Cholecystokinin (CCK): a neuromodulator with therapeutic potential in Alzheimer's and Parkinson's disease

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Abstract

Cholecystokinin (CCK) is a neuropeptide modulating digestion, glucose levels, neurotransmitters and memory. Recent studies suggest that CCK exhibits neuroprotective effects in Alzheimer's disease (AD) and Parkinson's disease (PD). Thus, we review the physiological function and therapeutic potential of CCK. The neuropeptide facilitates hippocampal glutamate release and gates GABAergic basket cell activity, which improves declarative memory acquisition, but inhibits consolidation. Cortical CCK alters recognition memory and enhances audio-visual processing. By stimulating CCK-1 receptors (CCK-1Rs), sulphated CCK-8 elicits dopamine release in the substantia nigra and striatum. In the mesolimbic pathway, CCK release is triggered by dopamine and terminates reward responses via CCK-2Rs. Importantly, activation of hippocampal and nigral CCK-2Rs is neuroprotective by evoking AMPK activation, expression of mitochondrial fusion modulators and autophagy. Other benefits include vagus nerve/CCK-1R-mediated expression of brain-derived neurotrophic factor, intestinal protection and suppression of inflammation. We also discuss caveats and the therapeutic combination of CCK with other peptide hormones.

Keywords

CCK; Alzheimer's disease; Parkinson's disease; memory formation; neuroprotective; dopamine; cognitive decline; insulin resistance; neuroinflammation; BDNF

1 Introduction

Cholecystokinin (CCK) is a gut-brain peptide with many roles. It modulates metabolic processes, acts as a neuromodulator and as a growth factor in the brain (Rehfeld, 2017). CCK is widely synthesised across the body, such as by intestinal endocrine l-cells mainly located in the duodenum, jejunum and ileum, as well as by peripheral nerves and immune cells. Furthermore, greater than in the periphery, CCK is expressed at high levels in almost every brain area, e.g. the hypothalamus, hippocampus, cerebral cortex, striatum and spinal cord (summarised in (Rehfeld, 2017)). While region-specific, the magnitude of cerebral CCK expression is much greater than that of other neuropeptides (Crawley, 1985; Rehfeld, 1978), highlighting the importance of CCK. An exception is the cerebellum, where only pro-CCK is expressed especially in fetal tissue, but conversion to bioactive CCK (with α-amidated COOH terminus 'Trp-Met-Asp-Phe') is virtually absent (Rehfeld, 1978; Rehfeld et al., 1992).

As stimulated by food intake, intestinal cells release different variants of CCK into the circulatory system, including predominantly CCK-33 and CCK-22, with lower secretion of CCK-58 and CCK-8 (Rehfeld, 1998; Rehfeld et al., 2001). Important for receptor interactions, shorter plasma CCKs such as CCK-8 (88 %) are more strongly tyrosine-O-sulphated compared to longer forms, for example CCK-58 (62 %) (Agersnap & Rehfeld, 2015). As demonstrated by Agersnap et al. (2016), there are only minor proportions of non-sulphated CCKs in the brain (excluding the cerebellum and dependent on the animal species and brain region, only ≤ 10 % of all CCKs, and ~1.5 % of CCK-8, are non-sulphated). The predominant neuropeptide variant in the brain is sulphated CCK-8 (CCK-8S; 'Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe'), e.g. shown to account for a striking ~96.4 % of all CCKs in the porcine cortex (Agersnap et al., 2016; Rehfeld, 2017). Additionally, due to lack of tyrosine, non-sulphated CCK-5 ('Gly-Trp-Met-Asp-Phe') acts as neuromodulator and is present in modest quantities, while CCK-7 and CCK-4 peptides are found at trace and low levels, respectively (Rehfeld, 2017; Rehfeld & Hansen, 1986). The aforementioned differences in CCK forms are due to differential processing of the 95 amino acid pro-CCK peptide by prohormone convertases (PCs), with dominant expression of

PC1/3 in the gut and PC2 in cerebral neurons (Rehfeld et al., 2008). PC5/6 also contribute to the intestinal production of CCK-22. Besides CCK, its structurally related family member gastrin(-17/34), e.g. largely produced in antro-duodenal G-cells, shares the bioactive C-terminal sequence of CCKs ('Trp-Met-Asp-Phe') (Rehfeld, 2019).

There is some controversy regarding whether CCK crosses the blood brain barrier (BBB) (Hommer, Palkovits, et al., 1985; Ouerdane et al., 2022). A study in dogs demonstrated that circulatory CCK-8 and CCK-33/39 are not transported into, at least, the cerebrospinal fluid (CSF) (Zhu et al., 1986). It is likely that only short and/or sulphated forms of CCK translocate into brain tissue. CCK-8S is likely the primary BBB-penetrating form, as its peripheral injection was shown to rapidly alter cerebral neurotransmitters, amino acid levels and hippocampal plasticity within 5 - 10 min *in vivo* (Acosta, 1998, 2001; Dolatabadi & Reisi, 2014; Reisi et al., 2015). CCK-4 presumably also crosses the BBB, as the peptide triggers panic attacks in humans following injection (for a historical overview, see Rehfeld (2021)) (Bradwejn, 1993). When comparing the cerebral effects of short CCKs, an *in vivo* study suggests that mainly peripheral CCK-8S, but less so unsulphated CCK-8 and CCK-4, effectively enters the brain (Altar & Boyar, 1989). As direct proof, a synthetic CCK-8 analogue was confirmed to diffuse across the BBB into the hippocampus, cortex, substantia nigra (SN) and striatum (Z. Zhang et al., 2022; Z. Zhang et al., 2023).

CCK binds to two principal G-protein-coupled receptors (GPCRs), including CCK-1R and CCK-2R. Importantly, sulphation increases receptor affinity and only sulphated CCKs effectively bind CCK-1Rs, while both sulphated and non-sulphated CCKs as well as gastrin interact with CCK-2Rs (Dufresne et al., 1996; S. C. Huang et al., 1989). CCK-1Rs are located in the stomach and gastric mucosa, (exocrine) pancreas, gallbladder smooth muscle cells, ovary, spleen, thymus, gut and on vagal afferent fibres and brain capillary endothelial cells (May et al., 2016; Moriarty et al., 1997; Morisset et al., 2003; Rettenbacher & Reubi, 2001; Reubi et al., 1997; Reubi et al., 1999; Schmitz, Goke, et al., 2001; Tokunaga et al., 1993; Weinberg et al., 1997). Although RT-PCR has detected CCK-1R in the kidney, protein expression has not been confirmed (Dufresne et al., 2006). Studies in rats, pigs and

monkeys suggest that CCK-1Rs are also present in the brain, including the area postrema, nucleus tractus solitarius (NTS), interpeduncular nucleus, dorsal motor nucleus of the vagus, hypothalamic regions (supraoptic, arcuate, paraventricular nuclei and preoptic area), dorsomedial, infundibular and supramammillary nuclei, mammillary bodies, neurohypophysis, SNpc, VTA, caudate nucleus and ventral putamen (Hill et al., 1987; Hill et al., 1990; Honda et al., 1993; Moran et al., 1986). There seem to be differences between rodents and monkeys, however, with primates showing greater cerebral expression levels and wider distribution of CCK-1Rs (Hill et al., 1990). CCK-2Rs are expressed in the pancreas, stomach (gastric fundus) and kidney, but not in other peripheral tissue (Ito et al., 1993; Y. M. Lee et al., 1993; von Schrenck et al., 2000). Instead, CCK-2R is regarded as the brain-specific receptor and ubiquitously expressed across the central nervous system (CNS), e.g. located in the cerebral cortex, hippocampus, amygdala, striatum, midbrain, olfactory regions, pons, spinal cord, anterior pituitary and septum spinal tract of the trigeminal nerve (Hill et al., 1987; Honda et al., 1993; Ito et al., 1993; Moran et al., 1986; Van Dijk et al., 1984). Interestingly, a novel CCKR, originally GPR173, has recently been identified, which was shown to potentiate inhibitory gamma-aminobutyric acid (GABA) transmission by cortical interneurons (He et al., 2023). Relative to other organs, the human protein atlas reported that expression of GRP173 is the highest in the brain, also present in regions such as the hippocampus and midbrain (Uhlen et al., 2015). Moreover, GPR173 is expressed in peripheral tissue, including the ovaries, pancreas and heart (McIlwraith et al., 2022). If activated by another neuropeptide, phoenixin, GPR173 regulates follicular development, reproduction, inflammation, water and food intake (see Liang et al. (2022) and McIlwraith et al. (2022) for details). Thus, GPR173 could play a significant role in some of the peripheral, cognitive, memory- and motor-associated effects of CCK.

CCK-1Rs typically couple to $G\alpha_{q/11}$, but also $G\alpha_{s}$, $G\alpha_{i}$, and $G\alpha_{13}$, whereas CCK-2R activation mainly leads to $G\alpha_{q/11}$-, or alternatively $G\alpha_{i}$-, signalling (see Figure 1 for Alzheimer's disease (AD)- and Parkinson's disease (PD)-related pathways) (Y. Ding et al., 2022; Q. Liu et al., 2021; X. Zhang et al., 2021). Thus, the downstream signalling of CCKRs may vary, and are dependent on cell type, brain

region (or tissue type) and presence of other GPCRs and/or modulating proteins. GPR173 (potentially a novel CCKR), at least when induced by phoenixin, was demonstrated to induce $G\alpha_s$/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)-signalling in hypothalamic gonadotropin-releasing hormone and kisspeptin neurons (Treen et al., 2016). GPR173 was also suggested to couple $G\alpha_{q/11}$ (not shown) (Larco et al., 2013). More studies are necessary to verify relevant CCK-binding, receptor function/interactions and downstream signalling of GPR173.

On a physiological level, CCK acts as a hormone that promotes digestive processes in the periphery. This includes the stimulation of bile release from the liver and gallbladder, production and secretion of pancreatic enzymes, improvement of gut motility and blood flow as well as satiety-signalling across CCK-1Rs located on vagal afferent nerves (Rehfeld, 2017). CCK also inhibits gastric acid secretion through CCK-1R-mediated somatostatin release (D. Chen et al., 2004).

Because CCK elicits CCK-2R-mediated insulin release by pancreatic β-cells, the therapeutic utility of gastrin or non-sulphated CCK-8 derivates (desulphated to prevent CCK-1R-mediated gallbladder contraction) have been investigated in obesity and type 2 diabetes mellitus (T2DM) animal models (reviewed in Pathak et al. (2018) and Rehfeld (2019)). Given that obesity (J. Chen et al., 2014; R. Kim & Jun, 2020; Park et al., 2022; Zhuang et al., 2021; Zuin et al., 2021) and, especially, T2DM (Athanasaki et al., 2022; Athauda et al., 2022; Maluf et al., 2019) are risk factors for AD and PD, the anorexigenic and incretin-like effects of CCK might indirectly prevent neurodegeneration. Moreover, following meal intake, CCK release enhances the cerebral uptake of insulin across the BBB, presumably by binding to CCK-1Rs on capillary endothelial cells (May et al., 2016). Insulin acts as a key growth factor in the brain (Figure 2), and it was shown that intranasal insulin therapy enhanced cognition in healthy adults (Benedict et al., 2004; Reger et al., 2006), mild cognitive impairment (MCI) and mild-moderate AD patients (particularly, if apolipoprotein E4-negative) (Long et al., 2022) and possibly PD patients (Novak et al., 2019). Importantly, brain insulin resistance is an independent key pathologic event in AD and PD (Holscher, 2020). Thus, co-treatment of CCK with glucagon-like peptide-1 (GLP-1) could be highly promising in ameliorating the chronic inflammatory response that

leads to desensitisation of insulin (see Reich & Holscher (2022b) for an extensive review, or (Holscher, 2019)). Pro-inflammatory cytokines, by acting on their respective receptors on neurons, result in activation of kinases (inhibitor of κB–kinase β, protein kinase R and c-Jun N-terminal kinase (JNK)) that phosphorylate, and thus inactivate, the immediate downstream effector of the insulin receptor: insulin receptor substrate 1 (IRS-1) (Figure 2) (Reich & Holscher, 2022b).

Importantly, CCK plays key roles in mood, plasticity and memory formation, as evident by co-localisation with cell bodies of glutamatergic pyramidal (Morino et al., 1994), GABAergic (Somogyi et al., 1984), dopaminergic (Hokfelt et al., 1980) and serotonergic neurons (van der Kooy et al., 1981). Our group has recently demonstrated that CCK has protective effects in animal models of neurodegenerative diseases (Z. Zhang et al., 2022; Z. Zhang et al., 2023). As such, this review aims to illustrate the implications of CCK in the brain. This includes the neuropeptide's physiological impact on hippocampal plasticity and memory formation and regulation of the nigrostriatal and mesolimbic dopamine release. We further describe the neuroprotective effects, with a focus on AD and PD. Finally, we cover related key aspects of CCK, including colonic protection, brain-derived neurotrophic factor (BDNF)/nerve growth factor (NGF) expression and anti-inflammatory properties, as well as the therapeutic opportunity for growth factor combinations.

2 Physiological modulation of plasticity, learning and memory by cholecystokinin

2.1 Cholecystokinin and receptor expression in the hippocampus

CCK, particularly the CCK-8S form, is one of the most expressed genes in the hippocampus (cornu ammonis (CA)1), indicating a key role in memory formation (M. A. Meyer, 2014). The cell bodies of CCK-immunoreactive neurons are located in the entorhinal cortex, subiculum, stratum pyramidale, amongst dentate granule cells and within the inner molecular layer of the dentate gyrus (Greenwood et al., 1981). CCK-producing neurons are exclusively GABAergic and regulated by incoming CCK-positive synaptic boutons, while CCK neurons form synapses with local pyramidal and

non-pyramidal neurons (Nunzi et al., 1985; Somogyi et al., 1984). CCK binding sites and expression of both CCK-1Rs and CCK-2Rs has been reported for all major subregions of the hippocampus, including the (pre/para-)subiculum, dentate gyrus, CA1, CA2 and CA3 (Honda et al., 1993; Kritzer et al., 1988). CCK-2Rs are present on excitatory pyramidal neurons and GABAergic interneurons (S. Y. Lee et al., 2011) and expressed at greater levels compared to CCK1Rs (Honda et al., 1993). Hippocampal CCK-2Rs principally contribute to memory formation, whereas peripheral CCK-1Rs expressed on vagal afferent fibres seem to be indirectly involved by enhancing hippocampal BDNF expression (section 5.1) (Lemaire, Barneoud, et al., 1994; Peters et al., 2006; Tirassa & Costa, 2007; Tirassa et al., 1998).

2.2 Transient facilitation of glutamatergic neurotransmission

CCK modifies both hippocampal presynaptic glutamate release and postsynaptic excitation. CCK-8, CCK-8S or a CCK-2R agonists were shown to elicited the endogenous release of glutamate, but not GABA, in hippocampal slices or into synaptosomes in a CCK-2R and extracellular Ca^{2+}-dependent manner (Breukel et al., 1997; Migaud et al., 1994). *In vivo*, however, peripheral CCK-8S administration resulted in reduced hippocampal glutamate levels 30 min post injection (Acosta, 1998). This suggests that CCK-mediated glutamate release is time-dependent and initially heightened, but then decreased. A study using cultured rat brain slices has confirmed that the addition of CCK, or endogenously released CCK, acutely elevates synaptic vesicle numbers and glutamate release probability in the hippocampus (Deng et al., 2010). These effects were conveyed by CCK-2Rs, involving phospholipase C beta (PLCβ), Ca^{2+} and protein kinase C (PKC)-signalling. CCK-indued PKC activation in the hippocampus likely prevents neuropeptide Y receptor 1/2/5-mediated inhibition of voltage-gated Ca^{2+} channels and presynaptic glutamate release (Figure 1) (Silva et al., 2003; Silva et al., 2007).

Regarding excitability, CCK treatment had depolarising effects in dentate granule cells (Brooks & Kelly, 1985; Sinton, 1988). Similarly, CCK promoted excitation in CA3 pyramidal neurons in a CCK-2R-,

but not CCK-1R-, mediated fashion (Gronier & Debonnel, 1995). Hippocampal CCK-2Rs are canonically $G\alpha_{q/11}$-coupled (S. Y. Lee et al., 2011), which promotes excitability via PLCβ-induced generation of IP3, release of Ca^{2+} from ER stores and PLCβ/diacylglycerol (DAG)-mediated inhibition of TWIK-related acid-sensitive K^+ channels (TASK)-1 and TASK-3 (Figure 1) (Wilke et al., 2014). However, in CA1 pyramidal neurons, only sulphated, but not unsulphated, CCK-8S seems to enhance excitability, suggesting that CCK-1Rs might play a role (Boden & Hill, 1988; Dodd & Kelly, 1981; Jaffe et al., 1987). An *ex vivo* study further showed that administered or endogenous CCK enhances α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-driven excitatory post-synaptic currents across hippocampal perforant path-dentate gyrus granule cell, CA3-CA3 and Schaeffer collateral-CA1 synapses in a CCK-2R-dependent manner (Deng et al., 2010). This postsynaptic facilitation likely involves PKC activation and phosphorylation of AMPARs at Ser^{831}, which decreases AMPAR activation threshold (Figure 1) (Kristensen et al., 2011).

There are time-associated effects of CCK on hippocampal plasticity *in vivo*, however. CCK-8S was shown to transiently enhance tonic excitatory postsynaptic potential and population spikes 5 - 10 min post i.p. injection, followed by their return to baseline from 15 min (Dolatabadi & Reisi, 2014). Moreover, relative to controls, CCK-8S-treated animals showed enhanced paired-pulse responses in the dentate gyrus at 40 ms, but deteriorated ones between 70 - 300 ms. Because CCK was shown to promote presynaptic glutamate release, but not vesicle recovery (Deng et al., 2010), this suggests that the neuropeptide acutely triggers a burst release of glutamate that leads to depletion of this neurotransmitter in response to prolonged stimulation.

2.3 Basket cell gating and regulation of GABA release

There are GABAergic parvalbumin- and CCK-expressing basket cells that modulate the output of principal excitatory pyramidal neurons in the hippocampus (reviewed in detail in Armstrong & Soltesz (2012)). These basket cells form synapses with dendrites of CA1/CA3 pyramidal neurons and

dentate granule cells in order to regulate (perisomatically inhibit) firing of these excitatory neurons, thus controlling oscillary network rhythm and mood (Freund & Katona, 2007; Ribak & Seress, 1983; Takacs et al., 2015). Parvalbumin$^+$ basket cells (~15.6 % of CA1 interneurons (Bezaire & Soltesz, 2013)) are fast firing and stimulation of extrasynaptic CCK-2Rs leads to noncanonical $G_{i/o}$-mediated opening of transient receptor channels and GABA release in a P/Q-type Ca^{2+} channel-dependent manner (Armstrong & Soltesz, 2012; S. Y. Lee et al., 2011). By contrast, CCK$^+$ basket cells (~8 % of CA1 interneurons (Bezaire & Soltesz, 2013)), due to receiving less excitatory input, have a comparably slower firing pattern, while GABA projection onto pyramidal neurons requires N-type Ca^{2+} channels (Armstrong & Soltesz, 2012; Karson et al., 2008). Notably, there are other less well characterised CCK interneurons, such as Schaffer collateral-associated cells, that modulate hippocampal memory formation (Cope et al., 2002).

In both the CA1 (*ex vivo*) and dentate gyrus (*in vivo*), CCK-2R activation on interneurons was demonstrated to induce K^+ channel inhibition, spontaneous GABA release and increased inhibitory post-synaptic current (iPSC) frequencies 2 - 4 min post administration, followed by a persistent iPSC reduction from 10 min (Deng & Lei, 2006; K. K. Miller et al., 1997). Interestingly, via CCK-2Rs, either CCK, conotoxin (N-type Ca^{2+} channel inhibitor) or endocannabinoids were shown to depress iPSCs induced by carbachol in CA1-located interneurons, whereas iPSCs mediated by CCK were inhibited by agatoxin (a P/Q-type Ca^{2+} channel inhibitor) (Karson et al., 2008). This indicates that CCK has a bidirectional effect on hippocampal GABA transmission. Other studies specified that CCK-2R activation on parvalbumin$^+$ basket cells enhanced GABA release, whereas GABA exocytosis by their CCK$^+$ counterparts was inhibited by CCK through endocannabinoid-signalling (Foldy et al., 2007). In this context, the cannabinoid receptor 1 (CB1R) is exclusively present on axonal terminals of CCK$^+$, but not parvalbumin$^+$, basket cells, while pyramidal neurons also express dendritic CCK-2Rs. Postsynaptic receptor activation on pyramidal neurons was shown to result in $G\alpha_{q/11}$/PLCβ-mediated endocannabinoid synthesis (Figure 1), retrograde activation of CB1Rs on presynaptic boutons of CCK$^+$ basket cells and, thus, inhibition of GABA release (S. H. Lee & Soltesz, 2011; Neu et al., 2007).

As such, the activity of CCK^+ basket cells is inversely correlated with that of both $parvalbumin^+$ basket and pyramidal cells in the hippocampus (Dudok et al., 2021). Furthermore, the CCK-mediated gating towards $parvalbumin^+$ basket cell activity potentially enhances performance in tasks needing precise timing and integration of information in short time windows (Armstrong & Soltesz, 2012).

2.4 Impact on hippocampal and cortical memory formation

Animal studies indicate that CCK distinctly affects the different stages of hippocampal memory formation. Peripheral (i.p.) and intrahippocampal injections of a CCK-2R agonist, but not administration into the caudate/putamen or prefrontal cortex, resulted in better object recognition memory in rats (Sebret et al., 1999). This effect occurred when the CCK-2R agonist was injected 30 min prior to the retrieval trial and 6 h after the initial training session. Interestingly, endogenous CCK immunoreactivity was also greater during the acquisition and retrieval phase, while the hippocampal administration of a CCK-2R antagonist at these time points impaired object memory. In aged Fischer 344 rats, daily systemic injections of CCK-8S prior to behavioural tests did not acutely influence cognitive or motor performance, but enhanced spatial memory retention in the probe trial of the Morris Water Maze (MWM) (Voits et al., 2001). Another study tested memory improvements in i.p. injected rats for 14 days with CCK-8S, with MWM training and the probe trial on days 10 - 14 (Reisi et al., 2015). On MWM days, CCK-8S was administered 3 - 4 h prior to the trials. Using this administration schedule, CCK-8S had no effect on spatial learning, suggesting that the neuropeptide was given too far away from the trial. Interestingly, combining CCK-1/2R dual agonist or, more strongly, CCK-4 injections with scopolamine, a sedative drug, before training sessions impaired food pellet (spatial working) memory in the radial maze (Harro & Oreland, 1993). There is evidence that hippocampal CCK-1R activation promotes, but that of CCK-2R suppresses, olfactory recognition in rats, however (Lemaire, Barneoud, et al., 1994; Lemaire, Bohme, et al., 1994). This suggests that CCK-4 (CCK-2R agonist) given prior to trials did not impede the learning process in the study of Harro

and Oreland (1993), but reduced radial maze performance by inhibiting sense of smell. On the other hand, administration of either a CCK-1/2R agonist or antagonist immediately after every training session mostly had no impact on spatial working memory in the radial maze over a 2 week period, suggesting that memory consolidation was unaffected (Harro & Oreland, 1993). In fact, prolonged peripheral, daily CCK-8S treatment after passive avoidance learning sessions lowered memory on the test day, suggesting that the gut-brain peptide could inhibit the consolidation step in the hippocampus (Sadeghi et al., 2015).

The chemogenetic activation of CCK-GABA neurons in mice resulted in improved hippocampus-associated memory and cognitive function, including greater social and object recognition, contextual fear conditioning, contextual discrimination and problem-solving, but with a mild increase in anxiety (Whissell et al., 2019). As such, enhancing the activity of GABAergic CCK^+ interneurons facilitates memory formation. On the other hand, loss of CCK-2R-expressing $parvalbumin^+$ and CCK^+ basket cells in hippocampal regions has been associated with learning deficits in a traumatic brain injury rat model (B. Zhang et al., 2011). Rodent studies have further confirmed that genetic knockout of either CCK (Lo et al., 2008), CCK-1R (Otsuka Long-Evans Tokushima fatty/OLETF rats; also a T2DM model (Kawano et al., 1994)) (X. L. Li et al., 2002; Matsushita et al., 2003; Nomoto et al., 1999) or CCK-2R (Sebret et al., 1999) impairs hippocampus-associated memory formation in passive avoidance, object recognition and spatial MWM paradigms.

Collectively, this suggests that the presence of endogenous or administered CCK in the hippocampus, or CCK-2R stimulation close to a training session, enhances declarative learning. This is in agreement with the fact that systemic CCK-8S administration elevates spontaneous glutamate release via CCK-2Rs (Breukel et al., 1997; Migaud et al., 1994) and increases baseline postsynaptic plasticity at 5 - 10 min post injection (at least in the dentate gyrus) (Dolatabadi & Reisi, 2014). Additionally, CCK diminishes activity of GABAergic CCK^+, but enhances that of $parvalbumin^+$, basket cells. Since plasticity in hippocampal early- and late-born $parvalbumin^+$ basket cells mediates knowledge exploitation during learning and memory acquisition, respectively (Donato et al., 2015),

basket cell gating by CCK further facilitates learning. Endogenous CCK release appears to enhance hippocampal memory retrieval, but CCK does not affect, or potentially impairs, memory consolidation. More studies are necessary to investigate these aspects.

The neocortical levels of CCK are 10-fold higher than that in the duodenum (Sanders et al., 1982), suggesting that the neuropeptide also plays a memory-regulating role in the neocortex. CCK was shown to be endogenously released in response to N-methyl-D-aspartate receptor (NMDAR) activity in the neocortex (X. Chen et al., 2019). CCK immunoreactive neurons were identified in the perirhinal and entorhinal cortices, with entorhinal CCK^+ neurons projecting to the auditory cortex in order to potentiate auditory, and visual cortex-derived, responses (X. Li et al., 2014; Z. Zhang et al., 2020). By activating CCK-2Rs, CCK infusion into the neocortex or auditory cortex enhanced long-term potentiation and visuo-auditory associative memory formation, which was inversely impaired after intracortical administration of a CCK-2R antagonist or CCK knockout (X. Chen et al., 2019; X. Li et al., 2014). Thus, the CCK system plays a key role in cortical visuo-auditory memory. While the amygdaloid impact of CCK on anxiety and fear memory is not in scope of this review (see e.g. S. J. Ballaz & Bourin (2021)), entorhinal CCK+ neurons also project CCK to the lateral amygdala, contributing to auditory (trace) fear memory formation (H. Feng et al., 2021). Interestingly, CCK-expressing basket cells in the cortex equally coordinate pyramidal neuron activity in the hippocampus (Del Pino et al., 2017). Genetic disruption of cortical CCK^+ basket cells was demonstrated to negatively affect specific aspects of spatial memory, including novel object recognition, spatial learning and short-term memory organisation.

There are also human studies investigating the cognitive impact of CCK. Peripheral or oral administration of the CCK analogue ceruletide or a CCK-2R antagonist was well tolerated and had no effect on attention, short-term and remote memory (Grasing et al., 1996; Hommer, Pickar, et al., 1985), but evoked fatigue (Hommer, Pickar, et al., 1985). Intravenous ceruletide infusions reduced food reward formation memory, but elevated neutral recognition memory (as expected for an anorexigenic peptide) (Pietrowsky et al., 1994), while CCK-4 impaired recall and recognition of words

during the administration process (Shlik et al., 1998). Schneider et al demonstrated that intranasal CCK-8S administration promoted automatic (familiarity-based) recognition memory shortly after administration (Schneider et al., 2009), but impaired controlled (recollection-based) recognition memory when administered during the consolidation phase (Schneider et al., 2005). These results are in agreement with animal studies, which show that entorhinal CCK facilitates relay of visuo-auditory responses (i.e. recognition) in the cortex (X. Chen et al., 2019; X. Li et al., 2014; Z. Zhang et al., 2020), whereas the presence of CCK might block hippocampal memory consolidation (Sadeghi et al., 2015). Reflective of improvements in cortical processing, intranasal CCK-8S was reported to transiently increase auditory event-related brain potentials (P3 complex) for about 120 min in humans (Denecke et al., 2002; Denecke et al., 2004; Pietrowsky et al., 2001; Pietrowsky et al., 1996).

3 Cholecystokinin in Alzheimer's disease

3.1 Pathological impairments in cholecystokinin secretion and hyperphagia

Bile acids are known to inhibit the intestinal release of CCK triggered by ingestion of triglycerides, amino acids or full liquid meals (Gomez et al., 1986; Gomez et al., 1988; Koop et al., 1989). Interestingly, plasma levels of certain bile acid metabolites have been shown to be elevated in MCI and AD patients (Greenberg et al., 2009; Marksteiner et al., 2018; Olazaran et al., 2015). Serum levels of some bile acid metabolites have been associated with amyloid beta $(A\beta)_{1\text{-}42}$, total Tau, phospho-Tau (Thr^{181}) in the CSF, glucose metabolism and neuronal degeneration in MCI and AD patients (Nho et al., 2019). Moreover, a higher ratio of circulatory deoxycholic acid, a bacterial product, versus cholic acid, as reduced in AD, was associated with cognitive decline (MahmoudianDehkordi et al., 2019; X. Pan et al., 2017). Bile acids seem to cross the BBB and their deregulation has additional adverse effects in AD, PD and other neurodegenerative diseases (reviewed in Xing et al. (2023)). The latter authors suggested that the bile acid-induced impairment

of CCK release, possibly due to intestinal dysbiosis or poor nutrition, might negatively affect CCK levels and disease progression.

Regarding CCK secretion, dietary changes affect the gut microbiota composition in as little as 24 h (Ley et al., 2006). In addition to inhibitory bile acids, there is *in vivo* evidence that nutritional changes alter the intestinal composition of bacteria and their secretion of metabolites, e.g. propionate, which increases the enteroendocrine expression of CCK (X. Zhang et al., 2019). Interestingly, ketones seem to promote intestinal CCK release (Paoli et al., 2015). This indicates that some of the cognitive, and possibly motor, benefits of ketogenic diets in AD and PD (A. Choi et al., 2021; Lilamand et al., 2021) might be due to peripheral production of CCK and associated benefits.

