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Pain and reward: How the affective-motivational system is perturbed in chronic pain

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Abstract
Chronic pain is a debilitating, persistent disease that remains poorly managed in many patients. Part of the problem of current analgesics is their focus on reducing the sensory discriminative element of pain, but pain has an equally important aspect relating to the affective quality, or how much the pain 'bothers' you. Drugs that target both the sensory and affective elements of pain, such as opioids, are generally more effective analgesics. However, opioids have inherent rewarding properties, in addition to their pain relieving qualities, which complicate the interaction between analgesia and pain affect. Further, despite their outstanding analgesic efficacy in acute pain settings, opioids are less effective in relieving chronic pain. While the exact mechanisms of why this may be remain debated, alterations in the limbic system resulting from a chronic pain state is a logical possibility. In this review, limbic processing of pain affect in acute and chronic pain conditions will be reviewed, with a particular emphasis placed on examining how the limbic system changes in a chronic pain state. Ultimately, better understanding of how the limbic system changes in chronic pain will further expand our understanding of the chronic pain brain, and identify novel therapeutic targets to improve the analgesic efficacy of the ubiquitous opioids.

Introduction
Chronic pain is a disease of the nervous system, distinct from acute pain. While acute pain serves a physiological purpose that warns the body of potential or actual tissue damage, chronic pain is a condition where the pain sensation is disconnected from the external stimuli, and evolves into a disease state in and of itself. In support of this idea are the numerous studies over several decades that have described countless adaptations in the sensory system under conditions of chronic pain. However, the majority of these studies have focused on how these changes relate to the sensory aspect of pain, and consequently, most new drugs developed for the treatment of chronic pain target these sensory elements. However, pain is composed of two distinct components: the sensory-discriminative and affective-emotional. The sensory-discriminative component carries information regarding the type, location, and intensity of the painful stimulus, and is encoded primarily in the primary and secondary somatosensory cortices. The emotional-affective component of pain provides the unpleasant quality to the pain experience, and is encoded by the limbic brain region. Opioids are some of the strongest pain relievers available, and part of the reason for their high analgesic efficacy is their ability to target the emotional affective, as well as sensory, components of pain. However, for reasons that remain unknown, opioid analgesia is less effective in chronic pain conditions. One possibility is that adaptations in the limbic system due to a chronic pain state may undermine the hedonic attributes of opioids, and play a role in the loss of analgesic efficacy of these drugs.

This review will discuss various salient points and contentious issues relating to the affective emotional system and chronic pain. First, it will review the normal processing of the limbic system in response to acute pain stimuli, and review evidence for how this system may change in chronic pain states. The contribution of some neuromodulators, including dopamine, serotonin and norepinephrine, will be discussed. Finally, it will review the evidence that the rewarding properties of opioids are altered in chronic pain, and discuss the implications this may have on opioid analgesic efficacy.

The Limbic System

The limbic system attributes emotional salience to stimuli encountered in the environment. Therefore, the limbic system can be seen as a filter through which neutral stimuli are given an emotional valence in order to direct movement towards stimuli that are positive (ie: palatable food), and away from ones that are negative (ie: pain). Behaviors that produce a positive outcome are more likely to be repeated, and those that produce a negative outcome will be discouraged (Skinner 1972). At its most basic then, emotional affect can be considered as the motivational drive to encourage behavior that promotes survival.

The most likely reaction to a pain stimulus is a motor response, usually a movement away from the offending stimulus. Pain is also a strong reinforcing stimulus, such that one encounter with a painful stimulus will significantly discourage the likelihood of repeating that same behavior. One has to touch a hot iron only once to remember to never repeat that behavior again. From these examples, it is clear the limbic contribution to the experience of pain is very strong.

