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Invited review

Imaging opioid analgesia in the human brain and its potential relevance for understanding opioid use in chronic pain

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ABSTRACT

Opioids play an important role for the management of acute pain and in palliative care. The role of long-term opioid therapy in chronic non-malignant pain remains unclear and is the focus of much clinical research. There are concerns regarding analgesic tolerance, paradoxical pain and issues with dependence that can occur with chronic opioid use in the susceptible patient. In this review, we discuss how far human neuroimaging research has come in providing a mechanistic understanding of pain relief provided by opioids, and suggest avenues for further studies that are relevant to the management of chronic pain with opioids.

This article is part of a Special Issue entitled 'Neuroimaging'.

1. Introduction

Basic science has advanced our understanding of nociception and suggests numerous receptors that can be targeted by drugs for pain relief in humans. Unfortunately, few novel compounds have emerged as clinically useful analgesics (Mogil, 2009). Opioids are the mainstay for the management of acute pain (Wu and Raja, 2011) and in palliative care (Portenoy, 2011), where the duration of treatment is limited.

The role of opioids for the treatment of chronic non-malignant pain remains debatable (Chou et al., 2009a). Chronic pain, by definition, persists beyond 3 months. In many patients, the fluctuations in the severity of such pain are not clearly correlated with demonstrable changes in a peripheral or central disease process. There are concerns that opioid-based medications may fail to maintain their efficacy when used indefinitely to relieve such pain. Robust data on opioid treatment efficacy in these patients are lacking (Noble et al., 2010), and concerns have grown over the escalating death rates from prescription-opioid overdose reported in the United States (Okie, 2010). Nonetheless, there is still general consensus amongst clinicians, that long-term management of pain with opiates can be beneficial, or at least safe with appropriate patient selection and dose titration (British Pain Society, 2010; Chou et al., 2009b; Kahan et al., 2011a, 2011b).

Opioid receptors are distributed throughout the nervous system. Experimental studies have demonstrated analgesic effects via stimulation of opioid receptors that are peripheral or centrally located (Dickenson and Kieffer, 2013). There are key spinal and supraspinal actions of opioids and the latter involves descending pathways. Furthermore, recent clinical trials with methylnaltrexone, a peripherally restricted mu-opioid-receptor antagonist, suggest that the effects within the central nervous system are important to pain relief afforded by systemic delivery of opioids in palliative care and chronic non-malignant pain (Anissian et al., 2012; Michna et al., 2011; Thomas et al., 2008). Thus, human brain neuroimaging studies may further our understanding of the central processes through which opiates operate to provide pain relief.

Most human neuroimaging research in humans is focussed on the acute effects of opioids on experimentally induced pain in humans. Far less is known about the effects of chronic opioid analgesic therapy on the central nervous system in humans. Analgesic tolerance is a long-held limitation of chronic opioid therapy. More recent data now suggests that chronic opioid administration or withdrawal cause a hyperalgesic state (Bannister and Dickenson, 2010) where opioids can paradoxically worsen pain. Furthermore, there may be risks of cognitive decline (Kendall et al., 2010)

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and medication misuse, particularly in the vulnerable (Pergolizzi et al., 2012).

Here, we discuss how far human neuroimaging research has come in translating mechanistic data from other species, suggest avenues for further studies that are relevant to the long-term management of pain with opioids.

2. Neuroimaging opioid-based analgesia

2.1. Acute administration of opioids

Neuroimaging research suggests that the experience of pain emerges from an extensive network of brain regions (Apkarian et al., 2005), which is unsurprising given how complex pain really is (Tracey, 2005). The International Association for the Study of Pain (IASP) defines pain as 'an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (IASP, 1994). This definition is based on the concept of pain as a specific consciousness comprising of sensory, emotional and cognitive aspects. Brain imaging has provided evidence for neural mechanisms that contribute to pain perception and its modulation, but the neuro-signature of pain itself remains elusive (Tracey and Mantyh, 2007).

Nearly all neuroimaging studies of opioid analgesia have been performed in healthy volunteers, in whom the effects of opioids on pain from brief non-injurious noxious stimuli are examined (Adler et al., 1997; Oertel et al., 2008; Petrovic et al., 2002; Wagner et al., 2007; Wise et al., 2002). Experimentally induced pain cannot replicate the distress experienced by patients with long-term pain that is often difficult to treat. Nonetheless, studies in healthy volunteers allow for more precise stimulation of the nociceptive system and pharmacological modulation of the resultant experience of pain without illness, disease and treatment confounds. In these highly controlled experiments, short-acting intravenous opioids, for example remifentanil or alfentanil, are often employed to minimise variability from pharmacokinetics between individual subjects.

