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Opioids: From Physical Pain to the Pain of Social Isolation

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Abstract

The opioid systems play an important role in mediating both physical pain and negative affects (eg, the pain of social isolation). From an evolutionary perspective, it is not surprising that the neurocircuitry and neurochemistry of physical pain would overlap with that involved in complex social emotions. Exposure to trauma as well as a range of gene variants in the opioid system may be associated with alterations in opioid systems function, with changes in reward processing, and with vulnerability to substance abuse. A role for interventions with opioid agents in depression and anxiety disorders has been suggested.

Case Report

Quinn is a 33-year-old man who presented with a history of heroin abuse. He had first started using heroin in the context of being rejected by his lover. He had been able to wean himself off heroin during an inpatient hospitalization and remained drug-free with supportive psychotherapy. However, Quinn continued to feel intermittently depressed and craved heroin at times of stress. Social rejection was a particularly important kind of stress for him. He presented for psychopharmacology evaluation, and buprenorphine was prescribed. During the next few months Quinn reported an increased mood, decreased craving, and overall improved sense of resilience.

Cognitive-Affective Neuroscience

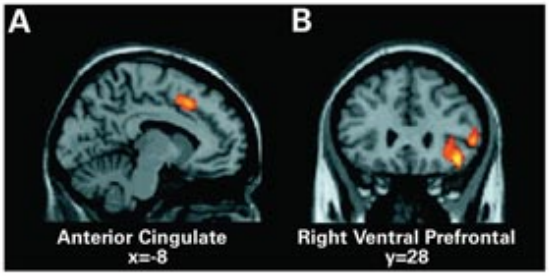
Neuroanatomy/Neurochemistry

The opioid systems comprise a number of G-protein receptor subtypes, including μ for morphine, κ for ketocyclazocine, δ for vas deferens, and ORL-1 for opioid receptor-like.[1,2] The endogenous neuropeptide ligands for these receptors include the endorphins (eg, endomorphin), the enkephalins, the dynorphins, and the orphanin FQ or nociceptin (N/OFQ) family. These endogenous neuropeptides are, in turn, derived, respectively, from the precursors prepropiomelanocortin, preproenkephalin, preprodynorphin, and proorphanin.

μ-opioid receptors are found in particularly high densities in cingulate cortex, thalamus, periaqueductal gray, and caudate nucleus in auto-radiography and positron emission tomography studies.[3-5] Activation of μ-opioid receptors leads to altered activity in neurons in lateral amygdala, periaqueductal gray, and ventral pallidum[6,7] by direct and indirect mechanisms. In limbic regions, increased μ-opioid receptor binding is associated with decreased perfusion, consistent with an inhibitory role.[8] Other opioid receptor subtypes have somewhat different anatomical distributions and functional networks. Opioid receptor density is also influenced by gender and age.[9]

The opioid systems play a key role in mediating both analgesia and social attachment.[10,11] Similarly, in keeping with its role as an alarm/conflict monitor,[12] activation of cingulate is associated with the affective distress of both physical pain[13,14] and social isolation (Figure 1).[15] In general, opioid systems function to signal reward, with release of endogenous opioids during the consummatory phase of motivated behavior. Exogenous opioids are analgesics and weaken the response to social separation.[16] Administration of μ-opioid agonists is associated with activation of areas that are rich in these receptors, and of reward circuitry (Figures 2 and 3).[17-22]

FIGURE 1.
Increased fMRI activation in (A) anterior cingulate cortex and (B) right ventral prefrontal cortex during social exclusion relative to social inclusion*[15]



* RVPFC appeared to regulate the distress of social exclusion by disrupting anterior cingulate activity.

fMRI=functional magnetic resonance imagery.

From Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An fMRI study of social exclusion. *Science.* 2003;302:290-292. Reprinted with permission from The American Association for the Advancement of Sciences, Copyright (2003).

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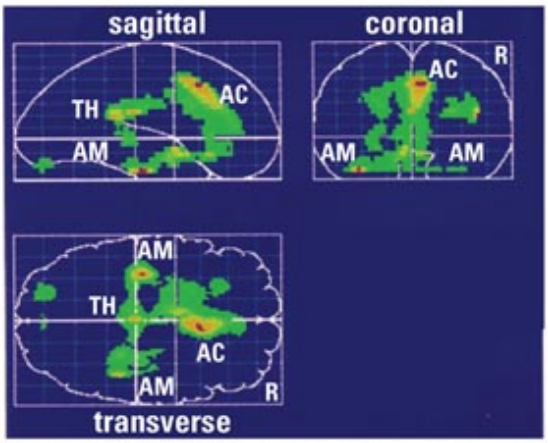
FIGURE 2.
SPECT regional cerebral blood flow increases one hour after administration of hydromorphone, a μ-opioid receptor agonist[17]



SPECT=single photon emission computed tomography; AC=anterior cingulate; TH=thalamus; AM=amygdala; R=right.

