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# Modulation of pain, nociception, and analgesia by the brain reward center

**Vasiliki Mitsi**[1,2] and **Venetia Zachariou**[2]

[1]Department of Basic Sciences, Faculty of Medicine, University of Crete, Heraklion, Crete, Greece, 71003

[2]Fishberg Department of Neuroscience, Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY 10029

## Abstract

The midbrain dopamine center comprises a key network for reward, salience, motivation, and mood. Evidence from various clinical and preclinical settings points to the midbrain dopamine circuit as an important modulator of pain perception and pain-induced anxiety and depression. This review summarizes recent findings that shed light to the neuroanatomical, electrophysiological and molecular adaptations that chronic pain conditions promote in the mesolimbic dopamine system. Chronic pain states induce changes in neuronal plasticity and functional connectivity in several parts of the brain reward center, including nucleus accumbens, the ventral tegmental area and the prefrontal cortex. Here, we discuss recent findings on the mechanisms involved in the perception of chronic pain, in pain-induced anxiety and depression, as well as in pain-killer addiction vulnerability. Several new studies also show that the mesolimbic dopamine circuit potently modulates responsiveness to opioids and antidepressants used for the treatment of chronic pain. We discuss recent data supporting a role of the brain reward pathway in treatment efficacy and we summarize novel findings on intracellular adaptations in the brain reward circuit under chronic pain states.

### Keywords

Antidepressants; Dopamine; Nucleus Accumbens; Pain-killers; Prefrontal Cortex; Ventral Tegmental Area

## Chronic pain: Beyond the spinal cord

Chronic pain affects millions of people around the world (Murray and Lopez 2013), and is often accompanied by dramatic changes in the quality of life that result from insomnia, immunosuppression, eating disorders, problems in cognitive function, maladaptive stress

Author for correspondence: Venetia Zachariou, PhD, Associate Professor, Fishberg Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, 10029. venetia.zachariou@mssm.edu.

responses, and major depression (Bair et al., 2003, Johannes et al., 2010, Fine 2011, Berryman et al., 2013). The treatment of chronic pain is a major challenge in therapeutics, as most of the available medications show poor efficacy, are accompanied by severe side effects with chronic use, or, in the case of opioids, may lead to the development of dependence or addiction (Jensen and Finnerup 2007, Toblin et al. 2011). In fact, the number of dependence or overdose cases from painkillers such as oxycodone has dramatically increased over the last decade (Kenan et al., 2012, Morlion et al., 2015). Research efforts have been directed towards novel medications for the treatment of pain, with the idea that non-opioid drugs can target several spinal and supraspinal sites that affect pain transmission and perception, and can be given chronically while remaining tolerable, safe, and without risk for abuse.

Much of our knowledge on chronic pain mechanisms concerns studies in the dorsal root ganglia, spinal cord, or the classical descending modulatory pathway, which involves brainstem and midbrain neurons. However, it is common among chronic pain patients to suffer comorbid emotional disorders (*e.g.*, anxiety, depression) and cognitive deficits (*e.g.*, memory impairment), suggesting critical involvement of higher-order neuronal brain processing. Indeed, alterations in the function of several brain networks in chronic pain patients have been documented and linked to emotional and cognitive deficits, or poor analgesic efficacy (Borsook 2012, Bushnell et al., 2013). Clinical studies suggest that sleep deprivation, anxiety and depression are among the factors that prevent recovery from pain or significantly reduce the efficacy of analgesic medications (Legrain et al., 2011, Baliki and Apkarian, 2015). Thus, pharmacologic interventions for the treatment of chronic pain should not only target circuits that control sensory transmission, but also those mediating salience, affect, mood, and motivation.

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Merskey and Boduk, 1994). Although this definition implies the involvement of networks controlling mood emotions and cognition, the complete mechanisms are not well understood. Nevertheless, evidence from clinical studies links chronic pain conditions to aberrant functioning of circuits involved in mood and motivation, including the dopamine brain reward center (Le Magnen et al, 1980, Mouraux et al., 2011, Oluigbo et al., 2012, Berryman et al., 2013, Baliki et al., 2015). This network includes neurons of the ventral tegmental area (VTA) and their projections to the nucleus accumbens (NAc) and several other brain regions, including the prefrontal cortex (PFC). This network plays a key role in mood, habit formation, salience, motivation, and reward (Berridge and Kringelbach, 2015).

## Chronic pain modulates the mesolimbic circuitry

Aberrant dopaminergic transmission in the mesolimbic network underlies several mood disorders (Russo and Nestler, 2013). Evidence from a number of groups also suggests that the mesolimbic dopamine system modulates the perception of nociceptive information, the efficacy of pain medications, and the affective symptoms of chronic pain (Baliki et al., 2010, Cahill et al., 2013, Terzi et al., 2014). Dennis and Melzack (1983) first demonstrated that dopaminergic agents improve symptoms of pain and promote analgesia. On the other hand, malfunction of mesolimbic dopaminergic regions, such as the striatum and the VTA, results

in excessive pain (Saadé et al., 1997). Notably, several diseases associated with aberrant dopaminergic transmission are comorbid with chronic pain, including Parkinson's disease (Sophie and Ford, 2012), drug addiction, and major depression (Jarcho et al., 2012).

