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Mini Review

CCK2 receptors in chronic pain

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ABSTRACT

The cholecystokinin receptor system, specifically cholecystokinin 2 receptor (CCK2R) is a historic target for pain management that has shown limited success. However, new approaches to target CCK2R have incited fresh enthusiasm for this target. In this mini-review, we discuss what is known about CCK2R in peripheral and central circuits under naïve physiological conditions and under conditions of chronic pain, the interactions of CCK2Rs with opioids and briefly, recent efforts to develop new treatments targeting CCK2R for chronic pain.

Introduction

Chronic pain is a very common disease which affects 28% of adults globally, equaling about 100 million adults affected in the United States alone(Zimmer et al., 2022) with 10% suffering from high impact chronic pain. Furthermore, between 2002 and 2018 there was a significant increase in the percentage of Americans suffering from pain, and this was disproportionally affected by various factors including sex, race, region, education and income(Zajacova et al., 2021). The pathophysiology of chronic pain is complex, with both sensory and affective components. Although opioids are effective at treating acute pain, they do not work well for many chronic pain conditions and have serious negative side effects including tolerance, addiction, and respiratory depression. Although novel therapeutics for the treatment of pain have been investigated, success has been limited. The cholecystokinin receptor system, specifically cholecystokinin 2 receptor (CCK2R) is a historic target for pain management that has shown limited success. However, new approaches to target CCK2R have incited fresh enthusiasm for this target. In this mini-review we discuss the cholecystokinin receptor system, its involvement in pain and analgesia, and briefly, recent drug discovery efforts to target CCK2R for treating chronic pain.

Molecular physiology

The cholecystokinin system is a gastrointestinal and neuropeptide signaling network found through the viscera and peripheral and central nervous systems. Cholecystokinin (CCK) and gastrin were initially discovered as modulators of digestive processes(Edkins, 1906; Ivy and Oldberg, 1928). CCK was then identified in hog antral mucosa(Gregory and Tracy, 1964) and determined to be a physiologically relevant gastrin-like peptide(Tracy and Gregory, 1964). Later, CCK was identified in human antral mucosa (Gregory et al., 1966) and in the vertebrate nervous system (Vanderhaeghen et al., 1975). Although CCK and gastrin are relevant in a variety of physiological and pathological processes, the focus of this review will encompass the physiological role and pharmacological targeting of CCK2R in pain.

The peptides ligands targeting CCK receptors are derived from the genes discovered for gastrin (Wiborg et al., 1984) and for cholecystokinin (Takahashi, 1985). Both genes produce prepropeptides that are further cleaved into active peptide products. These active CCK peptides can activate both CCK1R and CCK2R to differing degrees (Dufresne et al., 2006). Most predominantly found processed peptides are CCK-8 in the central nervous system and CCK-33 in circulating plasma and intestine (Rehfeld et al., 2001). Gastrin only activates CCK2R; thus, within the gastrointestinal system CCK2R can be considered the "gastrin receptor". Although several active peptides are derived from the pro-CCK sequence, we will focus on CCK-8 in this review as it remains the most abundant in nervous tissues.

The CCK receptors are both members of the rhodopsin-like seven transmembrane G protein-coupled receptors (GPCRs). GPCRs canonically couple to heterotrimeric G proteins, among other proteins, to exert effects on their downstream targets. Recent structural studies have demonstrated that CCK1R preferentially couple to $G\alpha_q$, but can couple to $G\alpha_s$ and $G\alpha i$(Liu, 2021), and that CCK2R predominantly couples to the $G\alpha_q$ family of G proteins. The $G\alpha_q$ family of G proteins activate phospholipase C (PLC) which in turn leads to the formation of inositol triphosphate (IP_3) and diacylglycerol (DAG) from phosphatidylinositol 4,5-bisphosphate (PIP_2). IP_3 activates its cognate receptors, the IP family

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of receptors, found on the endoplasmic reticulum (ER) which results in a massive efflux of Ca^{2+} from the ER into the cytoplasm. In the context of neuronal cellular physiology, this results in a depolarization of the cell, as well as activation of a plethora of Ca^{2+}-dependent signaling cascades (see Fig. 1). The complex downstream signaling mechanisms through CCK1R and CCK2R are beyond the scope of this review (see review Zeng et al., 2020). However, overall activation of these receptors and their downstream targets leads to increased excitability of neurons.

