Cholecystokinin antagonists: Can they augment opioid-derived analgesia?

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INTRODUCTION

Cholecystokinin (CCK), originally thought to be confined to the gastrointestinal tract, is now known to be colocalized in the gastrointestinal tract and the central nervous system (CNS). In animal models, levels are increased after neural injury and with opioid administration. CCK acts as an antiopioid, and as its levels increase, the extent of opioid-derived antinociception decreases.

Coadministration of a CCK antagonist along with an opioid is associated with an improved level of antinociception. Furthermore, CCK antagonists may prevent antinociceptive tolerance with opioids and even reverse established tolerance. Human studies have now confirmed the proanalgesic effect of some CCK antagonists; however, human investigation of the effect of CCK antagonists on analgesic tolerance has yet to be performed.

Few would argue about the crucial role played by opioids in modern pain management. That said, concerns still remain regarding the partial analgesic efficacy of these opioids and issues such as analgesic tolerance with sustained use, particularly in the field of chronic pain management. Consequently, much investigation is focused on ways of minimizing these concerns.

One line of investigation has been into the role of CCK in the nociceptive processing systems. In contrast to many other areas of study, the insight into its function is matched by the availability of a group of therapeutic entities, the CCK antagonists, which are already extensively investigated. The initial findings from human studies confirm the strong impression from the animal literature that CCK has an integral part in nociceptive processing and that antagonists of its action have a useful proanalgesic effect.

The aim of this review is to outline the results of the extensive investigation that has already been made into the function and action of CCK and its antagonists and hopefully stimulate further interest in the application of this knowledge into human clinical practice.

ORIGINAL DESCRIPTION OF CHOLECYSTOKININ

Following work by Boyden in 1926,[1] which showed that transfusion of blood from cats that had just been fed into other cats made their gall bladders contract, Ivy and Oldberg[2] suggested the existence of a hormone released after feeding that causes gall bladder contraction. They showed that in anesthetized dogs whose carotid arteries were connected to allow cross-circulation between two animals, feeding of one led to gall bladder contraction in both. They named this hormonal substance "cholecystokinin."

CENTRAL LOCALIZATION OF CHOLECYSTOKININ

Some 50 years after the original description of CCK, immunochemical studies started to reveal that not only was CCK present in gut tissues, but also in the CNS.[3-5] In addition, nerves containing CCK were found to be particularly numerous in the guinea pig neocortex, hippocampus, amygdaloid nuclei, hypothalamus, and spinal cord.[6] Further work has confirmed the presence of cells containing mRNA encoding CCK in the rat[7] and human[8] CNS. Levels of CCK in the rostroventral medulla are elevated in cases of neuropathic pain and tolerance.[9] What emerges is that CCK has extensive CNS as well as gastrointestinal representation. There are, however, some differences in the structure of CCK found in the alimentary tract of rodents and that found in the CNS. That predominating in the alimentary system is known as "CCK A," while that localized predominately in the CNS is known as "CCK B" (brain).

In rodent and murine models, "peripheral" CCK, or CCK A, is indeed found predominately in the periphery, but also has some CNS representation. The localization of CCK A varies among differing rodents.[10] In contrast, the density of CCK A receptors in the CNS is significantly higher in primate models.[11] Indeed, Verge and colleagues have shown that 20 percent of monkey dorsal root ganglion neurones express mRNA for CCK irrespective of spinal level. In contrast, mRNA for CCK is found at very

low levels in uninjured rats, and it is only after neural injury that its levels increase substantially.[12] Tissue levels of CCK are unaltered at the site of neural injury, and it is only at the dorsal root ganglion level that increases in CCK are seen. This increase is in mRNA levels for CCK[13-15] and in the extent of CCK binding.[15]

Not only neural injury can increase CCK levels. Gustafsson and colleagues used microdialysis techniques to show that systemic administration of antinociceptive doses of morphine induces a dose-dependent release of CCK-like immunoreactivity in the dorsal horn of the rat spinal cord.[16] Similarly, Zhou and colleagues have demonstrated an 89 percent increase in CCK immunoreactivity in the perfusate of the rat spinal cord after morphine administration.[17] Wiesenfeld-Hallin and colleagues have confirmed these findings and shown that morphine causes release of CCK after axotomy but not during carrageenan-induced inflammation.[18] In rodents, even a single dose of morphine can cause up to a threefold increase in the concentration of brain and spinal cord CCK.[19]

EFFECT OF ELEVATION OF CENTRAL NERVOUS SYSTEM CHOLECYSTOKININ LEVELS

If we accept that CCK is found in both the gastrointestinal tract and CNS and that its levels are elevated after neural injury or opiate administration, then the question of the relevance of such elevated levels arises.