Of the circulatory CCKs, animal studies suggest that CCK-8, especially the sulphated form, might pass the BBB (Acosta, 1998, 2001; Dolatabadi & Reisi, 2014; Reisi et al., 2015). Once in the brain, CCK exerts direct protective effects, but also indirect ones, such as through vagus nerve-mediated upregulation of BDNF and NGF expression in the brain (section 5.1). However, CCK-8 levels in the blood stream are low (~10 % of all CCKs (Rehfeld et al., 2001)), suggesting that they only mildly contribute to cerebral CCK levels. On the other hand, due to its protective effects in the gut, CCK indirectly benefits cognitive health by reducing intestinal inflammation and enhancing growth factor secretion. For example, a CCK analogue improved BDNF release in the gut of a PD animal model (Su et al., 2022), while BDNF can exert its neuroprotective effects by crossing the BBB (Bathina & Das, 2015; W. Pan et al., 1998). It is also well established that intestinal, or microbiota-gut-brain axis, dysfunction is linked to the development of AD and PD (H. Wang et al., 2021).

Interestingly, there is a pathologic connection between loss of CCK, hyperphagia, obesity and AD. The persistent ingestion of energy-dense foods can affect endocannabinoid-signalling, the gut microbiome, release of their metabolites (e.g. bile acids or propionate) and promote chronic inflammation, thus resulting in downregulation of vagal CCK-1Rs, desensitisation to circulatory CCK, reduced satiety and obesity (reviewed in Cawthon & de La Serre (2021)). In rats, supplementation

with CCK was shown to reduce meal size and induce weight loss, but these satiating effects only persisted while peptide was administered (Gibbs et al., 1973; West et al., 1984). Inversely, CCK-1R knockout rats display more aggressive food intake and become obese (Bi et al., 2007; Moran et al., 1998), although lack of this receptor can be compensated for by other satiety mechanisms (Kopin et al., 1999). Notably, genetic deletion of CCK-2Rs also results in obesity due to loss of feeding inhibition in the hypothalamus (Clerc et al., 2007; Weiland et al., 2004). Likewise, a high-fat diet was demonstrated to lower cerebral CCK expression in hypothalamic regions in mice, indicating decreased satiety-signalling (M. J. Morris et al., 2008). In humans, metabolic syndrome evokes reductions in postprandial CCK secretion (Zwirska-Korczala et al., 2007), while plasma levels of bile acids were found to correlate with a poorer ability to abstain from food and greater body mass indexes (Prinz et al., 2015). Possibly linked to CCK, some AD animal models also show hyperphagia (Knight et al., 2012; Pugh et al., 2007; Vloeberghs et al., 2008), and so do ~18.6 % of AD patients (mostly male subjects) (Shea et al., 2018). Moreover, 3xTgAD mouse model were resistant to the anorexigenic effects of CCK injections and exhibited a lower c-Fos response in the paraventricular hypothalamic nucleus (PVN), which was inversely correlated with meal intake (Adebakin et al., 2012). C-Fos activities in other feeding-regulating regions, including the supraoptic nucleus of the hypothalamus, NTS and area postrema, were not affected, however. In summary, this suggests that poor dietary choices may promote obesity by impairing intestinal CCK secretion, thus reducing satiety-signalling across CCK-1Rs on vagal afferent nerves, and by decreasing hypothalamic CCK expression. Obesity is a clear risk factor for AD (Zhuang et al., 2021; Zuin et al., 2021), but independent of body weight, circulatory and/or cerebral CCK reductions in AD might promote hyperphagia.

3.2 Evidence for pathological alterations of cerebral cholecystokinin and its receptors

In favour of a disease-modifying role, it has recently been suggested that CCK levels may serve as a biomarker for AD (Plagman et al., 2019). Furthermore, evidence for reductions in the cerebral CCK levels are given in both animal and human AD studies. Aging has been shown to diminish cerebral CCK expression and number of binding sites in the rat hippocampus (Greenstein et al., 1991; Harro & Oreland, 1992). Additionally, the hippocampal CCK mRNA levels in APP/PS1 mice were reported to be halved relative to age-matched wild-type littermates, suggesting that lack of CCK might predispose to neurodegeneration and negatively affects cognition in AD (Y. J. Liu et al., 2021). Indeed, dysfunction of hippocampal CCK^{+} interneurons, which are the local source of CCK, was associated with more advanced stages of AD (Reid et al., 2021). Similar to AD animals, post-mortem studies in AD patients have revealed that CCK expression in the cerebral cortex is lower compared to healthy controls (Perry et al., 1981), with a 24 - 38 % downregulation of CCK immunoreactivity in some, but not all, cortical regions (Mazurek & Beal, 1991). However, unaltered levels of CCK derivates or CCKR binding in the cerebral cortex of AD patients have also been reported (Lofberg et al., 1996). Importantly, higher CSF levels of CCK were positively correlated with a reduced risk of MCI and AD, better cognitive function and more gray matter volume in several brain areas, such as the posterior cingulate cortex, parahippocampal gyrus and medial prefrontal cortex (Plagman et al., 2019). CSF CCK pools further correlated with Tau and phospho-Tau (Thr^{181}) levels, while greater Tau loads attenuated the memory-improving association of higher CCK levels. In agreement with a beneficial role of CCK, genetic screens in MCI or AD patients have identified a downregulated expression of cerebral CCK-1Rs and hippocampal CCK-2Rs relative to healthy controls (Hokama et al., 2014; Lin et al., 2014), and a link between hippocampal CCK expression and cognition (Y. J. Liu et al., 2021).

Notably, altered CCK-2R expression was also associated with Huntington's disease and obesity (Hokama et al., 2014). The latter, especially when combined with metabolic syndrome and/or type 2

diabetes, represents an additional risk factor for cognitive decline (Jung & Mok, 2022; Veronese et al., 2017), AD (Zhuang et al., 2021; Zuin et al., 2021) and PD (J. Chen et al., 2014; R. Kim & Jun, 2020; Park et al., 2022).

3.3 Neuroprotective effects of cholecystokinin in Alzheimer's disease

Classically, the neuropathology in AD has been summarised as the triad of extracellular Aβ plaques, intracellular neurofibrillary Tau tangles and synapse loss (Breijyeh & Karaman, 2020). This is only a subset of the AD pathology promoting neurodegeneration and cognitive decline, however. Other pathologic events include, for example, oxidative stress, mitochondrial damage, dysfunctional autophagy, loss of hippocampal neurogenesis and BBB and microvascular injury (Reich & Holscher, 2020). Importantly, chronic inflammation likely plays a key role in AD, resulting in cerebral insulin resistance, growth factor desensitisation and glucose hypometabolism (see also Figure 2) (Holscher, 2019; Neth & Craft, 2017). Such insulin receptor (IRS-1/phosphoinositide 3-kinase (PI3K)/Akt) pathway defects have been confirmed in the brains of AD patients, which led to the designation of AD as 'type 3 diabetes', even though the mechanism driving insulin desensitisation is different from that in true diabetes (Moloney et al., 2010; Steen et al., 2005; Talbot et al., 2012). The consequences of cerebral insulin resistance in AD patients include decreased brain blood flow and glucose hypometabolism (Drzezga et al., 2003; Hoyer et al., 1988; Lying-Tunell et al., 1981; Mosconi et al., 2008; Ogawa et al., 1994), impaired expression of glucose-metabolising enzymes and enhanced formation of oxidation products (Iwangoff et al., 1980; Zhao et al., 2015). T2DM is also a well-established risk factor for AD (Athanasaki et al., 2022). Therefore, it is intuitive to test drugs that re-sensitise insulin-signalling in peripheral tissue and the brain. This has been done with success, using the incretin hormones GLP-1 and glucose-dependent Insulinotropic polypeptide (GIP), or both, in AD animal models and clinical trials (Reich & Holscher, 2022b). CCK and gastrin also exert an incretin, i.e. insulin-releasing, effect that is comparably modest, however (see Rehfeld (2011) and Rehfeld

(2019)). Nevertheless, studies employing peptide co-treatment or dual agonists have shown that gastrin potentiates the beneficial effects of other incretins (GLP-1) in diabetes models (Dalboge et al., 2014; Fosgerau et al., 2013; Suarez-Pinzon et al., 2008). As such, CCK could have therapeutic potential in AD.

In vitro, in both hippocampal CCK neurons derived from wild-type and APP/PS1 mice, CCK-8S exposure for multiple weeks promoted the density of dendritic filopodia and spines in a CCK-2R-dependent manner (L. L. Zhang et al., 2013). Treatment with CCK-8S also changed membrane parameters, increased firing frequency, facilitated excitatory synaptic transmission and heightened postsynaptic density protein-95 (PSD-95) expression, while decreasing synaptic inhibition. This suggests that CCK can potentially improve the synaptic pathology in AD. There is also evidence that cortical CCK-2R activation protects from glutamate-, kainate or NMDA-induced excitotoxicity (Akaike et al., 1991; Tamura et al., 1992), which is another pathologic event in the cortex (and other brain regions) in AD (Y. Chen et al., 2021; Ong et al., 2013).

In the hippocampus, $G\alpha_{q/11}$-recruiting CCK-2Rs are expressed on excitatory pyramidal neurons and both parvalbumin$^+$ and CCK$^+$ basket cells (S. Y. Lee et al., 2011). For the first time, our group has demonstrated that a CCK-2R-binding, unsulphated CCK-8 analogue has neuroprotective effects in an Aβ-based AD animal model. Initially, we demonstrated that a proteolytically resistant, carboxyfluorescein-labelled CCK analogue crossed the BBB after injection, diffusing into the hippocampus and cortex (Z. Zhang et al., 2023). Similar to *in vitro* studies (L. L. Zhang et al., 2013), hippocampal dendritic spine density, synapse numbers, morphology, various synaptic proteins (microtubule-associated protein 2, synaptophysin and postsynaptic density protein 95 (PSD-95)) and long-term potentiation were recovered in CCK analogue-treated APP/PS1 mice relative to untreated littermates (Z. Zhang et al., 2023). Synaptic protection resulted in improved spatial learning and memory (Morris Water Maze), working memory (Y Maze) and exploratory behaviour (Hao et al., 2023; Z. Zhang et al., 2023). These pro-cognitive effects of CCK involved a reduction in $A\beta_{1\text{-}42}$ production and deposition (Hao et al., 2023; Z. Zhang et al., 2023). Moreover, in contrast to

untreated APP/PS1 mice, CCK administration normalised the downregulated phosphorylation (activation) of the PI3K/Akt and PKA/cAMP response element-binding protein (CREB) pathways and expression of both BDNF and tyrosine kinase B (TrkB) in the hippocampus (Z. Zhang et al., 2023).

The CCK analogue further protected from morphological changes in hippocampal mitochondria in APP/PS1 mice (Hao et al., 2023). As co-confirmed in amyloid precursor protein-overexpressing N2a cells *in vitro*, this mitoprotective effect *in vivo* was dependent on CCK-2R and downstream 5' adenosine monophosphate-activated protein kinase (AMPK) activation in hippocampal neurons, which reversed the reduced expression of the mitochondrial fusion proteins mitofusin 2 (Mfn2) and optic atrophy 1 (OPA1), while preventing abnormal upregulation of the fission-inducers mitochondrial E3 ubiquitin ligase 1 (MUL1) and dynamin-related protein 1 (Drp-1). AMPK activation leads to activation of the mitochondrial biogenesis-associated transcription factor peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), which expresses fusion-enhancing modulators (Mfn2, OPA1 etc), but suppresses that of fission proteins (Drp-1) (Cannavino et al., 2015; J. Huang et al., 2019; Peng et al., 2017; Soriano et al., 2006). Genetic or pharmacological inhibition of Drp-1 has been linked to reduced mitochondrial damage and fragmentation, oxidative stress and cognitive decline in the APP/PS1 mouse model (Baek et al., 2017), as well as decreased loss of dopaminergic neurons, their processes and motor function in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD (Filichia et al., 2016). As such, CCK induces the AMPK/PGC-1α pathway to restore mitochondrial fusion/fission dynamics (Figure 1), offering protection against pathological hyperfission observed in AD animal models and patients (Cho et al., 2009; Y. J. Liu et al., 2020; X. Wang et al., 2009; X. Wang et al., 2008). Utility of a CCK antagonist and intrahippocampal receptor knockdown confirmed that all aforementioned effects, including improvements in synaptic markers, cognition, mitochondria and protein pathway activation, were dependent on hippocampal CCK-2Rs (Hao et al., 2023; Z. Zhang et al., 2023).

Considering that AMPK activation results in inhibition of mammalian target of rapamycin complex 1 (mTORC1) and, thus, induction of autophagy (Y. Li & Chen, 2019), this effect was likely responsible

for Aβ degradation seen in CCK-8 analogue-treated APP/PS1 mice (Figure 1) (Hao et al., 2023; Z. Zhang et al., 2023). Another study showed that CCK-8S administrations stimulated neural stem cell proliferation (Ki-67), while reducing apoptosis, in the rat dentate gyrus (Reisi et al., 2015). As such, CCK may promote hippocampal neurogenesis, which was shown to involve the CCK-mediated stimulation of glutamate release by, and inflammatory suppression of, local astrocytes (Asrican et al., 2020). Because indirect CCK-1R-signalling across vagal afferent nerves triggers hippocampal BDNF and NGF production *in vivo* (section 5.1) (Tirassa & Costa, 2007; Tirassa et al., 1998), sulphated CCK-8 mimetics could show better effects regarding memory and/or neuroprotection, but at the cost of more peripheral side effects (i.e. gallballder complications) (Rehfeld, 2019). Interestingly, CCK, whose intestinal release is evoked by food intake, seems to activate the same neuroprotective $G\alpha_{q/11}$-associated pathways in the hippocampus that acylated ghrelin, the 'hunger' hormone released during fasting, does (reviewed in Reich & Holscher (2020)).

Various AD mouse models, including APP/PS1 mice, develop cerebral insulin resistance, which is reflected by impaired PI3K and Akt activation (Batista et al., 2018; Long-Smith et al., 2013; Paladugu et al., 2021). This inactivation involves Aβ-induced inflammation and aberrant stimulation of the JNK/tumour necrosis factor alpha (TNF-α) pathway (Bomfim et al., 2012; Q. L. Ma et al., 2009). GLP-1 agonists such as liraglutide can restore neuronal insulin sensitivity in such animals by decreasing Aβ generation, mending dysfunctional autophagy and suppressing inflammation (reviewed in Reich & Holscher (2022b)). Besides normalising BDNF and TrkB expression, CCK might also improve cerebral insulin-signalling (PI3K/Akt phosphorylation) due to reducing Aβ deposition and inhibiting pro-inflammatory responses by microglia and astrocytes (Figure 2 and section 5.2).

4 Cholecystokinin in Parkinson's disease

4.1 Physiological modulation of the nigrostriatal and mesolimbic dopamine pathways

CCK is involved in modulating dopamine transmission across the movement-inducing nigrostriatal (SN pars compacta (SNpc) to caudate-putamen) and reward-regulating mesolimbic (ventral tegmental area (VTA) to nucleus accumbens) pathways (Luo & Huang, 2016). CCK-1R-dependent activation by CCK-8S, but not by non-sulphated CCK-4, has been shown to increase dopamine, aspartate and dynorphin B levels in the SN *in vivo* (from 10 μM) (You et al., 1996). At higher CCK-8S concentrations (100 μM), dopamine, but also glutamate and GABA, pools were heightened in the neostriatum (caudate, putamen and nucleus accumbens). Vice versa, the nigrostriatal release of CCK was dependent on dopamine (Sierralta & Gysling, 1990), likely mediated by dopamine D2 receptors (D_2Rs) located on axons and nerve terminals in the caudate-putamen (X. Z. Ding & Mocchetti, 1992; D. K. Meyer & Krauss, 1983). Curiously, CCK-1R knockout mice displayed higher basal dopamine levels in the caudate-putamen, but not nucleus accumbens (Feifel et al., 2003). This could indicate that CCK-1Rs stimulate dopamine production and transmission in the SNpc, but suppress dopamine release in the caudate-putamen. Alternatively, baseline dopamine release might be increased as a compensatory measure due to the lack of CCK-1Rs.

Regarding the mesolimbic pathway, when dopamine-releasing drugs (amphetamine and methamphetamine) were administered, CCK was shown to be expressed in the VTA and projected to the medial nucleus accumbens, with extracellular CCK levels paralleling those of dopamine (Hurd et al., 1992; Martin et al., 2012). As such, likely similar to the nigrostriatal pathway, endogenous CCK production and accumbal neuropeptide release are caused by a rise in dopamine levels (Hurd et al., 1992; Sierralta & Gysling, 1990). Animal studies have further revealed the principal mesolimbic function of CCK-1Rs and CCK-2Rs. CCK-1Rs present in the posterior, but not anterior, part of the nucleus accumbens enhanced stimulus-evoked dopamine release (Marshall et al., 1991). Furthermore, injection of CCK into the nucleus accumbens promoted locomotion and stereotypy in a

CCKR-dependent manner, when a dopamine agonist was co-administered (Crawley et al., 1985). Because this effect was not observed when CCK was desulphated or a non-sulphated CCK analogue was employed (Crawley et al., 1985), this suggests that accumbal CCK-1Rs selective for sulphated versions of CCK facilitate reward responses. Congruently, studies employing CCK-1R antagonists demonstrated that systemic or nucleus accumbens-specific inhibition of this receptor counteracts locomotion induced by (chronically administered) amphetamine (DeSousa et al., 1999; Phillips et al., 1993; Wunderlich et al., 2004). On the other hand, amphetamine-evoked dopamine release in the neostriatum of mice was blocked following central or peripheral CCK-8S injections via CCK-2Rs, but not CCK-1Rs (Altar & Boyar, 1989). Furthermore, CCK-2R agonism reinforced amphetamine ingestion, indicating that the effect of this dopamine-increasing drug was impaired (Bush et al., 1999). In line with inhibitory properties, CCK-2R antagonism prevented the CCK-induced reduction in dopamine release in the anterior nucleus accumbens following stimulation (Marshall et al., 1991). Pharmacological blockade of CCK-2Rs also potentiated locomotor behaviour triggered by amphetamine (Higgins et al., 1994). Therefore, CCK-1Rs located in the posterior nucleus accumbens augment dopamine-induced reward responses, whereas CCK-2Rs in the anterior nucleus accumbens inhibit them. The ultimate effect of CCK was suggested to be dependent on the magnitude of its release or the presynaptic vs. postsynaptic and region-specific presence of stimulatory CCK-1Rs vs. inhibitory CCK-2Rs (Y. Ma & Giardino, 2022). Additionally, given that the neuropeptide's sulfation state was e.g. shown to influence gastric acid secretion (Maeda et al., 2000), it matters whether a sulphated (CCK-1&2R-binding) or non-sulphated (only CCK-2R-interacting) form of CCK is released.

Since the mesolimbic CCK release reflects that of, and is seemingly triggered by, dopamine (Hurd et al., 1992; Martin et al., 2012; Sierralta & Gysling, 1990), the physiological purpose of CCK appears to be the termination of dopamine-induced reward behaviour via CCK-2Rs (Y. Ma & Giardino, 2022). This is supported by the fact that CCK-2Rs suppress neostriatal dopamine release, especially when dopamine pools are elevated (Altar & Boyar, 1989). Moreover, VTA neurons were shown to somatodendritically release CCK in response to optogenetic stimulation (Martinez Damonte et al.,

2023). This physiological release, or VTA infusion of CCK, encouraged long-term potentiation in GABA synapses in a CCK-2R-dependent manner, lowered local dopamine (Ca^{2+})-signalling and reduced the appetite of mice.

Collectively, particularly at higher neuropeptide concentrations, CCK-1R activation by sulphated CCKs can augment extracellular dopamine levels across the movement-coordinating nigrostriatal pathway. By contrast, baseline dopamine levels are not affected by CCK in the mesolimbic pathway. However, CCK-2Rs in the VTA and nucleus accumbens terminate dopamine release and reward behaviour following a stimulus. Selective expression of CCK-1Rs in the posterior nucleus accumbens may promote reward-associated behaviours, however. This indicates that CCKR-modulating drugs could be promising agents for the treatment of PD, but also other disorders such as schizophrenia or addiction, as reviewed elsewhere (S. Ballaz, 2017; Y. Ma & Giardino, 2022).

4.2 The disease-associated impact of cholecystokinin

Compared to AD, the pathological role of CCK is less prominent in PD. In the 6-hydroxydopamine (6-OHDA) animal model of PD, increased levels of two CCK derivatives were found in the lesioned hemisphere (Nilsson et al., 2009). Similarly, in 6-OHDA-injected rats, CCK expression in the SN was enhanced and further potentiated via l-3,4-dihydroxyphenylalanine (L-DOPA), while L-DOPA administrations elevated striatal CCK levels ipsilateral to the lesion (Taylor et al., 1992). This lesion-induced increase in CCK could be a consequence of feedback loss from dopaminergic neurons, or a protective compensatory response, as suggested for Tau pathology in AD (Plagman et al., 2019). Notably, L-DOPA treatment also heightened CCK levels in the SN of sham-operated animals (Taylor et al., 1992). Because nigrostriatal CCK expression is stimulated by the activation of neuronal dopamine D_2Rs (X. Z. Ding & Mocchetti, 1992; D. K. Meyer & Krauss, 1983), dopamine replacement therapy could upregulate CCK levels in relevant brain regions in PD patients (at least transiently, before desensitisation to L-DOPA etc. occurs (Beckers et al., 2022)). On the other hand, lack of

dopamine impairs striatal CCK production (Sierralta & Gysling, 1990), which could negatively affect disease progression.

Interestingly, it was shown that DJ-1 interacts with Ras-responsive element-binding protein 1 to induce the transcription of CCK from rev response elements and Sp1-binding sites (Yamane et al., 2013). DJ-1 upregulates antioxidant expression, thus detoxifying reactive oxygen species (ROS), induces intracellular dopamine degradation and regulates the immune system, while a loss-of-function mutation in DJ-1 (L166P) leads to early-onset PD and other complications (L. L. Liu et al., 2023; Moore et al., 2003; L. Zhang et al., 2020). Considering the anti-inflammatory actions of CCK (section 5.2), this DJ-1-associated reduction in CCK expression might participate in deregulation of the immune system (L. Zhang et al., 2020).

Genetically, in humans, CCK, CCK-1R or CCK-2R polymorphisms do not increase PD risk. However, a genetic variant of CCK (-45C>T), even more so when combined with the CCK-1R 779T>C polymorphism, has been linked to a higher occurrence of visual hallucinations amongst L-DOPA-treated PD patients (Fujii et al., 1999; Goldman et al., 2004; J. Wang et al., 2003).

4.3 Protection of dopaminergic neurons by cholecystokinin in Parkinson's disease

PD is characterised by the selective loss of SNpc-located dopaminergic neurons that project to the putamen to control movements (nigrostriatal pathway towards dorsal striatum) (Dickson, 2012). Up to ~30 % of dopaminergic SNpc neurons, ~60 % of their striatal processes and ~70 % of dopamine release in the dorsal striatum are lost when PD motor symptoms emerge (Cheng et al., 2010). The adjacent VTA is also negatively affected, but regresses slower than the SNpc (Alberico et al., 2015). There are numerous non-motor symptoms in PD (see Schapira et al. (2017)), such as apathy, which is related to dysregulation of mesolimbic (and mesocortical) reward pathways emanating from the VTA. A side product of neuronal degeneration may be the intracellular formation of Lewy bodies or Lewy neurites consisting of alpha-synuclein (α-syn) (Dickson, 2012). While all neurons are subjected

to the aging process and associated complications, dopaminergic SNpc neurons are specifically vulnerable due to high energy demands, oxidative phosphorylation and concomitant mitochondrial ROS production, catecholamine synthesis (thus increasing danger of reactive dopamine quinone formation), modest ROS and Ca^{2+}-buffering capabilities and poorly myelinated axons (Bose & Beal, 2016; Giguere et al., 2019; Pacelli et al., 2015; Sulzer & Surmeier, 2013). Likewise, toxins (i.e. pesticides) and genetic mutations in various genes, including DJ1, leucine-rich-repeat kinase 2, PTEN-induced kinase 1, Parkin, glucocerebrosidase or α-syn, cause early- or late-onset PD by exacerbating oxidative stress, mitochondrial dysfunction, autophagy defects, protein aggregation and inflammation (Simon et al., 2020).

A root cause of sporadic PD, however, might be metabolic deficiency (Muddapu et al., 2020). Responsible for such an impairment is the development of cerebral insulin resistance, as evident in the SNpc, basal ganglia and other brain regions in PD patients, with a loss of insulin receptor expression and downstream pathway inactivation by pro-inflammatory cytokines (Figure 2) (Holscher, 2019; Moroo et al., 1994; J. K. Morris et al., 2014; Takahashi et al., 1996; Tong et al., 2009). Additionally, expression of glucose-metabolising enzymes, i.e. those of the pentose phosphate pathway, are downregulated at an early stage during PD, which aggravates depletion of antioxidants and promotes glucose hypometabolism in the dorsal striatum (Dunn et al., 2014; Y. Xu et al., 2015). Similar to AD, T2DM is also a risk factor for PD (Hassan et al., 2020). Insulin re-sensitising GLP-1 agonists have shown great promise in treating PD in animal models and human clinical trials (reviewed in Reich & Holscher (2022b)), suggesting that CCK, like GLP-1, could also be used therapeutically.

We have shown that CCK has therapeutic potential in PD animal models. Biodistribution studies confirmed that an unsulphated CCK-8 analogue, which only binds CCK-2Rs, translocated into the SN and striatum following i.p. injection, suggesting that key brain regions were reached (Z. Zhang et al., 2022). In MPTP-administered mice, 14 days of CCK analogue treatment restored the levels of the mitochondrial biogenesis marker PGC-1α and its translation product, the fusion-modulator Mfn2,

while preventing deformation and loss of mitochondria in the SNpc (Figure 1) (Z. Zhang et al., 2022). Use of the CCK analogue also prevented endoplasmic reticulum (ER) stress (downregulation of inositol-requiring transmembrane kinase/endoribonuclease 1α/IRE1α expression), the MPTP-evoked abnormal increase in the macroautophagy markers autophagy-related 7 and Beclin 1 and the accumulation of damaged, autophagosome-engulfed mitochondria in the SNpc, further supporting that mitochondria were protected. Moreover, CCK mimetic administration blunted the MPTP-induced reduction in CREB phosphorylation and prevented the pro-apoptotic increase in the Bcl-2-associated X protein (Bax)/B-cell lymphoma 2 (Bcl-2) ratio. Microglial ionized calcium-binding adaptor molecule 1 (IBA-1) and astrocyte glial fibrillary acidic protein (GFAP) immunoreactivity in the SNpc were also reduced by the CCK analogue in MPTP-treated mice. Jointly, these anti-inflammatory, anti-apoptotic and mitoprotective effects of CCK resulted in reduced synaptic degeneration and death of tyrosine hydroxylase-positive dopamine neurons in the SNpc, leading to improved motor function and exploratory behaviour. The underlying neuroprotective signalling pathways of CCK in the SNpc were likely mediated by local CCK-2Rs and $G\alpha_{q/11}$-signalling in our study (see Figure 1), since the CCK-8 analogue was unsulphated and, thus, had low affinity for CCK-1Rs (Z. Zhang et al., 2022). As such, the protective effects of the CCK-8 analogue in the MPTP mouse model parallel those seen in the hippocampus of APP/PS1 mice (Figure 1) (Hao et al., 2023; Z. Zhang et al., 2023).

However, CCK-1Rs could play an indirect role in neuroprotection by modulating dopamine release. The study of Hill et al (1990) suggests that CCK-1Rs are expressed at high densities in the SNpc (and VTA), with higher densities in primates compared to rodents, whereas low or no expression of CCK-2Rs was detected in the SNpc (more pronounced in the striatum) (Hill et al., 1987; Hill et al., 1990; Honda et al., 1993; Ito et al., 1993; Moran et al., 1986; Van Dijk et al., 1984). CCK-1R, but not CCK-2R, activation of nigral neurons leads to their depolarisation and local dopamine release (Wu & Wang, 1994b; You et al., 1996). Treatment with higher CCK-8S concentrations also stimulated dopamine release across the neostriatum *in vivo* (You et al., 1996). Therefore, low CCK concentrations induce

CCK-1R-mediated somatodendritic dopamine release by SNpc neurons, whereas higher doses of CCK trigger axonal dopamine release in striatal regions. Mechanistically, similar to the CCK-2R/$G\alpha_{q/11}$-mediated increase in excitability in some hippocampal subregions (Figure 1) (Gronier & Debonnel, 1995; Wilke et al., 2014), CCK-1R activation appears to induce $G\alpha_{q/11}$-signalling, cationic currents (TASK-1/3 opening) and enhanced excitability in SN dopaminergic neurons (at least *in vitro*) (Wu & Wang, 1994a). It has been suggested that dopamine release by SNpc neurons is impeded by inhibition of vesicular monoamine transporter 2 (VMAT2; responsible for dopamine-packing into vesicles), while N-type and P/Q-type Ca^{2+} channel inhibition blocks the axonal liberation of dopamine (Rice & Patel, 2015; Sulzer et al., 2016). Because VMAT2 activity and N-type Ca^{2+} channel opening seem to be decreased by $G\alpha_{q/11}$-signaling (Holtje et al., 2003; Zamponi & Currie, 2013), this might explain why lower CCK concentrations induce local somatodendritic dopamine release in the SNpc, but not axonal release in the striatum. Depending on the conditions, CCK-1Rs can recruit a range of G proteins, including $G\alpha_{q/11}$, $G\alpha_s$, $G\alpha_i$, and $G\alpha_{13}$ (Y. Ding et al., 2022; Q. Liu et al., 2021; X. Zhang et al., 2021). Because high extracellular CCK levels elicit axonal dopamine release in the striatum *in vivo* (You et al., 1996), there could be a CCK concentration-dependent, or temporally regulated, switch in G proteins downstream of the CCK-1R in SNpc dopaminergic neurons.