Localization and pain

The CCK receptor designations were initially based on their localization with CCKAR labeled "A" for alimentary and CCKBR labeled "B" for brain. However, the Concise Guide to Pharmacology in conjunction with the International Union of Basic and Clinical Pharmacology (IUPHAR) Committee on Receptor Nomenclature and Drug Classification designate these receptors CCK1 and CCK2(Alexander, 2019), respectively. The majority of CCK1Rs are found in the peripheral areas of the body throughout the alimentary canal, stomach, intestines, pancreas, gallbladder and to a lesser extent in the peripheral and central nervous systems (Wank, 1995; Hill et al., 1987; Mercer and Beart, 2004). The receptors have critical functions in enzymatic and peptide secretions from these visceral organs but also modulate satiety. In nervous system locations, CCK1Rs increase dopamine release and decrease opioid analgesia. CCK2Rs are found throughout the peripheral and central nervous system with some distribution in stomach and immune cells (Wank, 1995). However, due to the relative abundance of the CCK2R ligands including sulfonated gastrin-17 and sulfonated CCK-8 in the periphery and central nervous system, respectively, it is suggested that CCK2Rs in these locations are fundamentally different due to the cognate ligand interacting with them in these areas(Dufresne et al., 2006). Thus, peripheral CCK2R is otherwise known as the "gastrin receptor".

In the nervous system CCKRs are distributed in a variety of areas including the cortex, amygdala, anterior cingulate cortex (ACC), substantia nigra, ventral tegmental area (VTA), periaqueductal grey (PAG), rostral ventromedial medulla (RVM), and the spinal cord(Hill et al., 1987; Mercer and Beart, 2004; Gutierrez-Mecinas, 2019; Sjöstedt, 2020). Within the spinal cord, CCK^{+} neurons are known to play a role in mechanical allodynia in both inflammatory and neuropathic models (Peirs et al., 2021). Interpretation of these studies is difficult as CCK^{+} (not $CCK2R^{+}$) neurons or only mRNA (not protein) levels are studied. Although a small portion of rat dorsal root ganglion (DRG) cells respond to CCK-8, the CCK2R selective antagonist LY225910 was not able to block the response, suggesting a lack of CCK2Rs in the DRG(Ma, 2006). Recent single-cell RNA sequencing efforts of human DRG show expression of CCK2R enriched in low-threshold mechanoreceptors, albeit low compared to nociceptive markers such as TRPV1 and SCN9A(Tavares-Ferreira et al., 2022). Levels of CCK and CCK2R may be low in naïve states examined in the aforementioned studies; however, upon injury CCK(Kim, 2009) or CCK2R(Antunes Bras, 1999) levels increase in the DRG and spinal cord, depending on the study (Fig. 2). Transcriptomic data in human DRGs of patients with chronic pain or no pain showed little difference between groups in terms of CCK2R and CCK mRNA levels(North et al., 20192019). There is substantial literature demonstrating a role for CCK2Rs supraspinally in anxiety and fear regulation (Andre, 2005; Bowers et al., 2012). CCK2Rs have an effect opposite that of CCK1Rs on dopamine release and a similar negative effect on opioid-induced analgesia. It should be noted that most of our localization evidence is via autoradiography, mRNA levels, or pharmacological approaches, as antibodies against these receptors lack specificity thus hindering interpretation of the data. More rigorous insight into the localization of CCKRs will come as better tools are developed. What is clear, is that CCK2R localization is well suited for it as a pain target.

A major site of CCKR location, the RVM, was heavily examined in for its role in pain regulation. Specifically, microinjection of CCK-8 into the RVM results in a pronociceptive phenotype via CCK2Rs(Zhang, 2009). Ablation of RVM cells containing CCK2Rs did not alter baseline nociceptive thresholds, nor alter the initial development of neuropathic pain, but did result in a more rapid recovery from the pain states. Although the pronociceptive actions of the RVM in pain states(Heinricher et al., 2001; Heinricher and Neubert, 2004), and the involvement of CCK2Rs in these actions, have been heavily investigated with use of pharmacology and ablation studies, little is still known on how these

