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Selected Landmark Studies in the Role of the Mesolimbic System

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ABSTRACT

The mesolimbic system has been demonstrated to have a major role in the perception of pain, but the mechanisms by which this occurs are poorly understood. In this paper, we review selected landmark studies that have contributed to our present understanding of the role of the mesolimbic system. The included studies outline the molecular mechanisms of the mesolimbic system's role in analgesia, pain relief, and feelings of decreased motivation and depression as a result of chronic pain. Because chronic pain is among the most highly-cited reasons for decreased quality of life, advancing our understanding of the function and mechanism of the mesolimbic system may be critical to improving the quality of life for millions of people around the globe.

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Introduction

The mesolimbic pathway is a dopaminergic pathway that includes a projection from the ventral tegmental area to the ventral striatum, which consists of the nucleus accumbens and olfactory tubercle [1]. The mesolimbic reward circuitry is involved in pain sensation and perception. Furthermore, mesolimbic system dysfunction has been linked to a variety of disorders including mood-related disorders, Parkinson's disease, and substance abuse [2]. Given that pain is a subjective experience, investigating the role of this pathway can provide insight into the pain experience and potentially improve pain treatment. In this review, we discuss a few notable discoveries along with an in-depth analysis of the logic behind some landmark studies in understanding the mesolimbic pathway in the context of pain.

In Chronic Neuropathic Pain, BDNF Mediates Nociception

The specific role of the mesolimbic system in pain is still not clear. Some studies demonstrate increased nucleus accumbens activation after noxious stimuli and that blocking nucleus accumbens activation leads to reduced hyperalgesia [3-6]. However, the mesolimbic system has also been implicated in analgesia, with pain relief leading to DA release in nucleus accumbens [7]. Given the variety of roles the mesolimbic system plays, studies are needed into specific mechanisms to elucidate neural processes. Writing in Biological Psychiatry, Zhang et al. research VTA-nucleus accumbens circuitry in a neuropathic pain model [8].

The VTA contains a variety of neuron types, including DA-releasing, glutamate-releasing, and GABA-releasing neurons, with DA-releasing neurons being the most abundant [9]. Previous research has found VTA-nucleus accumbens dopaminergic neuron activation leads to elevated nucleus accumbens BDNF levels in socially stressed mice [10]. This increased BDNF signaling is tied to stress susceptibility, with the opposite results when BDNF levels are decreased [11,12].

Zhang et al. modeled chronic neuropathic pain with chronic constrictive injury [CCI] [8]. As expected, these mice exhibited decreased paw withdrawal latency [PWL] only in the ipsilateral hind paw. Measuring VTA neuronal activation through c-Fos expression, an increase was found only in the contralateral side. It is worth noting that although c-Fos was expressed in VTA, very few were found in substantia nigra, which also contains many DA neurons. Immunofluorescence [tyrosine hydroxylase] confirmed

c-Fos expression in dopaminergic neurons. Thus, VTA DA neurons had increased c-Fos expression after CCI.

To understand firing rates, Zhang et al. recorded VTA slices in vitro. Results indicated that CCI led to increased firing rate in VTA DA neurons only on the contralateral side [8]. Furthermore, paw withdrawal threshold and VTA DA firing rate were negatively correlated, with firing rate being either tonic firing [single spike] or bursting firing [high frequency]. In vivo, single-unit recordings confirmed the increased contralateral firing rate. Specifically, the proportion of spikes that were bursts increased contralaterally. Similar to in vitro, in vivo results found a correlation between firing rate and pain latency. These tests, therefore, demonstrate that CCI leads to increased VTA DA firing contralaterally, driven by increased bursting firing.

Zhang et al. [8] then proceeded to pharmacologically inhibit VTA DA neurons. This led to analgesia, but not when drugs were infused to substantia nigra rather than VTA. This finding suggests that VTA DA neurons are related to CCI pain sensation, as inhibition led to a reversal of thermal hyperalgesia.

To specifically understand this relation, researchers then injected a retrograde tracer into nucleus accumbens prior to CCI. This revealed increased c-Fos expressing neurons [both number and proportion] in VTA-nucleus accumbens neurons after CCI. Furthermore, the proportion of c-Fos+ VTA neurons projecting to nucleus accumbens increased and c-Fos expression in nucleus accumbens contralateral to CCI increased. This rise could be partially reversed through pharmacologically inhibiting VTA DA neurons. Put together, these findings indicate that CCI leads to VTA-nucleus accumbens DA neuron activation contralaterally.