The early pharmacodynamic FMRI studies from our laboratory revealed that opioids decrease pain-related activations in a specific and dose dependent manner (Wise et al., 2002, 2004). Activations within the intra-calcarine cortex that are related to visual stimulation, a control task employed in these experiments, were not significantly affected by opioid administration. This finding suggests that the suppression of sensory-limbic activations was related to specific effects on neural processing, rather than global vascular effects from hypercarbia related to hypoventilation during opioid analgesia (Wise and Tracey, 2006). Furthermore, an investigation of the acute effects of remifentanil on FMRI activations after controlling for hypercarbia have not revealed direct effects of remifentanil on cerebral vascular reactivity itself (Pattinson et al., 2007). Interestingly, we found that activations evoked within the insular regions by noxious stimuli were particularly susceptible to remifentanil (Wise et al., 2002, 2004). The data are consisted with the known role of insular cortex in nociception and pain perception (Craig, 2003; Mazzola et al., 2009; Ostrowsky et al., 2002).

Oertel et al. (2008) have further demonstrated that opioid analgesic dose response functions differ between the posterior and anterior insula cortex. In their study, the posterior insula and other regions that encode the sensory aspects of pain, also demonstrate a linear reduction of activity with increasing intravenous opioids dose. However, they report that activations in the amygdala, anterior insula and cingulate cortices, which are regions implicated in the affective aspects of pain (Craig, 2009), are maximally suppressed at the lowest opioid dose. Their findings suggest that the limbic regions are exquisitely sensitive to opioid effects, consistent perhaps with their high opioid receptor densities (Fig. 1). The subjects only reported on the sensory aspects of pain in that study. Nonetheless, the FMRI data suggest that opioid analgesics can directly influence emotional responses at low doses that do not alter sensory aspects of pain (Fig. 2).

Opioid analgesia is not exclusively associated with suppression of brain activity. Wagner and colleagues found increased activation in the perigenual anterior cingulate cortex (ACC) and the periaqueductal grey (PAG) activations during opioid analgesia (Wagner et al., 2007). Converging evidence suggests that these regions comprise the neural circuit for the descending modulation of nociception, which include frontal-limbic and brainstem regions (Tracey, 2010). Baseline fluctuations of activity within regions in this circuit can predict moment-to-moment variation in the threshold of pain sensation within individuals, and relates to differences in trait anxiety and pain vigilance between individuals (Ploner et al., 2010). Endogenous opioids are known to contribute to the function of this descending neural circuit (Bencherif et al., 2002; Sprenger et al., 2006; Zubieta et al., 2001). Opioids can activate this same neural circuit for analgesic effects (Petrovic et al., 2002), which is shown to be active across FMRI studies during noxious stimulation itself (Fig. 2).

Interestingly, pain from noxious stimulation is also associated with activations in the several brain regions that are better known for their roles in processing rewards, such as monetary gain, palatable food, drugs and pleasurable social interactions (Becerra et al., 2001). These regions include the orbitofrontal cortex (OFC), nucleus accumbens (NA) and the ventral tegmental area (VTA), all of which are densely populated by opioid receptors. FMRI activations of these 'reward' regions during noxious stimulation may reflect increased endogenous opioidergic transmission for the regulation of pain. This increased opioidergic tone has been considered an opponent-process (pain-opposing) that persists briefly after cessation of the noxious stimulation to explain the experience of relief (from pain) (Leknes and Tracey, 2008; Seymour et al., 2005). Supporting the opponent-theory of pain are studies from our group and others studies demonstrating increased activations in similar reward regions when pain relief is experienced from the cessation or diminution of noxious stimulation (Baliki et al., 2010; Leknes et al., 2011). More recently, we demonstrated that pain relief related to opioids could be predicted from the baseline reactivity of 'reward-regions' within the brain in an FMRI study (Wanigasekera et al., 2012). In that study, activations within the OFC, NA and VTA evoked by painful noxious stimulation prior to opioid administration were positively correlated to reductions in subjective reports of pain intensity from identical noxious stimulation during opioid administration in healthy individuals. Opioid analgesia was also positively correlated with a psychometric measure of reward responsiveness, though neuroimaging data better accounted for the variance in opioid effects on pain ratings. Together these data suggest that opioid analgesia also involves neural mechanisms for reward processing. Interestingly, activity in these 'reward regions' evoked by noxious stimulation during opioid administration did not correlate with analgesic effect, suggesting that exogenous opioids do not directly modulate these reward regions for analgesic effect but may operate on shared mechanisms that are further downstream. For example, the baseline reactivity of the VTA also significantly predicted the opioid-induced changes in neuronal activity in the right amygdala and the left hippocampus, which may in turn influence the expression of behavioural analgesia in the study.

As with any treatment for pain, opioid analgesia can be influenced by the belief (expectancy) of efficacy held by the individual. Expectancy is often used to explain the placebo effect, which is now

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