The limbic system is formed of several brain regions, including the amygdala, anterior cingulate cortex (ACC), striatum, habenula and hippocampus. Together they mediate the motivation, emotion, learning and memory involved in directing behavior with respect to stimuli encountered in the environment. The majority of research describing limbic system structures has focused on their involvement in mediating reward stimuli; however, there is strong evidence to suggest acute pain stimuli engage overlapping brain regions. Acute pain stimuli activate neurons within the amygdala, striatum and ACC (Rainville *et al* 1997; Becerra *et al* 2001, Bernard *et al* 1992, for review see Ploghaus *et al* 2003 and Borsook *et al* 2010). In all cases, there are foci of neurons that are either activated or deactivated in response to pain, suggesting the limbic system is formed of a heterogeneous population of neurons that mediate aversion and reward (Becerra *et al* 2001). Certain brain areas, such as the habenula and parafascicular nucleus, are exclusively activated by aversive stimuli, such as pain, emphasizing that while aversion and reward may recruit overlapping brain regions, they represent distinct neurobiological processes (Xiao et al 2009, Stamatakis and Stuber 2012).

Changes in the affective-motivational system in chronic pain states

Chronic, inescapable pain leads to a permanent negative affect lasting over years. Also, pain can fluctuate throughout the day, depending on the time of day or certain movements that may precipitate the pain sensation. This leads to a continuous fluctuation between positive (pain off) and negative (pain on) affect that is pathological in nature. There is accumulating evidence to suggest that his constant fluctuation in negative affect has profound effects on the affective-motivational system.

First, chronic pain conditions can be associated with movement disorders, like loss of voluntary control, bradykinesia, dystonia, myoclonus, and tremor, suggesting a global dysregulation in dopaminergic signaling (Van Rijn *et al.* 2007, Schwartzman and Kerrigan 1990, for review see van Hilten 2010). Several human imaging studies found lowered grey matter density in the striatum and altered dopamine activity in response to aversive stimuli (Wood *et al.* 2009, Wood *et al.* 2007, see Borsook *et al.* 2010 for review). Chronic pain is associated with a strong affective phenotype, suggesting a limbic system dysfunction. Depression and anxiety are strong co-morbidities with chronic pain (Asmundson and Katz 2009). Mice developed an anxiety and depression phenotype 4-8 weeks after a nerve lesion (Yalcin *et al* 2011). These phenotypes were independent from stress hormones, as corticosterone levels did not differ in these animals in resting or stress induced conditions.

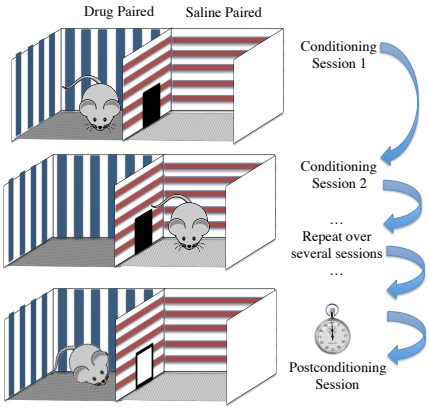

Figure 1: Conditioned Place Preference

Conditioned place preference (CPP) uses Pavlovian conditioning to measure the motivational or reinforcing attributes of a specific external stimulus (most often drugs). This paradigm can also be used for aversive stimuli, in which case it is called conditioned place aversion (CPA).

The CPP apparatus is formed of two chambers, differentiated based on visual (patterned walls) and sensory (floor textures) cues. A passageway that can be opened or closed connects these two chambers. In some cases, a third, 'neutral' chamber is present between the two outer chambers. During the conditioning days, animals are confined to one chamber and given either drug or saline. This conditioning session is repeated the following day on the other side, where the animals receive the other treatment. This is repeated for several days, so that the animal learns to pair a particular chamber with the given stimulus. On the final post-conditioning day, the passageway between the two chambers is opened, and the animal is able to choose in which chamber to be, and the time spent in the 'paired' chamber is recorded. Drugs with a positive affect will cause more time to be spent in the drug-paired chamber (a CPP), whereas negative affective stimuli (like pain) will discourage time spent in the paired chamber (a CPA).

The major advantage to this technique is that it is an easy, straightforward way to measure motivation in otherwise non-communicating animals (generally rats or mice). It also allows testing to be done in a drug free state, which avoids the common pitfalls of motor or cognitive impairment often associated with drug use. The main disadvantage is that animals passively receive drug during the conditioning sessions (via injection), which may not be generalizable to reward in humans, in which they generally seek and self-administer drugs.