Human brain imaging studies have provided important knowledge of the effects of chronic pain states on brain activity, and have documented neuronal activation of the mesolimbic dopamine system in chronic pain patients (Hagelberg et al., 2003a, 2003b, Wood et al., 2007). Using functional magnetic resonance imaging (fMRI) to investigate brain activity in chronic back pain patients, Baliki and colleagues (2006) demonstrated that chronic back pain results in increased activity in the PFC (including rostral anterior cingulate), and this activity is strongly related to pain intensity. Later on, studies conducted by the same group revealed that the functional connectivity of the PFC to NAc is stronger under chronic back pain states (Baliki et al., 2010), and it is positively correlated with pain chronification (Baliki et al., 2012). Rodent models of neuropathic pain also reveal changes in functional connectivity of the NAc with dorsal striatum and medial and orbital prefrontal cortices (Chang et al., 2014). The findings of another human fMRI study indicate that the functional and structural brain abnormalities in chronic pain patients are reversible, highlighting the fact that treatment of chronic pain is sufficient to restore normal human brain function (Seminowicz et al., 2011). In this case, investigators acquired MRI scans from chronic low back pain patients before and after treatment (spine surgery or facet joint injections), and compared findings to healthy controls. Their results showed that the left dorsolateral PFC of patients with chronic back pain was thinner compared to healthy controls, and that treatment increased cortical thickness, which correlated with the reduction of both pain and physical disability.

Recent work also reveals alterations in connectivity between the mPFC and the hippocampus in patients suffering from burning mouth syndrome (Khan et al., 2014), and alterations in dorsolateral PFC activity in anticipation or reception of a painful stimulus (Ritter et al., 2014). Such data not only demonstrate that chronic pain conditions elicit changes in neuronal activity, but they also link pain threshold to the circuitry between the ventral tegmental area/substantia nigra and NAc. This circuit is known to be modulated by several limbic and cortical inputs involved in remembering past experiences, values, expectations, and salience (Baliki and Apkarian 2015). Moreover, these data help explain individual differences in pain sensitivity, and provide insight into the role of environmental and disease-related factors in responses to nociceptive stimuli.

## A role of the mesolimbic dopamine system in analgesic/antinociceptive responses and pain relief

Noxious stimuli promote changes in the activity of several supraspinal structures, which in turn trigger endogenous antinociceptive responses. The physiologic role of the NAc in nociceptive control has been documented by many studies using evoked-pain approaches (**Table 1**). Although it was widely known that forebrain activation induces analgesic mechanisms, the first evidence for a role of the NAc came in the late '90s from experiments using localized infusions of dopamine or opioid receptor antagonists to prevent endogenous

antinociceptive responses (Gear et al., 1999). Acupuncture in rodent models has been shown to induce an ascending antinociceptive response in the orofacial formalin test, which is blocked by sciatic C-fiber depletion or by spinal administration of μ-opioid receptor (MOP) antagonists (Tobaldini et al., 2014). Furthermore, application of MOP antagonists in the NAc, blocks the effects of acupuncture, pointing to this brain region as an essential component of ascending modulatory pathways. The NAc also controls the development of hyperalgesia, one of the most prominent features of chronic pain conditions. For example, intra-accumbens injections of MOP agonists suppress mechanical hyperalgesia induced by repeated hindpaw injections of prostaglandin E2 (Miranda et al., 2015).

With regard to mechanisms, a number of studies documented changes in excitability of neurons within the mesolimbic circuit upon noxious stimulation or relief from pain-like states. Studies from Mirenowicz and Schultz (1996) were among the first to show that dopamine neurons are preferentially activated by appetitive versus aversive stimuli (Mirenowicz and Schultz, 1996). By using an acute aversive stimulus (foot pinch), Ungless et al (2004) later revealed uniform inhibition of dopamine neurons in the VTA and excitation of a non-dopaminergic neuronal population. Later on, electrophysiology studies in rodents revealed that dopamine neurons within this circuit, particularly in the dorsal VTA, are inhibited by noxious footshocks whilst in ventral VTA dopamine neurons, footshocks induce phasic excitation (Brischoux et al.,2009). These results suggest that the rewarding and aversive effects are mediated by two distinct dopamine populations in the VTA. The complexity of the mesolimbic circuit and the VTA dopamine neurons was also pointed in a primate study by Matsumoto and Hikosaka (2009). The authors identified a great number of dopamine neurons to be excited by both reward- and aversive -predicting stimuli. The activity pattern of the neurons correlated with differential distribution in the substantia nigra pars compacta and the VTA, suggesting once again, that dopamine neurons convey motivational signals in distinct manners (Matsumoto and Hikosaka, 2009). More recently, an optogenetic approach was used to identify dopamine neurons in the VTA under reward and punishment (Cohen et al., 2012). The study concluded that the VTA GABAergic neurons signal expected reward, assisting the dopaminergic neurons to calculate reward prediction error. Moreover, fear-conditioned rats exposed to aversive predicting stimuli, elicited three different dopamine biphasic responses, which when further analyzed, revealed that the duration of inhibition of VTA DA neurons is also a critical variable when encoding aversive stimuli from the environment (Mileykovskiy and Morales, 2011). A summary of selected studies on the role of VTA in nociception and pain is presented in **Table 2**.

