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A pain-induced tonic hypodopaminergic state augments phasic dopamine release in the nucleus accumbens

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Abstract

Diseases and disorders such as Parkinson's, schizophrenia, and chronic pain are characterized by altered mesolimbic dopaminergic neurotransmission. Dopamine release in the nucleus accumbens (NAc) influences behavior through both tonic and phasic signaling. Tonic dopamine levels are hypothesized to inversely regulate phasic signals via dopamine D2 receptor feedback inhibition. We tested this hypothesis directly in the context of ongoing pain. Tonic and phasic dopamine signals were measured using fast-scan controlled-adsorption voltammetry and fast-scan cyclic voltammetry, respectively, in the NAc shell of male rats with standardized levels of anesthesia. Application of capsaicin to the cornea produced a transient decrease in tonic dopamine levels. During the pain-induced hypodopaminergic state, electrically evoked phasic dopamine release was significantly increased when compared to baseline evoked phasic release. A second application of capsaicin to the same eye had a lessened effect on tonic dopamine suggesting desensitization of TRPV1 channels in that eye. Capsaicin treatment in the alternate cornea, however, again produced coincident decreased dopaminergic tone and increased phasic dopamine release. These findings occurred independently of stimulus lateralization relative to the hemisphere of dopamine measurement. Our data show that (a) the mesolimbic dopamine circuit reliably encodes acute noxious stimuli; (b) ongoing pain produces decreases in dopaminergic tone; and (c) pain-induced decreases in tonic dopamine correspond to augmented evoked phasic dopamine release. Enhanced phasic dopamine neurotransmission resulting from salient stimuli, may contribute to increased impulsivity and cognitive deficits often observed in conditions associated with decreased dopaminergic tone, including Parkinson's disease and chronic pain.

Summary

Ongoing pain produced a hypodopaminergic state and increased evoked phasic dopamine in the nucleus accumbens providing basis for pain-related changes in salience and cognition.

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Introduction

In both humans and animals, behavioral responses to salient events are reflected in activation of the meso-cortico-limbic reward valuation network [46,47]. Mesolimbic dopamine neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) via the medial forebrain bundle (MFB). In animals, activation of excitatory low affinity D1 receptors of the direct pathway and high affinity D2 receptors of the indirect pathway are essential in driving motivated behaviors and learning [39]. Dopaminergic dysfunction in several diseases in humans has been associated with behaviors such as impulsivity [22] as well as increased pain sensitivity [25,62].

The rat NAc shell has been shown to be vital in signaling both rewarding and aversive events [31,41]. Activity in the NAc shell can therefore reflect value predictions (e.g., gains and losses) in many diverse settings including for example, monetary gambling [7]. Unlike the NAc core, dopamine signals in the NAc shell of rats have been shown to play a differential and dynamic role in tracking reward information [55]. Additionally, modeling of VTA cell firing coupled with electrochemical dopamine detection in the rat has predicted that dopamine signaling may respectively arise from burst and constant firing in the NAc shell and core. [20]. Such hypothesized dynamic dopamine activity makes the NAc shell an area of interest for study in relation to changes in pain state.

We, and others, have previously reported that the saliency of relief of pain results in the activation of the mesolimbic dopamine pathway [44,46]. Persistent aversive states, including pain, in humans and animals are known to alter tonic levels of dopamine in the NAc [67,68]. While tonic dopamine levels have been hypothesized to modulate the magnitude of phasic release events through activation of the dopamine D2 receptor (D2), to our knowledge this concept has never been directly tested in a pain condition [42]. Elucidating the interplay of tonic and phasic dopaminergic signaling in the mesolimbic pathway is fundamental to understanding behaviors associated with many diseases that have altered dopaminergic tone such as schizophrenia [30] and Parkinson's disease [13], as well as in acute and chronic pain states [61].

Dopamine signaling can occur over different temporal domains. Tonic dopamine levels are measured on a time scale of minutes, or longer [23]. In contrast, phasic signals occur on second to sub-second time scales [66]. The large differences in temporal dynamics associated with phasic and tonic signals present technical barriers that prevent the use of methods such as positron emission tomography (PET) and microdialysis in the same experimental setting [17,34]. Fast-scan cyclic voltammetry (FSCV_{phasic}) is capable of capturing phasic changes with low micrometer spatial resolution but cannot be used for tonic measurements due to background subtraction [29]. Our laboratory has developed fast-scan controlled-adsorption voltammetry (FSCAV_{tonic}), that can be employed for tonic dopaminergic measurements using the same electrochemical probe as FSCV_{phasic} with temporal resolution extending from minutes to days [3,4,16].