To study causality, Zhang et al. used an optogenetic strategy wherein halo rhodopsin would be expressed only in VTA-nucleus accumbens neurons. Whole-cell current-clamp recordings were used to confirm that optical stimulation inhibited VTA-nucleus accumbens firing [8]. This inhibition led to a reversal of thermal hyperalgesia. Therefore, contralateral VTA-nucleus accumbens firing is shown to be necessary for CCI-induced hyperalgesia.

Because previous research indicates BDNF plays a key role in mesolimbic reward system modulation, Zhang et al. analyzed BDNF expression in the context of VTA-nucleus accumbens projections [8, 11,13-16]. Bdnf mRNA was upregulated for VTA-nucleus accumbens projections in CCI mice, shown through in situ hybridization. Tissue dissection revealed that although BDNF protein was expressed in both regions increased Bdnf mRNA was in VTA, not nucleus accumbens. BDNF protein increase in nucleus accumbens was prevented when pharmacologically inhibited. Blocking BDNF/tyrosine receptor kinase B signaling also led to analgesia. In context with other findings in this paper, these findings show in CCI mice, BDNF mesolimbic signaling can modulate nociception.

Normally, VTA is the key source for BDNF in nucleus accumbens, as baseline Bdnf transcription there is very low [11,13]. Thus, Zhang et al. tested whether BDNF release increases from VTA DA neurons is the key behind nucleus accumbens modifying the pain experience [8]. Using a protein synthesis inhibitor, researchers inhibited BDNF synthesis in VTA. This reduced CCI-induced hyperalgesia, though this could be reversed by injecting BDNF into nucleus accumbens. Using Cre recombinase technology to selectively knock-down BDNF expression in VTA-nucleus accumbens projections, researchers discovered CCI-induced hyperalgesia reversal. Therefore, VTA-nucleus accumbens circuitry leads to increased BDNF in nucleus accumbens and can impact CCI-induced chronic neuropathic pain.

Research shows a variety of conflicting findings regarding the role of the mesolimbic system in pain. For example, one study shows that a tail pinch causes the release of DA in nucleus accumbens whereas another study states blocking peripheral nerves peripheral nerve block in rats with incisional pain leads to DA release in nucleus accumbens [17]. Given that BDNF signaling in mesolimbic reward is linked to a variety of disorders, such work has high clinical relevance [2, 7, 9,11,13-15, 17 18,19]. Future work can build on this as we search for better ways to treat pain.

Decreased Motivation in Chronic Pain is Due to Nucleus Accumbens LTD

Individuals with chronic pain experience a decrease in quality of life and often exhibit depression and/or fatigue [20–23]. These symptoms represent a decline in motivation and can be viewed as maladaptive. A key region in the brain regulating motivation [that also plays a role in developing chronic pain] is the nucleus accumbens core [NAc] [4,24-26]. Writing in Science, Schwartz et al. investigate the molecular mechanism behind the reduced motivation accompanying chronic pain [27].

First, to confirm the role of chronic pain towards motivation, researchers induced chronic inflammatory pain through complete Freund's adjuvant [CFA] injection in hind paw. Sciatic nerve injury [SNI] was also used to induce neuropathic pain. Motivation was assessed by when the animal gave up when facing a test in which difficulty progressively increased. Results found that prior to chronic pain, animals had similar performances [measured with the number of nose pokes and the number of rewards]. However, after chronic pain induction, the next one to three weeks found the number of nose pokes declining by around forty percent. Because the animals still searched for a reward at the same frequency, physical ability and reward value were likely not altered. After three weeks, the reward given through nose pokes was switched to one reward per nose poke rather than the progressively difficult task. This returned groups to comparable levels and received a maximal level of reward. This suggests that motivation is the key difference, rather than some other factor. To confirm these findings, Schwartz et al. administered analgesics to animals after CFA and after SNI, based on the group. Yet, the disparity in progressively difficult task performance persisted. Put together, these results provide proof that chronic pain reduces motivation, at least in SNI and CFA models [27].