Importantly, CCK-evoked somatodendritic dopamine release by SNpc neurons will stimulate local dopamine DRs and, thus, influence downstream signalling and neuroprotection post CCKR activation. In the striatum, dopamine D_1Rs and D_2Rs are almost exclusively present on separate cells, with striatonigral neurons predominantly expressing dopamine D_1Rs (Gerfen, 2022). *In vivo*, 6-OHDA injections were shown to reduce dopamine D_1R levels in the SNpc, which was reversible with repeated administration of a dopamine D_1R agonist (Gerfen et al., 1990), suggesting that CCK could do the same by stimulating endogenous, somatodendritic dopamine release (You et al., 1996). By contrast, in PD patients, the expression of dopamine D_1Rs was shown to be upregulated amongst other cell survival-associated proteins in SNpc neurons (Simunovic et al., 2009). Dopamine D_1Rs are $G\alpha_{olf}$-coupled and result in induction of PKA and CREB (Jones-Tabah et al., 2021). Activation of the

latter transcription factor is neuroprotective and e.g. counteracts 6-OHDA-induced oxidative stress *in vitro* and in the SNpc *in vivo* (H. Kim et al., 2020). While mostly present in striatopallidal neurons (Gerfen, 2022), dopamine D_2R mRNA has also been detected in the SN (Le Moine et al., 1990). Dopamine D_2Rs are usually G_i-coupled and inhibit cAMP generation (Gerfen, 2022). Interestingly, in SN neurons, dopamine D_2Rs were shown to form heterodimers with the receptor for acylated ghrelin (growth hormone secretagogue receptor 1 alpha; GHS-R1α), changing downstream signalling (Tang et al., 2023). Activation of these receptor heterodimers by quinpirole (dopamine D2/3R agonist) protected from MPTP *in vitro* and *in vivo*, and enhanced TH and VMAT2 levels as well as CREB phosphorylation above baseline even in the SNpc of MPTP-untreated rats. Therefore, CCK-8S-induced dopamine release could be neuroprotective by activating dopamine D_1Rs and D_2Rs in the SNpc. Striatal dopamine release triggered by high CCK-8S doses could also acutely enhance motor function (You et al., 1996). Further studies are necessary to clarify the signalling mechanisms of nigral CCK-1Rs, receptor-driven dopamine release and the putative neuroprotective effects of dopamine $D_{1/2}$R activation, however.

Related to PD, methamphetamine use greatly increases the risk for developing Parkinsonism, resulting in oxidative and ER stress, neuroinflammation, excitotoxicity and degeneration of dopaminergic and other neurons (see Jayanthi et al. (2021)). In a respective mouse model, pre-treatment with CCK-8 decreased the methamphetamine-induced loss of tyrosine hydroxylase expression in the striatum and SN as well as that of dopamine transporters (striatum only) (Gou et al., 2015). This provides further evidence that CCK protects dopaminergic neurons from various toxic events.

A small trial tested the immediate impact of a single intranasal CCK-8 administration on motor function in PD patients, which had no effect (Smolnik et al., 2002). Curiously, acute intranasal CCK improved auditory brain potential (P3 complex; a measure of attention and information processing) in healthy controls, but impaired it in PD patients (Smolnik et al., 2002). Other studies support that intranasal CCK-8S transiently enhances the P3 complex in normal adults (Denecke et al., 2002;

Denecke et al., 2004; Pietrowsky et al., 2001; Pietrowsky et al., 1996). These attentional deficits specifically in CCK-8S-treated PD patients might be the consequence of CCK-induced GABA release in the striatum (Acosta, 1998; You et al., 1996), but without stimulation of the already lost dopaminergic SN/VTA neurons in PD.

4.4 Improvement of the gut pathology

PD patients show severe intestinal damage, including permeabilisation, changes in the gut microbiota, degeneration of enteric neurons and Lewy body formation in their nerve terminals (Scheperjans et al., 2018). These events are causative for the typical gastrointestinal symptoms in PD, usually preceding motor symptoms (Warnecke et al., 2022). The Intestinal pathology also contributes to that in the brain, for example by triggering systemic inflammation or via propagation of alpha synuclein (α-syn) seeds from the enteric nervous system and across the vagus nerve to the CNS (Klann et al., 2021; Rani & Mondal, 2021).

Besides the brain, CCK also ameliorates the gastrointestinal pathology in MPTP or human A53T α-syn transgenic PD mouse models. The 5 week-long administration of either a non-sulphated CCK-8 analogue or liraglutide was shown to prevent loss of the tight junction proteins occludin and zonula occludens-1 (ZO-1) and reduced the levels of the stress enzyme inducible nitric oxide synthase and pro-inflammatory cytokine TNF-α (Su et al., 2022). Moreover, administration of either of the peptides lowered the density of mono- and oligomeric α-syn species, while elevating TH levels, as indicative of decreased degeneration of enteric nervous system dopaminergic neurons, in the myenteric plexus (distal colon). The colonic reduction in BDNF levels in the PD mouse models was also partially prevented by neuropeptide injections. This restoration of gastrointestinal BDNF expression, which is impaired by inflammation, likely accounted for most of the protective effects of CCK and liraglutide, including the observed improvements in intestinal permeability, bowel and motor function and survival of dopaminergic neurons (Ahn et al., 2021; C. Li et al., 2018). An anti-

inflammatory effect is supported in the lipopolysaccharide-induced endotoxemia rat model, where injection of CCK-8S preserved gut integrity, prevented pro-inflammatory cytokine production and decreased bacterial invasion (Saia et al., 2020). CCK likely suppresses intestinal inflammation by acting on CCK-2R-expressing peripheral immune cells (Iwata et al., 1996; Schmitz, Schrader, et al., 2001), while sulphated peptide variants may additionally stimulate the vagus nerve (details in section 5.2) (Bozkurt et al., 2003; Luyer et al., 2005). Notably, in the mouse colon, BDNF transcription has been identified in epithelial cells and myenteric (GABAergic or dopaminergic) neurons (Lommatzsch et al., 1999; Lucini et al., 2002; Rao & Gershon, 2018). Our study in PD animal models employed a non-sulphated CCK-8 mimetic, suggesting that intestinal BDNF expression was restored by downregulating inflammation (Su et al., 2022). However, myenteric neurons express CCK-1Rs, indicating that sulphated CCKs might show additional benefits (Sternini et al., 1999).

5 Other beneficial therapeutic effects of cholecystokinin

5.1 Enhancement of nerve growth factor and brain-derived neurotrophic factor expression

BDNF is expressed in many tissues, including the brain and intestines, and acts as a protective growth factor, modulator of neurotransmission, plasticity and memory formation, neurogenesis-enhancer and more (see Bathina & Das (2015)). The neuroprotective effects of BDNF are exerted by binding to TrkB receptors, activating $IRS_{1/2}$/PI3K/Akt, src homology collagen peptide (Shc)/growth factor receptor-binding protein 2 (Grb2)/rat sarcoma (Ras)/rapidly accelerated fibrosarcoma (Raf)/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase 1/2 ($ERK_{1/2}$) and PLCβ-mediated IP3 and PKC signalling cascades. Stimulation of TrkB further leads to plasticity, stress resistance and survival gene expression through activation of CREB. BDNF expression is impaired in the hippocampus in AD, contributing to plasticity defects and memory decline (Banerjee & Shenoy, 2023), and the nigrostriatal pathway in PD, promoting neuronal atrophy

(Palasz et al., 2020). Enhancers of BDNF expression have been recognised as a potential therapeutic option for AD and PD (Banerjee & Shenoy, 2023; Palasz et al., 2020).

As BDNF, pro-NGF and its more mature form NGF are present in booth peripheral and cerebral tissues, both mediating regeneration and survival-signalling across TrkA receptors via the same neuroprotective downstream pathways as TrkB (Marlin & Li, 2015; Mitra et al., 2019). However, defects in cortical and hippocampal pro-NGF release as well as extracellular processing to NGF by plasmin in the forebrain negatively affect survival of local cholinergic neurons and cognition in AD (reviewed in Mitra et al. (2019)). This involves loss of principal TrkA receptor expression, pathologic binding of these receptors by Aβ (which also induces inflammation), lowered (apoptosis-provoking) ratios of TrkA vs. p75 neurotrophin receptors (p75NTRs) and poor retrograde NGF transport from axons to the nucleus in cholinergic neurons. Interestingly, peripheral NGF production was shown to be elevated in MCI and AD patients (Shen et al., 2019), whereas pro-NGF generation was impaired, but NGF elimination enhanced, in cortical regions (Pentz et al., 2021). NGF seems to be less involved in the cerebral pathology of PD compared to AD, although some studies have shown reduced pro-NGF and NGF levels in the serum of PD patients (Lorigados Pedre et al., 2002; X. M. Xu et al., 2018). NGF delivery or upregulation strategies in the brain and NGF mimetics have been tested as treatment options for AD (see Mitra et al. (2019)).

Interestingly, peripheral CCK might indirectly upregulate BDNF levels in selected brain regions. In noradrenergic LC3541 neurons, CCK-8S treatment was shown to enhance Akt and $ERK_{1/2}$ phosphorylation, thus increasing BDNF expression (Hwang et al., 2013). Akt and $ERK_{1/2}$ are kinases that indirectly, via mTORC1 or 90 kDa ribosomal s6 kinase, respectively, elicit the activation of the BDNF-regulating transcription factor CREB (phosphorylation at Ser^{133}; see also Figure 2) (Frodin & Gammeltoft, 1999; Reich & Holscher, 2022b; Velmurugan et al., 2012). CCK-8S also prevented downregulation of BDNF and caspase 3 activation in response to oxidative stress (H_2O_2) (Hwang et al., 2013). In agreement with protective effects in these neurons, CCK-signalling increased baseline expression of the anti-apoptotic protein Bcl-2 (CREB-mediated (Mabuchi et al., 2001)) and the

mitochondrial biogenesis inducer PGC-1α (Hwang et al., 2013), whose expression is, amongst other pathways, stimulated by cooperation of Akt/mTORC1 and yin-yang 1 (Blattler et al., 2012; Reich & Holscher, 2022b). The *in vitro* results were repeated *in vivo*, with i.p. injections of CCK-8S promoting c-Fos expression in the locus coeruleus (~40 % of these were tyrosine hydroxylase-positive noradrenergic neurons) (Monnikes, Lauer, & Arnold, 1997). This induction of c-Fos involved CCK-1R activation on vagal afferent nerves, also occurring in the dorsal vagal complex (DVC), NTS and PVN (Monnikes, Lauer, & Arnold, 1997; Monnikes, Lauer, Bauer, et al., 1997). Because CREB mediates c-Fos expression (Gandolfi et al., 2017), CCK likely also induces BDNF production in these brain regions. This further suggests that CCK-driven Akt and $ERK_{1/2}$ activation in noradrenergic neurons *in vivo* is dependent on the vagus nerve and indirect. Notably, in the mouse brain, GABAergic interneurons in the locus coeruleus were shown to express CCK-2Rs and GPR173 (a putative CCK-3R (He et al., 2023)) (Caramia et al., 2023). Besides vagal CCK-1Rs, local CCK-2Rs were confirmed not to be involved in BDNF expression in the locus coeruleus (Monnikes, Lauer, & Arnold, 1997; Monnikes, Lauer, Bauer, et al., 1997), while the role of GPR173 remains to be determined. Other animal studies have confirmed that repeated i.p. injections of CCK-8S for 3 weeks increased BDNF pools in the septum and, importantly, hippocampus (Tirassa & Costa, 2007). Vice versa, transcranial magnetic stimulation of the vagus nerve resulted in enhanced hippocampal BDNF and CCK expression, supporting a mechanistic link (M. B. Muller et al., 2000). Notably, peripheral CCK (or leptin) administrations transiently increase BDNF levels in the DVC and hypothalamus, which, at least in part, mediates CCK's anorexigenic effects (Bariohay et al., 2005). Given that the vagus nerve regulates hippocampal BDNF expression (M. B. Muller et al., 2000; O'Leary et al., 2018), it can be inferred that CCK-induced BDNF expression across the brain is based on CCK-1R-signalling across vagal afferents.

CCK also affects cerebral NGF expression. Peripheral CCK-8S injections transiently elevated NGF transcription and concentrations in the hypothalamus and pituitary (3-fold increased), hippocampus (+ 50 - 60 %) and septum, but not cortex, 15 - 60 min post administration or following prolonged

treatment from 3 days (Tirassa et al., 1999; Tirassa & Costa, 2007; Tirassa et al., 1998). Interestingly, CCK-1Rs were responsible for elevating NGF expression in the hypothalamus and pituitary and CCK-2Rs in the hippocampus, with vagus nerve inhibition by atropine reducing NGF expression in all brain regions (Tirassa et al., 1998). Because NGF expression in the CNS (cortex) was found to be dependent on promotor binding by both CREB and CCAAT/enhancer-binding protein delta (C/EBPdelta) (Figure 1) (McCauslin et al., 2006), this suggests that CCK-evoked CREB expression elicits that of NGF in the same brain region. Interestingly, CCK-8S administrations were shown to reduce expression of TrkA and p75NTR, but elevate that of TrkB, in the hippocampus and septum (Tirassa & Costa, 2007). Thus, relevant in the context of AD, CCK modifies hippocampal neurotrophin receptors and weakens NGF- and apoptosis-, but potentiates BDNF-, signalling.

5.2 Suppression of cerebral and systemic inflammation

Neuroinflammation, or the chronic activation of microglia and astrocytes, is a hallmark of both AD and PD (Stephenson et al., 2018). Inflammation involves nuclear factor-kappa B (NF-κB)-mediated transcription of pro-inflammatory cytokines (interleukin (IL)-1β, IL-6, IL-12, interferon γ, TNF-α, etc) as well as production of chemokines, nitric oxide and ROS (Morales et al., 2014). Glial inflammatory stimuli may be oligomeric Aβ (El Khoury et al., 2003; Johnstone et al., 1999; Lim et al., 2013; Meda et al., 1995; Reed-Geaghan et al., 2009; Sheedy et al., 2013; Stewart et al., 2010) oxidised low density lipoprotein (Sheedy et al., 2013; Stewart et al., 2010), aggregated Tau (Morales et al., 2013), α-syn species (C. Kim et al., 2013; H. J. Lee et al., 2010), damage-associated molecular patterns (DAMPs; e.g. matrix metalloproteinase-3 (MMP3) (Chung et al., 2013; Y. S. Kim et al., 2007; Y. S. Kim et al., 2005) or mitochondrial derivatives (Bajwa et al., 2019)) and, in rarer cases, pathogen-associated molecular patters due to bacterial and viral infections (Vigasova et al., 2021). Additionally, systemic inflammation (Furman et al., 2019), BBB damage (Sweeney et al., 2018), aberrant activation of

peripheral immune cells (adaptive immunity) and infiltration of these into the brain play important roles in the pathologies of AD and PD (Anderson et al., 2014).

CCK exerts direct immunosuppressive effects in the body. Peripheral immune cells, including human myeloid cells (e.g. THP-1 monocytes), T and B lymphocytes and mononuclear blood cells isolated from patients, were shown to express CCK-2Rs (Iwata et al., 1996; Schmitz, Schrader, et al., 2001). Lymphocyte exposure to CCK-8S inhibited mitogen-induced proliferation and mobility, while CCK-8S decreased the expression of pro-inflammatory cytokines (TNF-α) via CCKR activation on THP-1 cells *in vitro* (De la Fuente et al., 1998; Miyamoto et al., 2012). Administration of the neuropeptide also prevented systemic and peripheral tissue (kidney, lung, spleen, gut) as well as immune cell inflammation in a T1DM mouse model or following lipopolysaccharide injection *in vivo* (Meng et al., 2002; Miyamoto et al., 2012) (Saia et al., 2020). A fundamental exception is the pancreas, however. In this organ, CCK evokes inflammation by stimulating, in particular, local acinar cells and stellate cells (see Smith & Solomon (2014) and section 6.2). As such, CCK has been used to induce pancreatitis models (Gorelick & Thrower, 2009; H. Kim, 2008).

CCK also stimulates anti-inflammatory signalling across the vagus nerve. A recent drug screen identified both CCK and dopamine agonists as intestinal anti-inflammatory agents in a zebrafish enterocolitis model. Reversely, use of CCK receptor antagonists aggravated colitis (Oehlers et al., 2017). Interestingly, CCK-1Rs are present on vagal afferent neurons projecting from the gut, in particular the duodenum, to the brain (Peters et al., 2006). CCK-8S treatment was demonstrated to quench colonic inflammation in a CCK-1R-dependent manner, but only when vagal afferent nerves were intact (Bozkurt et al., 2003). Additionally, electrical, anti-inflammatory vagus nerve activation, which involved participation of the hypothalamic-pituitary-adrenal (HPA) axis, was inhibited by cerebral administration of a CCK-2R antagonist (Gulpinar et al., 2004). There are three anti-inflammatory vagus nerve pathways (reviewed in Bonaz et al. (2016)), including the intestine-associated HPA axis-cortisol, cholinergic and splenic sympathetic pathways. In this context, food (fat) intake stimulates CCK release (Liddle, 1997), and it was shown that the enteral infusion of dietary fat

prior to haemorrhagic shock prevented systemic pro-inflammatory cytokine production and subsequent intestinal permeabilization (Luyer et al., 2005). This anti-inflammatory effect was abolished when CCK-1R, CCK-2R or nicotinic receptor antagonists were co-administered, however (Luyer et al., 2005). As such, this suggests that intestinal CCK-1R-signalling across vagal afferent fibres results in reciprocal, vagal efferent nerve-mediated activation of enteric neurons, acetylcholine release and anti-inflammatory α-7-nicotinic acetylcholine receptor activation on macrophages (Bonaz et al., 2016). On the other hand, plasma corticosterone (rodent variant of cortisol) levels were heightened by haemorrhagic shock, but unaltered by co-injection of CCKR antagonists (Luyer et al., 2005). This indicates that CCKR-signalling does not induce the anti-inflammatory HPA axis-cortisol pathway, but CCK-2Rs may be involved in its execution (Gulpinar et al., 2004; Luyer et al., 2005).

Other studies also shed light on the anti-inflammatory mechanisms of CCK, which may combat the development of insulin resistance in the brain (Figure 2). The expression of CCK-2R was confirmed in N9 murine microglial cells (Gou et al., 2020). Moreover, CCK-8S treatment prevented methamphetamine-induced inflammation, such as reduced activation of the pro-inflammatory transcription factor NF-κB, both *in vitro* and *in vivo*. Similar to microglia, the presence of functional CCK-2Rs has been confirmed in primary mouse and rat astrocytes (W. Muller et al., 1997). Furthermore, astrocyte CCK-signalling was shown to play a bidirectional role in hippocampal neurogenesis *in vivo* (Asrican et al., 2020). The latter group showed that CCK released by local interneurons stimulates glutamatergic input from astrocytes to neural stem cells in the dentate gyrus, leading to progenitor neuron proliferation. Inversely, the depletion of CCK induced astrogliosis (increased GFAP immunoreactivity) and activated pro-inflammatory genes, with inflammation known to inhibit neural stem cell proliferation (Asrican et al., 2020; Ekdahl et al., 2003). A direct anti-inflammatory effect is supported, since microglial IBA-1 and astrocyte GFAP immunoreactivity were reduced in CCK-8 analogue-treated MPTP mice (Z. Zhang et al., 2022). CCK might also quench

inflammation indirectly, by reducing neuronal apoptosis and the associated release of DAMPs, such as MMP3 derived from dopaminergic neurons (D. H. Choi et al., 2008).

In summary, CCK directly quenches systemic inflammation by activating CCK-2Rs on peripheral immune cells, microglia and astrocytes, while stimulating the cholinergic anti-inflammatory vagus nerve pathway via CCK-1Rs. By contrast, in the pancreas, CCK evokes inflammation.

6 Therapeutic caveats

6.1 Failed previous efforts to develop anti-obesity drugs

There are some caveats regarding the therapeutic use of CCK. In light of the CCK-1R-mediated satiating effects of CCK, as confirmed by use of selective antagonists (Hewson et al., 1988; Weatherford et al., 1992) and receptor knockout in rodents (Bi et al., 2007; Moran et al., 1998), pharmaceutical companies have developed CCK-1R agonists for the treatment of obesity. This includes, for example, GI181771X (Jordan et al., 2008) or compound 4a (Elliott et al., 2010). Favourably, 4a is orally available, thus avoiding the parenteral or intracerebral administration routes typically seen in CCK-based studies. The vast majority of studies have utilised CCK-8-based mimetics that induce satiety, although more recent evidence suggests that CCK-58 might be more effective due to additionally prolonging intermeal intervals (L. J. Miller et al., 2021; Overduin et al., 2014; Sayegh et al., 2014). Such CCK-1R analogues were tested in clinical trials, but have not been approved, however, due to producing insufficient weight loss, promoting pancreatic cancer and showing undesirable side effects such as nausea, diarrhea, stomach cramping/peptic ulcers and gallbladder complications (cholelithiasis) (see L. J. Miller & Desai (2016) and L. J. Miller et al. (2021)) (Rehfeld, 2019).

6.2 Pancreatitis and cancer

Another caveat is the known association between CCK, pancreatitis and, consequentially, a greater risk of pancreatic cancer (Smith & Solomon, 2014). In fact, supraphysiological CCK concentrations (at least 10-fold greater than following meal intake) and the CCK-1R/CCK-2R agonist cerulein have been used to generate pancreatitis models *in vitro* and *in vivo* (Gorelick & Thrower, 2009; H. Kim, 2008). In the pancreas, the collective evidence suggests that CCK-1Rs are dominant in humans, whereas rodents mainly express CCK-2Rs (reviewed in Smith & Solomon (2014)). However, both receptors are involved, exerting different pathologic responses. Activation of CCK-1Rs on pancreatic acinar cells is presumably linked to digestive enzyme secretion and, thus, inflammation (pancreatitis), while stimulation of CCK-2Rs drives hyperplasia. Moreover, stimulation of stellate cells by CCK results in collagen production, fibrosis and an acetylcholine-mediated augmentation of enzyme secretion by acinar cells. However, it has been suggested that high dose CCK administrations are not sufficient to induce (pancreatic) cancer, and that an additional pathologic factor must be present, for example co-exposure to carcinogens, a high fat diet, obesity, other inflammatory diseases or genetic predispositions.

From a therapeutic standpoint, CCK-2R agonists are preferable for long-term treatment, given that peripheral CCK-1Rs are linked to a range of other adverse effects (see section 6.1). Use of a CCK-2R agonist will likely diminish the side effect profile relative to a CCK-1R/CCK-2R-co-stimulating CCK mimetic in the pancreas, but the higher expression of CCK-2R in humans might lead to unforeseen complications (Smith & Solomon, 2014). Besides the pancreas, adenocarcinomas in the stomach, liver, rectum, colon, oesophagus, lung and medullary thyroid were shown to overexpress CCK-1Rs and/or CCK-2Rs, with CCK and gastrin aggravating pathogenesis (compiled in Zeng et al. (2020)). Whether long-term administration of CCK-2R mimetics is safe in elderly AD and PD patients remains to be determined, and concomitant cancer screens might be necessary.

6.3 Panic and anxiety

By activating central CCK-2Rs (Bradwejn et al., 1994), human studies have shown that exogenous CCK-4 has panicogenic effects in humans (Bradwejn, 1993; Bradwejn et al., 1990; de Montigny, 1989). In fact, intravenous CCK-4 injections have been validated as a human panic model (see also Rehfeld (2021)) (Eser et al., 2007; Goettel et al., 2023). The intensity of such panic attacks is dose-dependent. Moreover, as Rehfeld describes, panic lasts about 20 - 28 min following CCK-4 administration and includes 'intense anxiety, with a fear of dying, and a strange sense of the world sliding away, accompanied by palpitations, sweating, and faintness' (Rehfeld, 2021). Some studies suggest that patients with various disorders (social phobia, major depression, anxiety, panic and obsessive compulsive disorder) are more susceptible to the panicogenic effects of CCK-4 and its analogue pentagastrin compared healthy individuals (Brawman-Mintzer et al., 1997; deLeeuw et al., 1996; Koszycki et al., 2004; McCann et al., 1997; van Vliet et al., 1997). The cause of this enhanced sensitivity is not fully understood, and could be due to greater CCK-2R sensitivity and/or a synergistic effect with pre-existing anxiety in these patients. In the context of panic disorder, genetic studies have further shown that CCK polymorphisms may facilitate panic (Garvey et al., 1998; Hansen et al., 2000; Hosing et al., 2004; Z. Wang et al., 1998), but some can also be protective (Koefoed et al., 2010). Furthermore, an aggravating (Hosing et al., 2004), or no (Hattori et al., 2001), impact of genetic CCK-2R variants on panic disorder has been reported.

The CCK system has not only been associated with panic, but also anxiety. Unlike CCK-4, there does not seem to be any evidence for panicogenic effects of CCK-8. However, CCK-8S, or its mimetic caerulein, may trigger anxiety *in vivo* (Koks et al., 2000; Pérez de la Mora et al., 2007; Rex et al., 1994). An *in vivo* study administering cerulein showed that anxiety only materialised when rats were pre-stressed, suggesting that these anxiogenic effects of the CCK mimetic synergise with other sources of anxiety (Koks et al., 2000). Overexpression and knockout studies suggest that, at least in

the forebrain, the magnitude of CCK-2R activation correlates with the expression of anxiety in rodents (Q. Chen et al., 2006; Raud et al., 2005).

Interestingly, when directly compared *in vivo*, CCK-8S is less anxiogenic than CCK-4 (Rex et al., 1994). It was hypothesised that CCK-4 is more potent due to exposition of its N-terminal tryptophan residue, possibly allowing binding of additional receptors, such as GPR142 on pancreatic islets (Rehfeld, 2021). Additionally, sulphated CCK-8 mimetics might be less anxiogenic than unsulphated CCK-8 variants due to CCK-1R activation. The available evidence supports that CCK-1Rs are anxiolytic (compiled in Zwanzger et al. (2012)), while a CCK-1R haplotype has been associated with reduced risk of panic disorder in women (Koefoed et al., 2010). Activation of CCK-1Rs has further been linked to enhanced reward and lessened anxiety-like behaviour following drug withdrawal (see Y. Ma & Giardino (2022)).

Regarding anxiety-associated brain regions, CCK is strongly expressed in various subregions of the amygdala (a key player in fear expression and memory, and modulated by gut-brain peptides (Reich & Holscher, 2022a)), the hippocampus and cerebral cortex, but is also present at notable levels in the hypothalamus, thalamus and olfactory bulb. Similarly, CCK-2Rs are expressed in these brain areas, and multiple CCK projections between regions are involved (mapped in Zwanzger et al., (2012)).

fMRI scans have confirmed that panic-triggering CCK-4 injections stimulate amygdaloid activity (Eser et al., 2009), and enhance blood flow in other anxiety/fear-processing brain areas, including the thalamus (also activated by placebo, but weaker), cerebellar vermis, ventral anterior cingulate cortex, left and right insula, anterior cingulate/middle and superior frontal/middle and superior temporal/inferior frontal gyrus, sublobar areas, occipital lobe, cerebellum and brainstem (Eser et al., 2009; Schunck et al., 2006). CCK-4-induced panic, or CCK-2R-mediated anxiety, were shown to be partly mediated by β-adrenergic receptors (Le Melledo et al., 1998), but counteracted by administration of selective serotonin reuptake inhibitors (Shlik et al., 1997; van Megen et al., 1997)

and GABA(A) receptor-signalling (Raud et al., 2005). Other neuromodulators interacting with CCK-mediated anxiety appear to be neuropeptide Y, neuropeptide S, melatonin and endocannabinoids (see Zwanzger et al. (2012)). The panicogenic effects of CCK-4 further involve sympathetic and HPA axis activation, leading to Increased heart rate, diastolic blood pressure and plasma release of adrenocorticotropic hormone, prolactin, growth hormone, epinephrine and cortisol (Eser et al., 2009; Kellner et al., 1997; Khan et al., 2004; Koszycki et al., 1998; Strohle et al., 2000). Considering that the CCK system induces anxiety and panic, CCK-2R antagonists have been clinically tested for these conditions (Rehfeld, 2021).

Collectively, the evidence suggests that, unlike CCK-4, CCK-8 analogues (especially if sulphated) are less likely to trigger panic, and rather elicit anxiety. However, these dose-dependent anxiogenic effects may still interfere with the clinical utility of (unsulphated) CCK-2R analogues, given that an estimated 40 % of AD and 20 - 50+ % of PD patients already exhibit symptoms of anxiety (J. J. Chen & Marsh, 2014; Mendez, 2021).

7 Sex differences

Some studies have shown gender-specific differences in the CCK system. Comparison of both sexes has shown that CCK (intestinal) and CCK-1R (pancreatic) transcription shows an age-dependent decline in males, but not in female rats (Miyasaka et al., 1995). In ovariectomised animals, estradiol injections were shown to increase the number of CCK-1R binding sites in the pancreas (Geary et al., 1996), suggesting that sex hormones affect the CCK system. As such, considering that CCK-1R activation on acinar cells has been linked to pancreatitis (Smith & Solomon, 2014), susceptibility to this adverse effect could differ between male and female subjects of varying age.

It has also been reported that only male lean and obese Zucker rats, but not their respective female littermates, showed increased food intake in response to administration of a CCK-1R antagonist (Strohmayer & Greenberg, 1996). This sex difference is likely also explained by the higher circulatory

levels of estrogens in females, which enable and potentiate CCK-mediated satiation in the estrus, but not in other, phases of the ovarian cycle (reviewed in Geary (2001)). Estrogens also modulate female reproductive behaviour via the CCK and endogenous opioid systems, involving estrogen-driven CCK expression in the limbic-hypothalamic lordosis circuit (see Micevych & Sinchak (2001)) (Holland et al., 1998).

It is not known whether such gender-associated differences in e.g. estradiol levels affect the cognitive or neuroprotective effects of CCK. It must be noted that our studies testing a non-sulphated CCK-8 analogue in AD and PD models employed male mice (Hao et al., 2023; Z. Zhang et al., 2022; Z. Zhang et al., 2023). As such, it cannot be ruled out that female rodents, possibly in an ovarian cycle-associated manner, show a different response to exogenous CCK in the brain.