The complexity of the VTA responses is also reflected in the NAc, as well as its subregions, the NAc core and shell. One of the first studies used a microdialysis approach in the rat NAc to show that immediately after footshock termination, extracellular dopamine levels were increased in the NAc-shell but remained unaltered in the NAc-core (Kalivas and Duffy, 1995). Such reward circuitry activation, especially in the ventral striatum and NAc was also observed after the application of acute noxious (thermal) stimulus (Becerra et al., 2001), while mere anticipation of an aversive stimulus activates ventral striatum in humans (Jensen et al., 2003). Voltammetry studies in rodents have shown changes in NAc dopamine release upon termination of a noxious stimulus (tail pinch, Bertolucci et al., 1990) and this effect

was more prominent in the NAc-core compared to NAc-shell (Budygin et al., 2012). Dopamine release in the NAc is promoted by noxious tail stimulation and local VTA microinjection of capsaicin. Capsaicin activates transient potential vanilloid-1 channels which are also implicated in nociceptive transmission in the spinal cord and midbrain pathways. Application of capsaicin in brain slices also increases the firing rate of VTA dopamine neurons (Marinelli at el., 2005). On the other hand, non-dopaminergic neurons in the VTA of anesthetized rats are excited by aversive stimuli, including pain. Thus, distinct neuronal populations can be excited by aversive versus rewarding stimuli. Recently, Leitl and colleagues (2014) applied a rat model of intrancranial self-stimulation along with microdialysis to show that a noxious visceral stimulus reduces both dopamine levels in the NAc and the rate of self-stimulation. Moreover, fMRI studies show that the offset of a noxious stimulus results in increased activation of the mesolimbic dopamine system in both humans and rodents (Berger et al., 2014, Baliki and Aplkarian, 2015). Finally, more recent findings from microdialysis studies further support the hypothesis that pain alleviation is modulated by changes in dopamine levels in the NAc (Navratilova et al., 2015).

At the behavioral level, rodents learn to pair a certain environment with pain relief, and when given a choice between different environments, prefer the space associated with pain relief (Navratilova et al., 2012). Place conditioning to pain relief has been reported using a variety of models, including the spared nerve injury model of neuropathic pain, the complete Freund's adjuvant model of inflammatory pain, and post-surgical, cancer, and osteoarthritic pain models (Navratilova and Porreca, 2014). In all cases, treatment with compounds possessing analgesic (but not rewarding) properties, such as lidocaine or the alpha-2 adrenoreceptor agonist clonidine, produce place preference only in the presence of pain-like conditions (King et al., 2009). Moreover, a study using a rat model of cephalic pain investigated dopaminergic neurotransmission in the NAc under pain relief (De Felice et al., 2013). The authors found that the same treatments effective in alleviating headache in humans elicited conditioned place preference and dopamine efflux in the NAc of rats in cephalic pain states. Taken together, these preclinical and clinical studies suggest that the management of chronic pain should include agents that target dopaminergic transmission in the NAc.

Peripheral neuropathy leads to dysfunction of hyperpolarization-activated cyclic nucleotide-gated channels in the mPFC (Cordeiro Matos et al., 2015). These channels also play a role in nociceptive transmission in the dorsal root ganglia. The dysfunction of these channels is driven by alterations in the activity of the protein kinase A/cAMP pathway under chronic pain states, thus contributing to the hyperexcitability and persistent firing of pyramidal neurons, which likely affect the perception of pain-like and mood-related symptoms. Neuropathic pain induced by the spared nerve injury model also leads to changes in synaptic proteins involved in mPFC plasticity (Hung et al., 2014). Specifically, spared nerve injury leads to an increase in synaptotagmin, synaptobrevin, and synaptophysin, and promoted time-dependent phosphorylation of extracellular regulated kinases 1 and 2 and CaMKII, as well as an increase in glutamate release. Several recent studies also link changes in DNA methylation to adaptations in the mPFC in response to nerve injury. For example, six months after peripheral nerve injury, a time point when both sensory deficits (mechanical and cold allodynia) and anxiodepressive behaviors are observed, there is a decrease in global gene

methylation in the PFC (Tajerian et al., 2013, see also **Table 3** summary). Other brain areas, such as anterior cingulate cortex, amygdala, and hippocampus, also control the affective and motivational properties of the NAc through glutamatergic inputs, and are reviewed extensively elsewhere (Fasick et al., 2015, Neugebauer 2015).