Using bacterial artificial chromosome [BAC] transgenic animals, researchers then prepared brain slices and performed whole-cell recordings on medium spiny neurons [MSNs] part of either the direct or indirect pathway [D1 receptors versus D2 receptors]. Schwartz et al. proceeded to measure AMPA receptor-mediated EPSCs and NMDA receptor-mediated EPSCs, and calculated the ratio between the two [27]. The AMPAR/NMDAR ratio was lower [measured 7-12 days after] in both CFA and SNI groups, but only in D2-MSNs. This drop was attributed to reduced AMPARs, but because D2-MSN mEPSC amplitudes decreased less than the AMPAR/NMDAR ratio decreased, pharmacologically isolated NMDARs were also recorded. Results indicated that only D2-MSNs had an increased time constant of delays. Previous studies suggest this increased time constant usually occurs as a result of the GluN2B subunit being present in an increased percentage of NMDARs [28]. Based on these findings, Schwartz et al. [27] used GluN2B antagonist ifenprodil and confirmed that the antagonist

led to larger D2-MSN depressions in SNI and CFA rodents relative to controls. Previous work has also found that during drug withdrawal, MSN-NMDARs undergo changes, followed by AMPAR-mediated transmission [29]. To study whether a similar phenomenon occurs in pain response, Schwartz et al. studied synaptic function after CFA injection and observed prolonged decay in NMDAR D2-MSN EPSCs. Through these experiments, Schwartz et al. conclude that chronic pain leads to synaptic changes in the nucleus accumbens [27].

Previous research regarding the neuropeptide galanin found it plays a role in chronic pain comorbidities, reward response activity in nucleus accumbens, and long-term stress [30-33]. Specific to rodents, performance on tasks with progressively increasing difficulty is worsened after galanin infusion and projections to nucleus accumbens demonstrate up-regulated galanin in pain models [34-37]. Building on this previous work, researchers injected a rabies virus into nucleus accumbens and observed galanin-positive neurons. Galanin led to transient presynaptic excitatory transmission decrease in both D1-MSNs and D2-MSNs, in line with previous literature [38]. This remained true even when postsynaptic GPCR signaling was inhibited [38]. Regarding decay kinetics, only D2-MSN NMDA EPSCs had prolonged constants, blocked with postsynaptic GPCR signaling inhibition and exhibiting increased depression with ifenprodil. To study the necessity of galanin signaling in the context of D2-MSNs, Schwartz et al. infused a galanin receptor antagonist into the nucleus accumbens of one group of mice both before and after CFA injection [27]. In the other group, short hairpin RNA [shRNA] for GalR1 was used [as GalR1 specifically plays a role in motivation] to prevent expression [39]. In both groups, modified decay kinetics were no longer found and GalR1 knockdowns did not exhibit the increased ifenprodil sensitivity. Based on these tests, the general pathway seems to be galanin activating GalR1, which increases GluN2B levels in D2-MSNs. This eventually leads to reduced AMPAR-mediated transmission. Schwartz et al. demonstrate that galanin is necessary for the nucleus accumbens synaptic changes that occur in response to pain [27].

To tie these changes together with motivation, animals were injected in nucleus accumbens with eGFP, GalR1 shRNA, or GalR1 shRNA with GalR1-eGFP replacement construct. These animals underwent a variety of behavioral tests. Results found through testing with progressively more difficult tasks that GalR1 knockdown mice reduced the motivation decrease from the chronic pain models, whereas the replacement construct mice resembled controls. To express replacement GalR1 only in the indirect pathway, researchers used a Cre-dependent construct. After SNI, these animals had reduced nose pokes relative to controls. NMDAR-dependent LTD relies on the precise placement of calcineurin near a scaffolding protein. Knocking down the scaffolding protein and replacing it with a mutant, Schwartz et al. blocked LTD in nucleus accumbens [27]. The change in AMPAR to NMDAR ratio associated with CFA did not occur. Furthermore, mutant scaffold protein rodents did not show the decline in motivation in nose poking that controls did. Thus, Schwartz et al. proved through GalR1 knockdowns and mutated scaffolding protein that for the decline in motivation because of chronic pain, nucleus accumbens synaptic modification are necessary [27].

These findings provide valuable information about nucleus accumbens D2-MSNs and their role in motivation. Chronic pain is often comorbid with mood disorders and is the second largest cause of suicide among medical illnesses [2]. Given these findings, and that other work has linked galanin to depression-like behavior, these findings offer a valuable opportunity to help many individuals with chronic pain who suffer from this lack of motivation [40].