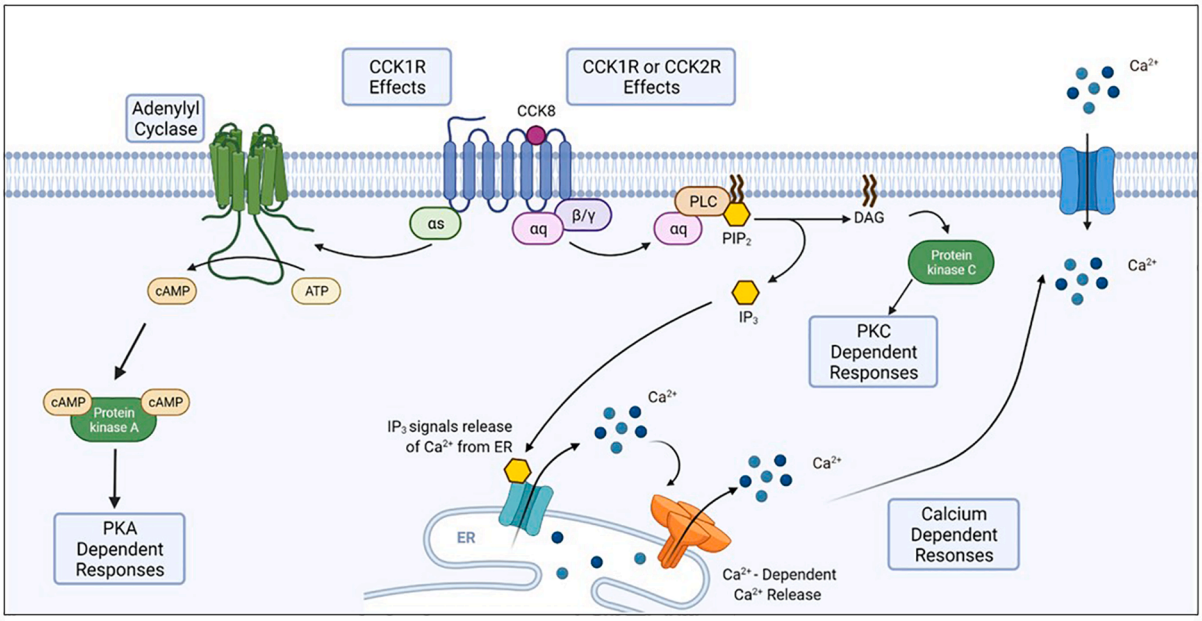

Fig. 1. Signaling Mechanisms of CCK1R and CCK2R. Activation of CCK1R by CCK8 can result in activation of $G\alpha_s$-dependent signaling. This activates adenylyl cyclase which leads to Protein Kinase A (PKA) activation and downstream effectors. CCK1R activation can also lead to $G\alpha_q$-dependent signaling which activates phospholipase C (PLC) and through multiple mechanisms results in increases in cytosolic calcium and calcium-dependent signaling cascades. CCK2R primarily activates $G\alpha_q$-dependent signaling. Created with Biorender.com.