## The impact of chronic pain on mood and motivation

Clinical studies over the last 40 years reveal that the comorbidity between chronic pain and depression is close to 50% (Bair et al., 2003, Chopra and Arora, 2014). Chronic pain conditions promote a number of neuroendocrine adaptations throughout the CNS networks that modulate mood and cognition, including the mesolimbic dopamine circuitry. In humans, maladaptations in NAc plasticity have been associated with depression and other mood disorders. In animal models, chronic stress leads to depressive states and a number of synaptic and intracellular adaptations in the NAc, including changes in phosphoprotein levels, and BDNF, transcription factor and epigenetic modifier activities (Berton et al., 2006a and 2006b, Lim et al., 2014). Importantly, the NAc is connected to several other brain regions that modulate pain perception and mood, including the PFC, the amygdala, and the hippocampus (Pezawas et al., 2005, Bär et al., 2007, MacQueen and Frodl 2011, Kim et al., 2012). Very few studies have examined the impact of chronic pain-induced depression in brain reward circuit plasticity. Recent studies using animal models of neuropathic pain link changes in dopamine receptor signal transduction, the amount of released dopamine and other neurochemical adaptations in the midbrain dopamine circuit with depression-like behaviors and reduced motivation (Ozaki et al., 2002, 2004, Terzi et al., 2014, Schwartz et al., 2014, Xie et al. 2014, Sagheddu, et al., 2015).

Studies by Schwartz and colleagues (2014) demonstrate that neuropathic pain in mice leads to decreased motivation, resulting from long-term depression of excitatory synaptic transmission in the medium spiny neurons of the indirect pathway. One of the key adaptations in these neurons concerns the expression and function of galanin receptor 1 (Schwartz et al., 2014). Recent work from our group using next-generation sequencing, also showed adaptations in the galaninergic system in the NAc of mice at one month after nerve injury (Mitsi et al., 2015). Notably, the galaninergic system dynamically modulates sensory transmission in the spinal cord under neuropathic pain states (Holmes et al., 2003). It will be interesting to further understand the role of galanin in anxiodepressive symptoms of neuropathic pain, and to also determine if this neuropeptide affects depression-like behaviors in other chronic pain models. Based on the evidence that the galanin system affects motivation as well as sensitized responses, galanin receptors constitute an interesting new target for the treatment of neuropathic pain.

Spared nerve injury in a rat model of neuropathic pain also promotes the expression of calcium-permeable (GluA1-containing) AMPA receptors in NAc synapses, which display inward rectification and have higher channel conductance compared to the GluR2-containing AMPA receptors. This switch in AMPA receptor composition may be an adaptive response to prevent the development of depression, as application of an AMPA-receptor potentiator directly into the NAc ameliorates, whereas blockade exacerbates, depression-like behaviors associated with neuropathic pain states (Goffer et al., 2013). In accordance to

these findings, depression-like conditions have been shown to downregulate AMPA receptor subunits and alter glutamatergic signaling in several brain regions. For example, chronic stress leads to a reduction in GluA2 subunits levels in the NAc (Vialou, et al. 2010, Lim et al., 2014). Evidence from genetic mouse models also supports a role of GluA1 subunits in depression vulnerability. On the other hand, antidepressant drug treatment promotes the expression of GluA1 and GluA2 subunits in the NAc (Tan et al., 2006). Therefore, adaptations to AMPA receptors in the NAc in models of depression differ from those observed following chronic pain. It remains to be elucidated if other adaptive changes in synaptic plasticity in NAc neurons occur in similar or opposite directions. Furthermore, manipulations of AMPA receptor activity in the NAc have no effect on sensitized responses, such as mechanical allodynia (Goffer et al., 2013). While this finding does not exclude the possibility that AMPA receptors in this brain region are involved in other sensory symptoms or in spontaneous pain, they clearly show that neuropathic pain conditions promote adaptations in the NAc that affect depression-like symptoms.

More recent work from our group applied genetic mouse models to investigate the intracellular adaptations in the NAc at several time points after the induction of neuropathic pain (Terzi et al., 2014). Using the spared nerve injury model, we examined the regulation of regulator of G protein signaling 9-2 (RGS9-2), a GPCR modulator, at early and later time points after nerve injury. Our Western blot analyses revealed that RGS9-2 levels were reduced in the spinal cord six days after spared nerve injury, but at this early time point, they remained unchanged in the NAc. However, RGS9-2 levels in the NAc were reduced at the 30-day time point, suggesting that this molecule may be modulating anxiodepressive and/or motivational behaviors of neuropathic pain. In support of this hypothesis, we showed that *RGS9*-knockout mice develop depression-like behaviors earlier than their wildtype controls (at six weeks after spared nerve injury, whereas wildtype mice show these behaviors at eight weeks). Importantly, genetic manipulations of RGS9-2 in the NAc did not affect the development or the intensity of mechanical allodynia (Mitsi et al., 2015). These data further support the hypothesis that neuropathic pain promotes long-term adaptations in the brain reward center. Future work should provide a better understanding of the signal transduction and epigenetic adaptations chronic pain states promote in the NAc and other brain regions associated with mood and motivation.

