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Review

Pro-nociceptive action of cholecystokinin in the periaqueductal grey: A role in neuropathic and anxiety-induced hyperalgesic states

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Abstract

The perception of pain is a dynamic process that is subject to ongoing modulation by central pro- and anti-nociceptive control systems. Diverse factors that may be genetic, gender specific, environmentally determined, psychological or, indeed, engendered by already existing pain-related neuronal activity influence the level of descending control on spinal nociceptive processing. In particular, pain is exacerbated by anxiety. This review examines the evidence for cholecystokinin (CCK)-evoked activation of descending pro-nociceptive facilitatory pathways from the midbrain periaqueductal grey matter (PAG) in mediating anxiety-induced hyperalgesia as well as in the development and maintenance of hyperalgesia associated with peripheral neuropathy. CCK drives a spinal-PAG-medullo-spinal pro-nociceptive positive feedback loop that potentiates spinal transmission of nociceptive afferent input, whilst at the same time suppressing activity in the opioid-driven anti-nociceptive descending pathway from the PAG. In females, responsiveness of PAG neurones to CCK is further modulated by changes in the levels of circulating ovarian hormones, an effect that could underlie the changes in pain sensitivity and responsiveness to opiates that occur during the menstrual cycle and postpartum period.

Keywords: Cholecystokinin; Anxiety; Hyperalgesia; Neuropathic pain; Periaqueductal grey; Nocebo effect; Ovarian hormones; Opiates; Maternal behaviour

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1. Introduction

The perception of pain is a dynamic process that is subject to ongoing modulation by pro- and anti-nociceptive control systems, which influence the transmission of sensory input at the spinal level. It has been proposed that both pro- and anti-nociceptive control systems are active under normal conditions, but that a small net facilitatory influence predominates (Bee and Dickenson, 2007; Kovelowski et al., 2000). The balance between the level of activity in the pro- and anti-nociceptive descending pathways is not static, however, but appears to be in a state of dynamic flux, due to the influence of a wide range of factors. These may be genetic, gender specific, environmentally determined, psychological or, indeed, engendered by already existing pain-related neuronal activity. By tipping the balance between the levels of activity in pro- and anti-nociceptive descending control pathways in favour of the hyperalgesic or analgesic state, such factors play a critical role in determining the final pain experience.

Over the past 30 years, considerable effort has been directed towards identifying sources of descending control of spinal nociceptive processing and investigating their mechanism(s) of action and the factors that determine their level of activity. Perhaps because of its obvious potential for harnessing as a therapeutic tool, the central descending inhibitory control system has received the most attention. The periaqueductal grey matter (PAG) of the midbrain is recognised as a major source of inhibitory control and it is now well established that descending pathway(s) from the PAG, which relay in the rostral ventral medulla (RVM) produce hypoalgesia by inhibiting nociceptive sensory processing within the dorsal horn of the spinal cord (e.g., Jones and Gebhart, 1988). At least two pharmacologically distinct opiate-sensitive and non-opiate-sensitive descending pathways emanate from the PAG. These pathways appear to be activated in response to high levels of aversive physical or psychological stress that pose an actual or perceived threat to the individual. Activation of these pathways in emergency situations contributes to the changes in sensory responsiveness that form part of the functional adaptation of the animal to a change in its environmental status (Loivck, 1996).

In addition to its well-documented role in anti-nociception, the PAG is a source of descending *facilitation* of spinal nociceptive processing (Vanegas and Schaible, 2004). Recent studies in animals have identified a descending facilitatory projection from the PAG, which like the descending inhibitory system, relays in the RVM but produces pro-nociceptive effects by *enhancing* spinal transmission of inputs from peripheral pain receptors (Carlson et al., 2007; Heinricher et al., 2004; Gebhart, 2004; Tillu et al., 2007). In the clinical situation, it is well recognised that anxiety is associated with exacerbation of pain symptoms (Kain et al., 2000; Lautenbacher et al., 1999; Taenzer et al., 1986). Activation of the descending facilitatory system from the PAG may be relevant to this phenomenon. Indeed, a recent imaging study in human subjects has indicated that the PAG becomes active in environmental situations that induce hyperalgesia in response to anxiogenic stress (Fairhurst et al., 2007).

The development of effective animal models is an essential pre-requisite for investigating the cellular basis of the anxiety-induced changes in somatosensory processing. Importantly, a significant number of studies in animals now report that acute stress can induce hyperalgesia. In contrast to the aversive stressful stimuli such as footshocks that consistently evoke hypoalgesia in animals (Gebhart, 2004), exposure to relatively mild non-noxious stressors such as vibration, mild restraint, odours, etc., were able to evoke a transient hyperalgesia (Jørum, 1988; Vidal and Jacob, 1982). In other studies, brief exposure to moderately stressful stimuli (which might have been expected to induce analgesia in the short term) were shown to produce a hyperalgesic state that was delayed in onset but long lasting. Thus, rats exposed to a diverse range of stressors that included 15 min of foot shock stress, (Geerse et al., 2006), forced swim sessions (Quintero et al., 2000) or a social conflict situation (Andre et al., 2005) showed enhanced responsiveness to nociceptor stimulation which developed over a period of hours/days but persisted for 1–4 weeks. The factors that determine whether an individual will respond to stress with hyper- or hypoalgesia are not clear. In the short term, the valency of the stress-evoked changes in sensory responsiveness appears to be related at least in part, to the intensity and/or aversiveness of the stressful stimulus. However, there are considerable differences between individual animals suggesting that emotional status could be an important factor as well. In several studies, the greatest degree of hyperalgesia was exhibited in those animals in which the stress evoked the highest levels of anxiety (Andre et al., 2005; Jørum, 1988; Quintero et al., 2000).

In contrast to its hypoalgesic counterpart, the neurophysiological basis of stress-induced hyperalgesia has received relatively little attention until lately. However, the involvement of the brain-gut peptide cholecystokinin (CCK) appears to be a critical event. CCK has been shown to have both pro-nociceptive and anxiogenic properties (Berna1 et al., 2007a, b). In humans, anxiety-induced hyperalgesia (the nocebo response) can be reduced in the presence of CCK_2 antagonists (Benedetti et al., 2006, 2007). CCK_2 antagonists can also be effective in an animal model of stress-evoked hyperalgesia (Andre et al., 2005). Animal studies have also shown that CCK is intimately involved in generating the hyperalgesia that characterises chronic pain states (Kovelowski et al., 2000).

A considerable body of evidence is accumulating that indicates that the anxiogenic and pro-nociceptive properties of CCK are inextricably linked at the level of the PAG. This review will focus on the role played by CCK in the modulation of descending control systems that originate in the midbrain and modulate transmission of nociceptive information within spinal and brainstem circuits. A fuller