Specific changes within the limbic system of a chronic pain state have been described as well. Decreased *c-fos* activation in the rodent ventral tegmental area (VTA) and nucleus accumbens following nerve ligation has been described (Narita *et al* 2003). In human fMRI studies, significant changes in limbic system signaling have been identified in chronic back pain patients (Baliki *et al.* 2010). In healthy controls, an acute pain stimulus caused a decrease in the nucleus accumbens blood oxygen level dependent (BOLD) signal, followed by an increase in signal that coincided with the anticipation of pain offset. In chronic back pain patients, this BOLD signal was reversed, and the pain offset was associated with decreased nucleus accumbens activity (Baliki *et al.* 2010).

Furthermore, a novel functional link between the nucleus accumbens and medial prefrontal cortex was identified in chronic back pain patients that was absent in healthy controls (Baliki *et al* 2012)

So far these changes have been restricted to the midbrain and striatum, but changes in other limbic brain regions under chronic pain conditions have also been described. Rodent amygdalar neurons show increased firing rates related to the upregulation of glutamatergic receptor subunit expression (Neugebauer *et al.* 2003). Experimental arthritis induced upregulation of glutamatergic activity in parabrachial neurons that project directly to the central amygdala. This resulted in an increase

protein kinase A (PKA) mediated phosphorylation of NR1 subunits within ionotropic glutamatergic receptors, and this effect was blocked by administration of N-methyl-D-aspartate (NMDA) antagonists (Bird *et al* 2005). Chronic pain patients showed behavioral deficits in the Iowa Gambling Task, in which subjects learn to make responses that lead to rewards of lower value, but with high probability of reinforcement. These deficits were similar to what is seen in patients with lesions to the prefrontal cortex or amygdala (Apkarian *et al.* 2004). This change in the Iowa Gambling Task was related to increased inhibitory influence of the basolateral amygdala on the medial prefrontal cortex.

Neuromodulators in acute and chronic pain

Neuromodulatory transmitters refer to neurotransmitters such as dopamine, norepinephrine, and serotonin that control neural activity within the brain. Release of these neuromodulators can either excite or inhibit postsynaptic neurons, and are thought to be at the basis of arousal, attention and motivation in an animal. Given their strong integration in the motivational system, they have long been implicated in acute pain signaling; however, how these systems change in pathology and their contribution to chronic pain conditions is a topic of new and exciting research.

Dopamine

Dopamine is the hallmark neurotransmitter in the affective-motivational system, and has long been equated with pleasure and reward. Rewarding stimuli, including most drugs of abuse, stimulate dopamine release in the striatum. These early observations led to the initial "anhedonia theory" of dopamine signaling, which posited dopaminergic systems directly mediate pleasure. However, further research has questioned this direct link. For example, animals with chemically lesioned VTA neurons will still self-administer heroin, a strong opioid (Pettit *et al* 1984). Further, transgenic mice bred without dopamine still express opioid CPP, a behavioral test of reward-like behavior (Figure 1) (Hnasko *et al* 2005). A more recent hypothesis has proposed that dopamine attributes incentive salience to otherwise neutral stimuli (Berridge and Robinson, 1998). In other words, dopamine will transform a neutral stimulus into an attractive/wanted incentive that will grab attention and turn the object into something an animal will work towards. Yet another hypothesis has posited that dopamine encodes the prediction or error in predicting a rewarding stimulus, based on the evidence that dopaminergic neurons are stimulated by unexpected rewards or reward predicting stimuli (Schultz 1998, for review see Ungless *et al.* 2010).

