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Topical Review

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Mesolimbic dopamine signaling in acute and chronic pain: implications for motivation, analgesia, and addiction

Anna M.W. Taylor[a,*], Susanne Becker[b], Petra Schweinhardt[c], Catherine Cahill[d]

1. Introduction

The mesolimbic dopamine system comprises neurons in the ventral tegmental area (VTA) and substantia nigra (SN), projecting to the ventral striatum. This system was originally described to mediate pleasure and goal-directed movement associated with rewarding stimuli.[70] However, it is now clear that dopamine, although crucial for reward processing, drives not the hedonic experience of reward ("liking") but rather the instrumental behavior of reward-driven actions ("wanting").[6] Phasic dopamine acts as an incentive salience signal underlying reinforcement learning.[57,59] Moreover, aversive stimuli, such as pain, also stimulate dopamine, further diminishing the idea of dopamine as a "reward" signal.[9,10] Recent studies suggest that dopamine neurons in the VTA and SN form a heterogeneous population tuned to either (or both) aversive or rewarding stimuli.[3,8,30,39] This review will summarize our current understanding of the role of the mesolimbic dopamine system in acute pain and the changes that occur in chronic pain.

2. Dopamine signaling, reward, and punishment

Although nociceptive events and their conditioned predictive cues depress activity in most dopaminergic neurons,[68] 5% to 15% of VTA dopaminergic neurons fire preferentially for aversive stimuli,[8,13,30,39,41] or for both aversive and rewarding stimuli.[30] These neurons are probably responsible for the dopamine release after aversive stimuli, such as psychosocial stress[3,53] or pain.[61,73]

The heterogeneity of dopamine neurons in response to aversive and rewarding stimuli suggests that they serve unique functional roles. Cells activated by reward and inhibited by punishment are well suited to code motivational valence, whereas neurons activated by both rewarding and punishing stimuli are likely to code motivational salience.[9] Neurons coding motivational valence would provide a signal for reward seeking, evaluation, and value learning, in line with current theories on the role of dopamine in reward processing.[7,58] In contrast, neurons coding motivational salience would provide a signal for detection and prediction of highly important events independent of valence, pursuant to dopamine's role in salience processing.[54] These distinct aspects of dopamine neurotransmission might be neuroanatomically separate: dopaminergic neurons coding motivational valence have been found more commonly in the ventromedial SN and lateral VTA with projections to nucleus accumbens shell, whereas neurons coding motivational salience are more often reported in the dorsolateral SN with projections to the nucleus accumbens core (**Fig. 1**).[10,39,41,49]

3. Dopamine signaling in pain: antinociception or motivational salience?

A common suggestion, based on animal studies focusing on pain behavior, some clinical data, and genetic associations, is that dopamine is antinociceptive by D2 receptors.[24,27,33,52,71] Some experimental works in humans supports this notion by showing increased affective pain ratings after dietary dopamine depletion[65] and increased conditioned pain modulation with D2-receptor activation.[67] However, more often, no effects of dopaminergic manipulations on a variety of pain tests have been reported.[5,65–67] It seems that ascribing an antinociceptive role to dopamine is too simplistic. Examining under which conditions antinociception is mostly observed suggests that the common feature is a motivational–emotional component of the pain tests. In rodent studies, tonic pain assays such as the formalin or writhing test reveal more often decreases in pain behavior with D2-receptor activation than brief phasic pain stimuli, such as tail flick, hot plate, or paw pressure.[2] In a study in rats with ongoing postsurgical pain, blocking dopamine release prevented conditioned place preference (CPP) associated with peripheral analgesia, clearly indicating the importance of dopamine for motivated behavior.[46] Similarly, in humans, dopaminergic manipulations have only been found to affect the affective component of pain[65] or strong behaviorally relevant stimuli such as immersion of the hand in ice water.[66] Interestingly, even with this stimulus, cold pain tolerance initially decreased with D2-receptor activation and increased only after 2 hours.[66] Moreover, striatal dopamine release positively correlates with the magnitude of perceived pain,[61,73] which strongly contradicts direct antinociceptive effects of dopamine release. Finally, we reported that increasing synaptic dopamine levels by a pharmacological intervention augmented endogenous pain inhibition induced by reward, and enhanced endogenous pain facilitation by punishment,[5] again opposing a simplistic view of dopamine as an antinociceptive agent.