Here, we used FSCAV_{tonic} and FSCV_{phasic} to measure tonic and phasic dopaminergic neurotransmission, following induction of a noxious stimulus. We hypothesized that changes

in baseline dopaminergic tone induced by pain would directly influence the magnitude of phasic dopamine events. We found that transient ongoing pain decreases tonic dopamine levels in the NAc shell, resulting in amplification of electrically evoked phasic dopamine release.

Materials and Methods

Animals.

Adult, male Sprague Dawley rats (280–350 g, Envigo, Haslett, MI) were used in all experiments. All procedures were performed in accordance with the policies of the National Institutes of Health guidelines for laboratory animals under protocols approved by the University of Arizona Institutional Animal Care and Use Committee and were in accordance with International Association of the Study of Pain guidelines. Prior to surgery animals were group-housed in a temperature and humidity-controlled environment, on a 12-hour light—dark cycle (lights on at 0700) with food and water provided *ad libitum*. All experiments were performed during the light stage of the cycle.

Electrodes and electrode placement.

Carbon-fiber microelectrodes were constructed as previously described [65]. Additional details can be found in the SI.

Anesthesia Standardization.

Following electrode placement and before capsaicin experiments, the depth of anesthesia was standardized using a behavioral response. The latency to tail flick from an acutely noxious thermal stimulus was measured. Anesthesia was adjusted to elicit a tail-flick latency of approximately six seconds (6.3 ± 0.2 s, mean $\pm$ SEM).

Measurement of Tonic Dopamine Levels.

All dopamine measurements were made in animals under stable anesthesia while they were in a stereotaxic frame. We measured tonic dopamine levels using FSCAV_{tonic}, a technique developed in our laboratory [3,4] (see additional details in SI). Discrimination between dopamine and its metabolites was achieved by analyzing the tenth scan after the application of the holding period as previously reported [4].

Procedure of Transient Ongoing Pain and Tonic Dopamine Measurements.

Prior to pain induction, a 10-minute baseline was collected followed by application of saline (~15 μ L drop via transfer pipette) to the cornea of one eye. Dopamine levels were then recorded for 10 minutes. Capsaicin (Sigma-Aldrich, St. Louis, MO, USA; 0.01%, 15 μ L) was then applied to the same eye as saline. Ten minutes following the first capsaicin application and upon return of tonic dopamine levels to pre-capsaicin baselines, the same concentration and volume of capsaicin was administered a second time to the same eye. The same sequence was then applied to the alternate eye and dopamine levels were recorded (Figure 1A). Application order to the left and right eyes was randomized between animals in order to control for potential lateralization effects.

Measurement of Phasic Dopamine Signals.

All dopamine measurements were made in animals with stable anesthesia while placed in a stereotaxic frame. Phasic dopamine measurements were made using FSCV_{phasic}, a well-established technique for monitoring neurotransmitters *in vivo* [53] (see SI for additional details).

Electrically Evoked Phasic Dopamine Measurement During Transient Ongoing Pain.

We designed our experimental paradigm to electrically evoke phasic dopamine release that coincided with a two-minute period of ongoing pain following capsaicin (see below). Electrical stimulation of the MFB, which contains dopaminergic axons that project to the NAc, was chosen to elicit phasic dopamine release. Two important considerations were made when selecting the stimulation parameters including: (a) the evoked dopamine release should be transient so that it could be produced repeatedly without change in magnitude every two minutes for the duration of the experiment; and (b) the stimulation pattern should mimic spontaneous burst firing [66] rather than increasing the general activity of the neurons to ensure that we did not confound our results with increases in dopaminergic tone [23].

Once every two minutes the MFB was electrically stimulated (6 pulses, 30 Hz, 4 ms biphasic pulses, 380 μ A) to produce a phasic dopamine release event in the NAc shell. Five baseline stimulated release events were recorded; then following application of saline to the same cornea, five more stimulated phasic release events were measured. Capsaicin was then applied to the same cornea and five more phasic release events were measured.

Histology.

Following experimentation, electrolytic lesions were made with the working electrode to allow visualization of the electrode tract. Electrolytic lesioning consisted of a slow increase in current applied to the CFME from 0 – 800 μ A over the course of 10 minutes (see SI for additional details).

Data Analysis.