Xu and colleagues[20] studied rats, of which some had a spinal cord injury inflicted. Of these, some exhibited behavioral signs of allodynia. They measured the circulating level of CCK in the cerebrospinal fluid and found that the levels in uninjured animals were almost exactly the same as those in animals with a spinal injury, but not exhibiting signs of allodynia. In contrast, those animals that were spinally injured and did show evidence of allodynia were found to have a very marked increase in level of circulating CCK.

Kovelowski and colleagues[21] have also investigated the role of CCK in neuropathic pain. We know that the CNS exerts facilitatory and inhibitory drives that regulate pain. In animals, spinal section at T8 blocks tactile allodynia, but not thermal hyperalgesia after spinal nerve ligation, suggesting a supraspinal integration of allodynia. They found that injection of CCK-8 into the rostroventromedial medulla was associated with a robust tactile allodynic effect and produced a more modest hyperalgesia. They also showed that the antinociceptive effect of morphine injected into the periaqueductal gray region was substantially reduced in spinal nerve-ligated rats, but that its effect was restored by the concomitant administration of a CCK antagonist. They concluded that activation of descending nociceptive facilitatory pathways is important in the maintenance of neuropathic pain, and that this is dependent on CCK release.

If CCK is injected systemically or perispinally, the antinociception produced by morphine is antagonized.[22] Furthermore, if CCK is injected into the inflamed paws of rats, the antinociceptive effect of fentanyl is reduced and this reduction is blocked by CCK A, but not CCK B antagonists in this species.[23]

EFFECT OF CHOLECYSTOKININ ANTAGONISTS ON OPIOID–DERIVED ANTINOCICEPTION

The studies presented previously imply a role for CCK in nociceptive processing. Although this is of interest, it is of clinical relevance only if it suggests a therapeutic intervention that may produce patient benefit. In fact, there is a depth of evidence to support the concept that the use of CCK antagonists may improve opioid-derived antinociception in a variety of animal models. Perhaps the first of these pieces of evidence dates from 1985, when Watkins and colleagues showed that proglumide given systemically, intrathecally, or intracerebrally enhanced morphine-derived antinociception in a rat radiant heat pain model.[24] That this effect was mediated by CCK was confirmed by Suh and colleagues,[25] who showed that intracerebroventricular injection of CCK-8 antagonized the antinociceptive effect of morphine in a mouse tail-flick test. The antagonistic effect of CCK-8 on morphine was blocked by the specific CCK B antagonist PD135,158, but not by the CCK A antagonist lorglumide.

While the majority of studies suggest that CCK B antagonists such as L365,260,[26,27] PD134, 308,[28-30] and PD135, 158[31] have the greatest enhancing effect on opioid-derived antinociception, other isolated reports confirm an enhancing effect with the mixed CCK A and B antagonist proglumide[32,33] and even with the specific A antagonist L364,718.[34] Although this evidence tends to point toward CCK B antagonists as having the more pronounced effect on the antinociceptive effects of morphine, we will see later that there are important interspecies variations.

The magnitude of effect produced by a CCK antagonist on morphine antinociception is typified by the results of Nichols and colleagues.[27] They examined rats that underwent an L5-L6 spinal nerve ligation. Allodynia was assessed using von Frey filaments. Neither administration of morphine nor the CCK B antagonist L365,260 alone had any effect on allodynia. When they were coadministered, however, a significant antiallodynic effect was observed. The δ-opioid receptor antagonist naltrindole NTI blocked this antiallodynic effect.

CHOLECYSTOKININ AND OTHER NEUROACTIVE SUBSTANCES

Dynorphin

CCK is not the only antiopioid peptide found in the

CNS. Dynorphin A, when given in very small doses intrathecally, reduces the antinociceptive effects of morphine.[35,36] This effect seems not to be a direct action, but rather, one that is mediated by CCK. The antinociceptive effect of morphine is reduced by intrathecal dynorphin, producing a rightward shift of the morphine dose-response curve. This effect is prevented by administration of a CCK antagonist and by pretreatment with CCK antiserum. On the other hand, the antianalgesic effect of CCK is not affected by pretreatment with dynorphin antiserum, suggesting that dynorphin A has an indirect effect mediated by spinal CCK.[37] In a similar fashion, the antianalgesic effects of pentobarbital[38,39] and neurotensin[40-42] seem to be mediated by spinal release of CCK.