8 Combination of growth factors as a therapeutic opportunity

Interestingly, the protective effects of the CCK analogue in the brain and colon of AD or PD animal models were on par with those of liraglutide (Hao et al., 2023; Su et al., 2022; Z. Zhang et al., 2022). The latter is a GLP-1 receptor agonist activating the neuroprotective PI3K/Akt, $ERK_{1/2}$ and cAMP/PKA pathways, with robust neuroprotective effects in AD/PD *in vivo* models and in clinical trials (reviewed in Reich & Holscher (2022b)). In T2DM animal models, co-administration of CCK and the GLP-1 analogue exendin-4 was more effective in ameliorating weight loss and T2DM-associated plasma glucose deregulation (Irwin et al., 2013; Trevaskis et al., 2015). Moreover, a GLP-1/gastrin (CCK-2R-binding) dual agonist has shown promising results in db/db (leptin receptor-deficient) mice (Dalboge et al., 2014; Fosgerau et al., 2013). CCK also synergises with leptin, whose receptor is co-expressed on vagal afferent nerves (at least in the absence of food (Burdyga et al., 2002; Buyse et al., 2001)), in reducing gastric emptying, food intake and inflammation (Bozkurt et al., 2003; Peters et al., 2006). Importantly, GLP-1/GIP receptor dual agonists have demonstrated superior neuroprotective effects in AD and PD animal models compared to single receptor agonists such as

liraglutide (P. Feng et al., 2018; Lv et al., 2021; Maskery et al., 2020; Salles et al., 2020; Yuan et al., 2017; L. Y. Zhang et al., 2021). This suggests that a combination of incretins and related growth factors released following food intake or during fasting, i.e. in form of multi-receptor agonists, are a promising therapeutic strategy for AD and PD (Reich & Holscher, 2022b). Such combinations can be beneficial in various ways. First, neuroprotective pathways can be synergistically activated to achieve a greater effect. For example, co-activation of hippocampal or nigral CCK-2Rs and GHS-1Rα (ghrelin receptor) could theoretically potentiate neuroprotective $G\alpha_{q/11}$-signalling, AMPK/PGC-1α activation and autophagy (S. Y. Lee et al., 2011; Reich & Holscher, 2020). This requires that there are no counterregulatory effects, however. Our own observations support that the activation of opposing pathways in the same neurons, e.g. mTORC1-stimulating Akt vs. mTORC1-inhibiting AMPK activation (Saxton & Sabatini, 2017), should be avoided. Second, dependent on receptor distributions in the brain, a wider range of neurons and brain regions may be covered, if multiple GPCR agonists are utilised. Third, side effects could potentially be reduced by using lower doses (due to synergistic effects), or possibly by employing growth factors that reciprocally cancel adverse effects. An example could be the possible neutralisation of the anorexigenic and glucose-lowering effects of CCK (Pathak et al., 2018) by the appetite- and hyperglycemia-stimulating properties of co-administered ghrelin (Reich & Holscher, 2020).

9 Conclusion

CCK is a multi-functional peptide hormone. Impaired release and/or expression of CCK, CCK-1Rs and CCK-2Rs contributes to neurodegeneration in AD, while deregulation of the CCK system seems to be involved in visual hallucinations in PD. Brain-penetrant forms, in particular long-lasting synthetic CCK8 analogues, bind to neuronal CCK-2Rs in the hippocampus (AD) and SNpc (PD), resulting in AMPK activation and neuroprotection. This includes synaptic protection, restoration of the mitochondrial fusion/fission dynamics, autophagy and a reduction in systemic and cerebral inflammation. Similar to peptide hormones such as GLP-1, the anti-inflammatory effects of glial CCK-2R activation could prevent insulin resistance in neurons, a key pathologic feature in AD and PD. Sulphated CCK-8 likely offers additional therapeutic benefits by inducing CCK-1Rs, but at the cost of long-term side effects such as gallstones. Improved weight loss, glucose regulation and intestinal protection indirectly benefit AD and PD. Combinatorial use of CCK-8 and other growth factors, such as acylated ghrelin, could yield synergistic therapeutic benefits. Although CCK may stimulate pancreatitis, tumour growth, anxiety and panic attacks, studies testing CCK-8 in patients with neurodegenerative disorders are warranted.

10 Abbreviations

AD	Alzheimer's disease
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AMPK	5' adenosine monophosphate-activated protein kinase
α-syn	Alpha synuclein

Aβ	Amyloid beta
Bax	B-cell lymphoma 2-associated X protein
BBB	Blood brain barrier
Bcl-2	B-cell lymphoma 2
BDNF	Brain-derived neurotrophic factor
CA1-3	Cornu ammonis 1-3
cAMP	Cyclic adenosine monophosphate
CB1R	Cannabinoid receptor 1
CCK	Cholecystokinin
CCK-1/2R	Cholecystokinin receptor 1/2
CCK-8S	Sulphated cholecystokinin-8
C/EBPdelta	CREB and CCAAT/enhancer-binding protein delta
CREB	cAMP response element-binding protein
CSF	Cerebrospinal fluid
DAG	Diacylglycerol
DAMP	Damage-associated molecular pattern
Drp-1	Dynamin-related protein 1
Dopamine $D_{1/2/3}R$	Dopamine D1/2/3 receptor
DVC	Dorsal vagal complex
ER	Endoplasmic reticulum

$ERK_{1/2}$	Extracellular signal-regulated kinase 1/2
GABA	Gamma-aminobutyric acid
GFAP	Glial fibrillary acidic protein
GHS-R1α	Growth hormone secretagogue receptor 1 alpha
GIP	Glucose-dependent Insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GPCR	G-protein-coupled receptor
Grb2	Growth factor receptor-binding protein 2
HPA	Hypothalamic-pituitary-adrenal
IBA-1	Ionized calcium-binding adaptor molecule 1
IL	Interleukin
IRS-1	Insulin receptor substrate 1
JNK	c-Jun N-terminal kinase
L-DOPA	L-3,4-dihydroxyphenylalanine
MCI	Mild cognitive impairment
MEK	Mitogen-activated protein kinase kinase
Mfn2	Mitofusin 2
MMP3	Matrix metalloproteinase-3
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTORC1	Mechanistic target of rapamycin complex 1

MUL1	Mitochondrial E3 ubiquitin ligase 1
MWM	Morris Water Maze
NGF	Nerve growth factor
NTS	Nucleus tractus solitarius
NF-κB	Nuclear factor-kappa B
OPA1	Optic atrophy 1
PC	Prohormone convertases
PD	Parkinson's disease
PGC-1α	Peroxisome proliferator-activated receptor-γ coactivator 1 alpha
PI3K	Phosphoinositide 3-kinase
PKA	Protein kinase A
PKC	Protein kinase C
PLCβ	Phospholipase C beta
PSD-95	Postsynaptic density protein-95
PVN	Paraventricular hypothalamic nucleus
p75NTR	p75 neurotrophin receptor
Raf	Rapidly accelerated fibrosarcoma
Ras	Rat sarcoma
ROS	Reactive oxygen species
Shc	Src homology collagen peptide

SNpc	Substantia nigra pars compacta
TASK-1/3	TWIK-related acid-sensitive K^+ channel 1/3
TNF-α	Tumour necrosis factor alpha
TrkA/B	Tyrosine kinase A/B
T2DM	Type 2 diabetes mellitus
VMAT2	Vesicular monoamine transporter 2
VTA	Ventral tegmental area
ZO-1	Zonula occludens-1
6-OHDA	6-hydroxydopamine

11 Author contributions

The manuscript and the figures were generated by NR. CH reviewed and revised the paper.

12 Acknowledgements

The figures were made with BioRender.com.

13 Conflict of interest

The authors declare no conflict of interest.

14 References

Acosta, G. B. (1998). Administration of cholecystokinin sulphated octapeptide (CCK-8S) induces changes on rat amino acid tissue levels and on a behavioral test for anxiety. *Gen Pharmacol, 31*(4), 637-641. doi:10.1016/s0306-3623(98)00075-5

Acosta, G. B. (2001). A possible interaction between CCKergic and GABAergic systems in the rat brain. *Comp Biochem Physiol C Toxicol Pharmacol, 128*(1), 11-17. doi:10.1016/s1532-0456(00)00175-7

Adebakin, A., Bradley, J., Gumusgoz, S., Waters, E. J., & Lawrence, C. B. (2012). Impaired satiation and increased feeding behaviour in the triple-transgenic Alzheimer's disease mouse model. *Plos One, 7*(10), e45179. doi:10.1371/journal.pone.0045179

Agersnap, M., & Rehfeld, J. F. (2015). Nonsulfated cholecystokinins in the small intestine of pigs and rats. *Peptides, 71*, 121-127. doi:10.1016/j.peptides.2015.07.010

Agersnap, M., Zhang, M. D., Harkany, T., Hokfelt, T., & Rehfeld, J. F. (2016). Nonsulfated cholecystokinins in cerebral neurons. *Neuropeptides, 60*, 37-44. doi:10.1016/j.npep.2016.08.003

Ahn, E. H., Kang, S. S., Liu, X., Cao, X., Choi, S. Y., Musazzi, L., Mehlen, P., & Ye, K. (2021). BDNF and Netrin-1 repression by C/EBPbeta in the gut triggers Parkinson's disease pathologies, associated with constipation and motor dysfunctions. *Progress in Neurobiology, 198*, 101905. doi:10.1016/j.pneurobio.2020.101905

Akaike, A., Tamura, Y., Sato, Y., Ozaki, K., Matsuoka, R., Miura, S., & Yoshinaga, T. (1991). Cholecystokinin-induced protection of cultured cortical neurons against glutamate neurotoxicity. *Brain Research, 557*(1-2), 303-307. doi:10.1016/0006-8993(91)90149-p

Alberico, S. L., Cassell, M. D., & Narayanan, N. S. (2015). The Vulnerable Ventral Tegmental Area in Parkinson's Disease. *Basal Ganglia, 5*(2-3), 51-55. doi:10.1016/j.baga.2015.06.001

Altar, C. A., & Boyar, W. C. (1989). Brain CCK-B receptors mediate the suppression of dopamine release by cholecystokinin. *Brain Research, 483*(2), 321-326. doi:10.1016/0006-8993(89)90176-5

Anderson, K. M., Olson, K. E., Estes, K. A., Flanagan, K., Gendelman, H. E., & Mosley, R. L. (2014). Dual destructive and protective roles of adaptive immunity in neurodegenerative disorders. *Transl Neurodegener, 3*(1), 25. doi:10.1186/2047-9158-3-25

Armstrong, C., & Soltesz, I. (2012). Basket cell dichotomy in microcircuit function. *J Physiol, 590*(4), 683-694. doi:10.1113/jphysiol.2011.223669

Asrican, B., Wooten, J., Li, Y. D., Quintanilla, L., Zhang, F., Wander, C., Bao, H., Yeh, C. Y., Luo, Y. J., Olsen, R., Lim, S. A., Hu, J., Jin, P., & Song, J. (2020). Neuropeptides Modulate Local Astrocytes to Regulate Adult Hippocampal Neural Stem Cells. *Neuron, 108*(2), 349-366 e346. doi:10.1016/j.neuron.2020.07.039

Athanasaki, A., Melanis, K., Tsantzali, I., Stefanou, M. I., Ntymenou, S., Paraskevas, S. G., Kalamatianos, T., Boutati, E., Lambadiari, V., Voumvourakis, K. I., Stranjalis, G., Giannopoulos, S., Tsivgoulis, G., & Paraskevas, G. P. (2022). Type 2 Diabetes Mellitus as a Risk Factor for Alzheimer's Disease: Review and Meta-Analysis. *Biomedicines, 10*(4). doi:10.3390/biomedicines10040778

Athauda, D., Evans, J., Wernick, A., Virdi, G., Choi, M. L., Lawton, M., Vijiaratnam, N., Girges, C., Ben-Shlomo, Y., Ismail, K., Morris, H., Grosset, D., Foltynie, T., & Gandhi, S. (2022). The Impact of Type 2 Diabetes in Parkinson's Disease. *Mov Disord, 37*(8), 1612-1623. doi:10.1002/mds.29122

Baek, S. H., Park, S. J., Jeong, J. I., Kim, S. H., Han, J., Kyung, J. W., Baik, S. H., Choi, Y., Choi, B. Y., Park, J. S., Bahn, G., Shin, J. H., Jo, D. S., Lee, J. Y., Jang, C. G., Arumugam, T. V., Kim, J., Han, J. W., Koh, J. Y., Cho, D. H., & Jo, D. G. (2017). Inhibition of Drp1 Ameliorates Synaptic Depression,

Abeta Deposition, and Cognitive Impairment in an Alzheimer's Disease Model. *Journal of Neuroscience, 37*(20), 5099-5110. doi:10.1523/JNEUROSCI.2385-16.2017

Bajwa, E., Pointer, C. B., & Klegeris, A. (2019). The Role of Mitochondrial Damage-Associated Molecular Patterns in Chronic Neuroinflammation. *Mediators Inflamm, 2019*, 4050796. doi:10.1155/2019/4050796

Ballaz, S. (2017). The unappreciated roles of the cholecystokinin receptor CCK(1) in brain functioning. *Rev Neurosci, 28*(6), 573-585. doi:10.1515/revneuro-2016-0088

Ballaz, S. J., & Bourin, M. (2021). Cholecystokinin-Mediated Neuromodulation of Anxiety and Schizophrenia: A "Dimmer-Switch" Hypothesis. *Curr Neuropharmacol, 19*(7), 925-938. doi:10.2174/1570159X18666201113145143

Banerjee, M., & Shenoy, R. R. (2023). Emphasizing roles of BDNF promoters and inducers in Alzheimer's disease for improving impaired cognition and memory. *J Basic Clin Physiol Pharmacol, 34*(2), 125-136. doi:10.1515/jbcpp-2021-0182

Bariohay, B., Lebrun, B., Moyse, E., & Jean, A. (2005). Brain-derived neurotrophic factor plays a role as an anorexigenic factor in the dorsal vagal complex. *Endocrinology, 146*(12), 5612-5620. doi:10.1210/en.2005-0419

Bathina, S., & Das, U. N. (2015). Brain-derived neurotrophic factor and its clinical implications. *Arch Med Sci, 11*(6), 1164-1178. doi:10.5114/aoms.2015.56342

Batista, A. F., Forny-Germano, L., Clarke, J. R., Lyra, E. S. N. M., Brito-Moreira, J., Boehnke, S. E., Winterborn, A., Coe, B. C., Lablans, A., Vital, J. F., Marques, S. A., Martinez, A. M., Gralle, M., Holscher, C., Klein, W. L., Houzel, J. C., Ferreira, S. T., Munoz, D. P., & De Felice, F. G. (2018). The diabetes drug liraglutide reverses cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non-human primate model of Alzheimer's disease. *Journal of Pathology, 245*(1), 85-100. doi:10.1002/path.5056

Beckers, M., Bloem, B. R., & Verbeek, M. M. (2022). Mechanisms of peripheral levodopa resistance in Parkinson's disease. *NPJ Parkinsons Dis, 8*(1), 56. doi:10.1038/s41531-022-00321-y

Benedict, C., Hallschmid, M., Hatke, A., Schultes, B., Fehm, H. L., Born, J., & Kern, W. (2004). Intranasal insulin improves memory in humans. *Psychoneuroendocrinology, 29*(10), 1326-1334. doi:10.1016/j.psyneuen.2004.04.003

Bezaire, M. J., & Soltesz, I. (2013). Quantitative assessment of CA1 local circuits: knowledge base for interneuron-pyramidal cell connectivity. *Hippocampus, 23*(9), 751-785. doi:10.1002/hipo.22141

Bi, S., Chen, J., Behles, R. R., Hyun, J., Kopin, A. S., & Moran, T. H. (2007). Differential body weight and feeding responses to high-fat diets in rats and mice lacking cholecystokinin 1 receptors. *Am J Physiol Regul Integr Comp Physiol, 293*(1), R55-63. doi:10.1152/ajpregu.00002.2007

Blattler, S. M., Verdeguer, F., Liesa, M., Cunningham, J. T., Vogel, R. O., Chim, H., Liu, H., Romanino, K., Shirihai, O. S., Vazquez, F., Ruegg, M. A., Shi, Y., & Puigserver, P. (2012). Defective mitochondrial morphology and bioenergetic function in mice lacking the transcription factor Yin Yang 1 in skeletal muscle. *Molecular and Cellular Biology, 32*(16), 3333-3346. doi:10.1128/MCB.00337-12

Boden, P. R., & Hill, R. G. (1988). Effects of cholecystokinin and pentagastrin on rat hippocampal neurones maintained in vitro. *Neuropeptides, 12*(2), 95-103. doi:10.1016/0143-4179(88)90037-6

Bomfim, T. R., Forny-Germano, L., Sathler, L. B., Brito-Moreira, J., Houzel, J. C., Decker, H., Silverman, M. A., Kazi, H., Melo, H. M., McClean, P. L., Holscher, C., Arnold, S. E., Talbot, K., Klein, W. L., Munoz, D. P., Ferreira, S. T., & De Felice, F. G. (2012). An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers. *Journal of Clinical Investigation, 122*(4), 1339-1353. doi:10.1172/JCI57256

Bonaz, B., Sinniger, V., & Pellissier, S. (2016). Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. *J Physiol, 594*(20), 5781-5790. doi:10.1113/JP271539

Bose, A., & Beal, M. F. (2016). Mitochondrial dysfunction in Parkinson's disease. *Journal of Neurochemistry, 139 Suppl 1*, 216-231. doi:10.1111/jnc.13731

Bozkurt, A., Cakir, B., Ercan, F., & Yegen, B. C. (2003). Anti-inflammatory effects of leptin and cholecystokinin on acetic acid-induced colitis in rats: role of capsaicin-sensitive vagal afferent fibers. *Regul Pept, 116*(1-3), 109-118. doi:10.1016/s0167-0115(03)00194-0

Bradwejn, J. (1993). Neurobiological investigations into the role of cholecystokinin in panic disorder. *J Psychiatry Neurosci, 18*(4), 178-188.

Bradwejn, J., Koszycki, D., Couetoux du Tertre, A., van Megen, H., den Boer, J., & Westenberg, H. (1994). The panicogenic effects of cholecystokinin-tetrapeptide are antagonized by L-365,260, a central cholecystokinin receptor antagonist, in patients with panic disorder. *Arch Gen Psychiatry, 51*(6), 486-493. doi:10.1001/archpsyc.1994.03950060050005

Bradwejn, J., Koszycki, D., & Meterissian, G. (1990). Cholecystokinin-tetrapeptide induces panic attacks in patients with panic disorder. *Can J Psychiatry, 35*(1), 83-85. doi:10.1177/070674379003500115

Brawman-Mintzer, O., Lydiard, R. B., Bradwejn, J., Villarreal, G., Knapp, R., Emmanuel, N., Ware, M. R., He, Q., & Ballenger, J. C. (1997). Effects of the cholecystokinin agonist pentagastrin in patients with generalized anxiety disorder. *Am J Psychiatry, 154*(5), 700-702. doi:10.1176/ajp.154.5.700

Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules, 25*(24). doi:10.3390/molecules25245789

Breukel, A. I., Lopes da Silva, F. H., & Ghijsen, W. E. (1997). Cholecystokinin (CCK-8) modulates vesicular release of excitatory amino acids in rat hippocampal nerve endings. *Neuroscience Letters, 234*(1), 67-70. doi:10.1016/s0304-3940(97)00678-2

Brooks, P. A., & Kelly, J. S. (1985). Cholecystokinin as a Potent Excitant of Neurons of the Dentate Gyrus of Rats. *Annals of the New York Academy of Sciences, 448*(Jul), 361-374. doi:10.1111/j.1749-6632.1985.tb29931.x

Burdyga, G., Spiller, D., Morris, R., Lal, S., Thompson, D. G., Saeed, S., Dimaline, R., Varro, A., & Dockray, G. J. (2002). Expression of the leptin receptor in rat and human nodose ganglion neurones. *Neuroscience, 109*(2), 339-347. doi:10.1016/s0306-4522(01)00474-2

Bush, D. E., DeSousa, N. J., & Vaccarino, F. J. (1999). Self-administration of intravenous amphetamine: effect of nucleus accumbens CCKB receptor activation on fixed-ratio responding. *Psychopharmacology (Berl), 147*(3), 331-334. doi:10.1007/s002130051176

Buyse, M., Ovesjo, M. L., Goiot, H., Guilmeau, S., Peranzi, G., Moizo, L., Walker, F., Lewin, M. J., Meister, B., & Bado, A. (2001). Expression and regulation of leptin receptor proteins in afferent and efferent neurons of the vagus nerve. *Eur J Neurosci, 14*(1), 64-72. doi:10.1046/j.0953-816x.2001.01628.x

Cannavino, J., Brocca, L., Sandri, M., Grassi, B., Bottinelli, R., & Pellegrino, M. A. (2015). The role of alterations in mitochondrial dynamics and PGC-1alpha over-expression in fast muscle atrophy following hindlimb unloading. *J Physiol, 593*(8), 1981-1995. doi:10.1113/jphysiol.2014.286740

Caramia, M., Romanov, R. A., Sideromenos, S., Hevesi, Z., Zhao, M., Krasniakova, M., Xu, Z. D., Harkany, T., & Hokfelt, T. G. M. (2023). Neuronal diversity of neuropeptide signaling, including galanin, in the mouse locus coeruleus. *Proc Natl Acad Sci U S A, 120*(31), e2222095120. doi:10.1073/pnas.2222095120

Cawthon, C. R., & de La Serre, C. B. (2021). The critical role of CCK in the regulation of food intake and diet-induced obesity. *Peptides, 138*, 170492. doi:10.1016/j.peptides.2020.170492

Chen, D., Zhao, C. M., Hakanson, R., Samuelson, L. C., Rehfeld, J. F., & Friis-Hansen, L. (2004). Altered control of gastric acid secretion in gastrin-cholecystokinin double mutant mice. *Gastroenterology, 126*(2), 476-487. doi:10.1053/j.gastro.2003.11.012

Chen, J., Guan, Z., Wang, L., Song, G., Ma, B., & Wang, Y. (2014). Meta-analysis: overweight, obesity, and Parkinson's disease. *International Journal of Endocrinology, 2014*, 203930. doi:10.1155/2014/203930

Chen, J. J., & Marsh, L. (2014). Anxiety in Parkinson's disease: identification and management. *Ther Adv Neurol Disord, 7*(1), 52-59. doi:10.1177/1756285613495723

Chen, Q., Nakajima, A., Meacham, C., & Tang, Y. P. (2006). Elevated cholecystokininergic tone constitutes an important molecular/neuronal mechanism for the expression of anxiety in the mouse. *Proc Natl Acad Sci U S A, 103*(10), 3881-3886. doi:10.1073/pnas.0505407103

Chen, X., Li, X., Wong, Y. T., Zheng, X., Wang, H., Peng, Y., Feng, H., Feng, J., Baibado, J. T., Jesky, R., Wang, Z., Xie, H., Sun, W., Zhang, Z., Zhang, X., He, L., Zhang, N., Zhang, Z., Tang, P., Su, J., Hu, L. L., Liu, Q., He, X., Tan, A., Sun, X., Li, M., Wong, K., Wang, X., Cheung, H. Y., Shum, D. K., Yung, K. K. L., Chan, Y. S., Tortorella, M., Guo, Y., Xu, F., & He, J. (2019). Cholecystokinin release triggered by NMDA receptors produces LTP and sound-sound associative memory. *Proc Natl Acad Sci U S A, 116*(13), 6397-6406. doi:10.1073/pnas.1816833116

Chen, Y., Dang, M., & Zhang, Z. (2021). Brain mechanisms underlying neuropsychiatric symptoms in Alzheimer's disease: a systematic review of symptom-general and -specific lesion patterns. *Molecular Neurodegeneration, 16*(1), 38. doi:10.1186/s13024-021-00456-1

Cheng, H. C., Ulane, C. M., & Burke, R. E. (2010). Clinical progression in Parkinson disease and the neurobiology of axons. *Annals of Neurology, 67*(6), 715-725. doi:10.1002/ana.21995

Cho, D. H., Nakamura, T., Fang, J., Cieplak, P., Godzik, A., Gu, Z., & Lipton, S. A. (2009). S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. *Science, 324*(5923), 102-105. doi:10.1126/science.1171091

Choi, A., Hallett, M., & Ehrlich, D. (2021). Nutritional Ketosis in Parkinson's Disease - a Review of Remaining Questions and Insights. *Neurotherapeutics, 18*(3), 1637-1649. doi:10.1007/s13311-021-01067-w

Choi, D. H., Kim, E. M., Son, H. J., Joh, T. H., Kim, Y. S., Kim, D., Flint Beal, M., & Hwang, O. (2008). A novel intracellular role of matrix metalloproteinase-3 during apoptosis of dopaminergic cells. *Journal of Neurochemistry, 106*(1), 405-415. doi:10.1111/j.1471-4159.2008.05399.x

Chung, Y. C., Kim, Y. S., Bok, E., Yune, T. Y., Maeng, S., & Jin, B. K. (2013). MMP-3 contributes to nigrostriatal dopaminergic neuronal loss, BBB damage, and neuroinflammation in an MPTP mouse model of Parkinson's disease. *Mediators Inflamm, 2013*, 370526. doi:10.1155/2013/370526

Clerc, P., Coll Constans, M. G., Lulka, H., Broussaud, S., Guigne, C., Leung-Theung-Long, S., Perrin, C., Knauf, C., Carpene, C., Penicaud, L., Seva, C., Burcelin, R., Valet, P., Fourmy, D., & Dufresne, M. (2007). Involvement of cholecystokinin 2 receptor in food intake regulation: hyperphagia and increased fat deposition in cholecystokinin 2 receptor-deficient mice. *Endocrinology, 148*(3), 1039-1049. doi:10.1210/en.2006-1064

Cope, D. W., Maccaferri, G., Marton, L. F., Roberts, J. D., Cobden, P. M., & Somogyi, P. (2002). Cholecystokinin-immunopositive basket and Schaffer collateral-associated interneurones target different domains of pyramidal cells in the CA1 area of the rat hippocampus. *Neuroscience, 109*(1), 63-80. doi:10.1016/s0306-4522(01)00440-7

Crawley, J. N. (1985). Comparative distribution of cholecystokinin and other neuropeptides. Why is this peptide different from all other peptides? *Ann N Y Acad Sci, 448*, 1-8. doi:10.1111/j.1749-6632.1985.tb29900.x

Crawley, J. N., Stivers, J. A., Blumstein, L. K., & Paul, S. M. (1985). Cholecystokinin potentiates dopamine-mediated behaviors: evidence for modulation specific to a site of coexistence. *Journal of Neuroscience, 5*(8), 1972-1983. doi:10.1523/JNEUROSCI.05-08-01972.1985

Dalboge, L. S., Almholt, D. L., Neerup, T. S., Vrang, N., Jelsing, J., & Fosgerau, K. (2014). The novel GLP-1-gastrin dual agonist ZP3022 improves glucose homeostasis and increases beta-cell mass without affecting islet number in db/db mice. *Journal of Pharmacology and Experimental Therapeutics, 350*(2), 353-360. doi:10.1124/jpet.114.215293

De la Fuente, M., Carrasco, M., Del Rio, M., & Hernanz, A. (1998). Modulation of murine lymphocyte functions by sulfated cholecystokinin octapeptide. *Neuropeptides, 32*(3), 225-233. doi:10.1016/s0143-4179(98)90041-5

de Montigny, C. (1989). Cholecystokinin tetrapeptide induces panic-like attacks in healthy volunteers. Preliminary findings. *Arch Gen Psychiatry, 46*(6), 511-517. doi:10.1001/archpsyc.1989.01810060031006

Del Pino, I., Brotons-Mas, J. R., Marques-Smith, A., Marighetto, A., Frick, A., Marin, O., & Rico, B. (2017). Abnormal wiring of CCK(+) basket cells disrupts spatial information coding. *Nature Neuroscience, 20*(6), 784-792. doi:10.1038/nn.4544

deLeeuw, A. S., DenBoer, J. A., Slaap, B. R., & Westenberg, H. G. M. (1996). Pentagastrin has panic inducing properties in obsessive compulsive disorder. *Psychopharmacology, 126*(4), 339-344. doi:10.1007/Bf02247385

Denecke, H., Czehak, N., & Pietrowsky, R. (2002). Dose-response relationships of intranasal cholecystokinin and the P300 event-related brain potential. *Pharmacol Biochem Behav, 73*(3), 593-600. doi:10.1016/s0091-3057(02)00823-7

Denecke, H., Meyer, F., Feldkamp, J., Fritzen, R., & Pietrowsky, R. (2004). Repetitive intranasal administration of cholecystokinin potentiates its central nervous effects. *Physiol Behav, 83*(1), 39-45. doi:10.1016/j.physbeh.2004.07.021

Deng, P. Y., & Lei, S. (2006). Bidirectional modulation of GABAergic transmission by cholecystokinin in hippocampal dentate gyrus granule cells of juvenile rats. *J Physiol, 572*(Pt 2), 425-442. doi:10.1113/jphysiol.2005.104463

Deng, P. Y., Xiao, Z., Jha, A., Ramonet, D., Matsui, T., Leitges, M., Shin, H. S., Porter, J. E., Geiger, J. D., & Lei, S. (2010). Cholecystokinin facilitates glutamate release by increasing the number of readily releasable vesicles and releasing probability. *Journal of Neuroscience, 30*(15), 5136-5148. doi:10.1523/JNEUROSCI.5711-09.2010

DeSousa, N. J., Wunderlich, G. R., De Cabo, C., & Vaccarino, F. J. (1999). The expression of behavioral sensitization to amphetamine: role of CCK(A) receptors. *Pharmacol Biochem Behav, 62*(1), 31-37. doi:10.1016/s0091-3057(98)00107-5

Dickson, D. W. (2012). Parkinson's disease and parkinsonism: neuropathology. *Cold Spring Harb Perspect Med, 2*(8). doi:10.1101/cshperspect.a009258

Ding, X. Z., & Mocchetti, I. (1992). Dopaminergic regulation of cholecystokinin mRNA content in rat striatum. *Brain Res Mol Brain Res, 12*(1-3), 77-83. doi:10.1016/0169-328x(92)90070-r

Ding, Y., Zhang, H., Liao, Y. Y., Chen, L. N., Ji, S. Y., Qin, J., Mao, C., Shen, D. D., Lin, L., Wang, H., Zhang, Y., & Li, X. M. (2022). Structural insights into human brain-gut peptide cholecystokinin receptors. *Cell Discov, 8*(1), 55. doi:10.1038/s41421-022-00420-3

Dodd, J., & Kelly, J. S. (1981). The actions of cholecystokinin and related peptides on pyramidal neurones of the mammalian hippocampus. *Brain Research, 205*(2), 337-350. doi:10.1016/0006-8993(81)90344-9

Dolatabadi, L. K., & Reisi, P. (2014). Acute effect of cholecystokinin on short-term synaptic plasticity in the rat hippocampus. *Res Pharm Sci, 9*(5), 331-336.