Chronic Back Pain is Linked to Altered Mesolimbic Neurotransmission

In the clinic, back pain is a common chronic pain problem. The striatum, a region of the brain that includes the nucleus accumbens, is a key region tied to chronic back pain formation [3,4,41]. This region of the brain is controlled by the midbrain, which sends dopaminergic projections, and relates to pain because of the presence of opioid receptors [42-44]. In this region, dopamine is thought to regulate pain through D2R [45-47]. Previous studies on humans with PET scans indicate that D2Rs play a role in pain sensitivity, with different studies on different illnesses showing differences in D2R expression [48-50]. Other work indicates that D2/D3R availability in striatum [measured with binding potential: BPND] exhibits positive correlation with pain sensitivity [51]. Activation is shown through reduced BPND and is correlated with higher reported pain [52].

Writing in The Journal of Neuroscience, Martikainen et al. investigate dopamine receptors in chronic neuropathic back pain and study the role of mu opioid receptors [MORs] in such neurotransmission [53].

Studying D2/D3R [D2/D3R BPND] binding potential using PET, they found declines in right ventral striatum, with the largest effect in the nucleus accumbens. Evaluating with an assessment known as Positive and Negative Affect Schedule [PANAS], D2/D3R BPND in ventral striatum was inversely related with positive affect ratings. It is worth noting that no such relation was found for negative affect ratings. Hypertonic saline infusion related to D2/D3R BPND, with negative correlations in an assay seeking to induce a certain level of pain. These findings help link D2/D3R BPND and personal affect.

When inducing pain with hypertonic saline, both healthy controls and chronic neuropathic back pain groups had increased D2/D3R neurotransmission, with key increases in left caudate, left putamen, and right nucleus accumbens. Furthermore, for healthy individuals, left caudate is correlated with pain unpleasantness [visual analog scale], but not intensity or PANAS, during pain-induced D2/D3R activation. For chronic neuropathic back pain subjects, dopamine release was smaller relative to healthy controls. These findings demonstrate regions tied to D2/D3R neurotransmission and pain perception.

Next, Martikainen et al. studied whether reduced D2/D3R BPND in ventral striatum is tied to modified MORs during pain [53]. The basis for this hypothesis comes from previous work showing increased MOR BPND in thalamus in chronic pain neuropathic models. Analyzing voxels after scanning, researchers found in amygdala that baseline MOR BPND is correlated with D2/D3R BPND in ventral striatum [54]. This D2/D3R BPND in ventral striatum negatively correlated with left amygdala MOR activation. Tying behavioral findings to scan results, researchers observed that positive affect [PANAS] was negatively related with right amygdala baseline MOR BPND. Profile of Mood States [POMS] was negatively related to baseline MOR BPND in amygdala and hypertonic saline volume required to induce pain. Left amygdala MOR activation inversely related with back pain affect [McGill Pain Questionnaire]. Putting these findings together, Martikainen et al. find key correlations in this chronic neuropathic back pain model, specifically linking MORs and D2/D3Rs [53] .

By obtaining binding potential, which indicates receptor availability, and the change of BPND from baseline to activated, which shows DA release, Martikainen et al. demonstrate key reductions in chronic neuropathic back pain subjects which were tied to more positive affect and higher pain tolerance. These D2/D3R BPND reductions correlate with opioid system activation in amygdala, further modifying pain perception. Given that chronic neuropathic back pain was proven in this work to be tied to D2/D3Rs in ventral striatum, such research provides a basis for future work in determining why only certain individuals are susceptible to such chronic back pain [53]. Furthermore, such imaging studies cannot prove causality, so future studies can potentially find a causal relation between D2/D3Rs and MORs.

Negative Reinforcement in Pain Relief is through Mesolimbic Circuitry

Previous studies with human imaging demonstrated that placebo analgesia and relief from acute noxious stimulus activate regions known to play a role in reward, specifically ventral tegmental area [VTA] and its dopaminergic projection to nucleus accumbens [3,55,56]. Disruption of this dopamine signaling leads to reduced conditioned place preference [CPP] [57,58]. Other research has indicated nucleus accumbens neurons play a role in decision-making and are involved in reward value [13,59-62]. Writing in PNAS, Navratilova et al. study whether pain relief activates the mesolimbic pathway and whether this pathway is required in the context of negative reinforcement [63].

Pain was induced through skin incisions and peripheral nerve block [PNB] was injected with lidocaine [numbs tissue] one day later. Looking at place preference, this led to a preference towards the chamber with PNB, whereas control sham-operated animals had no CPP. PNB also had no effect when it was administered to the contralateral paw. Given these findings, Navratilova et al. received confirmation of the rewarding nature of pain relief [63].