Optical methods have been used to understand how projections from the PFC to the NAc modulate sensory and affective symptoms of neuropathic pain (Lee et al., 2015). In these experiments, action potential spikes within the prelimbic PFC of rats were induced by light activation of neurons infected with adeno-associated viruses encoding channelrhodopsin-2. This activation promoted antinociceptive responses in both mechanical and cold allodynia assays. Using the place-conditioning paradigm, the investigators demonstrated that optical activation of these neurons lead to pain relief and promoted a preference for the compartment associated with this stimulation. Optical stimulation of the prelimbic PFC also reversed depression-like behaviors that were observed several weeks after nerve injury, namely reduced sucrose preference and increased immobility time in the forced swim assay. Subsequent experiments utilized photoactivation of channelrhodopsin-2-expressing NAc medium spiny neurons to confirm that the activation of projections from the prelimbic PFC

to the NAc were responsible for these effects, pointing to this corticostriatal circuit as an important target of neuromodulation therapy.

Chronic pain also induces impairments in noraderenergic circuits involving the locus coeruleus (LC) and the PFC (Alba-Delgado et al., 2013). Using the rat chronic constriction injury model, Albe-Delgado and colleagues (2013) demonstrated that a month after the induction of neuropathic pain, rats develop anxiodepressive behaviors. These behaviors correlated with increased bursting activity, expression of the noradrenaline synthesis enzyme tyrosine hydroxylase, and levels of noradrenaline transporter in the LC. In addition, the study used clonidine to show that under chronic constriction injury states, alpha-2 adrenoreceptors in the LC are supersensitive, and there is greater attenuation of noradrenaline release. This finding was further supported by electrophysiology studies showing a leftward shift in dose-response curves of alpha-2 agonists. Such adaptations occur at late stages of neuropathic pain, and therefore are more likely to result from changes in the activity of other brain regions modulating mood and anxiety. Indeed, similar adaptations in LC noradrenergic function have been associated with depression in both animal models and postmortem human tissue (Ordway et al., 1994 and 2003, Zhu et al., 1999).

## Brain reward center modulation of opiate actions under chronic pain states

Chronic pain-induced adaptations in the brain reward system also affect the responsiveness to opioid and non-opioid analgesics. Given the dramatic rise in painkiller-abuse incidents, it is essential to understand the mechanisms underlying addiction vulnerability under chronic pain states. Surprisingly, while painkillers such as oxycodone have been prescribed for years for the alleviation of chronic pain, very few studies have examined the impact of pain in opiate addiction vulnerability and the cellular mechanisms underlying this effect. Furthermore, there is very little information on the actions of opiate analgesics in the brain reward circuit under chronic pain states, and most of the published studies concern behavioral findings. Initial evidence came from a study showing that blockade of dopamine receptors in the NAc prevented the analgesic effects of morphine in the formalin test in rats (Altier and Stewart, 1996). Furthermore, blockade of dopamine D2-type receptors in the NAc shell by raclopide prevented the effects of morphine and substance P-analogs, providing the first evidence of tonic pain inhibition by the mesolimbic dopamine system. The same group has also provided evidence for roles of substance P and opioid receptors in VTA in stress-induced analgesia (Altier and Stewart 1998).

The impact of pain in opiate addiction vulnerability was recently assessed using a rat model of inflammatory pain in combination with heroin self-administration. Rats suffering from inflammatory pain showed decreased sensitivity to self-administration of low heroin doses, but at higher doses, the loss of MOP function in the brain reward center led to increased drug intake (Hipolito et al., 2015). Sensitivity to morphine reward is also reduced upon sciatic nerve injury. Using the conditioned place preference test, investigators showed that the loss of morphine reward sensitivity is accompanied by cellular adaptations in the VTA, including adaptations in G-protein coupled extracellular kinase-2 and in the extracellular signal regulated kinase pathway (Ozaki et al., 2002, 2004). Nerve injury in mice is also accompanied by upregulation of TNF-α in the NAc, and genetic or pharmacologic

inactivation of this TNF-α restores their sensitivity to morphine place preference (Wu et al., 2014). These data help define how adaptations within the endogenous opiate system under pain-like states can alter sensitivity to opiates. Future work may better elucidate the impact of the chronicity or type of pain (*e.g.,* inflammatory, neuropathic) in opiate addiction-related behaviors and in the efficacy of opioid and non-opioid medications.

There is additional evidence for a role of microglia in the mechanisms regulating dopamine transmission under chronic pain states. Specifically, Taylor and colleagues (2015) used a peripheral nerve injury model (applying polyethylene tubing to the sciatic nerve) and the place-conditioning paradigm to investigate the role of microglia in midbrain dopamine transmission in rodents. *In vivo* microdialysis and local drug microinjections were used to determine how changes in dopaminergic transmission under neuropathic states affect drug reward. They found that chronic pain activates microglia in the VTA, and the administration of the microglial inhibitor minocycline did not influence sensitized behaviors, such as mechanical allodynia. On the other hand, the microglial changes greatly altered the rewarding effects of opioid analgesics and other drugs targeting dopaminergic transmission. These effects were mediated by microglia-regulated activation of chloride channels in GABAergic VTA neurons and changes in BDNF levels.