Enkephalins

Radioimmunoassay and immunochemical studies have shown that enkephalins and CCK 8 have a similar distribution within many areas of the CNS.[43,44] Enkephalins act as endogenous opioids, while CCK has antiopioid properties. This has produced interest in the possible combined use of CCK antagonists and enkephalinase inhibitors, such as RB101, a complete inhibitor of the enkephalin-catabolizing enzymes.[45] Valverde and colleagues[46] have shown that RB101 does indeed have antinociceptive properties and that coadministration of the CCK antagonists L365,260, RB211, and PD134,308, along with RB101, increases the antinociception by 300, 500, and 800 percent, respectively, as compared with RB101 alone. The duration of action of RB101 is short, however, and this may limit its clinical usefulness. RB3007 has a longer duration of action, and recent work has confirmed its long-lasting antinociceptive properties and a significant potentiation by the CCK B antagonist PD134,308.[47]

Vanderah and colleagues[48] confirmed that the addition of a peptidase inhibitor (thiorphan) to L365,260 produced marked antinociception, while application of either alone produced no such decrease in nociceptive signaling. The effect of the combination of CCK antagonist and peptidase inhibitor was blocked by naltindole (a δ-opioid antagonist) and by antisera to [Leu5]enkephalin, but not by antisera to [Met5] enkephalin. This suggests that CCK may tonically inhibit [Leu5] enkephalin, which results in a subsequent enhancement of morphine activity.

This raises the question of the effect of CCK antagonists on placebo-mediated analgesia. It has been observed that the opioid antagonist naloxone is capable of reversing placebo analgesia.[49-52] Benedetti[53,54] examined human subjects with experimentally induced ischemic pain. He found that while the placebo response was indeed reversed by naloxone, proglumide enhanced it. This enhancement was seen only in placebo responders.

Opioid agonists

The knowledge of an interaction between CCK levels and the antinociceptive action of opioids has led to interest in the design of a novel peptide ligand for the CCK B receptor, which has potent agonist-binding affinity and bioactivity at δ-and μ-opioid receptors and simultaneous antagonist activity at CCK receptors.[55]

EFFECT OF CHOLECYSTOKININ ANTAGONISTS ON ANTINOCICEPTIVE TOLERANCE TO OPIOIDS

In keeping with much of the evidence relating to the actions of CCK and the effects of administration of its antagonists, referring to its effects on antinociceptive tolerance to opioids is not new. In 1984, Tang and colleagues demonstrated that the antinociceptive tolerance that developed after only seven or eight subcutaneous injections of morphine can be curtailed by treatment with proglumide without altering the half-life of the morphine.[56]

Similarly, in 1987, Panerai and colleagues studied rats that were fed morphine alone, morphine with proglumide, or morphine and benzotript (both CCK antagonists) dissolved in their drinking water.[57] The experiment lasted 27 days. The presence of tolerance to morphine was assessed by an evaluation of the analgesic responses evoked by graded doses of acutely injected morphine in the tail-flick and hotplate tests. Both proglumide and benzotript shifted the dose-response curve for morphine to the right when compared to those treated with morphine alone, suggesting that they had curtailed the development of tolerance. Neither proglumide nor benzotript had any effect when administered alone.

A recurring theme from animal experiments examining antinociceptive tolerance to opioids is that almost-complete tolerance is relatively easily obtained. This contrasts with human practice, in which many still maintain that even prolonged treatment with opioids is not commonly associated with such tolerance.

Tortorici and colleagues[58] have given some insight into the possible central location where tolerance is mediated through. They introduced a cannula into the periaqueductal gray area of rats. Microinjections of morphine produced antinociception, as quantified with the tail-flick and hotplate tests. When morphine microinjection was repeated twice daily, the antinociceptive effect disappeared within two days. If each morphine microinjection was preceded by a microinjection of proglumide into the same site, however, the microinjection of morphine always produced antinociception and did not induce tolerance. If the proglumide microinjections were suspended, subsequent morphine microinjections induced tolerance. In morphine-tolerant rats, a single microinjection of proglumide was enough to restore the antinociceptive effect of morphine.