Next, to study the necessity of the mesolimbic system in the context of CPP, dopaminergic neurons in the VTA were inactivated through lidocaine injection prior to PNB. This ended up preventing PNB-induced CPP. PNB-induced CPP was also not present after the use of a GABAB agonist that inhibited dopaminergic neuron firing and dopamine release. Researchers then measured VTA dopaminergic neuron activation through immunochemistry and cFos [marker for neuronal activity] expression. Results suggested that PNB increased FOS-expressing cells in VTA relative to controls. Confocal images also indicated that this increased FOS expression was preferentially in dopaminergic neurons. Using in vivo microdialysis, researchers then measured, following PNB, dopamine efflux in the nucleus accumbens shell. They observed during the time period after PNB, only injured rats had an increase in dopamine efflux. For a positive control, Navratilova et al. administered cocaine as well and found a large increase in extracellular dopamine for both sham and pain animals. This confirms this reward is completely different from opioid pathways [63]. To confirm the necessity of dopamine, researchers then proceeded to use a dopamine antagonist to block signaling. This also blocked CPP. This provided direct proof that dopamine signaling is required for negative reinforcement, measured with CPP, from pain relief. Put together, these findings elucidate the mesolimbic system's role in pain-relief-induced negative reinforcement.

Conclusion

Although the mesolimbic dopamine system was once thought to be solely involved in reward-processing, it is now also understood to play key roles in reward-driven actions and reinforcement learning [24,64-66]. Through D2 receptors, dopamine possesses antinociceptive properties [67-71]. This is in line with a study that found increased pain after dietary dopamine removal [72]. Activating D2 receptors also leads to heightened pain modulation [73]. However, dopamine has also been found to be released in response to pain [74,75]. This is because dopamine neurons in substantia nigra [SN] and ventral tegmental area [VTA] are tuned to either rewarding stimuli, aversive stimuli, or both [76-80]. This lack of homogeneity likely contributes to the varied responses and effects of the mesolimbic system. An immense amount of progress has been made in evolving our understanding of dopamine beyond just a mechanism of pleasure. Future work must stratify by neuron type to allow for more clarity regarding functions of specific brain regions or certain compounds.

Many studies exist on the mesolimbic system and its role in pain. Yet, although this selective review only analyzes a few studies, they provides key insights into the variety of roles the mesolimbic system plays. Zhang et al. demonstrated that nociceptive input leads to hypersensitivity through the mesolimbic system [8]. Schwartz et al. suggested chronic pain leads to decreased motivation through the mesolimbic system [27]. Despite both concerning the nucleus accumbens, these represent quite different functions. Martikainen et al. link increased D2/D3R activation in chronic neuropathic back pain patients to increased pain through the mesolimbic system and Navratilova et al. use the mesolimbic system to explain the negative reinforcement associated with pain relief [53,63]. This complexity of functions extends to subcomponents of the mesolimbic system as well. For example, Schwartz et al. prove the decline in motivation during chronic pain occurs through D2-MSRs while Martikainen et al. suggest increased D2/D3R activation is related to increased pain [27, 53]. Understanding the different roles of mesolimbic substructures represents the first step in understanding system-wide outputs that may initially seem contradictory or conflicting. Within this selective review, Navratilova et al. demonstrate how the mesolimbic system allows for negative reinforcement, which reduces future pain [63]. Yet in other studies, such as Zhang et al. the mesolimbic system leads to hypersensitivity, worsening the experience of pain [8].

Given that Schwartz et al. link chronic pain to decreased motivation through D2-MSNs, it should be noted that other work has found this signaling could potentially be interrupted [2,27]. Specifically, dopamine transmission is reduced in chronic pain states [2]. Testing with opioids and cocaine, Taylor et al. found that microglial activation [enhanced in VTA during chronic pain] is responsible for the reduced dopamine transmission, which disrupts reward circuitry [2]. This occurs through BDNF signaling. It should be noted, however, that this work focused solely on DA-stimulating drugs, limiting its generalizability.

As we seek to improve pain treatment for individuals, a more complete understanding of the mesolimbic system can improve our ability to provide personalized care. After all, given the literature reviewed, it seems plausible that different types of pain correspond to different mesolimbic pathways. It also seems possible that contextual or environmental differences, such as local protein expression, can vary the pain response in patients. Future research into the nuance of mesolimbic pathways relating to pain may provide immense clinical benefit to patients suffering from chronic or acute pain.

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