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REVIEW

Imaging opioid analgesia in the human brain

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SUMMARY

Opioids play an important role for the management of acute pain and in palliative care. In contrast, the role of long-term opioid therapy in chronic non-malignant pain remains unclear. 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.

1. Introduction

Basic science has advanced our understanding of nociception and suggests numerous receptors that can be targeted by drugs for pain relief. Unfortunately, few if any novel analgesics have emerged in clinical practise.[1] Opiates remain the mainstay for the management of acute pain[2] and in palliative care.[3]

The role of opioids for the treatment of chronic non-malignant pain is the focus of much research.[4] Chronic pain, by definition, persists beyond 3 months. In many patients, the fluctuations in the severity of such pain are not easily explained by demonstrable changes in a peripheral or central disease process. Robust data on opioid treatment efficacy in these patients are lacking,[5] and concerns grow over the escalating death rates from prescription-opioid overdose reported in the United States.[6] 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.[7–10]

Opioid receptors are distributed throughout the nervous system. Experimental studies demonstrate analgesic effects via stimulation of peripheral,[11] or centrally located[12] opioid receptors. However, recent clinical trials with methyl-naltrexone, a peripherally restricted mu-opioid-receptor antagonist, suggest that central effects are important to pain relief afforded by systemic opioids in palliative care and chronic non-malignant pain.[13,14] Thus, human brain neuroimaging studies may help further our understanding of the central processes through which opiates operate to provide pain relief in patients. Here, we discuss how far human neuroimaging research has come in translating mechanistic data from other species, and 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

Human brain imaging studies of opioid analgesia have been performed in healthy volunteers, in whom the effects of opioids on pain from brief non-injurious noxious stimuli were examined. Notwithstanding differences related to the neuroimaging technique and experimental paradigm, these studies consistently associate opioid analgesia with altered neuronal activation mainly in somatosensory and limbic regions.[15–21]

Functional magnetic resonance imaging (FMRI) demonstrates that opioids modulate brain activity associated with noxious stimuli in a dose dependent manner[19–22] that is unrelated to direct drug effect on cerebral vasculature.[23] However, these brain activities may not reflect analgesia from exogenous opioids alone. Positron emission tomography (PET) consistently demonstrates decreased opioid receptor occupancy during pain from noxious stimulation related to the release of endogenous opioids.[24–26] Placebo or nocebo effects further modulate the extent to which opioid receptor occupancy is altered during pain.[27] We have found that FMRI brain activations associated with the opioid analgesia are significantly altered by the effects of positive (placebo) and negative (nocebo) expectations of analgesic efficacy afforded by a fixed drug dose.[28] Thus, exogenous opioid effects may be determined by endogenous opioidergic tone.

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2.2. Long-term administration of opioids for pain

Neuroimaging studies on the effects of opioids are scant in patients with chronic non-malignant pain. However, central effects appear critical to opioid analgesia in humans. Thus studies regarding the distribution of opioid receptors in the brain in patient populations are instructive.

2.3. Opioid receptor availability – PET studies

Patients with chronic non-malignant pain are a heterogeneous group. Clinical trials have not revealed any pain phenotype for which opioids are particularly efficacious. The earliest PET study suggests that opioid receptor binding is decreased during a period of increased pain related to inflammation in a small group of patients with rheumatoid arthritis.[29] Similar PET studies of individuals with well-characterized neuropathic pain also reveal decreased opioid-receptor binding in patients compared to age-matched healthy controls.[30–32] Complex regional pain syndrome (CRPS) and fibromyalgia are currently diagnoses of exclusion: the contributing pathologies remain unclear in symptomatic individuals. In these pain syndromes, opioid receptor binding is altered primarily in the frontal and limbic regions, and partly account for the variance observed in the self-reports of affect and mood related to pain in patients.[33,34]

Altered opioid receptor binding has been offered as an explanation for the efficacy of exogenous opioids or the lack thereof in patients.[32,33] However, the bases for differences in opioid receptor binding in patients with chronic pain await further clarification. In PET studies, the binding potential is an estimate of unoccupied receptors.[35] A decreased binding potential may reflect an increase in receptor occupancy by endogenous opioid peptides or an absolute reduction in the quantity of receptors. Additionally, the action of different opioid agonists varies depending on differential binding to receptor subtypes.[36]

2.4. Opioid tolerance and drug-induced hyperalgesia

2.4.1. Analgesic tolerance

Opioid-induced tolerance is simply described as a shift to the right in the dose–response curve: a higher dose is required over time to maintain analgesic effect. Progressive disease may lead to higher opioid requirements. Tolerance also results from pharmacokinetic change, for example, when the drug up-regulates the activity of a metabolic process that facilitates its elimination from the body. For our review, "opioid tolerance" refers to pharmacodynamic tolerance, which reflects drug-activated changes in the response of the neural systems.