## The role of the midbrain dopamine pathway in treatment responsiveness

According to a study by Apkarian and colleagues (2013), the transition from acute to chronic pain can be predicted. Brain imaging studies from this group have focused mainly on chronic back pain patients, showing that the strength of functional connectivity between the NAc and PFC is proportional to the magnitude of pain (Baliki et al., 2010). At the same time, the chronification of pain induces brain maladaptations that could be partly responsible for decreased analgesic responsiveness. Furthermore, PET imaging in chronic back pain patients by Martikainen *et al* (2015) revealed altered ventral striatal D2/D3- and opioid receptor-binding potentials, suggesting that an interplay between dopamine and the endogenous opioid system is involved in the pathophysiology as well as the treatment of pain.

The brain reward center also modulates the actions of monoamine-targeting antidepressants (MTAs) used for the alleviation of neuropathic pain symptoms. Desipramine and other tricyclic antidepressants (TCAs) have been prescribed for neuropathic pain conditions due to their strong antiallodynic, mood-elevating, and pain-alleviating properties (Max et al., 1991). To date, TCAs and selective serotonin–norepinephrine uptake inhibitors (including duloxetine and venlafaxine) are among the most prescribed medications for the treatment of neuropathic pain (Cruccu, 2007). Although these classes of drugs are not devoid of side effects, they are better tolerated and can be chronically administered without the risk of addiction. On the downside, MTAs have a slow onset of action (several weeks). While it is clear that monoamine-targeting antidepressants have direct actions in the spinal cord, little is known about their actions in the brain reward center or the intracellular adaptations they trigger.

The ability of TCAs to potently ameliorate neuropathic pain symptoms resides in their actions in many different areas of the pain matrix, and their direct effects on dopaminergic signaling in the NAc. In fact, intracellular adaptations within the NAc may dynamically modulate both the onset of action and the efficacy of monoamine-targeting antidepressants in models of neuropathic pain (Mitsi et al., 2015). One of the most potent modulators of monoamine signal transduction in the NAc is RGS9-2. RGS9-2 shortens the duration of GPCR signal transduction by binding to activated G-alpha subunits and accelerating their GTPase activity. In addition, RGS9-2 prevents the activation of G-alpha subunit (but not beta–gamma complex)—effectors, thus controlling signal transduction events associated with receptor activation. RGS9-2 plays a major role in drug addiction (Traynor et al., 2009) and in responsiveness to antiparkinsonian and antipsychotic medications. We also recently demonstrated that global knockout of the *RGS9* gene does not have a prominent effect on sensory symptoms of neuropathic pain (Terzi et al., 2014), but it potently accelerates the onset of action of TCAs and serotonin–norepinephrine uptake inhibitors (Mitsi et al., 2015). In fact, prevention of RGS9-2 action leads to an earlier antiallodynic response to desipramine and other monoamine-targeting antidepressants, and also promotes the antidepressant efficacy of these drugs in the forced swim assay. These effects involve actions of RGS9-2 in the NAc, as local overexpression of *RGS9* prevents the effects of desipramine, and the phenotype of *RGS9*-knockout mice is rescued by expression of RGS9-2 in the NAc.

Our studies revealed that RGS9-2 in the NAc modulates several monoamine receptors and other GPCRs that are crucial for the actions of antidepressants, and provide evidence that mechanisms within the NAc may affect the actions of drugs that alleviate both sensory and affective components of neuropathic pain. Notably, data from next-generation sequencing analysis indicate that knockout of *RGS9* leads to alterations in gene expression in the NAc, and a large number of the affected genes are involved in pain transmission, pain perception, and antidepressant drug actions (Mitsi et al., 2015). Many of these genes are further up- or downregulated by antidepressants, suggesting that the knockout mice respond better to antidepressants because of adaptations in the expression of genes that are necessary for their actions. An opposite modulatory effect on antidepressant drug actions was observed in mice lacking the *RGS4* gene. Prevention of RGS4 action attenuates the antiallodynic effects of TCAs such as desipramine (Stratinaki et al., 2013). Although the exact mechanism of RGS4 action is not completely understood, the expression pattern of this G protein modulator in spinal and supraspinal areas involved in nociceptive transmission and mood suggests that this molecule may constitute a target for the treatment of chronic pain.

The opioid tramadol, which is prescribed for the treatment of chronic pain, also has antidepressant properties, and has been shown to downregulate alpha-2 adrenoreceptors in many brain areas, including the NAc (Faron-Gorecka et al., 2004a). Tramadol also promotes the expression of D2 and D3 dopamine receptors in the NAc, similar to what is observed with chronic antidepressant treatment (Faron-Gorecka et al., 2004b). Moreover, the potent and selective alpha-2B adrenoreceptor agonist A1262543 attenuates mechanical allodynia in a rat nerve injury model, and reduces the spontaneous firing of a population of pain-responsive mPFC neurons, an effect that is reproduced by another antidepressant drug (duloxetine) used for the treatment of neuropathic pain (Chu et al., 2014).