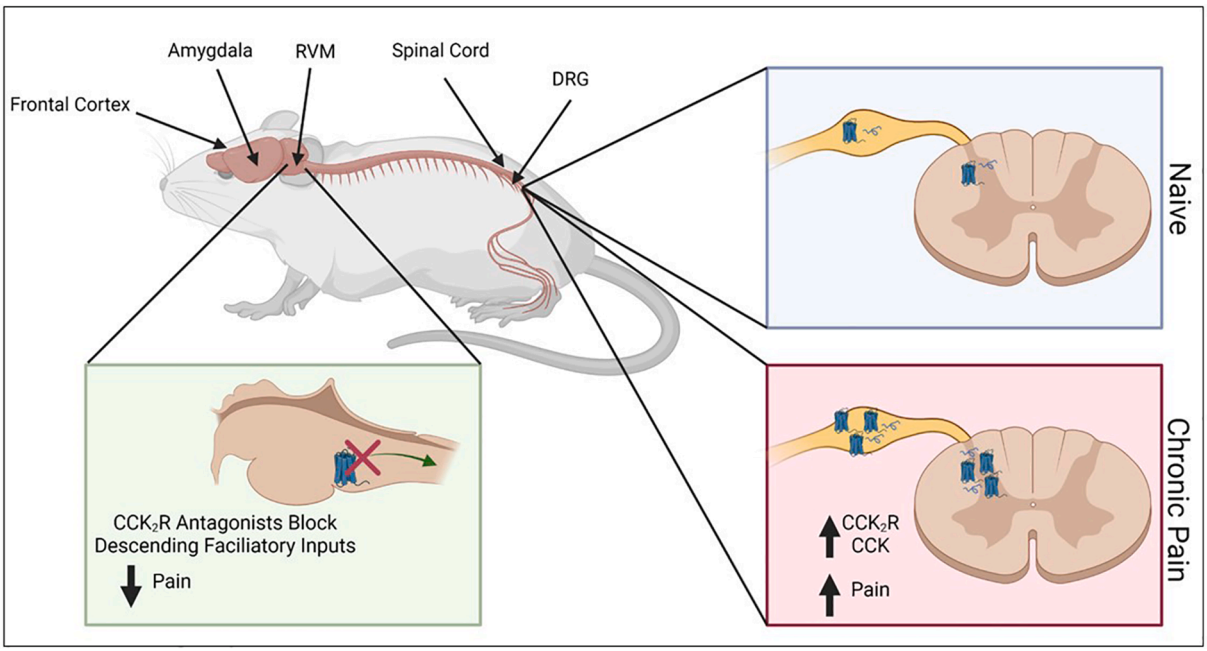

Fig. 2. CCK2R Receptors are Expressed Along the Pain Axis and Modulate Pain. Diagram depicts several areas of CCK2R expression which are linked to pain. In the spinal cord and DRG, CCK2R and CCK are expressed at low levels in naïve animals. In chronic pain models both CCK2R and CCK levels are increased in the spinal cord and DRG. In the RVM CCK2R antagonists block descending faciliatory pain signals, thus reduces pain. Created with Biorender.com.

CCK-8/CCK2Rs interactions are increased. The main source RVM CCK-8 inputs are from the dorsomedial hypothalamus (DMH), an area involved in stress responses and potentially involved in stress-induced pain facilitation, although a role for CCK receptors in this specific acute stress model was not found(Wagner et al., 2013). It is thus likely that facilitatory, pronociceptive inputs into RVM, coupled with anxiogenic properties in areas such as the amygdala(Bowers et al., 2012; Wang et al., 2005), all contribute to the pain promoting properties of the CCK system; indeed, antibody therapy has shown blockade of nociceptive, anxiety-like, and depression-like behaviors(Westlund et al., 2021).

CCK2R and opioid interactions

Due to the significant overlap of CCK2Rs in pathways modulating both sensory and affective components of pain processing (Fig. 2), a historically significant effort was taken to develop novel antagonists of CCKRs as adjunctive therapeutics with opioid analgesics(Hruby, 2003; Hanlon, 2011). Early pharmacological studies demonstrated that CCK receptor agonists can inhibit opioid agonist-induced antinociception (Faris et al., 1983; Barbaz et al., 1988; Li and Han, 1989; O'Neill et al., 1989) and conversely CCK receptor antagonists can potentiate opioid-induced antinociception(O'Neill et al., 1989; Watkins et al., 1985). Only two studies present weak evidence that CCK agonists can be analgesic themselves(Keppel Hesselink, 2020; Rattray et al., 1989) These studies were followed by a significant depth of literature consistently demonstrating an anti-opioid effect of CCK receptor agonists (Wang et al., 1990; Kellstein et al., 1991; Legido et al., 1995) and further elucidating that CCK2Rs appear to be the critical CCK receptor subtype in this phenomenon(Dourish, 1990; Wiesenfeld-Hallin et al., 1990; Zhou et al., 1993; Ossipov et al., 1994; Vanderah et al., 1996), although CCK1Rs may have a minimal contribution(Lavigne et al., 1992). These antinociceptive enhancements of CCK2R antagonists appear not only through application of exogenous opioids but also occur when endogenous opioid levels are increasing through inhibition of their degradation (Maldonado et al., 1993; Valverde et al., 1994; Le Guen et al., 2003). The exact mechanisms of these interactions remain somewhat of a controversy. Although initial evidence(Wang et al., 1990) suggested a role for mu and kappa opioid receptors (MOP and KOP, respectively), there is significant evidence to suggest involvement of enkephalins and the delta opioid receptor (DOP)(Ossipov et al., 1994; Vanderah et al., 1996; Gustafsson et al., 2001). Furthermore, whether heterodimerization of CCK receptors and opioid receptors mediates these interactions is inconclusive since some evidence suggests little, or ligand-induced, heterodimerization(Harikumar et al., 2010; Zheng, 2009), thus no physical modulation. One study did suggest heterodimerization of the MOP and CCK2Rs does relate to anti-opioid effects of CCK, however only one acute pain paradigm was utilized(Yang, 2018). Of note, the CCKR interplay with opioid receptors was shown in CCK2R knockout mice in which an upregulation of the endogenous opioid system was apparent (Pommier, 2002). Interestingly, in these knockout mice opioid receptors now stimulated adenylyl cyclase activity compared to inhibiting activity in naïve mice.