Schlaepfer TE, Strain EC, Greenberg BD, et al. Site of opioid action in the human brain: mu and kappa agonists' subjective and cerebral blood flow effects. *Am J Psychiatry.* 1998;155:470-473. Reprinted with permission from The American Psychiatric Association, Copyright (1998).

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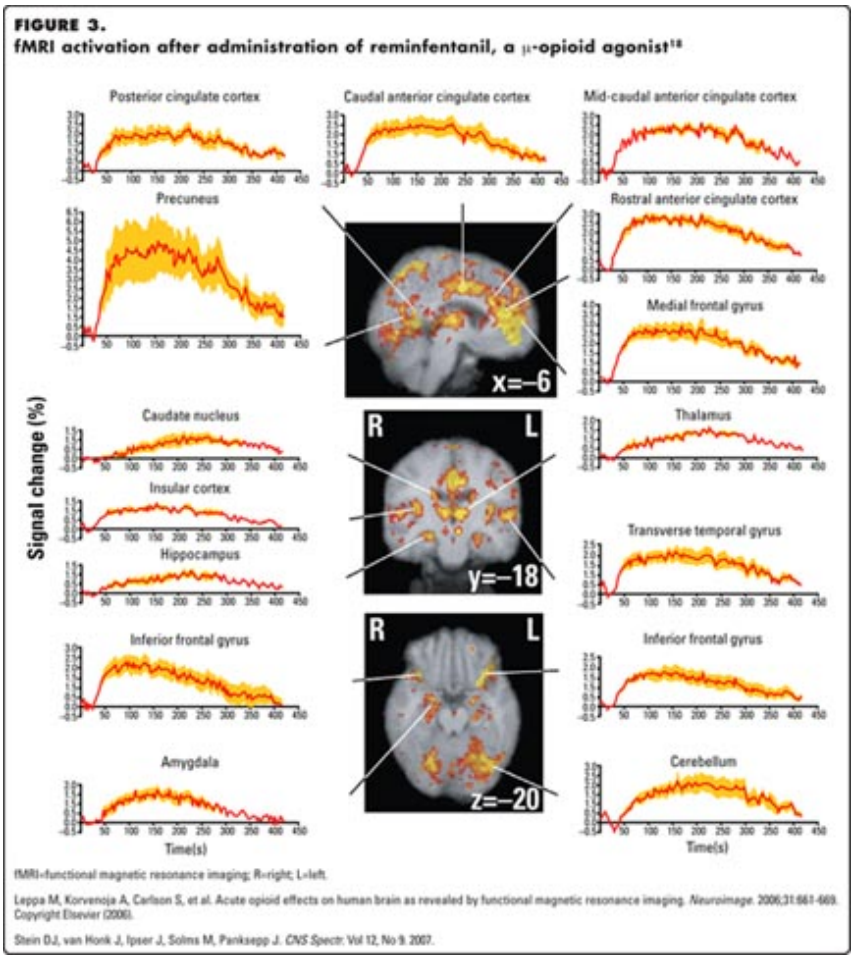

FIGURE 3.
fMRI activation after administration of reminfentanil, a μ-opioid agonist[18]

fMRI=functional magnetic resonance imaging; R=right; L=left.

Leppa M, Korvenoja A, Carlson S, et al. Acute opioid effects on human brain as revealed by functional magnetic resonance imaging. *Neuroimage*. 2006;31:661-669. Copyright Elsevier (2006).

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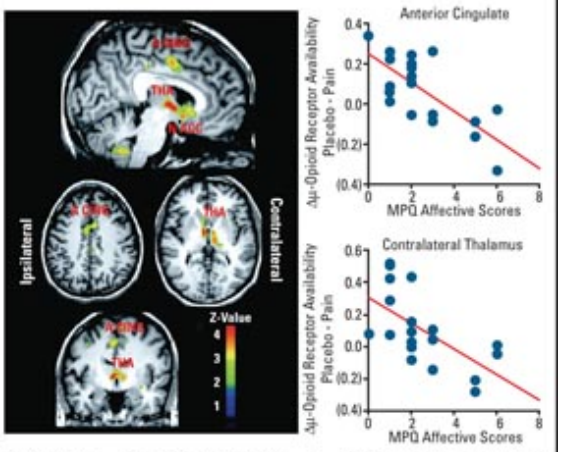
Physical pain leads to increased μ-opioid receptor-mediated neurotransmission (Figure 4),[23] and a similar phenomenon occurs during induced sadness in some cases of depression.[24] Indeed, opioid systems may be disrupted in a range of disorders, including depression, anxiety, autism, and self-injurious conditions.[25] In depression, an increase in μ-opioid receptor neurotransmission in anterior cingulate during induced sadness was associated with non-response to antidepressants.[24] Compared to controls with and without trauma exposure, patients with posttraumatic stress disorder (PTSD) had increased μ-opioid receptor-mediated neurotransmission in anterior cingulate, but also appeared unable to activate adequately μ-opioid receptors in amygdala and thalamus.[26]

FIGURE 4.
Sustained pain resulted in reduced μ-opioid receptor binding potential on positron emission tomography with [^{11}C]carfentanil, consistent with an increase in opioid neurotransmission[23]



MPQ=McGill Pain Questionnaire; A CING=anterior cingulate; THA=thalamus.