Interestingly, a recent fMRI study in healthy volunteers who received the opioid analgesic remifentanyl indicated that the magnitude of behavioral analgesia is positively correlated with the trait reward responsiveness, supporting the use of brain imaging to guide therapeutic decisions (Wanigasekera et al., 2012). Further identification of GPCRs, signal transduction pathways, and other intracellular molecules may lead to the development of novel, fast-acting, and efficacious therapeutic compounds.

## Conclusions

Evidence from clinical and preclinical models suggests that the brain reward center plays a key role in the modulation of nociception, and that adaptations in dopaminergic circuitry may affect several sensory and affective components of chronic pain syndromes. These adaptations involve changes in the levels of released dopamine, as well as postsynaptic changes in the levels of receptors and signal transduction molecules. Interestingly, while chronic pain states promote some unique adaptations in the brain reward pathway, several molecules regulated by chronic pain states in the NAc are also known to play roles in nociceptive transmission in the spinal cord and dorsal root ganglia, and in other structures of the pain matrix. These findings urge for a better understanding of the neuroanatomical and molecular mechanisms by which the brain reward center modulates chronic pain. This information can direct drug development efforts towards novel targets for chronic pain conditions. These novel approaches for the treatment of chronic pain should encompass several circuits, from the spinal cord to the brainstem and the brain reward center, and may involve more than one medication.

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This review summarizes recent findings that shed light on

1. Adaptations that chronic pain conditions promote in the brain reward network,
2. The mechanisms that affect the perception of chronic pain, anxiety and depression,
3. The actions of opioids and antidepressants under chronic pain states

**Table 1**

Summary of selected studies on the role of the striatum (mainly NAc) in chronic pain/nociception.

| STUDY | SPECIES | BRAIN REGION | METHOD | MODEL/ TREATMENT | FINDINGS |
|---|---|---|---|---|---|
| Gear et al., 1999 | Rat | NAc, RVM | Stereotaxic injections, JOR (jaw open reflex) | Subdermal injection of capsaicin, paw immersion in hot water Flupentixol Naloxone Muscimol | Painful stimuli may induce analgesia by activating forebrain structures |
| Tobaldini et al., 2014 | Rat | NAc, RVM | Acupuncture | Orofacial formalin test, intraplantar capsaicin, sciatic C-fibers depletion Bicuculline, Naloxone, Mecamylamine | Ascending nociceptive control contributes to the antinociceptive effect of acupuncture. |
| Miranda et al., 2015 | Rat | NAc | Randall–Selitto nociceptive paw-withdrawal test | Capsaicin-induced analgesia, Persistent hyperalgesia (chronic prostaglandin E2 (PGE2) injections into hind paw) Naloxone, intra-NAc morphine antagonist | Pain chronification and chronic pain reduce the duration of capsaicin-induced analgesia, without affecting its dependence on NAc MOP receptor mechanisms. |
| Kalivas et al., 1995 | Rat | NAc (Core/ Shell) | Microdialysis, HPLC Quantification of Dopamine | Footshock | Increase of extracellular dopamine in the NAc-shell immediately after discontinuing footshock. Unaltered dopamine levels in the NAc-core |
| Martikainen et al., 2015 | Human | Ventral striatum | PET scan | Chronic Non-neuropathic Back Pain patients, painful stimulation by intra-muscle saline infusion | Reductions in D2/D3R binding potential in the ventral striatum compared to controls. These reductions were associated with greater positive affect scores and pain tolerance measures. |
| Budygin et al., 2012 | Rat | NAc (core/ shell), dorsal striatum | FSCV (fast-scan-cyclic voltammetry) | Tail pinch | Dorsal striatum / NAc core: increased dopamine release during stimulus application NAc shell: dopamine concentration suppressed throughout stimulation, increased at offset of stimulus application |
| Becerra et al., 2001 | Human | NAc/ Ventral striatum | fMRI | Thermal noxious stimulus | Painful thermal stimulation activates the ventral striatum |
| Becerra et al., 2013 | Human, rat | NAc, ACC | fMRI | Thermal noxious stimulus | Similar NAc and ACC excitation at pain onset and offset in both species |