While these theories of dopamine function in the brain may vary, they all address incentive motivation through the lens of reward. The role of dopamine in mediating behavior under aversive states has had a much more contentious path of discovery. Both pain activated and pain inhibited neurons in the striatum have been identified in a variety of experimental animal models (Schultz and Romo 1987, Mantz *et al* 1989, Mirenowicz and Schultz 1996, Guarraci and Kapp 1999, Chiodo *et al* 1980). Human fMRI data have also identified foci of activation and deactivation throughout the striatum in response to noxious thermal stimuli (Becerra *et al.* 2001). Aversive events such as stress and pain stimulate dopamine release in the nucleus accumbens, as measured by microdialysis in rodents (Abercrombie *et al* 1989, Kalivas and Duffy 1995, Thierry *et al* 1976, for review see Joseph *et al* 2003). Given that the offset of an aversion can be considered rewarding, it has been argued that activation of dopamine in response to aversion happens when the aversive stimulus ends, or is anticipated to end. However, further microdialysis studies in rodents have shown that the offset of aversion is followed by its own separate activation of dopamine neurons, and so stimulation of dopaminergic neurons by aversive stimuli is still possible (Imperato *et al* 1992, Imperato *et al.* 1992).

The next logical question is what is the contribution of dopamine release in mediating pain? In general, increased dopamine is related to analgesia and decreased dopamine related to low pain tolerance (Gear *et al* 2012, for review Becker *et al.* 2012). Some patients with pathologically low dopamine levels (such as in Parkinson's disease) have decreased pain tolerance (for review Jarcho *et al* 2012). In some reports, the prevalence of chronic pain in Parkinson's patients was as high as 83% (Beiske *et al* 2009). Other reports have found Parkinson's patients to be more likely to suffer from fibromyalgia and chronic widespread pain (Toda and Harada 2010). While the relationship of dopamine to pain is not entirely direct, in that many Parkinson's patients who present with impaired motor function do not develop a pain condition, the collective data cited above certainly argues for dopamine to be playing a role, at least in part, in the regulation of pain. Animal studies have further supported this idea, where chemical lesions of dopamine neurons in the VTA and substantia nigra are associated with an increase in pain (Saade *et al.* 1997).

Increased dopamine receptor subtype 2 (D2) availability in the human putamen, as measured through positron emission tomography (PET) scans, is associated with decreased pain threshold (Hagelberg *et al* 2003). Injection of dopamine agonists into the rat striatum decreased clinical pain, and antagonists increased pain sensitivity (Lin *et al* 1981, Magnusson and Fisher 2000). Studies in rodents have identified the D2, and not the dopamine receptor subtype 1 (D1), as being responsible for mediating this analgesia (Taylor *et al.* 2003, Magnusson and Fisher 2000, Coffeen *et al* 2008). Levo-dopa, a synthetic dopamine analogue used in the treatment of Parkinson's disease is effective at treating some conditions of neuropathic pain in humans (Ertas *et al.* 1998; Kernbaum and Hauchecone *et al.* 1981). While these studies are intriguing, they have yet to determine whether dopamine is analgesic due to the effect on affect and motivation, or whether it is analgesic in its own right. Further behavioral studies are necessary to properly describe this contribution.

While the striatum represents the major dopaminergic target in the brain, other extrastriatal dopaminergic regions do exist, and seem to be important in mediating aversive stimuli. Dopamine in the rodent parafascicular nucleus excited pain responsive neurons and was directly involved in mediating some of the aversive qualities of pain (Cheng *et al.* 2009; Dafny *et al* 1990; Guo *et al* 2008). Also, dopaminergic input from the VTA has been shown to inhibit ACC activity, leading to a reduction in pain related behavior (Lopez-Avila et al. 2004). Microinjection of a dopamine agonist into the ACC decreased pain behavior. From these studies it is clear that while dopamine release in the striatum is related to analgesia, this is not necessarily the case in other brain regions. Caution needs to be taken when interpreting the contribution of neuromodulators to pain conditions, and analgesic or pronociceptive properties of neuromodulators will depend largely on where they are released.