Donato, F., Chowdhury, A., Lahr, M., & Caroni, P. (2015). Early- and late-born parvalbumin basket cell subpopulations exhibiting distinct regulation and roles in learning. *Neuron, 85*(4), 770-786. doi:10.1016/j.neuron.2015.01.011

Drzezga, A., Lautenschlager, N., Siebner, H., Riemenschneider, M., Willoch, F., Minoshima, S., Schwaiger, M., & Kurz, A. (2003). Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. *Eur J Nucl Med Mol Imaging, 30*(8), 1104-1113. doi:10.1007/s00259-003-1194-1

Dudok, B., Klein, P. M., Hwaun, E., Lee, B. R., Yao, Z., Fong, O., Bowler, J. C., Terada, S., Sparks, F. T., Szabo, G. G., Farrell, J. S., Berg, J., Daigle, T. L., Tasic, B., Dimidschstein, J., Fishell, G., Losonczy, A., Zeng, H., & Soltesz, I. (2021). Alternating sources of perisomatic inhibition during behavior. *Neuron, 109*(6), 997-1012 e1019. doi:10.1016/j.neuron.2021.01.003

Dufresne, M., Escrieut, C., Clerc, P., Le Huerou-Luron, I., Prats, H., Bertrand, V., Le Meuth, V., Guilloteau, P., Vaysse, N., & Fourmy, D. (1996). Molecular cloning, developmental expression and pharmacological characterization of the CCKB/gastrin receptor in the calf pancreas. *European Journal of Pharmacology, 297*(1-2), 165-179. doi:10.1016/0014-2999(95)00737-7

Dufresne, M., Seva, C., & Fourmy, D. (2006). Cholecystokinin and gastrin receptors. *Physiological Reviews, 86*(3), 805-847. doi:10.1152/physrev.00014.2005

Dunn, L., Allen, G. F., Mamais, A., Ling, H., Li, A., Duberley, K. E., Hargreaves, I. P., Pope, S., Holton, J. L., Lees, A., Heales, S. J., & Bandopadhyay, R. (2014). Dysregulation of glucose metabolism is an early event in sporadic Parkinson's disease. *Neurobiology of Aging, 35*(5), 1111-1115. doi:10.1016/j.neurobiolaging.2013.11.001

Ekdahl, C. T., Claasen, J. H., Bonde, S., Kokaia, Z., & Lindvall, O. (2003). Inflammation is detrimental for neurogenesis in adult brain. *Proceedings of the National Academy of Sciences of the United States of America, 100*(23), 13632-13637. doi:10.1073/pnas.2234031100

El Khoury, J. B., Moore, K. J., Means, T. K., Leung, J., Terada, K., Toft, M., Freeman, M. W., & Luster, A. D. (2003). CD36 mediates the innate host response to beta-amyloid. *J Exp Med, 197*(12), 1657-1666. doi:10.1084/jem.20021546

Elliott, R. L., Cameron, K. O., Chin, J. E., Bartlett, J. A., Beretta, E. E., Chen, Y., Jardine, P. D., Dubins, J. S., Gillaspy, M. L., Hargrove, D. M., Kalgutkar, A. S., LaFlamme, J. A., Lame, M. E., Martin, K. A., Maurer, T. S., Nardone, N. A., Oliver, R. M., Scott, D. O., Sun, D. X., Swick, A. G., Trebino, C. E., & Zhang, Y. X. (2010). Discovery of N-benzyl-2-[(4S)-4-(1H-indol-3-ylmethyl)-5-oxo-1-phenyl-4,5-dihydro-6H-[1,2,4]tri azolo[4,3-a][1,5 benzodiazepin-6-yl]-N-isopropylacetamide, an orally active, gut-selective CCK1 receptor agonist for the potential treatment of obesity. *Bioorganic & Medicinal Chemistry Letters, 20*(22), 6797-6801. doi:10.1016/j.bmcl.2010.08.115

Eser, D., Leicht, G., Lutz, J., Wenninger, S., Kirsch, V., Schule, C., Karch, S., Baghai, T., Pogarell, O., Born, C., Rupprecht, R., & Mulert, C. (2009). Functional neuroanatomy of CCK-4-induced panic attacks in healthy volunteers. *Hum Brain Mapp, 30*(2), 511-522. doi:10.1002/hbm.20522

Eser, D., Schule, C., Baghai, T., Floesser, A., Krebs-Brown, A., Enunwa, M., de la Motte, S., Engel, R., Kucher, K., & Rupprecht, R. (2007). Evaluation of the CCK-4 model as a challenge paradigm in a population of healthy volunteers within a proof-of-concept study. *Psychopharmacology (Berl), 192*(4), 479-487. doi:10.1007/s00213-007-0738-7

Feifel, D., Shilling, P. D., Kuczenski, R., & Segal, D. S. (2003). Altered extracellular dopamine concentration in the brains of cholecystokinin-A receptor deficient rats. *Neuroscience Letters, 348*(3), 147-150. doi:10.1016/s0304-3940(03)00767-5

Feng, H., Su, J., Fang, W., Chen, X., & He, J. (2021). The entorhinal cortex modulates trace fear memory formation and neuroplasticity in the mouse lateral amygdala via cholecystokinin. *Elife, 10*. doi:10.7554/eLife.69333

Feng, P., Zhang, X., Li, D., Ji, C., Yuan, Z., Wang, R., Xue, G., Li, G., & Holscher, C. (2018). Two novel dual GLP-1/GIP receptor agonists are neuroprotective in the MPTP mouse model of Parkinson's disease. *Neuropharmacology, 133*, 385-394. doi:10.1016/j.neuropharm.2018.02.012

Filichia, E., Hoffer, B., Qi, X., & Luo, Y. (2016). Inhibition of Drp1 mitochondrial translocation provides neural protection in dopaminergic system in a Parkinson's disease model induced by MPTP. *Sci Rep, 6*, 32656. doi:10.1038/srep32656

Foldy, C., Lee, S. Y., Szabadics, J., Neu, A., & Soltesz, I. (2007). Cell type-specific gating of perisomatic inhibition by cholecystokinin. *Nature Neuroscience, 10*(9), 1128-1130. doi:10.1038/nn1952

Fosgerau, K., Jessen, L., Lind Tolborg, J., Osterlund, T., Schaeffer Larsen, K., Rolsted, K., Brorson, M., Jelsing, J., & Skovlund Ryge Neerup, T. (2013). The novel GLP-1-gastrin dual agonist, ZP3022, increases beta-cell mass and prevents diabetes in db/db mice. *Diabetes Obesity & Metabolism, 15*(1), 62-71. doi:10.1111/j.1463-1326.2012.01676.x

Freund, T. F., & Katona, I. (2007). Perisomatic inhibition. *Neuron, 56*(1), 33-42. doi:10.1016/j.neuron.2007.09.012

Frodin, M., & Gammeltoft, S. (1999). Role and regulation of 90 kDa ribosomal S6 kinase (RSK) in signal transduction. *Molecular and Cellular Endocrinology, 151*(1-2), 65-77. doi:10.1016/s0303-7207(99)00061-1

Fujii, C., Harada, S., Ohkoshi, N., Hayashi, A., Yoshizawa, K., Ishizuka, C., & Nakamura, T. (1999). Association between polymorphism of the cholecystokinin gene and idiopathic Parkinson's disease. *Clinical Genetics, 56*(5), 394-399.

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D. W., Fasano, A., Miller, G. W., Miller, A. H., Mantovani, A., Weyand, C. M., Barzilai, N., Goronzy, J. J., Rando, T. A., Effros, R. B., Lucia, A., Kleinstreuer, N., & Slavich, G. M. (2019). Chronic inflammation in the etiology of disease across the life span. *Nature Medicine, 25*(12), 1822-1832. doi:10.1038/s41591-019-0675-0

Gandolfi, D., Cerri, S., Mapelli, J., Polimeni, M., Tritto, S., Fuzzati-Armentero, M. T., Bigiani, A., Blandini, F., Mapelli, L., & D'Angelo, E. (2017). Activation of the CREB/c-Fos Pathway during Long-Term Synaptic Plasticity in the Cerebellum Granular Layer. *Frontiers in Cellular Neuroscience, 11*, 184. doi:10.3389/fncel.2017.00184

Garvey, M. J., Crowe, R. R., & Wang, Z. (1998). An association of NAG levels and a mutation of the CCK gene in panic disorder patients. *Psychiatry Res, 80*(2), 149-153. doi:10.1016/s0165-1781(98)00063-8

Geary, N. (2001). Estradiol, CCK and satiation. *Peptides, 22*(8), 1251-1263. doi:10.1016/s0196-9781(01)00449-1

Geary, N., Smith, G. P., & Corp, E. S. (1996). The increased satiating potency of CCK-8 by estradiol is not mediated by upregulation of NTS CCK receptors. *Brain Research, 719*(1-2), 179-186. doi:10.1016/0006-8993(96)00099-6

Gerfen, C. R. (2022). Segregation of D1 and D2 dopamine receptors in the striatal direct and indirect pathways: An historical perspective. *Front Synaptic Neurosci, 14*, 1002960. doi:10.3389/fnsyn.2022.1002960

Gerfen, C. R., Engber, T. M., Mahan, L. C., Susel, Z., Chase, T. N., Monsma, F. J., Jr., & Sibley, D. R. (1990). D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science, 250*(4986), 1429-1432. doi:10.1126/science.2147780

Gibbs, J., Young, R. C., & Smith, G. P. (1973). Cholecystokinin decreases food intake in rats. *J Comp Physiol Psychol, 84*(3), 488-495. doi:10.1037/h0034870

Giguere, N., Delignat-Lavaud, B., Herborg, F., Voisin, A., Li, Y., Jacquemet, V., Anand-Srivastava, M., Gether, U., Giros, B., & Trudeau, L. E. (2019). Increased vulnerability of nigral dopamine neurons after expansion of their axonal arborization size through D2 dopamine receptor conditional knockout. *PLoS Genet, 15*(8), e1008352. doi:10.1371/journal.pgen.1008352

Goettel, M., Fuertig, R., Mack, S. R., Just, S., Sharma, V., Wunder, A., & den Boer, J. (2023). Effect of BI 1358894 on Cholecystokinin-Tetrapeptide (CCK-4)-Induced Anxiety, Panic Symptoms, and Stress Biomarkers: A Phase I Randomized Trial in Healthy Males. *CNS Drugs, 37*(12), 1099-1109. doi:10.1007/s40263-023-01042-3

Goldman, J. G., Goetz, C. G., Berry-Kravis, E., Leurgans, S., & Zhou, L. (2004). Genetic polymorphisms in Parkinson disease subjects with and without hallucinations: an analysis of the cholecystokinin system. *Arch Neurol, 61*(8), 1280-1284. doi:10.1001/archneur.61.8.1280

Gomez, G., Lluis, F., Guo, Y. S., Greeley, G. H., Jr., Townsend, C. M., Jr., & Thompson, J. C. (1986). Bile inhibits release of cholecystokinin and neurotensin. *Surgery, 100*(2), 363-368.

Gomez, G., Upp, J. R., Jr., Lluis, F., Alexander, R. W., Poston, G. J., Greeley, G. H., Jr., & Thompson, J. C. (1988). Regulation of the release of cholecystokinin by bile salts in dogs and humans. *Gastroenterology, 94*(4), 1036-1046. doi:10.1016/0016-5085(88)90564-1

Gorelick, F. S., & Thrower, E. (2009). The acinar cell and early pancreatitis responses. *Clin Gastroenterol Hepatol, 7*(11 Suppl), S10-14. doi:10.1016/j.cgh.2009.07.036

Gou, H., Sun, D., Hao, L., An, M., Xie, B., Cong, B., Ma, C., & Wen, D. (2020). Cholecystokinin-8 attenuates methamphetamine-induced inflammatory activation of microglial cells through CCK2 receptor. *Neurotoxicology, 81*, 70-79. doi:10.1016/j.neuro.2020.09.001

Gou, H., Wen, D., Ma, C., Li, M., Li, Y., Zhang, W., Liu, L., & Cong, B. (2015). Protective effects of cholecystokinin-8 on methamphetamine-induced behavioral changes and dopaminergic neurodegeneration in mice. *Behavioural Brain Research, 283*, 87-96. doi:10.1016/j.bbr.2015.01.028

Grasing, K., Murphy, M. G., Lin, J., Swigar, M., Freedholm, D., Clarke, L., Zhang, J., Wolkowitz, O. M., Weingartner, H., Putnam, K., & Seibold, J. R. (1996). Human pharmacokinetics and tolerability of L-365,260, a novel cholecystokinin-B antagonist. *Journal of Clinical Pharmacology, 36*(4), 292-300. doi:10.1002/j.1552-4604.1996.tb04204.x

Greenberg, N., Grassano, A., Thambisetty, M., Lovestone, S., & Legido-Quigley, C. (2009). A proposed metabolic strategy for monitoring disease progression in Alzheimer's disease. *Electrophoresis, 30*(7), 1235-1239. doi:10.1002/elps.200800589

Greenstein, R. J., Ybanez, M. M., Zhang, R. L., & Bauman, W. A. (1991). Is Aging Preprogrammed - Observations from the Brain Gut Axis. *Mechanisms of Ageing and Development, 61*(2), 113-121. doi:10.1016/0047-6374(91)90010-W

Greenwood, R. S., Godar, S. E., Reaves, T. A., Jr., & Hayward, J. N. (1981). Cholecystokinin in hippocampal pathways. *Journal of Comparative Neurology, 203*(3), 335-350. doi:10.1002/cne.902030303

Gronier, B., & Debonnel, G. (1995). CCKB receptors mediate CCK-8S-induced activation of dorsal hippocampus CA3 pyramidal neurons: an in vivo electrophysiological study in the rat. *Synapse, 21*(2), 158-168. doi:10.1002/syn.890210209

Gulpinar, M. A., Ozbeyli, D., Arbak, S., & Yegen, B. C. (2004). Anti-inflammatory effect of acute stress on experimental colitis is mediated by cholecystokinin-B receptors. *Life Sciences, 75*(1), 77-91. doi:10.1016/j.lfs.2003.12.009

Hansen, T. V., Rehfeld, J. F., & Nielsen, F. C. (2000). Function of the C-36 to T polymorphism in the human cholecystokinin gene promoter. *Mol Psychiatry, 5*(4), 443-447. doi:10.1038/sj.mp.4000705

Hao, L., Shi, M., Ma, J., Shao, S., Yuan, Y., Liu, J., Yu, Z., Zhang, Z., Hölscher, C., & Zhang, Z. (2023). A Cholecystokinin Analogue Ameliorates Cognitive Deficits and Regulates Mitochondrial Dynamics via the AMPK/Drp1 Pathway in APP/PS1 Mice [in press]. *J Prev Alz Dis. Available at https://www.researchgate.net/publication/375073338_A_Cholecystokinin_analogue_ameliorates_cognitive_deficits_and_regulates_mitochondrial_dynamics_via_the_AMPKDrp1_pathway_in_APPPS1_mice*.

Harro, J., & Oreland, L. (1992). Age-related differences of cholecystokinin receptor binding in the rat brain. *Prog Neuropsychopharmacol Biol Psychiatry, 16*(3), 369-375. doi:10.1016/0278-5846(92)90088-v

Harro, J., & Oreland, L. (1993). Cholecystokinin receptors and memory: a radial maze study. *Pharmacol Biochem Behav, 44*(3), 509-517. doi:10.1016/0091-3057(93)90160-u

Hassan, A., Sharma Kandel, R., Mishra, R., Gautam, J., Alaref, A., & Jahan, N. (2020). Diabetes Mellitus and Parkinson's Disease: Shared Pathophysiological Links and Possible Therapeutic Implications. *Cureus, 12*(8), e9853. doi:10.7759/cureus.9853

Hattori, E., Yamada, K., Toyota, T., Yoshitsugu, K., Toru, M., Shibuya, H., & Yoshikawa, T. (2001). Association studies of the CT repeat polymorphism in the 5' upstream region of the cholecystokinin B receptor gene with panic disorder and schizophrenia in Japanese subjects. *American Journal of Medical Genetics, 105*(8), 779-782. doi:10.1002/ajmg.10043

He, L., Shi, H., Zhang, G., Peng, Y., Ghosh, A., Zhang, M., Hu, X., Liu, C., Shao, Y., Wang, S., Chen, L., Sun, W., Su, J., Chen, X., Zhang, L., Chan, Y. S., Pei, D., Tortorella, M., Guo, Y., Yan, H., & He, J. (2023). A Novel CCK Receptor GPR173 Mediates Potentiation of GABAergic Inhibition. *Journal of Neuroscience, 43*(13), 2305-2325. doi:10.1523/JNEUROSCI.2035-22.2023

Hewson, G., Leighton, G. E., Hill, R. G., & Hughes, J. (1988). The cholecystokinin receptor antagonist L364,718 increases food intake in the rat by attenuation of the action of endogenous cholecystokinin. *Br J Pharmacol, 93*(1), 79-84. doi:10.1111/j.1476-5381.1988.tb11407.x

Higgins, G. A., Sills, T. L., Tomkins, D. M., Sellers, E. M., & Vaccarino, F. J. (1994). Evidence for the contribution of CCKB receptor mechanisms to individual differences in amphetamine-induced locomotion. *Pharmacol Biochem Behav, 48*(4), 1019-1024. doi:10.1016/0091-3057(94)90214-3

Hill, D. R., Campbell, N. J., Shaw, T. M., & Woodruff, G. N. (1987). Autoradiographic localization and biochemical characterization of peripheral type CCK receptors in rat CNS using highly selective nonpeptide CCK antagonists. *Journal of Neuroscience, 7*(9), 2967-2976. doi:10.1523/JNEUROSCI.07-09-02967.1987

Hill, D. R., Shaw, T. M., Graham, W., & Woodruff, G. N. (1990). Autoradiographical detection of cholecystokinin-A receptors in primate brain using 125I-Bolton Hunter CCK-8 and 3H-MK-329. *Journal of Neuroscience, 10*(4), 1070-1081. doi:10.1523/JNEUROSCI.10-04-01070.1990

Hokama, M., Oka, S., Leon, J., Ninomiya, T., Honda, H., Sasaki, K., Iwaki, T., Ohara, T., Sasaki, T., LaFerla, F. M., Kiyohara, Y., & Nakabeppu, Y. (2014). Altered expression of diabetes-related genes in Alzheimer's disease brains: the Hisayama study. *Cerebral Cortex, 24*(9), 2476-2488. doi:10.1093/cercor/bht101

Hokfelt, T., Rehfeld, J. F., Skirboll, L., Ivemark, B., Goldstein, M., & Markey, K. (1980). Evidence for coexistence of dopamine and CCK in meso-limbic neurones. *Nature, 285*(5765), 476-478. doi:10.1038/285476a0

Holland, K. L., Norby, L. A., & Micevych, P. E. (1998). Peripubertal ontogeny and estrogen stimulation of cholecystokinin and preproenkephalin mRNA in the rat hypothalamus and limbic system. *Journal of Comparative Neurology, 392*(1), 48-57.

Holscher, C. (2019). Insulin Signaling Impairment in the Brain as a Risk Factor in Alzheimer's Disease. *Frontiers in Aging Neuroscience, 11*, 88. doi:10.3389/fnagi.2019.00088

Holscher, C. (2020). Brain insulin resistance: role in neurodegenerative disease and potential for targeting. *Expert Opin Investig Drugs, 29*(4), 333-348. doi:10.1080/13543784.2020.1738383

Holtje, M., Winter, S., Walther, D., Pahner, I., Hortnagl, H., Ottersen, O. P., Bader, M., & Ahnert-Hilger, G. (2003). The vesicular monoamine content regulates VMAT2 activity through Galphaq in mouse platelets. Evidence for autoregulation of vesicular transmitter uptake. *Journal of Biological Chemistry, 278*(18), 15850-15858. doi:10.1074/jbc.M212816200

Hommer, D. W., Palkovits, M., Crawley, J. N., Paul, S. M., & Skirboll, L. R. (1985). Cholecystokinin-induced excitation in the substantia nigra: evidence for peripheral and central components. *Journal of Neuroscience, 5*(6), 1387-1392. doi:10.1523/JNEUROSCI.05-06-01387.1985

Hommer, D. W., Pickar, D., Crawley, J. N., Weingartner, H., & Paul, S. M. (1985). The effects of cholecystokinin-like peptides in schizophrenics and normal human subjects. *Ann N Y Acad Sci, 448*, 542-552. doi:10.1111/j.1749-6632.1985.tb29947.x

Honda, T., Wada, E., Battey, J. F., & Wank, S. A. (1993). Differential Gene Expression of CCK(A) and CCK(B) Receptors in the Rat Brain. *Molecular and Cellular Neuroscience, 4*(2), 143-154. doi:10.1006/mcne.1993.1018

Hosing, V. G., Schirmacher, A., Kuhlenbaumer, G., Freitag, C., Sand, P., Schlesiger, C., Jacob, C., Fritze, J., Franke, P., Rietschel, M., Garritsen, H., Nothen, M. M., Fimmers, R., Stogbauer, F., & Deckert, J. (2004). Cholecystokinin- and cholecystokinin-B-receptor gene polymorphisms in panic disorder. *J Neural Transm Suppl*(68), 147-156. doi:10.1007/978-3-7091-0579-5_17

Hoyer, S., Oesterreich, K., & Wagner, O. (1988). Glucose-Metabolism as the Site of the Primary Abnormality in Early-Onset Dementia of Alzheimer Type. *Journal of Neurology, 235*(3), 143-148. doi:Doi 10.1007/Bf00314304

Huang, J., Liu, W., Doycheva, D. M., Gamdzyk, M., Lu, W., Tang, J., & Zhang, J. H. (2019). Ghrelin attenuates oxidative stress and neuronal apoptosis via GHSR-1alpha/AMPK/Sirt1/PGC-1alpha/UCP2 pathway in a rat model of neonatal HIE. *Free Radic Biol Med, 141*, 322-337. doi:10.1016/j.freeradbiomed.2019.07.001

Huang, S. C., Yu, D. H., Wank, S. A., Mantey, S., Gardner, J. D., & Jensen, R. T. (1989). Importance of sulfation of gastrin or cholecystokinin (CCK) on affinity for gastrin and CCK receptors. *Peptides, 10*(4), 785-789. doi:10.1016/0196-9781(89)90114-9

Hurd, Y. L., Lindefors, N., Brodin, E., Brene, S., Persson, H., Ungerstedt, U., & Hokfelt, T. (1992). Amphetamine regulation of mesolimbic dopamine/cholecystokinin neurotransmission. *Brain Research, 578*(1-2), 317-326. doi:10.1016/0006-8993(92)90264-a

Hwang, C. K., Kim, D. K., & Chun, H. S. (2013). Cholecystokinin-8 induces brain-derived neurotrophic factor expression in noradrenergic neuronal cells. *Neuropeptides, 47*(4), 245-250. doi:10.1016/j.npep.2013.04.002

Irwin, N., Hunter, K., Montgomery, I. A., & Flatt, P. R. (2013). Comparison of independent and combined metabolic effects of chronic treatment with (pGlu-Gln)-CCK-8 and long-acting GLP-1 and GIP mimetics in high fat-fed mice. *Diabetes Obesity & Metabolism, 15*(7), 650-659. doi:10.1111/dom.12079

Ito, M., Matsui, T., Taniguchi, T., Tsukamoto, T., Murayama, T., Arima, N., Nakata, H., Chiba, T., & Chihara, K. (1993). Functional characterization of a human brain cholecystokinin-B receptor. A trophic effect of cholecystokinin and gastrin. *Journal of Biological Chemistry, 268*(24), 18300-18305.

Iwangoff, P., Armbruster, R., Enz, A., & Meier-Ruge, W. (1980). Glycolytic enzymes from human autoptic brain cortex: normal aged and demented cases. *Mechanisms of Ageing and Development, 14*(1-2), 203-209. doi:10.1016/0047-6374(80)90120-7

Iwata, N., Murayama, T., Matsumori, Y., Ito, M., Nagata, A., Taniguchi, T., Chihara, K., Matsuo, Y., Minowada, J., & Matsui, T. (1996). Autocrine loop through cholecystokinin-B/gastrin receptors involved in growth of human leukemia cells. *Blood, 88*(7), 2683-2689.

Jaffe, D. B., Aitken, P. G., & Nadler, J. V. (1987). The effects of cholecystokinin and cholecystokinin antagonists on synaptic function in the CA1 region of the rat hippocampal slice. *Brain Research, 415*(1), 197-203. doi:10.1016/0006-8993(87)90288-5

Jayanthi, S., Daiwile, A. P., & Cadet, J. L. (2021). Neurotoxicity of methamphetamine: Main effects and mechanisms. *Experimental Neurology, 344*, 113795. doi:10.1016/j.expneurol.2021.113795

Johnstone, M., Gearing, A. J., & Miller, K. M. (1999). A central role for astrocytes in the inflammatory response to beta-amyloid; chemokines, cytokines and reactive oxygen species are produced. *Journal of Neuroimmunology, 93*(1-2), 182-193. doi:10.1016/s0165-5728(98)00226-4

Jones-Tabah, J., Mohammad, H., Paulus, E. G., Clarke, P. B. S., & Hebert, T. E. (2021). The Signaling and Pharmacology of the Dopamine D1 Receptor. *Frontiers in Cellular Neuroscience, 15*, 806618. doi:10.3389/fncel.2021.806618

Jordan, J., Greenway, F. L., Leiter, L. A., Li, Z., Jacobson, P., Murphy, K., Hill, J., Kler, L., & Aftring, R. P. (2008). Stimulation of cholecystokinin-A receptors with GI181771X does not cause weight loss in overweight or obese patients. *Clin Pharmacol Ther, 83*(2), 281-287. doi:10.1038/sj.clpt.6100272

Jung, C. H., & Mok, J. O. (2022). Recent Updates on Associations among Various Obesity Metrics and Cognitive Impairment: from Body Mass Index to Sarcopenic Obesity. *J Obes Metab Syndr, 31*(4), 287-295. doi:10.7570/jomes22058

Karson, M. A., Whittington, K. C., & Alger, B. E. (2008). Cholecystokinin inhibits endocannabinoid-sensitive hippocampal IPSPs and stimulates others. *Neuropharmacology, 54*(1), 117-128. doi:10.1016/j.neuropharm.2007.06.023

Kawano, K., Hirashima, T., Mori, S., & Natori, T. (1994). OLETF (Otsuka Long-Evans Tokushima Fatty) rat: a new NIDDM rat strain. *Diabetes Res Clin Pract, 24 Suppl*, S317-320. doi:10.1016/0168-8227(94)90269-0

Kellner, M., Yassouridis, A., Jahn, H., & Wiedemann, K. (1997). Influence of clonidine on psychopathological, endocrine and respiratory effects of cholecystokinin tetrapeptide in patients with panic disorder. *Psychopharmacology (Berl), 133*(1), 55-61. doi:10.1007/s002130050371

Khan, S., Liberzon, I., & Abelson, J. L. (2004). Effects of propranolol on symptom and endocrine responses to pentagastrin. *Psychoneuroendocrinology, 29*(9), 1163-1171. doi:10.1016/j.psyneuen.2004.01.009

Kim, C., Ho, D. H., Suk, J. E., You, S., Michael, S., Kang, J., Joong Lee, S., Masliah, E., Hwang, D., Lee, H. J., & Lee, S. J. (2013). Neuron-released oligomeric alpha-synuclein is an endogenous agonist of TLR2 for paracrine activation of microglia. *Nature Communications, 4*, 1562. doi:10.1038/ncomms2534

Kim, H. (2008). Cerulein pancreatitis: oxidative stress, inflammation, and apoptosis. *Gut Liver, 2*(2), 74-80. doi:10.5009/gnl.2008.2.2.74

Kim, H., Park, J., Kang, H., Yun, S. P., Lee, Y. S., Lee, Y. I., & Lee, Y. (2020). Activation of the Akt1-CREB pathway promotes RNF146 expression to inhibit PARP1-mediated neuronal death. *Science Signaling, 13*(663). doi:10.1126/scisignal.aax7119

Kim, R., & Jun, J. S. (2020). Impact of Overweight and Obesity on Functional and Clinical Outcomes of Early Parkinson's Disease. *J Am Med Dir Assoc, 21*(5), 697-700. doi:10.1016/j.jamda.2019.11.019

Kim, Y. S., Choi, D. H., Block, M. L., Lorenzl, S., Yang, L., Kim, Y. J., Sugama, S., Cho, B. P., Hwang, O., Browne, S. E., Kim, S. Y., Hong, J. S., Beal, M. F., & Joh, T. H. (2007). A pivotal role of matrix metalloproteinase-3 activity in dopaminergic neuronal degeneration via microglial activation. *Faseb Journal, 21*(1), 179-187. doi:10.1096/fj.06-5865com

Kim, Y. S., Kim, S. S., Cho, J. J., Choi, D. H., Hwang, O., Shin, D. H., Chun, H. S., Beal, M. F., & Joh, T. H. (2005). Matrix metalloproteinase-3: a novel signaling proteinase from apoptotic neuronal cells that activates microglia. *Journal of Neuroscience, 25*(14), 3701-3711. doi:10.1523/JNEUROSCI.4346-04.2005

Klann, E. M., Dissanayake, U., Gurrala, A., Farrer, M., Shukla, A. W., Ramirez-Zamora, A., Mai, V., & Vedam-Mai, V. (2021). The Gut-Brain Axis and Its Relation to Parkinson's Disease: A Review. *Frontiers in Aging Neuroscience, 13*, 782082. doi:10.3389/fnagi.2021.782082

Knight, E. M., Verkhratsky, A., Luckman, S. M., Allan, S. M., & Lawrence, C. B. (2012). Hypermetabolism in a triple-transgenic mouse model of Alzheimer's disease. *Neurobiology of Aging, 33*(1), 187-193. doi:10.1016/j.neurobiolaging.2010.02.003

Koefoed, P., Woldbye, D. P., Hansen, T. O., Hansen, E. S., Knudsen, G. M., Bolwig, T. G., & Rehfeld, J. F. (2010). Gene variations in the cholecystokinin system in patients with panic disorder. *Psychiatric Genetics, 20*(2), 59-64. doi:10.1097/YPG.0b013e32833511a8

Koks, S., Mannisto, P. T., Bourin, M., Shlik, J., Vasar, V., & Vasar, E. (2000). Cholecystokinin-induced anxiety in rats: relevance of pre-experimental stress and seasonal variations. *J Psychiatry Neurosci, 25*(1), 33-42.