Mechanisms for analgesic tolerance include altered molecular signalling pathways and down-regulation of opioid receptors.[37] These mechanisms have largely been elucidated in *healthy* animals. Data regarding opioid tolerance in animal models of inflammation, injury and disease are few and inconsistent. Some behavioural studies suggest that tolerance to the anti-nociceptive effects (withdrawal effects) of opioids develop more slowly in inflammatory,[38,39] cancer[40] and neuropathic models[41] when compared to sham controls. Other studies demonstrate enhanced development of analgesic tolerance, particularly in neuropathic models.[42] The inconsistencies may relate to the species, disease model and the opioid and dose administered.[1]

2.5. Opioid-induced hyperalgesia

Distinct from tolerance, the *excitatory* effects of opioids at the cellular level are thought to cause opioid-induced hyperalgesia[43–46]. In clinical practise, opioid-induced hyperalgesia is diagnosed when generalised pain develops and worsens with escalating opioid dose.[47] Improvement following opioid dose reduction is recommended to help distinguish between opioid tolerance and excitatory effects.[48] However, discomfort related to withdrawal can negatively influence the overall pain experienced and cloud the diagnosis.

Opioid-induced hyperalgesia is mainly demonstrated after prolonged administration of opioids in healthy animals.[49,50] These data are mostly consistent with findings of decreased tolerance of noxious stimuli in human individuals maintained on long-term methadone to manage opioid dependence.[51–53] However, a recent study in which oxycodone was administered orally over days in healthy volunteers without a history of drug misuse revealed no analgesic tolerance or hyperalgesia.[54] The development of tolerance or hyperalgesia appear to vary with the duration of administration, dose and opioid chemistry.[55] Susceptibility to these effects may also differ between individuals.

In healthy volunteers, cessation of remifentanil (after about an hour of infusion) can induce[56–58] or enhance hyperalgesia[59,60] but not consistently. The phenomenon of opioid post-infusion hyperalgesia has been investigated recently in a combined psychophysical-fMRI study.[58] Only half of all subjects recruited developed post-infusion hyperalgesia to noxious thermal stimuli, implying considerable inter-individual variation for the phenomenon, possibly related to genetic susceptibility.[57] Midbrain reticular formation activation was significantly increased in the hyperalgesic subjects and correlated negatively with the degree of hyperalgesia, which suggest that brainstem activity regulates, rather than drives sensitisation effects during opioid withdrawal.

Further to its role in opioid-induced hyperalgesia,[61] the brainstem has been shown to mediate the physical signs of opioid withdrawal in rats. Several animal studies suggest that the brain sites that drive volitional drug self-administration differ from those mediating the development of physical dependence.[62] Bozarth and Wise first demonstrated this double dissociation in a series of experiments in laboratory rats implanted with intra-cerebral catheters.[63] The rodents avidly self-administer opiates to the brain's reward loci, but drug antagonism at those sites produced no signs of physical dependence. In contrast, rats do not self-administer opiates to the posterior brainstem loci (near the dorsal raphae nucleus), but cessation of opiates to that region produces physical signs of withdrawal.

In the human FMRI study,[58] subjects who developed opioid post-infusion hyperalgesia were indistinguishable from the rest of study cohort during remifentanil infusion: decreases in subjective ratings of pain during opioid infusion were similar in both groups. In subjects who subsequently developed post-infusion hyperalgesia, FMRI revealed increased activation in the midbrain reticular formation during the opioid infusion, suggesting initiation of pro-nociceptive processes in that brief period. As this was an acute administration study with an hour of opioid infusion, it remains unclear whether opioid-induced hyperalgesia would have occurred eventually had the infusion been prolonged in the susceptible individuals.

2.6. Opioid-induced hyperalgesia in injury or disease

Relatively few animal studies demonstrate opioid-induced hyperalgesia in the presence of tissue injury,[64–66] inflammation[67] or cancer,[68] suggesting that these pathological states are protective. Notably, the doses of opioids used to induce hyperalgesia in animal models of pain appear higher than those employed to study opioid tolerance.

Several clinical investigators have reported increased post-surgical pain scores and analgesic requirements following intra-