Norepinephrine and serotonin

Norepinephrine (NE) and serotonin (5HT) are equally important contributors to the motivational and affective systems in the brain; however, significantly less is known about their contribution to pain affect than their dopaminergic counterpart. A discussion on the NE and 5HT systems in chronic pain would be incomplete without mentioning their well documented involvement in descending noxious inhibitory control pathways from the rostral ventral medulla and periaqueductal grey (PAG) to the spinal cord. However, for the essence of space, these mechanisms will not be reviewed here, but the reader is pointed to other excellent reviews on the matter (Ossipov *et al.* 2010). This review will focus specifically on the contribution of ascending NE and 5HT projections in mediating pain affect and analgesia in acute and chronic pain states.

Noradrenergic and serotonergic pathways are well implicated in reward and motivated behavior, and some emerging evidence has supported their involvement in modulating affective aspects of pain. NE cells bodies in the locus coerulus (LC) project to affective brain regions such as the forebrain and amygdala (Page and Lucki 2002 Saito et al 2002, Tsuruoka *et al* 2003). Stress increases NE release in the rat amygdala, and clonidine, an adrenergic agonist that decreases endogenous NE release, injected directly into the central amygdala was analgesic (Ortiz et al 2007). In addition, excitatory parabrachial neurons projecting to the central amygdala were inhibited by NE acting through alpha2 adrenergic receptors (Delaney *et a*l 2007). NE injections into the hippocampus potentiated the response to pain and increased the aversive properties of an electric shock (Plaznik *et al* 1983)

In chronic pain conditions, the story is less clear. Unlike dopamine, humans with a NE deficiency are not known to have altered pain thresholds or be more prone to suffer from chronic pain conditions (for review Vincent and Robertson 2002). A rodent model of neuropathic pain was not found to cause changes in NE release in either the thalamus or hypothalamus following a noxious stimulus (Goettl *et al* 2002). However, in a diabetic neuropathy animal model, NE was decreased in the hypothalamus and increased in the corpus striatum (Chu *et al.* 1986). Further, formalin injection in the rat hindpaw stimulated NE release in the ventral bed nucleus of the stria terminalis (vBNST), and reduction of this release dose dependently attenuated formalin induced CPA without reducing spinal nociceptive behaviors (Deyama *et al* 2011, Deyama *et al* 2009) (See Figure 2 for a discussion on the formalin nociceptive assay). This was shown to be mediated through the beta 2 adrenergic receptor (Deyama *et al* 2008).

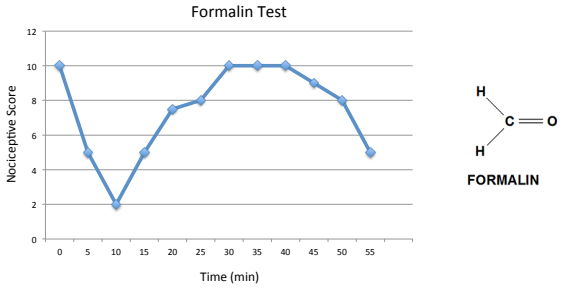

Figure 2: Formalin test of inflammatory pain
The formalin test is a popular test of acute and persistent nociception by which dilute formalin (~5%) is injected under the skin of the rodents' hind paw. This provokes an immediate withdrawal of the paw followed by several stereotypical behaviors such as flinching, licking, and biting of the affected paw. Two phases of the behavioral response to formalin have been described. The early phase occurs directly after injection and is associated with direct activation of nociceptors in the skin. The late phase occurs 15-20 minutes after injection and persists for up to an hour, and is thought to reflect secondary inflammatory responses in the spinal cord.

This test is often used to distinguish acute and persistent elements of the pain response, and drugs that are effective in the second phase of the formalin test are often effective analgesics in chronic pain. However, the formalin test should not be considered a true chronic inflammatory model since a full immunogenic response and accompanying neuroplastic changes have not yet come into effect, and care must be taken when interpreting results from this test of nociception.

The story of 5HT in acute and chronic pain processing is equally convoluted. Tracing studies have identified nucleus raphe serotonergic projections to the amygdala (Ma *et al* 1991). Also, the PAG sends serotenergic projections to forebrain regions such as the orbital frontal cortex, nucleus accumbens, and amygdala (Li *et al* 1993). In general, release of serotonin is considered to be antinociceptive in the healthy brain. Lowered serotonin metabolites in the rat hippocampus and amygdala were associated with higher nociceptive responses (Burke *et al* 2010). 5HT injection into the amygdala attenuated reactivity to pain, and the antinociceptive effect of 5HT in the nucleus accumbens could be blocked by naloxone (Plaznik *et al* 1985; Xuan *et al* 1986). In healthy humans, there was a negative correlation between tonic pain ratings and 5HT binding in the hypothalamus and right anterior insula (Kupers *et al* 2011).