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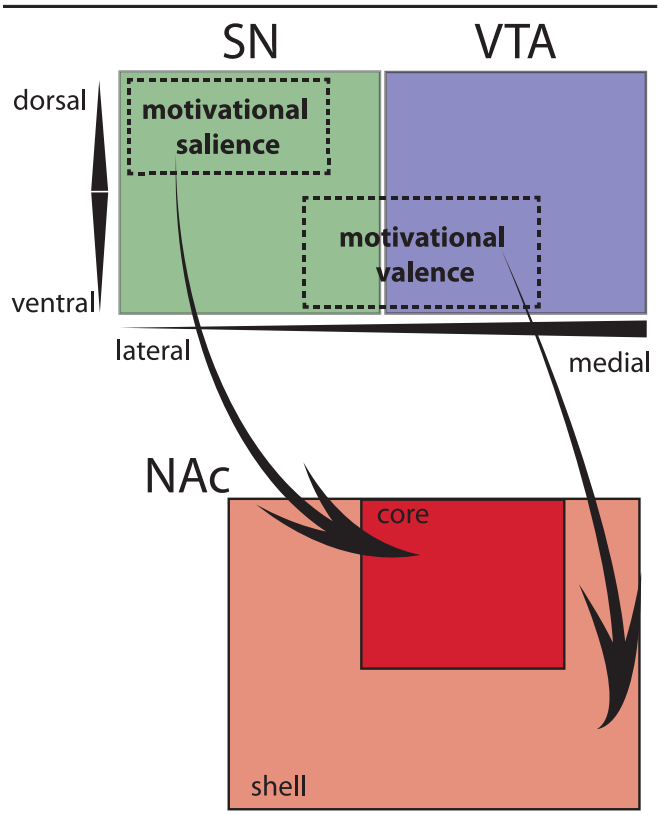

Figure 1. The role of mesolimbic dopamine neuron subpopulations in motivated behavior. Dopamine neurons in the dorsolateral substantia nigra (SN) project to the nucleus accumbens (NAc) core and encode motivational salience (stimulus awareness). Dopamine neurons in the ventromedial SN and lateral ventral tegmental area (VTA) project to the NAc shell and encode motivational valence (whether the stimulus is positive or negative in value).

When these results are considered as a whole, we posit that dopamine modulates the salience of pain stimuli and thereby mediates the motivation to avoid or endure pain depending on the situational context. The observation that mesolimbic dopamine neurons activated by aversive stimuli also respond to appetitive stimuli supports the idea that dopamine codes the motivational salience of pain and may act as a "decision aid" whether pain should be endured to obtain a reward. Thereby, they would subserve an important function of Fields' Motivation-Decision Model of Pain.[17] This framework means that dopamine would play a crucial role in pain avoidance and coping responses, 2 processes that are of high clinical importance.

4. Dopamine dysfunction in chronic pain

There is now ample evidence from both the animal and human literature to suggest that chronic pain results in a hypodopaminergic tone that impairs motivated behavior. Human imaging studies have found lowered responsiveness within the mesolimbic dopamine system in response to salient stimuli in patients with chronic pain.[34,36] For example, patients with chronic pain have lower D2-receptor binding[22,23,36,73] and presynaptic dopamine activity[26,72] in the striatum at rest and after an acute pain stimulus. In animal studies, chronic pain results in decreased c-Fos activation in the VTA[42] and decreased overall dopamine levels and striatal D2 receptors.[12,56,64,74]

Dopamine signaling is important for motivating approach or avoidance behavior following presentation of a salient stimulus, rather than the hedonic value. In this way, chronic pain results in behavior indicative of a hypodopaminergic state. When food rewards are easily available (ie, under a fixed ratio operant responding task), there is no difference in reward consumption between chronic pain and control groups.[37,69] However, as the energy required to solicit a food reward increases (eg, under a progressive ratio schedule), animals with chronic pain consume significantly less food than controls.[25,60] Thus, we conclude that although the hedonic value of food is unaffected in animals with chronic pain, the drive to obtain these rewards is reduced. Moreover, persistent and chronic pain decreases intracranial self-stimulation of the medial forebrain bundle,[31,32,51] an effect that can be recovered by pharmacological intervention that increases dopamine levels.[40,55] Taken together, these results indicate that chronic pain leads to a significant impairment of mesolimbic dopamine activity that interferes with motivated behavior.

5. Opioid reward and chronic pain

The mesolimbic dopamine system drives approach or avoidance behavior following a salient cue, such as acute pain. In conditions of chronic pain, deficits in dopamine signaling emerge that impair motivated behavior. Reinforcing drugs, such as opioids, also stimulate the dopamine system, a function that underscores their highly salient and rewarding attributes. Long-term exposure to opioids disrupts dopamine signaling,[21,62,76] a phenomenon that contributes to the downward shift in the allostatic state associated with addiction.[29] Coincident with the exponential rise of opioids for the treatment of chronic pain has been the growing concern of the risk of iatrogenic addiction in this population.[1] Given the association of dopamine signaling with addiction behaviors, it is possible that the chronic pain–induced disruptions in dopamine signaling may alter the addiction liability of opioids used for pain management. Recent research has begun to address these issues by assessing how opioids interact with the dopamine system in chronic pain models.

