plasticity, there should be renewed efforts to cure neuromas, to quiet ectopic discharge, to uncouple adrenergic receptors, and to remove inflammatory and other forms of persistent nociceptor activation.

Cholecystokinin (CCK): Negative feedback control for opioid analgesia

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Abstract: Negative feedback is an important mechanism whereby the organism maintains its balance in a complicated system. It may be regarded as a modern version of the ancient Eastern wisdom of Yin and Yang balance. Control of pain and analgesia, is no exception: CCK seems to serve as a built-in mechanism for the modulation of opioid analgesia system **[DICKENSON]**.

DICKENSON has provided a comprehensive account of the plasticity of nociceptive transmission in the dorsal horn of spinal cord as controlled by the interaction of many pharmacological systems, including opioid and nonopioid transmitters/mediators. Considerable attention has been paid to the interaction between opioids and cholecystokinin (CCK) since this has been amply shown to play a key role in determining the efficacy of opioid analgesia at both spinal and supra-spinal levels. Here I would like to make three points to supplement the opioid/CCK mechanisms for modulating pain and analgesia.

1. CCK reverses mu and kappa, but not delta opioid analgesia. In section 5.2, paragraph 1, DICKENSON pointed out that CCK prevents mu- but not delta-mediated neuronal inhibition. In our hands, CCK antagonizes not only mu, but also kappa, except for the delta receptor mediated opioid effect. Thus, i.t. injection of 4 ng of cholecystokinin octapeptide (CCK-8) produced a right shift of the dose-response analgesic curve induced by i.t. injection of mu agonist PL017 or kappa agonist 66A-078 [(N-MeTyr^1, N-MeArg^7, D-Ala^8)Dynorphin (1-8) amide], but not that induced by delta agonist DPDPE (Wang et al. 1990b)

2. Mechanisms of CCK antagonism of opioid effect. In section 5.2, paragraph 4, DICKENSON mentions a possible mechanism by which CCK attenuates the antinociceptive effect of morphine, that is, CCK mobilizes calcium from intracellular store (Wang et al. 1992) via IP_3 pathway (Zhang et al. 1992) to counter the opioid suppression of the rise in intracellular calcium produced by depolarization. We now have direct evidence that in a patch clamping study on dissociated rat dorsal root ganglion neuron, opioid-induced suppression of voltage-gated calcium current could be almost completely reversed by CCK-8. That the effect of CCK is achieved by the activation of the CCK receptor is shown by the fact that the CCK effect can be readily reversed by the CCK-B receptor antagonist L-365260. Again, CCK antagonizes mu (Liu et al. 1995) and kappa (Xu et al. 1996) rather than delta opioid effect.

Another aspect of CCK/opioid interaction seems to take place at the receptor level ("receptor-receptor cross-talk"). Wang et al. (1989) were the first to show that CCK suppressed brain membrane binding to ^{3}H-etorphine, the universal opioid agonist. Further study revealed that CCK decreased the Bmax of mu binding and increased the Kd of kappa binding without affecting delta binding (Wang et al. 1990a). Uncoupling of the opioid receptor from G protein may serve as another mechanism of CCK antagonism of opioid activity (Zhang et al. 1993). The molecular events underlying the anti-opioid effect of CCK in the CNS have been summarized in a recent review article (Han 1995a).

3. CCK as a negative feedback control for opioid analgesia. In paragraph 9 of section 5.2, DICKENSON concludes that CCK may be an endogenous "brake" applied to the antinociceptive action of morphine. In a recent review article (Han 1995b) I called this "negative feedback control," based on five lines of evidence: (1) Systemic morphine produced an 89% increase of the CCK immunoreactivity in the perfusate of the rat spinal cord, an effect completely reversed by naloxone (Zhou et al. 1993b). (2) Peripheral electrical stimulation produced a naloxone reversible analgesia accompanied by a marked increase of the content of CCK in rat spinal perfusate with a frequency rank order of 100 Hz = 15 Hz > 2 Hz; i.t. administration of CCK-B antagonist L-365260 markedly potentiated the stimulation-produced analgesia with the same rank order of 100 Hz > 15 Hz >> 2 Hz (Zhou et al. 1993). (3) An increase of CCK release in rat spinal perfusate can be triggered by mu- or kappa- but not delta-opioid agonist (Sheng et al. 1995). (4) Repeated morphine administration increased the abundance of brain CCK mRNA as measured by the Northern blotting (Zhou et al. 1992) or *in situ* hybridization (Pu et al. 1994). (5) I.c.v. injection of CCK antisense plasmid vector significantly delayed the development of morphine tolerance (Tang et al., in press).

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Pains are in the head, not the spine

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Abstract: The authors presume that activity in the dorsal horn or nociceptors is well correlated with pain sensations and behavior. This overlooks the myriad of interactions between cortex and our spinothalamic tract. It is better to think of our nociceptors, the dorsal horn, and the pain centers in our brain as all components in one larger and complex pain sensory system. **[BERKLEY; BLUMBERG et al.; CODERRE & KATZ; DICKENSON; MCMAHON; WIESENFELD-HALLIN et al.]**

Back in 1911, Head and Holmes proposed a dual system of afferent projections in our pain sensory system: an *epicritic* system that processes information regarding intensity and precise location, and a *protopathic* system that delivers the actual pain sensations. Eighty-five years later, we still believe they were fundamentally right. We have a "sensory discriminative" subsystem, originating with the A-δ fibers, that computes the location, intensity, duration, and nature (stabbing, burning, prickling) of stimuli. We also have an "affective-motivational" subsystem, beginning with the well-known C-fibers, which supports the unpleasant part of painful sensations. As the authors all indicate, each subsystem has a set of neurons that resides in the dorsal root ganglion of the spinal column. These neurons extend their axons to whatever tissue they innervate and receive input there; they also have a second axon that projects across to the dorsal horn. However, pain processing does not end there. The now classic view of our basic pain system continues up through cortex. In brief, the axons in the dorsal horn connect with a second set of neurons housed in the dorsal horn whose axons run out of the spinal column and up to the thalamus. And there is a third set of neurons that projects from the thalamus to the postcentral gyrus in cerebral cortex.

I trust that the six target article authors all know these facts; however, their writing does not reflect this and, in my humble opinion, it should. With two exceptions,[1] the authors assume that activity in the nociceptors, dorsal horn, or some interaction of the two is directly correlated with an animal's experience of pain (or, in some cases, with producing pain behavior in an animal). This assumption is mistaken. The authors show convincingly that our pain system is quite complex; however, they overlook that it gets even more complex once we move beyond the spine.

Very roughly speaking, once pain information exits the dorsal horn, it travels either to the reticular formation in the brain stem or