Chronic pain conditions generally have reductions in 5HT release throughout the brain. Diabetic rats had lowered 5HT levels in the hypothalamus and brain stem, but no changes in the corpus striatum (Chu *et al* 1986). Neuropathic rats had decreased 5HT release in the ventrobasal thalamus compared to controls. (Goettl *et al* 2002). 5HT reuptake inhibitors reduced pain scores in central poststroke pain patients (Shimodozono *et al* 2002). However, as with NE and dopamine, important differences between brain regions and 5HT signaling exist, as blocking 5HT signaling in the CA1 area and dentate gyrus decreased nociceptive behavior in both phases of the formalin test (Soleimannejad *et al* 2006). A new study has further elucidated the changes that occur in the serotonergic system in a chronic pain state. Indoleamine 2,3 dioxygenase (IDO1), the rate-limiting enzyme that converts tryptophan to serotonin, was found to be upregulated in the hippocampus of chronic pain animals. This was associated with a decreased serotonin/tryptophan ratio, and IDO1 knock out or antagonism attenuated nociceptive and depressive behaviors (Kim *et al* 2012). Finally, part of the changes in the serotonergic system following chronic pain conditions likely incorporate stress responses, as prolonged stress is also known to lead to a depletion of central 5HT expression (for review Stahl and Briley 2004).

Corticotropin releasing factor

Further emphasizing the link between stress and chronic pain is the contribution of corticotropin releasing factor (CRF) to acute and chronic pain signaling. CRF is produced by the hypothalamus and is intimately involved in the stress response. Its main role is to stimulate production of adrenocorticotropic hormone (ACTH) from the pituitary, and while this is not a classical neuromodulator in the motivational system, there is strong evidence to show it plays an important role in mediating the affective properties of acute and chronic pain.

Noxious stimulation of the rat viscera via colorectal distension increased CRF in the central amygdala and increased *c-fos* expression in CRF neurons (Kim *et al* 2010, Wang *et al* 2009). CRF mRNA expression also increased in the central amygdala of inflammatory pain states (Nishii *et al* 2007). The release of CRF seems to be an endogenous analgesic response, as injection of CRF into the central amygdala of naïve animals produced antinociception (Cui *et al* 2004).

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in chronic pain states has been proposed (Chlauw and Chrousos 1997). This dysregulation has profound effects on the function of CRF signaling in mediating pain. Whereas in acute pain CRF release is associated with analgesia, it switches to a pronociceptive role in chronic pain states. Administration of a CRF antagonist into the central amygdala decreased nociceptive responses and anxiety like behaviors in an animal model of arthritis (Ji *et al.* 2007). This was shown to be mediated through the CRF1 receptor (Bourbia *et al.* 2010, Ji *et al* 2007, Ji and Neugebauer 2007, Fu and Neugebauer 2008). In fact, it was found that

inflammation must be present if CRF release from the hypothalamus is to be analgesic (Lariviere and Melzack 2000). Further, while a CRF1 antagonist inhibited evoked responses in central amygdala neurons in an animal model of arthritis, it was without effect before the pain onset, further emphasizing the significant changes occurring in CRF signaling in chronic pain states (Ji and Neugebauer 2007). CRF was also elevated in the BNST in an animal model of chronic pain, but this was not mediated through the HPA axis or the Edinger-Westphal nucleus. This is in contrast to the contribution of CRF in acute pain settings, and suggests CRF contribution to chronic pain becomes dissociated from the normal HPA axis function (Rouwette *et al* 2012).