Koop, I., Koop, H., Gerhardt, C., Schafmayer, A., & Arnold, R. (1989). Do Bile-Acids Exert a Negative Feedback-Control of Cholecystokinin Release. *Scandinavian Journal of Gastroenterology, 24*(3), 315-320. doi:10.3109/00365528909093053

Kopin, A. S., Mathes, W. F., McBride, E. W., Nguyen, M., Al-Haider, W., Schmitz, F., Bonner-Weir, S., Kanarek, R., & Beinborn, M. (1999). The cholecystokinin-A receptor mediates inhibition of food intake yet is not essential for the maintenance of body weight. *Journal of Clinical Investigation, 103*(3), 383-391. doi:10.1172/JCI4901

Koszycki, D., Copen, J., & Bradwejn, J. (2004). Sensitivity to cholecystokinin-tetrapeptide in major depression. *J Affect Disord, 80*(2-3), 285-290. doi:10.1016/S0165-0327(03)00110-1

Koszycki, D., Zacharko, R. M., Le Melledo, J. M., & Bradwejn, J. (1998). Behavioral, cardiovascular, and neuroendocrine profiles following CCK-4 challenge in healthy volunteers: a comparison of panickers and nonpanickers. *Depress Anxiety, 8*(1), 1-7.

Kristensen, A. S., Jenkins, M. A., Banke, T. G., Schousboe, A., Makino, Y., Johnson, R. C., Huganir, R., & Traynelis, S. F. (2011). Mechanism of Ca2+/calmodulin-dependent kinase II regulation of AMPA receptor gating. *Nature Neuroscience, 14*(6), 727-735. doi:10.1038/nn.2804

Kritzer, M. F., Innis, R. B., & Goldman-Rakic, P. S. (1988). Regional distribution of cholecystokinin receptors in macaque medial temporal lobe determined by in vitro receptor autoradiography. *Journal of Comparative Neurology, 276*(2), 219-230. doi:10.1002/cne.902760206

Larco, D. O., Semsarzadeh, N. N., Cho-Clark, M., Mani, S. K., & Wu, T. J. (2013). beta-Arrestin 2 is a mediator of GnRH-(1-5) signaling in immortalized GnRH neurons. *Endocrinology, 154*(12), 4726-4736. doi:10.1210/en.2013-1286

Le Melledo, J. M., Bradwejn, J., Koszycki, D., Bichet, D. G., & Bellavance, F. (1998). The role of the beta-noradrenergic system in cholecystokinin-tetrapeptide-induced panic symptoms. *Biol Psychiatry, 44*(5), 364-366. doi:10.1016/s0006-3223(97)00536-2

Le Moine, C., Normand, E., Guitteny, A. F., Fouque, B., Teoule, R., & Bloch, B. (1990). Dopamine receptor gene expression by enkephalin neurons in rat forebrain. *Proc Natl Acad Sci U S A, 87*(1), 230-234. doi:10.1073/pnas.87.1.230

Lee, H. J., Suk, J. E., Patrick, C., Bae, E. J., Cho, J. H., Rho, S., Hwang, D., Masliah, E., & Lee, S. J. (2010). Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. *Journal of Biological Chemistry, 285*(12), 9262-9272. doi:10.1074/jbc.M109.081125

Lee, S. H., & Soltesz, I. (2011). Requirement for CB1 but not GABAB receptors in the cholecystokinin mediated inhibition of GABA release from cholecystokinin expressing basket cells. *J Physiol, 589*(Pt 4), 891-902. doi:10.1113/jphysiol.2010.198499

Lee, S. Y., Foldy, C., Szabadics, J., & Soltesz, I. (2011). Cell-type-specific CCK2 receptor signaling underlies the cholecystokinin-mediated selective excitation of hippocampal parvalbumin-positive fast-spiking basket cells. *Journal of Neuroscience, 31*(30), 10993-11002. doi:10.1523/JNEUROSCI.1970-11.2011

Lee, Y. M., Beinborn, M., McBride, E. W., Lu, M., Kolakowski, L. F., Jr., & Kopin, A. S. (1993). The human brain cholecystokinin-B/gastrin receptor. Cloning and characterization. *Journal of Biological Chemistry, 268*(11), 8164-8169.

Lemaire, M., Barneoud, P., Bohme, G. A., Piot, O., Haun, F., Roques, B. P., & Blanchard, J. C. (1994). CCK-A and CCK-B receptors enhance olfactory recognition via distinct neuronal pathways. *Learn Mem, 1*(3), 153-164.

Lemaire, M., Bohme, G. A., Piot, O., Roques, B. P., & Blanchard, J. C. (1994). CCK-A and CCK-B selective receptor agonists and antagonists modulate olfactory recognition in male rats. *Psychopharmacology (Berl), 115*(4), 435-440. doi:10.1007/BF02245565

Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Microbial ecology: human gut microbes associated with obesity. *Nature, 444*(7122), 1022-1023. doi:10.1038/4441022a

Li, C., Cai, Y. Y., & Yan, Z. X. (2018). Brain-derived neurotrophic factor preserves intestinal mucosal barrier function and alters gut microbiota in mice. *Kaohsiung J Med Sci, 34*(3), 134-141. doi:10.1016/j.kjms.2017.11.002

Li, X., Yu, K., Zhang, Z., Sun, W., Yang, Z., Feng, J., Chen, X., Liu, C. H., Wang, H., Guo, Y. P., & He, J. (2014). Cholecystokinin from the entorhinal cortex enables neural plasticity in the auditory cortex. *Cell Res, 24*(3), 307-330. doi:10.1038/cr.2013.164

Li, X. L., Aou, S., Hori, T., & Oomura, Y. (2002). Spatial memory deficit and emotional abnormality in OLETF rats. *Physiol Behav, 75*(1-2), 15-23. doi:10.1016/s0031-9384(01)00627-8

Li, Y., & Chen, Y. (2019). AMPK and Autophagy. *Issues in Clinical Epileptology: A View from the Bench, 1206*, 85-108. doi:10.1007/978-981-15-0602-4_4

Liang, H., Zhao, Q., Lv, S., & Ji, X. (2022). Regulation and physiological functions of phoenixin. *Front Mol Biosci, 9*, 956500. doi:10.3389/fmolb.2022.956500

Liddle, R. A. (1997). Cholecystokinin cells. *Annual Review of Physiology, Vol 79, 59*, 221-242. doi:10.1146/annurev.physiol.59.1.221

Lilamand, M., Mouton-Liger, F., & Paquet, C. (2021). Ketogenic diet therapy in Alzheimer's disease: an updated review. *Curr Opin Clin Nutr Metab Care, 24*(4), 372-378. doi:10.1097/MCO.0000000000000759

Lim, D., Iyer, A., Ronco, V., Grolla, A. A., Canonico, P. L., Aronica, E., & Genazzani, A. A. (2013). Amyloid beta deregulates astroglial mGluR5-mediated calcium signaling via calcineurin and Nf-kB. *Glia, 61*(7), 1134-1145. doi:10.1002/glia.22502

Lin, H., Zhang, T., Wu, Y., Wang, Y., Wang, W., & Wang, Q. (2014). Related genes and potential biomarkers for early diagnosis of Alzheimer's disease: a preliminary study based on DNA microarray. *Am J Alzheimers Dis Other Demen, 29*(1), 90-95. doi:10.1177/1533317513506774

Liu, L. L., Han, Y., Zhang, Z. J., Wang, Y. Q., Hu, Y. W., Kaznacheyeva, E., Ding, J. Q., Guo, D. K., Wang, G. H., Li, B., & Ren, H. G. (2023). Loss of DJ-1 function contributes to Parkinson's disease pathogenesis in mice via RACK1-mediated PKC activation and MAO-B upregulation. *Acta Pharmacologica Sinica, 44*(10), 1948-1961. doi:10.1038/s41401-023-01104-8

Liu, Q., Yang, D., Zhuang, Y., Croll, T. I., Cai, X., Dai, A., He, X., Duan, J., Yin, W., Ye, C., Zhou, F., Wu, B., Zhao, Q., Xu, H. E., Wang, M. W., & Jiang, Y. (2021). Ligand recognition and G-protein coupling selectivity of cholecystokinin A receptor. *Nat Chem Biol, 17*(12), 1238-1244. doi:10.1038/s41589-021-00841-3

Liu, Y. J., Liu, T. T., Jiang, L. H., Liu, Q., Ma, Z. L., Xia, T. J., & Gu, X. P. (2021). Identification of hub genes associated with cognition in the hippocampus of Alzheimer's Disease. *Bioengineered, 12*(2), 9598-9609. doi:10.1080/21655979.2021.1999549

Liu, Y. J., McIntyre, R. L., Janssens, G. E., & Houtkooper, R. H. (2020). Mitochondrial fission and fusion: A dynamic role in aging and potential target for age-related disease. *Mechanisms of Ageing and Development, 186*, 111212. doi:10.1016/j.mad.2020.111212

Lo, C. M., Samuelson, L. C., Chambers, J. B., King, A., Heiman, J., Jandacek, R. J., Sakai, R. R., Benoit, S. C., Raybould, H. E., Woods, S. C., & Tso, P. (2008). Characterization of mice lacking the gene for cholecystokinin. *Am J Physiol Regul Integr Comp Physiol, 294*(3), R803-810. doi:10.1152/ajpregu.00682.2007

Lofberg, C., Harro, J., Gottfries, C. G., & Oreland, L. (1996). Cholecystokinin peptides and receptor binding in Alzheimer's disease. *J Neural Transm (Vienna), 103*(7), 851-860. doi:10.1007/BF01273363

Lommatzsch, M., Braun, A., Mannsfeldt, A., Botchkarev, V. A., Botchkareva, N. V., Paus, R., Fischer, A., Lewin, G. R., & Renz, H. (1999). Abundant production of brain-derived neurotrophic factor by adult visceral epithelia. Implications for paracrine and target-derived Neurotrophic functions. *American Journal of Pathology, 155*(4), 1183-1193. doi:10.1016/S0002-9440(10)65221-2

Long-Smith, C. M., Manning, S., McClean, P. L., Coakley, M. F., O'Halloran, D. J., Holscher, C., & O'Neill, C. (2013). The diabetes drug liraglutide ameliorates aberrant insulin receptor localisation and signalling in parallel with decreasing both amyloid-beta plaque and glial pathology in a mouse model of Alzheimer's disease. *Neuromolecular Med, 15*(1), 102-114. doi:10.1007/s12017-012-8199-5

Long, C., Han, X., Yang, Y., Li, T., Zhou, Q., & Chen, Q. (2022). Efficacy of intranasal insulin in improving cognition in mild cognitive impairment or dementia: a systematic review and meta-analysis. *Frontiers in Aging Neuroscience, 14*, 963933. doi:10.3389/fnagi.2022.963933

Lorigados Pedre, L., Pavon Fuentes, N., Alvarez Gonzalez, L., McRae, A., Serrano Sanchez, T., Blanco Lescano, L., & Macias Gonzalez, R. (2002). Nerve growth factor levels in Parkinson disease and experimental parkinsonian rats. *Brain Research, 952*(1), 122-127. doi:10.1016/s0006-8993(02)03222-5

Lucini, C., Maruccio, L., de Girolamo, P., Vega, J. A., & Castaldo, L. (2002). Localisation of neurotrophin - containing cells in higher vertebrate intestine. *Anat Embryol (Berl), 205*(2), 135-140. doi:10.1007/s00429-002-0237-x

Luo, S. X., & Huang, E. J. (2016). Dopaminergic Neurons and Brain Reward Pathways: From Neurogenesis to Circuit Assembly. *American Journal of Pathology, 186*(3), 478-488. doi:10.1016/j.ajpath.2015.09.023

Luyer, M. D., Greve, J. W., Hadfoune, M., Jacobs, J. A., Dejong, C. H., & Buurman, W. A. (2005). Nutritional stimulation of cholecystokinin receptors inhibits inflammation via the vagus nerve. *J Exp Med, 202*(8), 1023-1029. doi:10.1084/jem.20042397

Lv, M., Xue, G., Cheng, H., Meng, P., Lian, X., Holscher, C., & Li, D. (2021). The GLP-1/GIP dual-receptor agonist DA5-CH inhibits the NF-kappaB inflammatory pathway in the MPTP mouse model of Parkinson's disease more effectively than the GLP-1 single-receptor agonist NLY01. *Brain Behav, 11*(8), e2231. doi:10.1002/brb3.2231

Lying-Tunell, U., Lindblad, B. S., Malmlund, H. O., & Persson, B. (1981). Cerebral blood flow and metabolic rate of oxygen, glucose, lactate, pyruvate, ketone bodies and amino acids. *Acta Neurologica Scandinavica, 63*(6), 337-350. doi:10.1111/j.1600-0404.1981.tb00788.x

Ma, Q. L., Yang, F., Rosario, E. R., Ubeda, O. J., Beech, W., Gant, D. J., Chen, P. P., Hudspeth, B., Chen, C., Zhao, Y., Vinters, H. V., Frautschy, S. A., & Cole, G. M. (2009). Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. *Journal of Neuroscience, 29*(28), 9078-9089. doi:10.1523/JNEUROSCI.1071-09.2009

Ma, Y., & Giardino, W. J. (2022). Neural circuit mechanisms of the cholecystokinin (CCK) neuropeptide system in addiction. *Addict Neurosci, 3*. doi:10.1016/j.addicn.2022.100024

Mabuchi, T., Kitagawa, K., Kuwabara, K., Takasawa, K., Ohtsuki, T., Xia, Z., Storm, D., Yanagihara, T., Hori, M., & Matsumoto, M. (2001). Phosphorylation of cAMP response element-binding protein in hippocampal neurons as a protective response after exposure to glutamate in vitro and ischemia in vivo. *Journal of Neuroscience, 21*(23), 9204-9213. doi:10.1523/JNEUROSCI.21-23-09204.2001

Maeda, A., Akimoto, M., Goto, Y., Ogihara, Y., Debas, H. T., & Yamashiata, K. (2000). Reciprocal effect of unsulfated and sulfated forms of cholecystokinin-octapeptide on gastric acid secretion in the rat. *Pharmacol Res, 42*(4), 333-336. doi:10.1006/phrs.2000.0692

MahmoudianDehkordi, S., Arnold, M., Nho, K., Ahmad, S., Jia, W., Xie, G., Louie, G., Kueider-Paisley, A., Moseley, M. A., Thompson, J. W., St John Williams, L., Tenenbaum, J. D., Blach, C., Baillie, R., Han, X., Bhattacharyya, S., Toledo, J. B., Schafferer, S., Klein, S., Koal, T., Risacher, S. L., Kling, M. A., Motsinger-Reif, A., Rotroff, D. M., Jack, J., Hankemeier, T., Bennett, D. A., De Jager, P. L., Trojanowski, J. Q., Shaw, L. M., Weiner, M. W., Doraiswamy, P. M., van Duijn, C. M., Saykin, A. J., Kastenmuller, G., Kaddurah-Daouk, R., Alzheimer's Disease Neuroimaging, I., & the Alzheimer Disease Metabolomics, C. (2019). Altered bile acid profile associates with cognitive impairment in Alzheimer's disease-An emerging role for gut microbiome. *Alzheimers Dement, 15*(1), 76-92. doi:10.1016/j.jalz.2018.07.217

Maluf, F. C., Feder, D., & Carvalho, A. A. D. (2019). Analysis of the Relationship between Type II Diabetes Mellitus and Parkinson's Disease: A Systematic Review. *Parkinsons Disease, 2019*. doi:10.1155/2019/4951379

Marksteiner, J., Blasko, I., Kemmler, G., Koal, T., & Humpel, C. (2018). Bile acid quantification of 20 plasma metabolites identifies lithocholic acid as a putative biomarker in Alzheimer's disease. *Metabolomics, 14*(1), 1. doi:10.1007/s11306-017-1297-5

Marlin, M. C., & Li, G. (2015). Biogenesis and function of the NGF/TrkA signaling endosome. *Int Rev Cell Mol Biol, 314*, 239-257. doi:10.1016/bs.ircmb.2014.10.002

Marshall, F. H., Barnes, S., Hughes, J., Woodruff, G. N., & Hunter, J. C. (1991). Cholecystokinin modulates the release of dopamine from the anterior and posterior nucleus accumbens by two different mechanisms. *Journal of Neurochemistry, 56*(3), 917-922. doi:10.1111/j.1471-4159.1991.tb02009.x

Martin, T. A., Jayanthi, S., McCoy, M. T., Brannock, C., Ladenheim, B., Garrett, T., Lehrmann, E., Becker, K. G., & Cadet, J. L. (2012). Methamphetamine causes differential alterations in gene expression and patterns of histone acetylation/hypoacetylation in the rat nucleus accumbens. *Plos One, 7*(3), e34236. doi:10.1371/journal.pone.0034236

Martinez Damonte, V., Pomrenze, M. B., Manning, C. E., Casper, C., Wolfden, A. L., Malenka, R. C., & Kauer, J. A. (2023). Somatodendritic Release of Cholecystokinin Potentiates GABAergic Synapses Onto Ventral Tegmental Area Dopamine Cells. *Biol Psychiatry, 93*(2), 197-208. doi:10.1016/j.biopsych.2022.06.011

Maskery, M., Goulding, E. M., Gengler, S., Melchiorsen, J. U., Rosenkilde, M. M., & Holscher, C. (2020). The Dual GLP-1/GIP Receptor Agonist DA4-JC Shows Superior Protective Properties Compared to the GLP-1 Analogue Liraglutide in the APP/PS1 Mouse Model of Alzheimer's Disease. *Am J Alzheimers Dis Other Demen, 35*, 1533317520953041. doi:10.1177/1533317520953041

Matsushita, H., Akiyoshi, J., Kai, K., Ishii, N., Kodama, K., Tsutsumi, T., Isogawa, K., & Nagayama, H. (2003). Spatial memory impairment in OLETF rats without cholecystokinin - a receptor. *Neuropeptides, 37*(5), 271-276. doi:10.1016/s0143-4179(03)00083-0

May, A. A., Liu, M., Woods, S. C., & Begg, D. P. (2016). CCK increases the transport of insulin into the brain. *Physiol Behav, 165*, 392-397. doi:10.1016/j.physbeh.2016.08.025

Mazurek, M. F., & Beal, M. F. (1991). Cholecystokinin and somatostatin in Alzheimer's disease postmortem cerebral cortex. *Neurology, 41*(5), 716-719. doi:10.1212/wnl.41.5.716

McCann, U. D., Slate, S. O., Geraci, M., Roscow-Terrill, D., & Uhde, T. W. (1997). A comparison of the effects of intravenous pentagastrin on patients with social phobia, panic disorder and healthy controls. *Neuropsychopharmacology, 16*(3), 229-237. doi:10.1016/S0893-133X(96)00197-2

McCauslin, C. S., Heath, V., Colangelo, A. M., Malik, R., Lee, S., Mallei, A., Mocchetti, I., & Johnson, P. F. (2006). CAAT/enhancer-binding protein delta and cAMP-response element-binding protein mediate inducible expression of the nerve growth factor gene in the central nervous system. *Journal of Biological Chemistry, 281*(26), 17681-17688. doi:10.1074/jbc.M600207200

McIlwraith, E. K., Zhang, N., & Belsham, D. D. (2022). The Regulation of Phoenixin: A Fascinating Multidimensional Peptide. *J Endocr Soc, 6*(2), bvab192. doi:10.1210/jendso/bvab192

Meda, L., Cassatella, M. A., Szendrei, G. I., Otvos, L., Jr., Baron, P., Villalba, M., Ferrari, D., & Rossi, F. (1995). Activation of microglial cells by beta-amyloid protein and interferon-gamma. *Nature, 374*(6523), 647-650. doi:10.1038/374647a0

Mendez, M. E. (2021). The Relationship Between Anxiety and Alzheimer's Disease. *Journal of Alzheimers Disease Reports, 5*(1), 171-177. doi:10.3233/Adr-210294

Meng, A. H., Ling, Y. L., Zhang, X. P., & Zhang, J. L. (2002). Anti-inflammatory effect of cholecystokinin and its signal transduction mechanism in endotoxic shock rat. *World J Gastroenterol, 8*(4), 712-717. doi:10.3748/wjg.v8.i4.712

Meyer, D. K., & Krauss, J. (1983). Dopamine modulates cholecystokinin release in neostriatum. *Nature, 301*(5898), 338-340. doi:10.1038/301338a0

Meyer, M. A. (2014). Highly Expressed Genes within Hippocampal Sector CA1: Implications for the Physiology of Memory. *Neurol Int, 6*(2), 5388. doi:10.4081/ni.2014.5388

Micevych, P., & Sinchak, K. (2001). Estrogen and endogenous opioids regulate CCK in reproductive circuits. *Peptides, 22*(8), 1235-1244. doi:10.1016/s0196-9781(01)00447-8

Migaud, M., Roques, B. P., & Durieux, C. (1994). Effects of cholecystokinin octapeptide and BC 264, a potent and selective CCK-B agonist on aspartate and glutamate release from rat

hippocampal slices. *Neuropharmacology, 33*(6), 737-743. doi:10.1016/0028-3908(94)90113-9

Miller, K. K., Hoffer, A., Svoboda, K. R., & Lupica, C. R. (1997). Cholecystokinin increases GABA release by inhibiting a resting K+ conductance in hippocampal interneurons. *Journal of Neuroscience, 17*(13), 4994-5003. doi:10.1523/JNEUROSCI.17-13-04994.1997

Miller, L. J., & Desai, A. J. (2016). Metabolic Actions of the Type 1 Cholecystokinin Receptor: Its Potential as a Therapeutic Target. *Trends Endocrinol Metab, 27*(9), 609-619. doi:10.1016/j.tem.2016.04.002

Miller, L. J., Harikumar, K. G., Wootten, D., & Sexton, P. M. (2021). Roles of Cholecystokinin in the Nutritional Continuum. Physiology and Potential Therapeutics. *Front Endocrinol (Lausanne), 12*, 684656. doi:10.3389/fendo.2021.684656

Mitra, S., Behbahani, H., & Eriksdotter, M. (2019). Innovative Therapy for Alzheimer's Disease-With Focus on Biodelivery of NGF. *Front Neurosci, 13*, 38. doi:10.3389/fnins.2019.00038

Miyamoto, S., Shikata, K., Miyasaka, K., Okada, S., Sasaki, M., Kodera, R., Hirota, D., Kajitani, N., Takatsuka, T., Kataoka, H. U., Nishishita, S., Sato, C., Funakoshi, A., Nishimori, H., Uchida, H. A., Ogawa, D., & Makino, H. (2012). Cholecystokinin plays a novel protective role in diabetic kidney through anti-inflammatory actions on macrophage: anti-inflammatory effect of cholecystokinin. *Diabetes, 61*(4), 897-907. doi:10.2337/db11-0402

Miyasaka, K., Ohta, M., Masuda, M., Kawanami, T., Matsumoto, M., & Funakoshi, A. (1995). Sex difference in gene expressions of cholecystokinin (CCK) and CCK receptor in young and old rats. *Arch Gerontol Geriatr, 21*(2), 157-165. doi:10.1016/0167-4943(95)00635-x

Moloney, A. M., Griffin, R. J., Timmons, S., O'Connor, R., Ravid, R., & O'Neill, C. (2010). Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to

IGF-1 and insulin signalling. *Neurobiology of Aging, 31*(2), 224-243. doi:10.1016/j.neurobiolaging.2008.04.002

Monnikes, H., Lauer, G., & Arnold, R. (1997). Peripheral administration of cholecystokinin activates c-fos expression in the locus coeruleus/subcoeruleus nucleus, dorsal vagal complex and paraventricular nucleus via capsaicin-sensitive vagal afferents and CCK-A receptors in the rat. *Brain Research, 770*(1-2), 277-288. doi:10.1016/s0006-8993(97)00865-2

Monnikes, H., Lauer, G., Bauer, C., Tebbe, J., Zittel, T. T., & Arnold, R. (1997). Pathways of Fos expression in locus ceruleus, dorsal vagal complex, and PVN in response to intestinal lipid. *Am J Physiol, 273*(6), R2059-2071. doi:10.1152/ajpregu.1997.273.6.R2059

Moore, D. J., Zhang, L., Dawson, T. M., & Dawson, V. L. (2003). A missense mutation (L166P) in DJ-1, linked to familial Parkinson's disease, confers reduced protein stability and impairs homo-oligomerization. *Journal of Neurochemistry, 87*(6), 1558-1567. doi:10.1111/j.1471-4159.2003.02265.x

Morales, I., Guzman-Martinez, L., Cerda-Troncoso, C., Farias, G. A., & Maccioni, R. B. (2014). Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. *Frontiers in Cellular Neuroscience, 8*, 112. doi:10.3389/fncel.2014.00112

Morales, I., Jimenez, J. M., Mancilla, M., & Maccioni, R. B. (2013). Tau oligomers and fibrils induce activation of microglial cells. *Journal of Alzheimers Disease, 37*(4), 849-856. doi:10.3233/JAD-131843

Moran, T. H., Katz, L. F., Plata-Salaman, C. R., & Schwartz, G. J. (1998). Disordered food intake and obesity in rats lacking cholecystokinin A receptors. *Am J Physiol, 274*(3), R618-625. doi:10.1152/ajpregu.1998.274.3.R618

Moran, T. H., Robinson, P. H., Goldrich, M. S., & McHugh, P. R. (1986). Two brain cholecystokinin receptors: implications for behavioral actions. *Brain Research, 362*(1), 175-179. doi:10.1016/0006-8993(86)91413-7

Moriarty, P., Dimaline, R., Thompson, D. G., & Dockray, G. J. (1997). Characterization of cholecystokininA and cholecystokininB receptors expressed by vagal afferent neurons. *Neuroscience, 79*(3), 905-913. doi:10.1016/s0306-4522(96)00675-6

Morino, P., Herrera-Marschitz, M., Castel, M. N., Ungerstedt, U., Varro, A., Dockray, G., & Hokfelt, T. (1994). Cholecystokinin in cortico-striatal neurons in the rat: immunohistochemical studies at the light and electron microscopical level. *Eur J Neurosci, 6*(5), 681-692. doi:10.1111/j.1460-9568.1994.tb00980.x

Morisset, J., Julien, S., & Laine, J. (2003). Localization of cholecystokinin receptor subtypes in the endocine pancreas. *Journal of Histochemistry & Cytochemistry, 51*(11), 1501-1513. doi:10.1177/002215540305101110

Moroo, I., Yamada, T., Makino, H., Tooyama, I., McGeer, P. L., McGeer, E. G., & Hirayama, K. (1994). Loss of insulin receptor immunoreactivity from the substantia nigra pars compacta neurons in Parkinson's disease. *Acta Neuropathologica, 87*(4), 343-348. doi:10.1007/BF00313602

Morris, J. K., Vidoni, E. D., Perea, R. D., Rada, R., Johnson, D. K., Lyons, K., Pahwa, R., Burns, J. M., & Honea, R. A. (2014). Insulin resistance and gray matter volume in neurodegenerative disease. *Neuroscience, 270*, 139-147. doi:10.1016/j.neuroscience.2014.04.006

Morris, M. J., Chen, H., Watts, R., Shulkes, A., & Cameron-Smith, D. (2008). Brain neuropeptide Y and CCK and peripheral adipokine receptors: temporal response in obesity induced by palatable diet. *Int J Obes (Lond), 32*(2), 249-258. doi:10.1038/sj.ijo.0803716

Mosconi, L., Pupi, A., & De Leon, M. J. (2008). Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. *Ann N Y Acad Sci, 1147*, 180-195. doi:10.1196/annals.1427.007

Muddapu, V. R., Dharshini, S. A. P., Chakravarthy, V. S., & Gromiha, M. M. (2020). Neurodegenerative Diseases - Is Metabolic Deficiency the Root Cause? *Frontiers in Neuroscience, 14*. doi:10.3389/fnins.2020.00213

Muller, M. B., Toschi, N., Kresse, A. E., Post, A., & Keck, M. E. (2000). Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. *Neuropsychopharmacology, 23*(2), 205-215. doi:10.1016/S0893-133X(00)00099-3

Muller, W., Heinemann, U., & Berlin, K. (1997). Cholecystokinin activates CCKB-receptor-mediated Ca-signaling in hippocampal astrocytes. *Journal of Neurophysiology, 78*(4), 1997-2001. doi:10.1152/jn.1997.78.4.1997

Neth, B. J., & Craft, S. (2017). Insulin Resistance and Alzheimer's Disease: Bioenergetic Linkages. *Frontiers in Aging Neuroscience, 9*, 345. doi:10.3389/fnagi.2017.00345

Neu, A., Foldy, C., & Soltesz, I. (2007). Postsynaptic origin of CB1-dependent tonic inhibition of GABA release at cholecystokinin-positive basket cell to pyramidal cell synapses in the CA1 region of the rat hippocampus. *J Physiol, 578*(Pt 1), 233-247. doi:10.1113/jphysiol.2006.115691

Nho, K., Kueider-Paisley, A., MahmoudianDehkordi, S., Arnold, M., Risacher, S. L., Louie, G., Blach, C., Baillie, R., Han, X., Kastenmuller, G., Jia, W., Xie, G., Ahmad, S., Hankemeier, T., van Duijn, C. M., Trojanowski, J. Q., Shaw, L. M., Weiner, M. W., Doraiswamy, P. M., Saykin, A. J., Kaddurah-Daouk, R., Alzheimer's Disease Neuroimaging, I., & the Alzheimer Disease Metabolomics, C. (2019). Altered bile acid profile in mild cognitive impairment and Alzheimer's disease: Relationship to neuroimaging and CSF biomarkers. *Alzheimers Dement, 15*(2), 232-244. doi:10.1016/j.jalz.2018.08.012

Nilsson, A., Falth, M., Zhang, X., Kultima, K., Skold, K., Svenningsson, P., & Andren, P. E. (2009). Striatal alterations of secretogranin-1, somatostatin, prodynorphin, and cholecystokinin peptides in an experimental mouse model of Parkinson disease. *Mol Cell Proteomics, 8*(5), 1094-1104. doi:10.1074/mcp.M800454-MCP200

Nomoto, S., Miyake, M., Ohta, M., Funakoshi, A., & Miyasaka, K. (1999). Impaired learning and memory in OLETF rats without cholecystokinin (CCK)-A receptor. *Physiol Behav, 66*(5), 869-872. doi:10.1016/s0031-9384(99)00033-5

Novak, P., Pimentel Maldonado, D. A., & Novak, V. (2019). Safety and preliminary efficacy of intranasal insulin for cognitive impairment in Parkinson disease and multiple system atrophy: A double-blinded placebo-controlled pilot study. *Plos One, 14*(4), e0214364. doi:10.1371/journal.pone.0214364

Nunzi, M. G., Gorio, A., Milan, F., Freund, T. F., Somogyi, P., & Smith, A. D. (1985). Cholecystokinin-immunoreactive cells form symmetrical synaptic contacts with pyramidal and nonpyramidal neurons in the hippocampus. *Journal of Comparative Neurology, 237*(4), 485-505. doi:10.1002/cne.902370406

O'Leary, O. F., Ogbonnaya, E. S., Felice, D., Levone, B. R., L, C. C., Fitzgerald, P., Bravo, J. A., Forsythe, P., Bienenstock, J., Dinan, T. G., & Cryan, J. F. (2018). The vagus nerve modulates BDNF expression and neurogenesis in the hippocampus. *Eur Neuropsychopharmacol, 28*(2), 307-316. doi:10.1016/j.euroneuro.2017.12.004

Oehlers, S. H., Flores, M. V., Hall, C. J., Wang, L., Ko, D. C., Crosier, K. E., & Crosier, P. S. (2017). A whole animal chemical screen approach to identify modifiers of intestinal neutrophilic inflammation. *Febs Journal, 284*(3), 402-413. doi:10.1111/febs.13976

Ogawa, M., Fukuyama, H., Ouchi, Y., Yamauchi, H., & Kimura, J. (1994). [Altered energy metabolism in Alzheimer's disease]. *Rinsho Shinkeigaku, 34*(1), 27-31.