From Zubieta JK, Smith YR, Bueller JA, et al. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science.* 2001;293:311-315. Reprinted with permission from The American Association for the Advancement of Sciences, Copyright (2001).

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Gene/Environment

Reduced levels of endogenous opioids may result from social isolation.[11] Opioid system function is also influenced by a number of functional polymorphisms in opioid receptor genes.[27,28] Such environmental and genetic factors may in turn mediate vulnerability to pain symptoms, substance use disorders,[29,30] and other psychopathology.[31] In addition, gene variants in a range of other systems may impact on opioid function. For example, worrier individuals[32] homozygous for the met158 allele of the catechol-O-methyltransferase polymorphism have diminished regional μ-opioid system responses to pain and increased pain and distress ratings compared with heterozygotes.[33]

Evolutionary Approaches

From an evolutionary perspective, it would not be surprising if psychobiological research demonstrated that mechanisms involved in thermoregulation and energy balance later contributed to the monitoring of social presence, and if mechanisms involved in (especially visceral) pain later contributed to emotional distress during social separation.[11,16,34] Conversely, evolution psychology is considerably weakened when it excludes neurobiology.[35]

Indeed, opioid research highlights a close relationship between physical pain and emotions involved in social exclusion/rejection.[16] A range of other data strengthen the idea that physical and social pain operate via common proximal (psychobiological) and distal (evolutionary) mechanisms.[36] Concepts of social exclusion/rejection may be found in all times and places, and metaphors of "social pain" are present in many languages. Such ideas underpin evolutionary approaches to substance use disorders.[37-39]

Clinical Implications

DSM-IV-TR Diagnosis

The *DSM-IV-TR* provides diagnostic criteria for a range of opioid use disorders, including opioid abuse, dependence, intoxication, and withdrawal and opioid-induced psychotic and mood disorder. It has been suggested that the neurocircuitry underlying mother-infant attachment, in which the opioid system plays a central role, is important in mediating a range of psychopathology,[11] evident in current psychiatric nosology.

Assessment/Evaluation

Current psychiatric measures focus on symptoms characteristic of particular disorders. Rejection sensitivity has been described as a symptom of atypical depression, is increasingly being explored,[40] and a Rejection Sensitivity Questionnaire has been developed.[41] Panksepp[42] has further emphasized the importance of assessing core emotional feelings that are mediated by brainstem and limbic neural systems common to humans and lower animals. In patients with PTSD, it is important to assess opioid use.[43]

Pharmacotherapy/Psychotherapy

Morphine (named after Morpheus, the Greek god of dreams) was synthesized around 200 years ago. A range of opioids have been developed since and are used illicitly or as therapeutic agents. Higher concentrations of μ-opioid receptors in women may explain their higher sensitivity to μ-opioid agonists.[44]

Opioids play a particularly important role in the management of opioid detoxification and maintenance treatment[45,46] Buprenorphine, for example, binds with high affinity to both the μ-opioid receptor (as a partial agonist) and the κ-receptor (as an antagonist); it is able to displace heroin and other opioids that bind the μ-receptor, but has dose-limited agonist effects, and therefore, lower potential for abuse.[47] Systematic reviews of psychotherapy support its use in the integrated management of opioid use disorders.[48,49]

Opioid antagonists have proven effective for a number of substance use and impulse-control disorders, including alcohol dependence and pathological gambling.[50,51] They have also been used in autistic disorder and self-injurious behavior.[42,52,53] Buprenorphine seems to exert an antidepressant effect when used for the treatment of opioid abuse.[54,55] Furthermore, there is also preliminary evidence of the value of opioid agents in major depression,[56,57] PTSD,[58-61] and obsessive-compulsive disorder.[62]

Conclusion

Animal and human experiences of physical pain are embodied in a neural circuitry in which the opioid system plays a key role. In addition, more abstract cognitive-affective experiences, such as those cued by social isolation, seem to be mediated by similar circuitry. Therefore, it is perhaps not unexpected that in patients with disrupted social attachments, there are comorbid symptoms of depression and of pain, and abnormalities of the opioid system. These possibilities were anticipated by the first animal experiments in modern social neuroscience.[63,64] Further work is needed to delineate fully the role of the opioid system in various psychopathologies, and to determine whether opioid interventions can contribute to their treatment.

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