Opioids and pain

Opioid receptors are distributed throughout the neuroaxis, including the spinal cord, that directly inhibit activation of nociceptive pathways leading to analgesia. However, opioid receptors are also located in the mesolimbic dopaminergic system, and in particular on gamma-aminobutyric acid (GABA)-ergic inhibitory interneurons within the VTA that lead to the activation of dopaminergic neurons in this brain region. Therefore, opioid analgesia in chronic pain conditions is complicated by the fact that opioids have inherent rewarding properties as well as their analgesic properties. There is emerging evidence that suggests simple relief of pain is rewarding. In animal models of chronic pain, local relief of pain through a peripheral nerve block produces a CPP, and this CPP can be blocked by local deactivation of the VTA via microinjection of lidocaine (Navratilova *et al.* 2012). Further, fruit flies can be trained to approach an aversive stimulus if it is paired with pain relief (Tanimoto *et al.* 2004). Therefore, opioids taken in a pain state not only reduce the negative affect of pain due to their direct analgesic properties, but also induce their own positive affect based on their intrinsic rewarding effect. In acute pain states, this property leads to a profoundly effective analgesic with high abuse potential. In patients with chronic pain who require large doses of opioids over long periods of time, the potential for abuse is a significant concern. Chronic pain patients may also be considered even more at risk for abuse, since opioids will be reinforcing for their analgesic effects as well as their inherent rewarding properties. However, emerging evidence suggests this is not the case. Rates of opioid abuse among the chronic pain patient population do not seem to be any higher, and may in fact be lower, than the general population (Watson 2012). Further, animal studies have shown the rewarding properties of opioids are compromised in chronic pain models. For example, CPP to opioids is smaller than in naïve states (Narita *et al.* 2004). Animals in chronic pain also self administer less opioids than sham controls, and only doses high enough to significantly reduce hyperalgesia were still self-administered (Martin *et al.* 2007). This suggests the intrinsic rewarding properties of opioids are blunted in the chronic pain brain. In further support of this idea, administration of a non-rewarding analgesic drug (intrathecal clonidine) decreased heroin self-administration in chronic pain animals, but not sham controls, suggesting some, if not all of, the opioid self-administration in chronic pain animals is related to pain relief (Martin *et al* 2007). Finally, dopamine release in the nucleus accumbens in response to an analgesic dose of morphine was significantly lowered in chronic pain animals (Ozaki *et al* 2002). This blunted release of dopamine in chronic pain animals was reversed in transgenic beta-endorphin knocked out mice (Niikura *et al* 2008). This implied prolonged release of endogenous opioids might interfere with the intrinsic rewarding and analgesic properties of exogenous opiates. It also draws an intriguing parallel between opioid dependent and chronic pain states, and suggests chronic pain may mimic an opioid dependent state via release of endogenous opioids.

Conclusions and outstanding questions

Chronic pain leads to profound changes through the limbic system that alters the response to rewarding and aversive stimuli. Drugs with mixed reinforcing and analgesic properties, such as opioids, also produce reinforcing effects in chronic pain animals, although this reward seems to be lower than in healthy controls. This suggests changes in the normal reward pathway that may interfere with the intrinsic reinforcing properties of opioids in a chronic pain state. Further complicating this matter is that relief of pain is a sufficient motivating stimulus that can reinforce behavior, as demonstrated by several studies showing CPP to non-rewarding analgesic drugs in chronic pain animals. How relief of pain interacts with the inherent rewarding properties of opioids in a chronic pain state is an ongoing area of research. One question that remains to be answered is what proportion of opioid reinforcement is due to its analgesia, rather than its intrinsic positive affective attributes. Also, from the literature reviewed above, it is clear chronic pain states lead to significant changes in the limbic system. Could this altered limbic system processing be at the root of the reduced analgesic efficacy of opioids? And is the relief of pain sufficient to restore the changes in limbic system processing or are they permanent adaptations?

Ultimately, the goal is to improve the treatment for chronic pain, which currently goes poorly managed in most patients. Better understanding how limbic system changes contribute to the analgesic efficacy opioids may identify novel therapeutic targets that would improve the analgesic efficacy of the already available and ubiquitous opioid therapy.

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