Olazaran, J., Gil-de-Gomez, L., Rodriguez-Martin, A., Valenti-Soler, M., Frades-Payo, B., Marin-Munoz, J., Antunez, C., Frank-Garcia, A., Acedo-Jimenez, C., Morlan-Gracia, L., Petidier-Torregrossa, R., Guisasola, M. C., Bermejo-Pareja, F., Sanchez-Ferro, A., Perez-Martinez, D. A., Manzano-Palomo, S., Farquhar, R., Rabano, A., & Calero, M. (2015). A blood-based, 7-metabolite signature for the early diagnosis of Alzheimer's disease. *Journal of Alzheimers Disease, 45*(4), 1157-1173. doi:10.3233/JAD-142925

Ong, W. Y., Tanaka, K., Dawe, G. S., Ittner, L. M., & Farooqui, A. A. (2013). Slow excitotoxicity in Alzheimer's disease. *Journal of Alzheimers Disease, 35*(4), 643-668. doi:10.3233/JAD-121990

Ouerdane, Y., El-Nahas, Z. S., Ouerdane, F., Hamam, K. M., & Ebada, M. A. (2022). *Gut–Brain Axis in Alzheimer's Disease: Interplay Between Cholecystokinin, Dysbiosis, and Brain-Derived Neurotrophic Factor. In: Ashraf, G.M., Uddin, M.S. (eds) Current Thoughts on Dementia. Springer, Singapore.* https://doi.org/10.1007/978-981-16-7606-2_12.

Overduin, J., Gibbs, J., Cummings, D. E., & Reeve, J. R. (2014). CCK-58 elicits both satiety and satiation in rats while CCK-8 elicits only satiation. *Peptides, 54*, 71-80. doi:10.1016/j.peptides.2014.01.008

Pacelli, C., Giguere, N., Bourque, M. J., Levesque, M., Slack, R. S., & Trudeau, L. E. (2015). Elevated Mitochondrial Bioenergetics and Axonal Arborization Size Are Key Contributors to the Vulnerability of Dopamine Neurons. *Current Biology, 25*(18), 2349-2360. doi:10.1016/j.cub.2015.07.050

Paladugu, L., Gharaibeh, A., Kolli, N., Learman, C., Hall, T. C., Li, L. X., Rossignol, J., Maiti, P., & Dunbar, G. L. (2021). Liraglutide Has Anti-Inflammatory and Anti-Amyloid Properties in Streptozotocin-Induced and 5xFAD Mouse Models of Alzheimer's Disease. *International Journal of Molecular Sciences, 22*(2). doi:10.3390/ijms22020860

Palasz, E., Wysocka, A., Gasiorowska, A., Chalimoniuk, M., Niewiadomski, W., & Niewiadomska, G. (2020). BDNF as a Promising Therapeutic Agent in Parkinson's Disease. *International Journal of Molecular Sciences, 21*(3). doi:10.3390/ijms21031170

Pan, W., Banks, W. A., Fasold, M. B., Bluth, J., & Kastin, A. J. (1998). Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology, 37*(12), 1553-1561. doi:10.1016/s0028-3908(98)00141-5

Pan, X., Elliott, C. T., McGuinness, B., Passmore, P., Kehoe, P. G., Holscher, C., McClean, P. L., Graham, S. F., & Green, B. D. (2017). Metabolomic Profiling of Bile Acids in Clinical and Experimental Samples of Alzheimer's Disease. *Metabolites, 7*(2). doi:10.3390/metabo7020028

Paoli, A., Bosco, G., Camporesi, E. M., & Mangar, D. (2015). Ketosis, ketogenic diet and food intake control: a complex relationship. *Frontiers in Psychology, 6*, 27. doi:10.3389/fpsyg.2015.00027

Park, K. Y., Nam, G. E., Han, K., Park, H. K., & Hwang, H. S. (2022). Waist circumference and risk of Parkinson's disease. *NPJ Parkinsons Dis, 8*(1), 89. doi:10.1038/s41531-022-00353-4

Pathak, V., Flatt, P. R., & Irwin, N. (2018). Cholecystokinin (CCK) and related adjunct peptide therapies for the treatment of obesity and type 2 diabetes. *Peptides, 100*, 229-235. doi:10.1016/j.peptides.2017.09.007

Peng, K., Yang, L., Wang, J., Ye, F., Dan, G., Zhao, Y., Cai, Y., Cui, Z., Ao, L., Liu, J., Zou, Z., Sai, Y., & Cao, J. (2017). The Interaction of Mitochondrial Biogenesis and Fission/Fusion Mediated by PGC-1alpha Regulates Rotenone-Induced Dopaminergic Neurotoxicity. *Molecular Neurobiology, 54*(5), 3783-3797. doi:10.1007/s12035-016-9944-9

Pentz, R., Iulita, M. F., Ducatenzeiler, A., Bennett, D. A., & Cuello, A. C. (2021). The human brain NGF metabolic pathway is impaired in the pre-clinical and clinical continuum of Alzheimers disease. *Mol Psychiatry, 26*(10), 6023-6037. doi:10.1038/s41380-020-0797-2

Pérez de la Mora, M., Hernández-Gómez, A. M., Arizmendi-García, Y., Jacobsen, K., Lara-García, D., Flores-Gracia, C., Crespo-Ramírez, M., Gallegos-Cari, A., Nuche-Bricaire, A., & Fuxe, K. (2007). Role of the amygdaloid cholecystokinin (CCK)/gastrin-2 receptors and terminal networks in the modulation of anxiety in the rat. Effects of CCK-4 and CCK-8S on anxiety-like behaviour and [3H]GABA release. *Eur J Neurosci, 26*(12), 3614-3630. doi:10.1111/j.1460-9568.2007.05963.x

Perry, R. H., Dockray, G. J., Dimaline, R., Perry, E. K., Blessed, G., & Tomlinson, B. E. (1981). Neuropeptides in Alzheimer's disease, depression and schizophrenia. A post mortem analysis of vasoactive intestinal peptide and cholecystokinin in cerebral cortex. *J Neurol Sci, 51*(3), 465-472. doi:10.1016/0022-510x(81)90123-4

Peters, J. H., Simasko, S. M., & Ritter, R. C. (2006). Modulation of vagal afferent excitation and reduction of food intake by leptin and cholecystokinin. *Physiol Behav, 89*(4), 477-485. doi:10.1016/j.physbeh.2006.06.017

Phillips, G. D., Le Noury, J., Wolterink, G., Donselaar-Wolterink, I., Robbins, T. W., & Everitt, B. J. (1993). Cholecystokinin-dopamine interactions within the nucleus accumbens in the control over behaviour by conditioned reinforcement. *Behavioural Brain Research, 55*(2), 223-231. doi:10.1016/0166-4328(93)90118-a

Pietrowsky, R., Claassen, L., Frercks, H., Fehm, H. L., & Born, J. (2001). Time course of intranasally administered cholecystokinin-8 on central nervous effects. *Neuropsychobiology, 43*(4), 254-259. doi:10.1159/000054899

Pietrowsky, R., Specht, G., Fehm, H. L., & Born, J. (1994). Comparison of satiating effects of ceruletide and food intake using behavioral and electrophysiological indicators of memory. *Int J Psychophysiol, 17*(1), 79-89. doi:10.1016/0167-8760(94)90058-2

Pietrowsky, R., Thiemann, A., Kern, W., Fehm, H. L., & Born, J. (1996). A nose-brain pathway for psychotropic peptides: evidence from a brain evoked potential study with cholecystokinin. *Psychoneuroendocrinology, 21*(6), 559-572. doi:10.1016/s0306-4530(96)00012-1

Plagman, A., Hoscheidt, S., McLimans, K. E., Klinedinst, B., Pappas, C., Anantharam, V., Kanthasamy, A., Willette, A. A., & Alzheimer's Disease Neuroimaging, I. (2019). Cholecystokinin and Alzheimer's disease: a biomarker of metabolic function, neural integrity, and cognitive performance. *Neurobiology of Aging, 76*, 201-207. doi:10.1016/j.neurobiolaging.2019.01.002

Prinz, P., Hofmann, T., Ahnis, A., Elbelt, U., Goebel-Stengel, M., Klapp, B. F., Rose, M., & Stengel, A. (2015). Plasma bile acids show a positive correlation with body mass index and are negatively associated with cognitive restraint of eating in obese patients. *Frontiers in Neuroscience, 9*. doi:10.3389/fnins.2015.00199

Pugh, P. L., Richardson, J. C., Bate, S. T., Upton, N., & Sunter, D. (2007). Non-cognitive behaviours in an APP/PS1 transgenic model of Alzheimer's disease. *Behavioural Brain Research, 178*(1), 18-28. doi:10.1016/j.bbr.2006.11.044

Rani, L., & Mondal, A. C. (2021). Unravelling the role of gut microbiota in Parkinson's disease progression: Pathogenic and therapeutic implications. *Neuroscience Research, 168*, 100-112. doi:10.1016/j.neures.2021.01.001

Rao, M., & Gershon, M. D. (2018). Enteric nervous system development: what could possibly go wrong? *Nature Reviews Neuroscience, 19*(9), 552-565. doi:10.1038/s41583-018-0041-0

Raud, S., Innos, J., Abramov, U., Reimets, A., Koks, S., Soosaar, A., Matsui, T., & Vasar, E. (2005). Targeted invalidation of CCK2 receptor gene induces anxiolytic-like action in light-dark exploration, but not in fear conditioning test. *Psychopharmacology (Berl), 181*(2), 347-357. doi:10.1007/s00213-005-2255-x

Reed-Geaghan, E. G., Savage, J. C., Hise, A. G., & Landreth, G. E. (2009). CD14 and toll-like receptors 2 and 4 are required for fibrillar Abeta-stimulated microglial activation. *Journal of Neuroscience, 29*(38), 11982-11992. doi:10.1523/JNEUROSCI.3158-09.2009

Reger, M. A., Watson, G. S., Frey, W. H., 2nd, Baker, L. D., Cholerton, B., Keeling, M. L., Belongia, D. A., Fishel, M. A., Plymate, S. R., Schellenberg, G. D., Cherrier, M. M., & Craft, S. (2006). Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. *Neurobiology of Aging, 27*(3), 451-458. doi:10.1016/j.neurobiolaging.2005.03.016

Rehfeld, J. F. (1978). Immunochemical studies on cholecystokinin. II. Distribution and molecular heterogeneity in the central nervous system and small intestine of man and hog. *Journal of Biological Chemistry, 253*(11), 4022-4030.

Rehfeld, J. F. (1998). Accurate measurement of cholecystokinin in plasma. *Clinical Chemistry, 44*(5), 991-1001.

Rehfeld, J. F. (2011). Incretin physiology beyond glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide: cholecystokinin and gastrin peptides. *Acta Physiol (Oxf), 201*(4), 405-411. doi:10.1111/j.1748-1716.2010.02235.x

Rehfeld, J. F. (2017). Cholecystokinin-From Local Gut Hormone to Ubiquitous Messenger. *Front Endocrinol (Lausanne), 8*, 47. doi:10.3389/fendo.2017.00047

Rehfeld, J. F. (2019). Premises for Cholecystokinin and Gastrin Peptides in Diabetes Therapy. *Clin Med Insights Endocrinol Diabetes, 12*, 1179551419883608. doi:10.1177/1179551419883608

Rehfeld, J. F. (2021). Cholecystokinin and Panic Disorder: Reflections on the History and Some Unsolved Questions. *Molecules, 26*(18). doi:10.3390/molecules26185657

Rehfeld, J. F., Bundgaard, J. R., Hannibal, J., Zhu, X., Norrbom, C., Steiner, D. F., & Friis-Hansen, L. (2008). The cell-specific pattern of cholecystokinin peptides in endocrine cells versus neurons is governed by the expression of prohormone convertases 1/3, 2, and 5/6. *Endocrinology, 149*(4), 1600-1608. doi:10.1210/en.2007-0278

Rehfeld, J. F., & Hansen, H. F. (1986). Characterization of preprocholecystokinin products in the porcine cerebral cortex. Evidence of different processing pathways. *Journal of Biological Chemistry, 261*(13), 5832-5840.

Rehfeld, J. F., Mogensen, N. W., Bardram, L., Hilsted, L., & Monstein, H. J. (1992). Expression, but failing maturation of procholecystokinin in cerebellum. *Brain Research, 576*(1), 111-119. doi:10.1016/0006-8993(92)90615-g

Rehfeld, J. F., Sun, G., Christensen, T., & Hillingso, J. G. (2001). The predominant cholecystokinin in human plasma and intestine is cholecystokinin-33. *J Clin Endocrinol Metab, 86*(1), 251-258. doi:10.1210/jcem.86.1.7148

Reich, N., & Holscher, C. (2020). Acylated Ghrelin as a Multi-Targeted Therapy for Alzheimer's and Parkinson's Disease. *Front Neurosci, 14*, 614828. doi:10.3389/fnins.2020.614828

Reich, N., & Holscher, C. (2022a). Beyond appetite: Acylated ghrelin as a learning, memory and fear behavior-modulating hormone. *Neurosci Biobehav Rev, 143*, 104952. doi:10.1016/j.neubiorev.2022.104952

Reich, N., & Holscher, C. (2022b). The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: An in-depth review. *Front Neurosci, 16*, 970925. doi:10.3389/fnins.2022.970925

Reid, H. M. O., Chen-Mack, N., Snowden, T., & Christie, B. R. (2021). Understanding Changes in Hippocampal Interneurons Subtypes in the Pathogenesis of Alzheimer's Disease: A Systematic Review. *Brain Connect, 11*(3), 159-179. doi:10.1089/brain.2020.0879

Reisi, P., Ghaedamini, A. R., Golbidi, M., Shabrang, M., Arabpoor, Z., & Rashidi, B. (2015). Effect of cholecystokinin on learning and memory, neuronal proliferation and apoptosis in the rat hippocampus. *Adv Biomed Res, 4*, 227. doi:10.4103/2277-9175.166650

Rettenbacher, M., & Reubi, J. C. (2001). Localization and characterization of neuropeptide receptors in human colon. *Naunyn Schmiedebergs Arch Pharmacol, 364*(4), 291-304. doi:10.1007/s002100100454

Reubi, J. C., Waser, B., Laderach, U., Stettler, C., Friess, H., Halter, F., & Schmassmann, A. (1997). Localization of cholecystokinin A and cholecystokinin B-gastrin receptors in the human stomach. *Gastroenterology, 112*(4), 1197-1205. doi:10.1016/s0016-5085(97)70131-8

Reubi, J. C., Waser, B., Schmassmann, A., & Laissue, J. A. (1999). Receptor autoradiographic evaluation of cholecystokinin, neurotensin, somatostatin and vasoactive intestinal peptide receptors in gastro-intestinal adenocarcinoma samples: where are they really located? *Int J Cancer, 81*(3), 376-386. doi:10.1002/(sici)1097-0215(19990505)81:3<376::aid-ijc11>3.0.co;2-5

Rex, A., Barth, T., Voigt, J. P., Domeney, A. M., & Fink, H. (1994). Effects of cholecystokinin tetrapeptide and sulfated cholecystokinin octapeptide in rat models of anxiety. *Neuroscience Letters, 172*(1-2), 139-142. doi:10.1016/0304-3940(94)90681-5

Ribak, C. E., & Seress, L. (1983). Five types of basket cell in the hippocampal dentate gyrus: a combined Golgi and electron microscopic study. *J Neurocytol, 12*(4), 577-597. doi:10.1007/BF01181525

Rice, M. E., & Patel, J. C. (2015). Somatodendritic dopamine release: recent mechanistic insights. *Philos Trans R Soc Lond B Biol Sci, 370*(1672). doi:10.1098/rstb.2014.0185

Sadeghi, M., Radahmadi, M., & Reisi, P. (2015). Effects of repeated treatment with cholecystokinin sulfated octapeptide on passive avoidance memory under chronic restraint stress in male rats. *Adv Biomed Res, 4*, 150. doi:10.4103/2277-9175.161577

Saia, R. S., Ribeiro, A. B., & Giusti, H. (2020). Cholecystokinin Modulates the Mucosal Inflammatory Response and Prevents the Lipopolysaccharide-Induced Intestinal Epithelial Barrier Dysfunction. *Shock, 53*(2), 242-251. doi:10.1097/SHK.0000000000001355

Salles, G. N., Calio, M. L., Holscher, C., Pacheco-Soares, C., Porcionatto, M., & Lobo, A. O. (2020). Neuroprotective and restorative properties of the GLP-1/GIP dual agonist DA-JC1 compared with a GLP-1 single agonist in Alzheimer's disease. *Neuropharmacology, 162*, 107813. doi:10.1016/j.neuropharm.2019.107813

Sanders, D. J., Zahedi-Asl, S., & Marr, A. P. (1982). Glucagon and CCK in human brain: controls and patients with senile dementia of Alzheimer type. *Essence of Memory, 55*, 465-471. doi:10.1016/S0079-6123(08)64215-6

Saxton, R. A., & Sabatini, D. M. (2017). mTOR Signaling in Growth, Metabolism, and Disease. *Cell, 169*(2), 361-371. doi:10.1016/j.cell.2017.03.035

Sayegh, A. I., Washington, M. C., Raboin, S. J., Aglan, A. H., & Reeve, J. R., Jr. (2014). CCK-58 prolongs the intermeal interval, whereas CCK-8 reduces this interval: not all forms of cholecystokinin have equal bioactivity. *Peptides, 55*, 120-125. doi:10.1016/j.peptides.2014.02.014

Schapira, A. H. V., Chaudhuri, K. R., & Jenner, P. (2017). Non-motor features of Parkinson disease. *Nature Reviews Neuroscience, 18*(7), 435-450. doi:10.1038/nrn.2017.62

Scheperjans, F., Derkinderen, P., & Borghammer, P. (2018). The Gut and Parkinson's Disease: Hype or Hope? *J Parkinsons Dis, 8*(s1), S31-S39. doi:10.3233/JPD-181477

Schmitz, F., Goke, M. N., Otte, J. M., Schrader, H., Reimann, B., Kruse, M. L., Siegel, E. G., Peters, J., Herzig, K. H., Folsch, U. R., & Schmidt, W. E. (2001). Cellular expression of CCK-A and CCK-B/gastrin receptors in human gastric mucosa. *Regul Pept, 102*(2-3), 101-110. doi:10.1016/s0167-0115(01)00307-x

Schmitz, F., Schrader, H., Otte, J., Schmitz, H., Stuber, E., Herzig, K., & Schmidt, W. E. (2001). Identification of CCK-B/gastrin receptor splice variants in human peripheral blood mononuclear cells. *Regul Pept, 101*(1-3), 25-33. doi:10.1016/s0167-0115(01)00281-6

Schneider, R., Osterburg, J., Buchner, A., & Pietrowsky, R. (2009). Effect of intranasally administered cholecystokinin on encoding of controlled and automatic memory processes. *Psychopharmacology (Berl), 202*(4), 559-567. doi:10.1007/s00213-008-1332-3

Schneider, R., Stohr, C., & Pietrowsky, R. (2005). Intranasally administered Cholecystokinin decreases controlled memory. *Biological Psychology, 69*(3), 297-314. doi:10.1016/j.biopsycho.2004.08.006

Schunck, T., Erb, G., Mathis, A., Gilles, C., Namer, I. J., Hode, Y., Demaziere, A., Luthringer, R., & Macher, J. P. (2006). Functional magnetic resonance imaging characterization of CCK-4-induced panic attack and subsequent anticipatory anxiety. *Neuroimage, 31*(3), 1197-1208. doi:10.1016/j.neuroimage.2006.01.035

Sebret, A., Lena, I., Crete, D., Matsui, T., Roques, B. P., & Dauge, V. (1999). Rat hippocampal neurons are critically involved in physiological improvement of memory processes induced by cholecystokinin-B receptor stimulation. *Journal of Neuroscience, 19*(16), 7230-7237. doi:10.1523/JNEUROSCI.19-16-07230.1999

Shea, Y. F., Lee, S. C., & Chu, L. W. (2018). Prevalence of hyperphagia in Alzheimer's disease: a meta-analysis. *Psychogeriatrics, 18*(4), 243-251. doi:10.1111/psyg.12316

Sheedy, F. J., Grebe, A., Rayner, K. J., Kalantari, P., Ramkhelawon, B., Carpenter, S. B., Becker, C. E., Ediriweera, H. N., Mullick, A. E., Golenbock, D. T., Stuart, L. M., Latz, E., Fitzgerald, K. A., & Moore, K. J. (2013). CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. *Nature Immunology, 14*(8), 812-820. doi:10.1038/ni.2639

Shen, X. N., Niu, L. D., Wang, Y. J., Cao, X. P., Liu, Q., Tan, L., Zhang, C., & Yu, J. T. (2019). Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. *J Neurol Neurosurg Psychiatry, 90*(5), 590-598. doi:10.1136/jnnp-2018-319148

Shlik, J., Aluoja, A., Vasar, V., Vasar, E., Podar, T., & Bradwejn, J. (1997). Effects of citalopram treatment on behavioural, cardiovascular and neuroendocrine response to cholecystokinin tetrapeptide challenge in patients with panic disorder. *J Psychiatry Neurosci, 22*(5), 332-340.

Shlik, J., Koszycki, D., & Bradwejn, J. (1998). Decrease in short-term memory function induced by CCK-4 in healthy volunteers. *Peptides, 19*(6), 969-975. doi:10.1016/s0196-9781(98)00056-4

Sierralta, J., & Gysling, K. (1990). Effect of dopamine depletion upon the K(+)-evoked release of CCK from superfused striatal slices. *Neuroscience Letters, 112*(2-3), 313-317. doi:10.1016/0304-3940(90)90222-u

Silva, A. P., Carvalho, A. P., Carvalho, C. M., & Malva, J. O. (2003). Functional interaction between neuropeptide Y receptors and modulation of calcium channels in the rat hippocampus. *Neuropharmacology, 44*(2), 282-292. doi:10.1016/S0028-3908(02)00382-9

Silva, A. P., Lourenco, J., Xapelli, S., Ferreira, R., Kristiansen, H., Woldbye, D. P., Oliveira, C. R., & Malva, J. O. (2007). Protein kinase C activity blocks neuropeptide Y-mediated inhibition of glutamate release and contributes to excitability of the hippocampus in status epilepticus. *Faseb Journal, 21*(3), 671-681. doi:10.1096/fj.06-6163com

Simon, D. K., Tanner, C. M., & Brundin, P. (2020). Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. *Clin Geriatr Med, 36*(1), 1-12. doi:10.1016/j.cger.2019.08.002

Simunovic, F., Yi, M., Wang, Y., Macey, L., Brown, L. T., Krichevsky, A. M., Andersen, S. L., Stephens, R. M., Benes, F. M., & Sonntag, K. C. (2009). Gene expression profiling of substantia nigra dopamine neurons: further insights into Parkinson's disease pathology. *Brain, 132*(Pt 7), 1795-1809. doi:10.1093/brain/awn323

Sinton, C. M. (1988). Cholecystokinin modulates neurotransmission through the dentate gyrus. *Neuroscience Letters, 95*(1-3), 341-346. doi:10.1016/0304-3940(88)90682-9

Smith, J. P., & Solomon, T. E. (2014). Cholecystokinin and pancreatic cancer: the chicken or the egg? *Am J Physiol Gastrointest Liver Physiol, 306*(2), G91-G101. doi:10.1152/ajpgi.00301.2013

Smolnik, R., Fischer, S., Hagenah, J., Kis, B., Born, J., & Vieregge, P. (2002). Brain potential signs of slowed stimulus processing following cholecystokinin in Parkinson's disease. *Psychopharmacology (Berl), 161*(1), 70-76. doi:10.1007/s00213-002-1010-9

Somogyi, P., Hodgson, A. J., Smith, A. D., Nunzi, M. G., Gorio, A., & Wu, J. Y. (1984). Different populations of GABAergic neurons in the visual cortex and hippocampus of cat contain somatostatin- or cholecystokinin-immunoreactive material. *Journal of Neuroscience, 4*(10), 2590-2603. doi:10.1523/JNEUROSCI.04-10-02590.1984

Soriano, F. X., Liesa, M., Bach, D., Chan, D. C., Palacin, M., & Zorzano, A. (2006). Evidence for a mitochondrial regulatory pathway defined by peroxisome proliferator-activated receptor-gamma coactivator-1 alpha, estrogen-related receptor-alpha, and mitofusin 2. *Diabetes, 55*(6), 1783-1791. doi:10.2337/db05-0509

Steen, E., Terry, B. M., Rivera, E. J., Cannon, J. L., Neely, T. R., Tavares, R., Xu, X. J., Wands, J. R., & de la Monte, S. M. (2005). Impaired insulin and insulin-like growth factor expression and

signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? *Journal of Alzheimers Disease, 7*(1), 63-80. doi:10.3233/jad-2005-7107

Stephenson, J., Nutma, E., van der Valk, P., & Amor, S. (2018). Inflammation in CNS neurodegenerative diseases. *Immunology, 154*(2), 204-219. doi:10.1111/imm.12922

Sternini, C., Wong, H., Pham, T., De Giorgio, R., Miller, L. J., Kuntz, S. M., Reeve, J. R., Walsh, J. H., & Raybould, H. E. (1999). Expression of cholecystokinin A receptors in neurons innervating the rat stomach and intestine. *Gastroenterology, 117*(5), 1136-1146. doi:10.1016/s0016-5085(99)70399-9

Stewart, C. R., Stuart, L. M., Wilkinson, K., van Gils, J. M., Deng, J., Halle, A., Rayner, K. J., Boyer, L., Zhong, R., Frazier, W. A., Lacy-Hulbert, A., El Khoury, J., Golenbock, D. T., & Moore, K. J. (2010). CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. *Nature Immunology, 11*(2), 155-161. doi:10.1038/ni.1836

Strohle, A., Holsboer, F., & Rupprecht, R. (2000). Increased ACTH concentrations associated with cholecystokinin tetrapeptide-induced panic attacks in patients with panic disorder. *Neuropsychopharmacology, 22*(3), 251-256. doi:10.1016/S0893-133X(99)00115-3

Strohmayer, A. J., & Greenberg, D. (1996). Devazepide increases food intake in male but not female Zucker rats. *Physiol Behav, 60*(1), 273-275. doi:10.1016/0031-9384(96)83164-7

Su, Y., Liu, N., Zhang, Z., Li, H., Ma, J., Yuan, Y., Shi, M., Liu, J., Zhao, Z., Zhang, Z., & Holscher, C. (2022). Cholecystokinin and glucagon-like peptide-1 analogues regulate intestinal tight junction, inflammation, dopaminergic neurons and alpha-synuclein accumulation in the colon of two Parkinson's disease mouse models. *European Journal of Pharmacology, 926*, 175029. doi:10.1016/j.ejphar.2022.175029

Suarez-Pinzon, W. L., Power, R. F., Yan, Y., Wasserfall, C., Atkinson, M., & Rabinovitch, A. (2008). Combination therapy with glucagon-like peptide-1 and gastrin restores normoglycemia in diabetic NOD mice. *Diabetes, 57*(12), 3281-3288. doi:10.2337/db08-0688

Sulzer, D., Cragg, S. J., & Rice, M. E. (2016). Striatal dopamine neurotransmission: regulation of release and uptake. *Basal Ganglia, 6*(3), 123-148. doi:10.1016/j.baga.2016.02.001

Sulzer, D., & Surmeier, D. J. (2013). Neuronal vulnerability, pathogenesis, and Parkinson's disease. *Mov Disord, 28*(6), 715-724. doi:10.1002/mds.25187

Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat Rev Neurol, 14*(3), 133-150. doi:10.1038/nrneurol.2017.188

Takacs, V. T., Szonyi, A., Freund, T. F., Nyiri, G., & Gulyas, A. I. (2015). Quantitative ultrastructural analysis of basket and axo-axonic cell terminals in the mouse hippocampus. *Brain Structure & Function, 220*(2), 919-940. doi:10.1007/s00429-013-0692-6

Takahashi, M., Yamada, T., Tooyama, I., Moroo, I., Kimura, H., Yamamoto, T., & Okada, H. (1996). Insulin receptor mRNA in the substantia nigra in Parkinson's disease. *Neuroscience Letters, 204*(3), 201-204. doi:10.1016/0304-3940(96)12357-0

Talbot, K., Wang, H. Y., Kazi, H., Han, L. Y., Bakshi, K. P., Stucky, A., Fuino, R. L., Kawaguchi, K. R., Samoyedny, A. J., Wilson, R. S., Arvanitakis, Z., Schneider, J. A., Wolf, B. A., Bennett, D. A., Trojanowski, J. Q., & Arnold, S. E. (2012). Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *Journal of Clinical Investigation, 122*(4), 1316-1338. doi:10.1172/JCI59903

Tamura, Y., Sato, Y., Akaike, A., & Shiomi, H. (1992). Mechanisms of cholecystokinin-induced protection of cultured cortical neurons against N-methyl-D-aspartate receptor-mediated

glutamate cytotoxicity. *Brain Research, 592*(1-2), 317-325. doi:10.1016/0006-8993(92)91691-7

Tang, T. T., Bi, M. X., Diao, M. N., Zhang, X. Y., Chen, L., Xiao, X., Jiao, Q., Chen, X., Yan, C. L., Du, X. X., & Jiang, H. (2023). Quinpirole ameliorates nigral dopaminergic neuron damage in Parkinson's disease mouse model through activating GHS-R1a/D(2)R heterodimers. *Acta Pharmacologica Sinica, 44*(8), 1564-1575. doi:10.1038/s41401-023-01063-0

Taylor, M. D., De Ceballos, M. L., Rose, S., Jenner, P., & Marsden, C. D. (1992). Effects of a unilateral 6-hydroxydopamine lesion and prolonged L-3,4-dihydroxyphenylalanine treatment on peptidergic systems in rat basal ganglia. *European Journal of Pharmacology, 219*(2), 183-192. doi:10.1016/0014-2999(92)90295-f

Tirassa, P., Aloe, L., Stenfors, C., Turrini, P., & Lundeberg, T. (1999). Cholecystokinin-8 protects central cholinergic neurons against fimbria-fornix lesion through the up-regulation of nerve growth factor synthesis. *Proc Natl Acad Sci U S A, 96*(11), 6473-6477. doi:10.1073/pnas.96.11.6473

Tirassa, P., & Costa, N. (2007). CCK-8 induces NGF and BDNF synthesis and modulates TrkA and TrkB expression in the rat hippocampus and septum: Effects on kindling development. *Neurochemistry International, 50*(1), 130-138. doi:10.1016/j.neuint.2006.07.008

Tirassa, P., Stenfors, C., Lundeberg, T., & Aloe, L. (1998). Cholecystokinin-8 regulation of NGF concentrations in adult mouse brain through a mechanism involving CCK(A) and CCK(B) receptors. *Br J Pharmacol, 123*(6), 1230-1236. doi:10.1038/sj.bjp.0701718

Tokunaga, Y., Cox, K. L., Coleman, R., Concepcion, W., Nakazato, P., & Esquivel, C. O. (1993). Characterization of cholecystokinin receptors on the human gallbladder. *Surgery, 113*(2), 155-162.