The work of Idanpaan-Heikkila and colleagues[59] confirms that the CCK B antagonist L365,260 curtails tolerance in a rat model of peripheral neuropathy, while the studies by Zarrindast[60,61] show that both the CCK A antagonist MK329 and the B antagonist L365,260 curtail antinociceptive tolerance to morphine in mice. Dourish and colleagues also show that both the CCK A antagonist L365,031 and the B antagonist L365,260 curtail antinociceptive tolerance in a rat radiant heat tail-flick model, although they did show the morphine-enhancing effect was greater with L365,260 than with L365,031.[62]

The majority of studies investigating antinociceptive tolerance have concentrated on morphine. Kissin and colleagues,[63] in contrast, studied the effect of intravenous infusion of the short-acting opioid analgesic alfentanil in a rat model. Within four hours of commencement of alfentanil infusion there had been an approximate cumulative reduction of initial analgesic effect of 95 percent. L365,260 administered with alfentanil attenuated this reduction to a value of approximately 65 percent after four hours. Most impressively, proglumide, when given with alfentanil, had the effect of allowing a cumulative reduction of initial analgesic effect of only 45 percent.

REVERSAL OF ESTABLISHED TOLERANCE

The majority of studies addressing the issue of antinociceptive tolerance have concentrated on prevention. In contrast, Hoffmann and Wiesenfeld-Hallin[64] looked at the effect of a CCK antagonist, CI988, on established tolerance. This was induced by twice-daily subcutaneous injections of morphine in rats. By this stage, tolerance was almost complete. Administration of further morphine with saline did not improve the level of antinociception as judged by a hotplate test. When CI988 was given with morphine, however, marked antinociception was observed, suggesting that this CCK antagonist had reversed established antinociceptive tolerance. Similarly, Watkins and colleagues[65] showed that proglumide not only increased the antinociceptive effect of morphine in a rat model, but also seemed to reverse established tolerance.

SAFETY OF CHOLECYSTOKININ ANTAGONISTS

As has been shown, a considerable body of evidence supports the contentions that CCK has an antiopioid effect, its levels are increased after neural injury and chronic opioid administration, and CCK antagonists have a pro-opioid analgesic effect. The use of opioids is not without risk, however, with the major concern after acute administration being respiratory depression. Efficacy matters little in the promotion of better analgesia if additional risk to the patient is accrued from their use. Dourish and colleagues[66] provide a degree of reassurance from one of the few studies actually done in primates. They examined the effect of morphine on respiratory depression in squirrel monkeys and demonstrated a reduction in respiratory frequency after morphine administration, as would be expected. Addition of devazepide, a CCK A antagonist to a similar dose of morphine, increased the antinociception obtained from morphine alone, but did not decrease the respiratory rate any more than morphine alone. It is also interesting that they demonstrated such an increase in antinociception with a CCK A antagonist, given that the majority of studies done in rodent and murine models suggest that the B antagonists have a greater effect on nociception than the A antagonists.

To date, only one study has been undertaken in human subjects addressing the issue of safety. McCleane[67] studied nine subjects, all of whom were unresponsive to previous analgesic intervention, and in whom a trial of strong opioids was indicated. All subjects were given a twice-daily dose of sustained-release morphine. After stabilization of this dose, subjects were divided into three groups. All received L365,260, with the first three getting two doses of 10 mg separated by a four-hour interval; of the remaining six, three received 30 mg and the other three 60 mg, in a similar fashion. Cardiovascular and respiratory parameters were measured at regular intervals for the 10 hours after drug administration. No alterations in these variables were observed, and side effects were infrequent and mild.

HUMAN EVIDENCE

Despite the abundance of studies examining the concepts surrounding the issue of CCK in animal models, relatively few human comparisons have been made.

In 1985, Price and colleagues[68] used a human experimental pain model (radiant heat stimulus to the forearm) to examine the effect of proglumide on morphine-induced analgesia. Each subject received intravenous morphine at a dose of 0.04 or 0.06 mg per kg. They were then given intravenous saline and 10 or 100 mcg of proglumide. Morphine with saline had a very modest analgesic effect; however, the quality and duration of analgesia was substantially improved by coadministration of proglumide with morphine. Although this paper was the first to demonstrate a useful improvement in analgesia when a CCK antagonist is given with morphine, the dose of proglumide used was exceptionally small. The majority of other human studies examine the use of proglumide with doses measured in milligrams, rather than micrograms. If nothing else, this highlights the lack of dose-finding studies in humans with this and all of the other CCK antagonists currently available.