Opioid and CCK interaction studies have not be limited to their involvement in pain. Although the previous discussion has demonstrated a significant reduction or increase in opioid-induced analgesia by CCK2R agonists or antagonists, respectively, there appears to be an interaction at the level of opioid tolerance and reward. Evidence consistently supports the idea that CCK antagonists can mitigate the tolerance associated with opioid use(Dourish, 1990; Kellstein and Mayer, 1991; Xu et al., 1992; Rezayat et al., 1994; Zarrindast, 1997). Antiserum against CCK has also produced a reversal of tolerance(Ding et al., 1986). In terms of the interactions at the level of reward, CCK2R antagonist, but not CCK1R antagonist, can block morphine-induced conditioned place preference (CPP) if the antagonist are administered after the acquisition phase, before the testing phase, into the anterior nucleus accumbens(Mitchell et al., 2006). However, it should be noted that administration of CCK-8 during the acquisition phase of morphine-induced CPP, decreases the acquisition and leads to a less pronounced conditioning to the morphine compared to morphine alone. Thus, there appears to be a temporally mediated change in the regulation of the CCK system during the acquisition, or chronic use of opioids, versus the retrieval of the conditioned response.

CCK2R drug discovery efforts

Early reviews begin exploring the role of cholecystokinin in pain.

However they either focused on the implications as an adjuvant for opioids(McRoberts, 1986) or providing valid skepticism on whether the cholecystokinin system plays any true physiological role in the pathophysiology of pain(Baber et al., 1989). The latter skepticism seems to hold partially true as it has been demonstrated that ablation of CCK2Rs in the RVM fail to alter baseline pain thresholds and the initial development of pain, but does result in a more rapidly recover in preclinical models(Zhang, 2009). Although many small molecules and peptide analogs have been developed (reviewed Dufresne et al., 2006) there have been no successful transitions to the clinic for pain.

A randomized, double blind, placebo-controlled crossover study of the CCK2R antagonist L-365,260 as an adjunct to morphine in patients with chronic neuropathic pain showed that it did not augment the analgesic effects of morphine(McCleane, 2003). There were no adverse negative side effects of L-365,260 noted in patients. The authors state that this finding is surprising given that proglumide, a non-specific CCK1R and CCK2R antagonist, does enhance the effects of morphine in neuropathic pain patients(McCleane, 1998). Lack of efficacy of L-365,320 may have been due to the type of pain that patients had, sex differences or route of administration. Lastly, a study examining the safety and tolerability of L-365,260 found patients may have some pain relief, however the study was open label and had a small number of patients, thus the author determined the results of this secondary outcome to have little scientific validity(McCleane, 2002). These clinical studies in chronic pain patients with the CCK2R antagonist seem to have discouraged the field from pursuing CCK2R antagonists for chronic pain further.

As discussed, there are few rigorous clinical trials examining the effects of CCK2R antagonists on chronic pain. Furthermore, most were in conjunction with an opioid and little investigation has been done on different pain types or utilizing CCK2R antagonists alone. With the current heavy stigma on opioid use, it is likely that the initial indication of CCK2R antagonists as an adjunctive therapy to morphine has hindered their further investigation. However, the preclinical literature is immense, demonstrating that CCK2R receptors are located along the pain access (including both sensory and affective-related areas), CCK2R and/or CCK may be further upregulated during pain states, and antagonists can mitigate pain behaviors. It's thus clear, that CCK2R remains a viability target for the treatment of chronic pain. Indeed, more recently, novel technologies that allow for brain-penetrance and/or higher specificity and nanomolar binding for CCK2R such as small antibody-based therapies(Westlund et al., 2021), may yield promise for translation to patients. Therapeutics outside the realm of small molecules, new tools to investigate the CCK system, and more rigorous approaches for clinical trials may bring CCK2R back into the spotlight of chronic pain therapeutics.

Declaration of interest

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CRediT authorship contribution statement

Justin E. LaVigne: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Sascha R.A. Alles:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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