Tong, M., Dong, M., & de la Monte, S. M. (2009). Brain insulin-like growth factor and neurotrophin resistance in Parkinson's disease and dementia with Lewy bodies: potential role of manganese neurotoxicity. *Journal of Alzheimers Disease, 16*(3), 585-599. doi:10.3233/JAD-2009-0995

Treen, A. K., Luo, V., & Belsham, D. D. (2016). Phoenixin Activates Immortalized GnRH and Kisspeptin Neurons Through the Novel Receptor GPR173. *Molecular Endocrinology, 30*(8), 872-888. doi:10.1210/me.2016-1039

Trevaskis, J. L., Sun, C., Athanacio, J., D'Souza, L., Samant, M., Tatarkiewicz, K., Griffin, P. S., Wittmer, C., Wang, Y., Teng, C. H., Forood, B., Parkes, D. G., & Roth, J. D. (2015). Synergistic metabolic benefits of an exenatide analogue and cholecystokinin in diet-induced obese and leptin-deficient rodents. *Diabetes Obesity & Metabolism, 17*(1), 61-73. doi:10.1111/dom.12390

Uhlen, M., Fagerberg, L., Hallstrom, B. M., Lindskog, C., Oksvold, P., Mardinoglu, A., Sivertsson, A., Kampf, C., Sjostedt, E., Asplund, A., Olsson, I., Edlund, K., Lundberg, E., Navani, S., Szigyarto, C. A., Odeberg, J., Djureinovic, D., Takanen, J. O., Hober, S., Alm, T., Edqvist, P. H., Berling, H., Tegel, H., Mulder, J., Rockberg, J., Nilsson, P., Schwenk, J. M., Hamsten, M., von Feilitzen, K., Forsberg, M., Persson, L., Johansson, F., Zwahlen, M., von Heijne, G., Nielsen, J., & Ponten, F. (2015). Proteomics. Tissue-based map of the human proteome. *Science, 347*(6220), 1260419. doi:10.1126/science.1260419

van der Kooy, D., Hunt, S. P., Steinbusch, H. W., & Verhofstad, A. A. (1981). Separate populations of cholecystokinin and 5-hydroxytryptamine-containing neuronal cells in the rat dorsal raphe, and their contribution to the ascending raphe projections. *Neuroscience Letters, 26*(1), 25-30. doi:10.1016/0304-3940(81)90420-1

Van Dijk, A., Richards, J. G., Trzeciak, A., Gillessen, D., & Mohler, H. (1984). Cholecystokinin receptors: biochemical demonstration and autoradiographical localization in rat brain and

pancreas using [3H] cholecystokinin8 as radioligand. *Journal of Neuroscience, 4*(4), 1021-1033. doi:10.1523/JNEUROSCI.04-04-01021.1984

van Megen, H. J., Westenberg, H. G., den Boer, J. A., Slaap, B., & Scheepmakers, A. (1997). Effect of the selective serotonin reuptake inhibitor fluvoxamine on CCK-4 induced panic attacks. *Psychopharmacology (Berl), 129*(4), 357-364. doi:10.1007/s002130050201

van Vliet, I. M., Westenberg, H. G., Slaap, B. R., den Boer, J. A., & Ho Pian, K. L. (1997). Anxiogenic effects of pentagastrin in patients with social phobia and healthy controls. *Biol Psychiatry, 42*(1), 76-78. doi:10.1016/S0006-3223(97)00185-6

Velmurugan, K., Bouchard, R., Mahaffey, G., & Pugazhenthi, S. (2012). Neuroprotective actions of glucagon-like peptide-1 in differentiated human neuroprogenitor cells. *Journal of Neurochemistry, 123*(6), 919-931. doi:10.1111/jnc.12036

Veronese, N., Facchini, S., Stubbs, B., Luchini, C., Solmi, M., Manzato, E., Sergi, G., Maggi, S., Cosco, T., & Fontana, L. (2017). Weight loss is associated with improvements in cognitive function among overweight and obese people: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 72*, 87-94. doi:10.1016/j.neubiorev.2016.11.017

Vigasova, D., Nemergut, M., Liskova, B., & Damborsky, J. (2021). Multi-pathogen infections and Alzheimer's disease. *Microb Cell Fact, 20*(1), 25. doi:10.1186/s12934-021-01520-7

Vloeberghs, E., Van Dam, D., Franck, F., Serroyen, J., Geert, M., Staufenbiel, M., & De Deyn, P. P. (2008). Altered ingestive behavior, weight changes, and intact olfactory sense in an APP overexpression model. *Behavioral Neuroscience, 122*(3), 491-497. doi:10.1037/0735-7044.122.3.491

Voits, M., Hasenohrl, R. U., Huston, J. P., & Fink, H. (2001). Repeated treatment with cholecystokinin octapeptide improves maze performance in aged Fischer 344 rats. *Peptides, 22*(8), 1325-1330. doi:10.1016/s0196-9781(01)00459-4

von Schrenck, T., Ahrens, M., de Weerth, A., Bobrowski, C., Wolf, G., Jonas, L., Jocks, T., Schulz, M., Blaker, M., Neumaier, M., & Stahl, R. A. (2000). CCKB/gastrin receptors mediate changes in sodium and potassium absorption in the isolated perfused rat kidney. *Kidney Int, 58*(3), 995-1003. doi:10.1046/j.1523-1755.2000.00257.x

Wang, H., Yang, F., Zhang, S., Xin, R., & Sun, Y. (2021). Genetic and environmental factors in Alzheimer's and Parkinson's diseases and promising therapeutic intervention via fecal microbiota transplantation. *NPJ Parkinsons Dis, 7*(1), 70. doi:10.1038/s41531-021-00213-7

Wang, J., Si, Y. M., Liu, Z. L., & Yu, L. (2003). Cholecystokinin, cholecystokinin-A receptor and cholecystokinin-B receptor gene polymorphisms in Parkinson's disease. *Pharmacogenetics, 13*(6), 365-369. doi:10.1097/00008571-200306000-00008

Wang, X., Su, B., Lee, H. G., Li, X., Perry, G., Smith, M. A., & Zhu, X. (2009). Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. *Journal of Neuroscience, 29*(28), 9090-9103. doi:10.1523/JNEUROSCI.1357-09.2009

Wang, X., Su, B., Siedlak, S. L., Moreira, P. I., Fujioka, H., Wang, Y., Casadesus, G., & Zhu, X. (2008). Amyloid-beta overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fission/fusion proteins. *Proc Natl Acad Sci U S A, 105*(49), 19318-19323. doi:10.1073/pnas.0804871105

Wang, Z., Valdes, J., Noyes, R., Zoega, T., & Crowe, R. R. (1998). Possible association of a cholecystokinin promotor polymorphism (CCK-36CT) with panic disorder. *American Journal of Medical Genetics, 81*(3), 228-234. doi:10.1002/(sici)1096-8628(19980508)81:3<228::aid-ajmg5>3.0.co;2-s

Warnecke, T., Schafer, K. H., Claus, I., Del Tredici, K., & Jost, W. H. (2022). Gastrointestinal involvement in Parkinson's disease: pathophysiology, diagnosis, and management. *NPJ Parkinsons Dis, 8*(1), 31. doi:10.1038/s41531-022-00295-x

Weatherford, S. C., Chiruzzo, F. Y., & Laughton, W. B. (1992). Satiety induced by endogenous and exogenous cholecystokinin is mediated by CCK-A receptors in mice. *Am J Physiol, 262*(4 Pt 2), R574-578. doi:10.1152/ajpregu.1992.262.4.R574

Weiland, T. J., Voudouris, N. J., & Kent, S. (2004). The role of CCK2 receptors in energy homeostasis: insights from the CCK2 receptor-deficient mouse. *Physiol Behav, 82*(2-3), 471-476. doi:10.1016/j.physbeh.2004.04.065

Weinberg, D. S., Ruggeri, B., Barber, M. T., Biswas, S., Miknyocki, S., & Waldman, S. A. (1997). Cholecystokinin A and B receptors are differentially expressed in normal pancreas and pancreatic adenocarcinoma. *Journal of Clinical Investigation, 100*(3), 597-603. doi:10.1172/JCI119570

West, D. B., Fey, D., & Woods, S. C. (1984). Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. *Am J Physiol, 246*(5 Pt 2), R776-787. doi:10.1152/ajpregu.1984.246.5.R776

Whissell, P. D., Bang, J. Y., Khan, I., Xie, Y. F., Parfitt, G. M., Grenon, M., Plummer, N. W., Jensen, P., Bonin, R. P., & Kim, J. C. (2019). Selective Activation of Cholecystokinin-Expressing GABA (CCK-GABA) Neurons Enhances Memory and Cognition. *Eneuro, 6*(1). doi:10.1523/ENEURO.0360-18.2019

Wilke, B. U., Lindner, M., Greifenberg, L., Albus, A., Kronimus, Y., Bunemann, M., Leitner, M. G., & Oliver, D. (2014). Diacylglycerol mediates regulation of TASK potassium channels by Gq-coupled receptors. *Nature Communications, 5*, 5540. doi:10.1038/ncomms6540

Wu, T., & Wang, H. L. (1994a). CCK-8-evoked cationic currents in substantia nigra dopaminergic neurons are mediated by InsP3-induced Ca2+ release. *Neuroscience Letters, 175*(1-2), 95-98. doi:10.1016/0304-3940(94)91087-1

Wu, T., & Wang, H. L. (1994b). CCK-8 excites substantia nigra dopaminergic neurons by increasing a cationic conductance. *Neuroscience Letters, 170*(2), 229-232. doi:10.1016/0304-3940(94)90325-5

Wunderlich, G. R., Rotzinger, S., Bush, D. E., DeSousa, N. J., & Vaccarino, F. J. (2004). Cholecystokinin modulation of locomotor behavior in rats is sensitized by chronic amphetamine and chronic restraint stress exposure. *Brain Research, 1001*(1-2), 95-107. doi:10.1016/j.brainres.2003.10.064

Xing, C., Huang, X., Wang, D., Yu, D., Hou, S., Cui, H., & Song, L. (2023). Roles of bile acids signaling in neuromodulation under physiological and pathological conditions. *Cell Biosci, 13*(1), 106. doi:10.1186/s13578-023-01053-z

Xu, X. M., Dong, M. X., Feng, X., Liu, Y., Pan, J. X., Jia, S. Y., Cao, D., & Wei, Y. D. (2018). Decreased serum proNGF concentration in patients with Parkinson's disease. *Neurol Sci, 39*(1), 91-96. doi:10.1007/s10072-017-3157-5

Xu, Y., Wei, X., Liu, X., Liao, J., Lin, J., Zhu, C., Meng, X., Xie, D., Chao, D., Fenoy, A. J., Cheng, M., Tang, B., Zhang, Z., Xia, Y., & Wang, Q. (2015). Low Cerebral Glucose Metabolism: A Potential Predictor for the Severity of Vascular Parkinsonism and Parkinson's Disease. *Aging and Disease, 6*(6), 426-436. doi:10.14336/AD.2015.0204

Yamane, T., Suzui, S., Kitaura, H., Takahashi-Niki, K., Iguchi-Ariga, S. M., & Ariga, H. (2013). Transcriptional activation of the cholecystokinin gene by DJ-1 through interaction of DJ-1 with RREB1 and the effect of DJ-1 on the cholecystokinin level in mice. *Plos One, 8*(11), e78374. doi:10.1371/journal.pone.0078374

You, Z. B., Herrera-Marschitz, M., Pettersson, E., Nylander, I., Goiny, M., Shou, H. Z., Kehr, J., Godukhin, O., Hokfelt, T., Terenius, L., & Ungerstedt, U. (1996). Modulation of neurotransmitter release by cholecystokinin in the neostriatum and substantia nigra of the

rat: regional and receptor specificity. *Neuroscience, 74*(3), 793-804. doi:10.1016/0306-4522(96)00149-2

Yuan, Z., Li, D., Feng, P., Xue, G., Ji, C., Li, G., & Holscher, C. (2017). A novel GLP-1/GIP dual agonist is more effective than liraglutide in reducing inflammation and enhancing GDNF release in the MPTP mouse model of Parkinson's disease. *European Journal of Pharmacology, 812*, 82-90. doi:10.1016/j.ejphar.2017.06.029

Zamponi, G. W., & Currie, K. P. (2013). Regulation of Ca(V)2 calcium channels by G protein coupled receptors. *Biochimica Et Biophysica Acta, 1828*(7), 1629-1643. doi:10.1016/j.bbamem.2012.10.004

Zeng, Q., Ou, L., Wang, W., & Guo, D. Y. (2020). Gastrin, Cholecystokinin, Signaling, and Biological Activities in Cellular Processes. *Front Endocrinol (Lausanne), 11*, 112. doi:10.3389/fendo.2020.00112

Zhang, B., Chen, X., Lin, Y., Tan, T., Yang, Z., Dayao, C., Liu, L., Jiang, R., & Zhang, J. (2011). Impairment of synaptic plasticity in hippocampus is exacerbated by methylprednisolone in a rat model of traumatic brain injury. *Brain Research, 1382*, 165-172. doi:10.1016/j.brainres.2011.01.065

Zhang, L., Wang, J., Wang, J., Yang, B., He, Q., & Weng, Q. (2020). Role of DJ-1 in Immune and Inflammatory Diseases. *Frontiers in Immunology, 11*, 994. doi:10.3389/fimmu.2020.00994

Zhang, L. L., Wei, X. F., Zhang, Y. H., Xu, S. J., Chen, X. W., Wang, C., & Wang, Q. W. (2013). CCK-8S increased the filopodia and spines density in cultured hippocampal neurons of APP/PS1 and wild-type mice. *Neuroscience Letters, 542*, 47-52. doi:10.1016/j.neulet.2013.03.023

Zhang, L. Y., Jin, Q. Q., Holscher, C., & Li, L. (2021). Glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide dual receptor agonist DA-CH5 is superior to exendin-4 in

protecting neurons in the 6-hydroxydopamine rat Parkinson model. *Neural Regeneration Research, 16*(8), 1660-1670. doi:10.4103/1673-5374.303045

Zhang, X., Grosfeld, A., Williams, E., Vasiliauskas, D., Barretto, S., Smith, L., Mariadassou, M., Philippe, C., Devime, F., Melchior, C., Gourcerol, G., Dourmap, N., Lapaque, N., Larraufie, P., Blottiere, H. M., Herberden, C., Gerard, P., Rehfeld, J. F., Ferraris, R. P., Fritton, J. C., Ellero-Simatos, S., & Douard, V. (2019). Fructose malabsorption induces cholecystokinin expression in the ileum and cecum by changing microbiota composition and metabolism. *Faseb Journal, 33*(6), 7126-7142. doi:10.1096/fj.201801526RR

Zhang, X., He, C., Wang, M., Zhou, Q., Yang, D., Zhu, Y., Feng, W., Zhang, H., Dai, A., Chu, X., Wang, J., Yang, Z., Jiang, Y., Sensfuss, U., Tan, Q., Han, S., Reedtz-Runge, S., Xu, H. E., Zhao, S., Wang, M. W., Wu, B., & Zhao, Q. (2021). Structures of the human cholecystokinin receptors bound to agonists and antagonists. *Nat Chem Biol, 17*(12), 1230-1237. doi:10.1038/s41589-021-00866-8

Zhang, Z., Li, H., Su, Y., Ma, J., Yuan, Y., Yu, Z., Shi, M., Shao, S., Zhang, Z., & Holscher, C. (2022). Neuroprotective Effects of a Cholecystokinin Analogue in the 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine Parkinson's Disease Mouse Model. *Front Neurosci, 16*, 814430. doi:10.3389/fnins.2022.814430

Zhang, Z., Yu, Z., Yuan, Y., Yang, J., Wang, S., Ma, H., Hao, L., Ma, J., Li, Z., Zhang, Z., & Holscher, C. (2023). Cholecystokinin Signaling can Rescue Cognition and Synaptic Plasticity in the APP/PS1 Mouse Model of Alzheimer's Disease. *Molecular Neurobiology, 60*(9), 5067-5089. doi:10.1007/s12035-023-03388-7

Zhang, Z., Zheng, X., Sun, W., Peng, Y., Guo, Y., Lu, D., Zheng, Y., Li, X., Jendrichovsky, P., Tang, P., He, L., Li, M., Liu, Q., Xu, F., Ng, G., Chen, X., & He, J. (2020). Visuoauditory Associative Memory Established with Cholecystokinin Under Anesthesia Is Retrieved in Behavioral Contexts. *Journal of Neuroscience, 40*(10), 2025-2037. doi:10.1523/JNEUROSCI.1673-19.2019

Zhao, W., Wang, J., Varghese, M., Ho, L., Mazzola, P., Haroutunian, V., Katsel, P. L., Gibson, G. E., Levine, S., Dubner, L., & Pasinetti, G. M. (2015). Impaired mitochondrial energy metabolism as a novel risk factor for selective onset and progression of dementia in oldest-old subjects. *Neuropsychiatr Dis Treat, 11*, 565-574. doi:10.2147/NDT.S74898

Zhu, X. G., Greeley, G. H., Jr., Lewis, B. G., Lilja, P., & Thompson, J. C. (1986). Blood-CSF barrier to CCK and effect of centrally administered bombesin on release of brain CCK. *Journal of Neuroscience Research, 15*(3), 393-403. doi:10.1002/jnr.490150310

Zhuang, Q. S., Meng, L., Wang, Z., Shen, L., & Ji, H. F. (2021). Associations Between Obesity and Alzheimer's Disease: Multiple Bioinformatic Analyses. *Journal of Alzheimers Disease, 80*(1), 271-281. doi:10.3233/JAD-201235

Zuin, M., Roncon, L., Passaro, A., Cervellati, C., & Zuliani, G. (2021). Metabolic syndrome and the risk of late onset Alzheimer's disease: An updated review and meta-analysis. *Nutr Metab Cardiovasc Dis, 31*(8), 2244-2252. doi:10.1016/j.numecd.2021.03.020

Zwanzger, P., Domschke, K., & Bradwejn, J. (2012). Neuronal network of panic disorder: the role of the neuropeptide cholecystokinin. *Depress Anxiety, 29*(9), 762-774. doi:10.1002/da.21919

Zwirska-Korczala, K., Konturek, S. J., Sodowski, M., Wylezol, M., Kuka, D., Sowa, P., Adamczyk-Sowa, M., Kukla, M., Berdowska, A., Rehfeld, J. F., Bielanski, W., & Brzozowski, T. (2007). Basal and postprandial plasma levels of PYY, ghrelin, cholecystokinin, gastrin and insulin in women with moderate and morbid obesity and metabolic syndrome. *Journal of Physiology and Pharmacology, 58 Suppl 1*, 13-35.

15 Figure captions

Figure 1: Neuroprotective signalling pathways of CCKRs in hippocampal and dopaminergic SNpc neurons. CCK-2Rs are expressed by pyramidal excitatory neurons and GABAergic interneurons (including basket cells) in the hippocampus. Nigral neurons express both CCK-1Rs and CCK-2Rs. In these neurons, CCK-2Rs are canonically $G\alpha_{q/11}$-coupled, stimulating the PLCβ-mediated conversion of PIP2 into the ER Ca^{2+} channel IP3 and DAG. In hippocampal pyramidal neurons, DAG is processed into endocannabinoids that induce retrograde inhibition of GABA release by CCK^{+} basket cells. Furthermore, DAG evokes gene expression by CREB, including that of plasticity (e.g. c-Fos) and survival genes (e.g. BDNF, NGF and Bcl-2), via the PKC/Raf/$ERK_{1/2}$ pathway. BDNF and NGF expression in various brain regions, such as the hippocampus, are predominantly driven by CCK-1R activation on vagal afferent nerves in the intestinal tract, however. Regarding plasticity, DAG inhibits K^{+} channels (TASK-1 and TASK-3), thus enhances excitability. CCK also promotes presynaptic glutamate release by hippocampal neurons, which likely involves DAG/PKC-mediated blockade of $NPYR_{1/2/5}/G_i$-induced voltage-gated Ca^{2+} channel inhibition. PKC further phosphorylates AMPARs (GluR1 subunit) at Ser^{831}, leading to increased postsynaptic excitability by improving channel conductance and lowering AMPAR activation threshold. The neuroprotective effects of CCK-2R activation parallel those of acylated ghrelin (see Reich & Holscher (2020); also for additional $G\alpha_{q/11}$-related pathways). IP3-mediated Ca^{2+} release leads to AMPK activation, which stimulates autophagy and induces PGC-1α, a transcription factor expressing genes associated with mitochondrial biogenesis and fusion. Injection of CCK-8 analogues in AD and PD animal models has shown that the neuropeptide is anti-inflammatory and anti-apoptotic, preventing synaptic damage, mitochondrial dysfunction, initiation of ER stress (IRE1α) and aberrant autophagy. The underlying neuroprotective signalling pathways need further characterisation. Notably, In SNpc neurons, CCK-1Rs elicit local somatodendritic and, at higher CCK concentrations, striatal dopamine release. The underlying signalling pathways and potential neuroprotective effects need further characterisation. Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR); 5' adenosine

monophosphate-activated protein kinase (AMPK); autophagy-related 7 (Atg7); Bcl-2-associated X protein (Bax); B-cell lymphoma 2 (Bcl-2); brain-derived neurotrophic factor (BDNF); cholecystokinin receptor 1/2 (CCK-1/2R); CCAAT/enhancer binding protein delta (C/EBPdelta); cAMP response element-binding protein (CREB); diacylglycerol (DAG); dynamin-related protein 1 (Drp-1); extracellular signal-regulated kinase 1/2 ($ERK_{1/2}$); AMPAR subunit glutamate receptor 1 (GluR1); inositol 1,4,5-triphosphate receptor (IP3); inositol-requiring enzyme type 1 alpha (IRE1α); microtubule-associated protein 1A/1B-light chain 3 (LC3-I/II); liver kinase B1 (LKB1); mitofusin 2 (Mfn2); mechanistic target of rapamycin complex 1 (mTORC1); mitochondrial E3 ubiquitin ligase 1 (MUL1); neuropeptide Y receptor 1/2/5 ($NPYR_{1/2/5}$); nerve growth factor (NGF); nuclear respiratory factor 1/2 (NRF1/2); optic atrophy 1 (OPA1); peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α); phosphatidylinositol 4,5-bisphosphate (PIP2); phospholipase C beta (PLCβ); protein kinase C (PKC); sirtuin 1 (SIRT1); TWIK-related acid-sensitive K^+ channel (TASK-1/3); mitochondrial transcription factor A (TFAM); tuberous sclerosis complex 1/2 ($TSC_{1/2}$); unc-51-like kinase 1/2 ($ULK_{1/2}$).

Figure 2: Neuronal insulin resistance and the anti-inflammatory effects of CCK. Insulin acts as an important growth factor in neurons. By activating CREB and mTORC1 through the Shc/Grb2/SOS/Ras/Raf/$MEK_{1/2}$/$ERK_{1/2}$ and IRS-1/PI3K/Akt/mTORC pathways, respectively, the insulin receptor induces expression of genes related to survival, plasticity, glucose metabolism and autophagy. The consequences of neuronal insulin resistance, including glucose hypometabolism and reduced blood flow, are seen in the brains of AD and PD patients. Akt also suppresses GSK-3β, a kinase involved in Tau hyperphosphorylation and synaptic dysfunction in AD. Causative of this desensitisation of insulin is the chronic (age-associated or pathologic) production of pro-inflammatory cytokines by microglia and astrocytes. By binding to neuronal PICRs, these cytokines induce kinases (IKKβ, PKR and JNK) that inactivate IRS-1 and, thus, block downstream PI3K/Akt-signalling. Neuroinflammation further enhances Aβ generation, for example via the JNK3-mediated

phosphorylation of APP at Thr^{668}, which encourages amyloidogenic processing. Vice versa, Aβ impairs insulin-signalling by aggravating inflammation and evoking insulin receptor clustering and endocytosis. Microglia and astrocytes both express CCK-2Rs, and their activation is anti-inflammatory. *In vivo* studies suggest that CCK quenches cerebral inflammation and restores insulin-signalling, similar to GLP-1. For details, see Reich & Holscher (2022b). Activator protein 1 (AP1); amyloid beta precursor protein (APP); autophagy-related 3/7 (Atg3/7); amyloid beta (Aβ); beta-secretase 1 (BACE1); brain-derived neurotrophic factor (BDNF); cholecystokinin receptor 2 (CCK-2R); cyclic AMP response-binding protein (CREB); extracellular signal-regulated kinase 1/2 ($ERK_{1/2}$); hypoxia-inducible factor 1 alpha (HIF-1α); IkappaB kinase beta (IKKβ); insulin receptor substrate 1 (IRS-1); c-Jun NH2-terminal kinase (JNK); mitogen-activated protein kinase kinase 1/2 ($MEK_{1/2}$); metabotropic glutamate receptor 1 (mGluR1); MAP kinase kinase (MKK); mammalian target of rapamycin complex 1 (mTORC1); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); N-methyl-D-aspartate receptor (NMDAR); Src homology collagen peptide (Shc); alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor subunit glutamate receptor 1 (GluR1-AMPAR); glucose transporter 3 (GLUT3); growth factor receptor-binding protein 2 (Grb2); glycogen synthase kinase 3 beta (GSK-3β); insulin-degrading enzyme 1 (IDE1); pro-inflammatory cytokine receptor (PIKR); phosphoinositide 3-kinase (PI3K); protein kinase R (PKR); postsynaptic density protein 95 (PSD95); 90 kDa ribosomal S6 kinase (p90RSK); rat sarcoma (Ras); rapidly accelerated fibrosarcoma (Raf); son of sevenless (SOS); sterol regulatory element-binding protein 1/2 ($SREBP_{1/2}$).