Lavigne and colleagues[69] studied 60 subjects undergoing impacted third molar extraction. Subjects received intravenous morphine at a dose of 4 or 8 mg or morphine

4 mg with proglumide at a dose of 0.05, 0.5, or 5 mg. Morphine 4 mg with proglumide 5 mg not only produced analgesia comparable to morphine 8 mg alone in terms of quality, but also of much greater duration.

In contrast to the studies with positive results, Lehmann and colleagues[70] were unable to demonstrate any improvement in pain scores or reduction in morphine consumption when they studied 80 subjects undergoing major abdominal or gynecological surgery. The morphine and proglumide administered in this study was given on demand using a patient-controlled analgesia device. It is hard to rationalize the failure to observe improvements in analgesic quality when proglumide was given, although four dose levels were examined. Also, the subjects were undergoing a variety of different procedures, so the comparability between subjects may not have been that great.

McCleane[71] studied 40 subjects who were already taking sustained-release morphine at a mean daily dose of 50 mg for a median time of 7.4 months (range, 0.3 to 72 months) for intractable pain. Subjects were blindly treated with proglumide 200 mg twice daily and placebo twice daily, in random order, for a two-week period each. Pain scores fell from a baseline of 8 on a 0 to 10-cm linear visual analog scale to 6 with proglumide treatment ($p < 0.002$), while no significant changes in pain score were seen with placebo. Side effects resultant from proglumide use were infrequent and minor. While morphine is occasionally considered as a possible treatment option in pain management, infinitely greater numbers of patients receive codeine-based preparations. McCleane[72] also examined the effect of proglumide on analgesia derived from a stable dose of dihydrocodeine in 30 adult subjects with pain of varied etiology using a double-blind, placebo-controlled crossover study. Pain scores were essentially unaltered by addition of placebo, but proglumide 200 mg twice daily produced a fall in pain scores of 1.23 on a 0 to 10-cm linear visual analog scale ($p < 0.05$).

Bernstein and colleagues[73] performed a double-blind, placebo-controlled crossover study of 60 subjects with cancer pain who were receiving morphine. Each patient received their usual daily dose of morphine along with placebo and half of their normal daily morphine dose with proglumide 50 mg. Forty-three patients completed the study. No differences in pain scores were observed between the two treatment periods, indicating that a substantially smaller dose of morphine could be used to achieve analgesia when proglumide was added. They also observed no side effects from the use of proglumide. The clinical implications of this study are obvious.

The majority of the murine and rodent studies suggest that antagonism of the CCK B receptors produces a more pronounced enhancement of opioid-derived antinociception. Few primate studies have been undertaken, but that of Dourish and colleagues[66] examined the effect of a CCK A antagonist in a squirrel monkey pain model. They observed impressive antinociception when the CCK A antagonist was added to morphine. McCleane[74] investigated the effect of the CCK B antagonist L365,260 on morphine-derived analgesia in humans with chronic neuropathic pain. Forty subjects were studied, all of whom were taking sustained-release morphine but obtaining incomplete pain relief. All subjects received placebo and L365,260 at three dose levels (30, 60, and 120 mg) in three divided doses daily for two weeks in random order separated by a washout period. Pain scores, activity levels, sleep, concomitant analgesic consumption, electrocardiographs, and serum biochemistry were all measured. No differences between the treatment periods (at any dose given) and the placebo period were observed, and few side effects were attributable to the use of L365,260. The study population was made up of patients with pain previously resistant to treatment, similar to other studies with proglumide in which definite reductions in pain levels were observed.[70,71] This implies that there may be species variations in the response to CCK antagonists and also raises the possibility that CCK A antagonists may be more efficacious in primate and human models.

To date, no randomized controlled trials have been reported that examine the effect of CCK antagonists on analgesic tolerance in humans. McCleane[75] reported an open-label series in which patients stabilized on proglumide 200 mg twice daily along with a fixed dose of morphine were followed for one year. At the end of this period all subjects were still receiving a similar level of analgesia from this fixed dose of morphine, and it was concluded that analgesic tolerance had not developed.

CONCLUSION

A significant body of evidence confirms that in animal pain models, CCK and its receptors play an important role in nociceptive processing. Again in these models, the addition of a CCK antagonist to an opioid enhances its antinociceptive effect and reduces the extent of antinociceptive tolerance with sustained use.

Human evidence is less complete and only partially suggests that the same effects are associated with CCK use. Therefore, the full story of the effect of CCK antagonists and their effects on opioid-derived analgesia in humans needs significant further research, but given the highly suggestive animal evidence, such human work is well merited.

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