| STUDY | SPECIES | BRAIN REGION | METHOD | MODEL/ TREATMENT | FINDINGS |
|---|---|---|---|---|---|
| Baliki et al., 2010 | Human | NAc, mPFC | fMRI | Thermal noxious stimulus on healthy subjects and chronic back pain patients | Pain offset differentially affects NAc activity in healthy versus CBP subject. |
| Navratilova et al., 2012 | Rat | NAc, VTA | Microdialysis and HPLC Quantification of Dopamine, Brain Microinjection, CPP, Hargreaves test | Hind paw incision (post-surgical pain) Baclofen, flupenthixol, lidocaine, naloxone | Relief of ongoing postsurgical pain produces CPP and activates the mesolimbic dopaminergic circuit |
| Xie et al., 2014 | Rat | NAc | Microdialysis and HPLC Quantification of Dopamine, CPP | Hind paw incision (post-surgical pain),SNL (neuropathic pain) Clonidine, gabapentin, ketorolac, naproxen | Spinal clonidine produced CPP and produced a dose-related increase in net NAc DA release in SNL rats. Gabapentin, increased NAc DA in rats with SNL. Ketorolac or naproxen produced increased NAc DA in animals with incisional but not neuropathic pain. |
| Navratilova et al., 2015 | Rat | NAc, ACC | In Vivo Microdialysis, CPP, Von Frey, Hargreaves test, Intracranial/ intrathecal cannulation | Hind paw incision (post-surgical pain) SNL (neuropathic pain) Flupenthixol, morphine, naloxone, saporin | Morphine into ACC: DA release in the NAc and promotion of CPP. Intrathecal clonidine: DA release in the NAc and promotion of CPP. |
| Hagelberg et al., 2003a | Human | Striatum | PET | Burning mouth syndrome | Decrease in the D1/D2 ratio may indicate a decline in endogenous dopamine levels in the putamen in burning mouth patients. |
| Hagelberg et al., 2003b | Human | Striatum | PET | Atypical facial pain | Changes in D2 receptor availability and D1/D2 ratio in the left putamen and the decrease in D1/D2 ratio in patients with atypical facial pain. |
| Jensen et al., 2003 | Human | Ventral striatum | fMRI (combination of 3 studies) | Cutaneous electrical stimulation | The first study to show that mere anticipation of an aversive stimulus activates ventral striatum in humans |
| Chang et al., 2014 | Rat | NAc | fMRI | SNI Intra-Nac lidocaine | The study demonstrated macroscopic (fMRI) and molecular reorganization of NAc and indicated that NAc neuronal activity is necessary for full expression of neuropathic pain-like behaviors. |

**Table 2**

Summary of selected studies on the role of VTA in nociception and pain

| STUDY | SPECIES | BRAIN REGION | METHOD | MODEL/ TREATMENT | FINDINGS |
|---|---|---|---|---|---|
| Ungless et al., 2004 | Rat | VTA | Electrophysiology | Foot pinch (15 sec) | Dopamine neurons are specifically excited by reward. A population of non-dopamine neurons is excited by aversive stimuli |
| Brischoux et al., 2009 | Rat | VTA (ventral/ dorsal) | Electrophysiology | Footshock | Inhibition of dorsal VTA dopamine neurons by noxious footshocks Phasic excitation of ventral VTA dopamine neurons by footshocks. |
| Matsumoto and Hikosaka, 2009 | Monkey (Macaca mulatta") | VTA, Substantia nigra pars compacta | Electrophysiology, monitoring of licking and blinking of the monkeys | Pavlovian procedure with appetitive and aversive outcomes (liquid rewards and airpuffs directed at the face) | Large number of dopamine neurons excited by both rewarding/aversive stimuli. Distinct anatomical place of these neurons. |
| Cohen et al., 2009 | Mouse | VTA | Electrophysiology, optogenetics | Odor cues | The first study to assess reward and punishment in optogenetically identified dopamine neurons. |
| Mileykovskiy and Morales, 2011 | Rat | VTA | Electrophysiology and Immunohisto-chemistry | Fear-conditioned rats exposed to stimuli predicting electrical shock | Duration of inhibition of VTA DA neurons encodes negative emotional values of signals predicting aversive events in the environment. |
| Taylor et al., 2015 | Mouse, Rat | VTA (focus on microglia) | In vivo microdialysis, CPP, brain microinjection | Peripheral nerve injury, tail withdrawal assay Inta-Nac cocaine, intra-VTA DAMGO | Peripheral nerve injury-induced activation of microglia within the reward circuit disrupts dopaminergic signaling and reward behavior |

**Table 3**

Summary of selected human imaging studies on the role of mPFC in chronic pain responses

| STUDY | SPECIES | BRAIN REGION | METHOD | MODEL | FINDINGS |
|---|---|---|---|---|---|
| Baliki et al., 2006 | Human | mPFC (including rostral anterior cingulate) | fMRI | Chronic back pain patients (trying to identify spontaneous pain) | Sustained chronic back pain resulted in increased activity in the mPFC; mPFC activity was strongly related to the intensity of chronic back pain. |
| Baliki et al., 2010 | Human | NAc, mPFC | fMRI | Thermal noxious stimulus on healthy (control) subjects and chronic back pain patients | Distinct NAc activities in healthy versus chronic pain subjects after relief of acute stimulation Functional Connectivity of NAc to mPFC is stronger in chronic back pain subjects |
| Baliki et al., 2012 | Human | NAc, insula, mPFC | fMRI | Sub-acute back pain patients followed for a year NSAID, Steroids, SNRIs, Muscle Relaxants. | NAC-mPFC functional connectivity positively correlates with pain chronification |
| Seminowicz et al., 2011 | Human | DL PFC | fMRI | Chronic back pain patients before and 6 months after (spine surgery or facet joint injections)treatment. | Increased cortical thickness in the left dorsolateral prefrontal cortex (DLPFC) after spine surgery |
| Khan et al., 2014 | Human | mPFC, Hippocampus | fMRI | Burning mouth syndrome | Patients show decreased grey matter volume in the mPFC and increased connectivity between mPFC and anterior cingulate cortex, occipital cortex, ventromedial PFC, and bilateral Hp/amygdala |