On a mechanistic level, opioids are less effective at stimulating mesolimbic dopamine neurons in chronic pain. For example, morphine-stimulated GTPγS (a measure of μ-opioid receptor activation) is significantly reduced in the VTA,[44] and systemic opioids fail to stimulate extracellular dopamine in the striatum in animals with chronic pain.[25,50,63]

The deficits in opioid-stimulated dopamine in chronic pain suggest alterations in salience and motivated behavior. However, assessing opioid reward in chronic pain has an added level of complexity, because systemic opioids will engage dopamine signaling and stimulate motivated approach behavior through 2 distinct mechanisms: direct activation of the mesolimbic dopamine neurons and indirectly through analgesic effects mediated by the inhibition of pain pathways throughout the peripheral and central nervous system. Direct inhibition of pain pathways is rewarding in the context of pain, as evidenced by the fact that peripherally or spinally restricted analgesics, such as lidocaine and intrathecal clonidine, stimulate dopamine release, are self-administered, and produce a place preference in animals with pain.[28,37,38,46,75] The rewarding effects of opioid analgesia also involve supraspinal circuits outside the VTA. For example, localized injection of opioids into the anterior cingulate cortex is sufficient to stimulate striatal dopamine and produce a place preference.[45] Therefore, the salience of opioids is context-dependent and may engage different circuits depending on the preexisting behavioral state of the subject.[17,19] The challenge in the chronic pain literature is to tease out these factors when assessing opioid reward in the whole animal.

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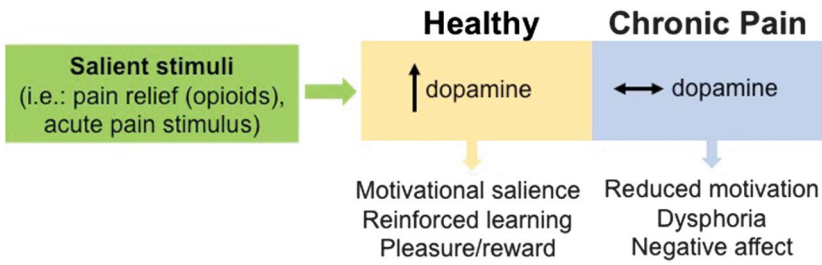

Figure 2. The mesolimbic dopamine system is formed of a heterogeneous population of neurons that respond to both appetitive and aversive stimuli and mediate motivated behavior. Release of dopamine after an acute painful stimulus acts as a salience cue, mediating the motivation to avoid or endure pain depending on the situational context. Conversely, relief of pain is normally interpreted as a positive salient stimulus and stimulates the release of dopamine in healthy individuals. Chronic pain, however, results in a hypodopaminergic state that impairs motivated behavior. Decreased reward responsivity may underlie a key system mediating the anhedonia and depression common with chronic pain.

When opioid reward is assessed using self-administration, motivated behavior is reduced only at doses that fail to effectively mitigate pain.[25,35,37,69] In fact, the presence of analgesia is required for opioid reward behavior in chronic pain, given that spinally blocking pain interferes with opioid self-administration and CPP.[35,37,38] Equivocal findings have been reported when opioid reward is assessed with the CPP assay,[11,43–45,48,50,63,77] perhaps because systemic drug administration is engaging circuits outside the midbrain dopamine system. However, when opioids are administered directly into the VTA, they do not produce a place preference,[47,63] and the potentiating effect of opioids on VTA intracranial self-stimulation is diminished in animals with chronic pain.[16] Taken together, we conclude that although the mesolimbic dopamine system is less responsive in chronic pain, systemic opioids remain reinforcing through their analgesic effects. Importantly, analgesia seems to be required for systemic opioids to be reinforcing in chronic pain.

6. Conclusions

Our understanding of the mesolimbic dopamine system has evolved significantly over the past decade, and now the integration of this system in the context of acute and chronic pain needs refinement. We no longer equate dopamine release with pleasure or reward but rather acknowledge that dopamine neurons are a heterogeneous population of neurons that respond to both appetitive and aversive stimuli to mediate motivated behavior. Release of dopamine after an acute painful stimulus acts as a salience cue and is critical for approach or avoidance behavior.

There are now multiple lines of evidence that show chronic pain leads to a hypodopaminergic state that impairs motivated behavior (**Fig. 2**). Decreased reward responsivity may underlie a key system mediating the anhedonia and depression common with chronic pain.[15,20,27] Strategies to restore dopamine signaling may represent a novel approach to manage these affective sequelae of chronic pain.

The story becomes more nuanced when assessing motivated behavior toward opioids in chronic pain. Research shows that the ability of opioids to stimulate the mesolimbic dopamine system is impaired, and this seems to translate into reduced responsiveness to appetitive stimuli. However, opioids maintain their reinforcement in subjects with chronic pain through their analgesic properties, emphasizing the notion that motivated behavior and reward are context-dependent.

A final question asks whether these changes affect opioid addiction liability. Unfortunately, it remains difficult to draw such conclusions from the animal literature, and clinical reports of rates of opioid addiction among the chronic pain population remain divisive[4,14] (for review, see Reference 18). One issue is that chronic pain states are not static, and as the pain condition progresses or resolves so might the function of the dopamine system. This idea is supported by an animal study that found self-administration of low doses of opioids returned to normal as the chronic pain state resolved.[35] This study highlights the fact that the motivational drive for opioids is constantly adapting with the internal states of the subject. Discussing addiction liability in a population with possibly fluctuating pain states is a difficult task requiring a nuanced appreciation of the motivational state in chronic pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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