Tonic dopamine measurements were made relative to the first data point. The percent change was calculated by comparing the dopaminergic low point observed during the first three minutes of each recording to the tonic dopamine measurement made directly prior to treatment. The length of the hypodopaminergic state was established as the time after which 40% of the decrease in dopaminergic tone was recovered (see SI for more details). Phasic dopamine measurements were made relative to the average of the first five (baseline) evoked phasic release events. Percent change for phasic dopamine release was calculated by comparing the average of the two phasic events prior to saline or capsaicin application to the phasic release one minute after the application.

Generation of two-dimensional color plots in LabVIEW software (National Instruments, Austin, TX, USA), which show phasic dopamine release, are described in detail elsewhere [18]. Briefly, time is represented on the abscissa and the voltammogram on the ordinate. Voltammetric current is represented in false color. Dopamine oxidation occurs at ~ 0.6 V vs.

Ag/AgCl and is denoted with a horizontal dashed line. Representative voltammograms were taken from the vertical dashed line on the color plots and graphed versus potential.

Tonic dopamine data were analyzed by repeated-measures analysis of variance (ANOVA) tests. Where significant main effects were observed, post-hoc analysis was conducted using Tukey's procedure to correct for multiple comparisons. For phasic experiments, paired t-tests were used to compare the percent change data between saline and capsaicin (or saline and saline) subsequent applications within individual animals. For both tonic and phasic dopamine measurements, unpaired t-tests were used to compare the percent change in response to capsaicin treatment between ipsilateral or contralateral control groups (data are presented in the SI). All data are represented as mean $\pm$ SEM. Statistical analyses were completed using GraphPad Prism (GraphPad Software, San Diego, CA, USA).

Results

1.0 FSCAV_{tonic} measures sub-minute changes in tonic dopamine.

Tonic dopamine levels were measured in the NAc shell using FSCAV_{tonic} in response to saline and capsaicin corneal treatment (Figures 1A–C). First, following a 10-minute tonic dopamine baseline measurement (Figure 1D), saline was applied (Figure 1E, vertical dotted line) to one cornea, randomized to the ipsilateral or contralateral hemisphere of the carbon-fiber microelectrode (CFME) placement. Ten minutes after the initial saline application, capsaicin (Figure 1F, vertical dotted line) was applied to the same cornea. After an additional ten minutes, a second drop of capsaicin was given in the same eye (Figure 1G). Results in Figure 1 include data from 10 animals.

1.1 A single application of capsaicin to the cornea decreases tonic dopamine levels.—To determine if capsaicin treatment had an effect on tonic dopamine levels, we calculated the maximum percent decrease during the first three minutes after each saline and capsaicin application. A significant main effect of treatment was observed (one-way ANOVA, $F_{3, 27} = 5.18$, $p < 0.01$; post-hoc analysis revealed a significant effect of the capsaicin application when compared to baseline and saline data, $p < 0.01$ and $p < 0.05$, respectively). Saline did not significantly affect tonic dopamine levels when compared to baseline (Figure 1H; $1 \pm 4\%$ decrease in tonic dopamine levels, post-hoc analysis, $p > 0.80$). The capsaicin application significantly decreased dopamine levels (Figure 1H, post-hoc analysis, $*p < 0.05$), resulting in a $22 \pm 8\%$ maximum decrease. Dopaminergic minima were observed 1.4 ± 0.2 minutes after capsaicin application (Table S1) and the decrease lasted 2.0 ± 0.3 minutes (Figure S1). Application of a second capsaicin treatment to the same cornea resulted in a $9 \pm 2\%$ decrease in dopamine level (Figure 1H). No significant change in dopamine level was observed when compared to saline (post-hoc analysis, $p > 0.40$). No significant effects of capsaicin lateralization were observed (unpaired t-test, $p > 0.8$, Figure S2).

1.2 FSCAV_{tonic} measures sub-minute dopaminergic changes in the alternate cornea.—Ten minutes following the second application of capsaicin to the first cornea, saline was applied to the alternate cornea (Figure 1I). Using the same protocol as above, capsaicin was then applied twice consecutively at 10-minute intervals. The first application

of capsaicin to the alternate eye produced a robust decrease in dopamine levels (Figure 1J), while the second application of capsaicin to the alternate cornea had a significantly lower effect (Figure 1K).

1.3 A hypodopaminergic response to capsaicin application is preserved in the alternate cornea.—Saline application in the alternate cornea did not cause a significant change in dopamine levels ($3 \pm 1\%$ decrease) when compared to the initial baseline recording (post-hoc analysis, $p > 0.75$). However, a significant effect of treatment on tonic dopamine levels in the alternate eye was observed following capsaicin (Figure 1L, one-way ANOVA, $F_{3, 27} = 7.14$, $p < 0.01$). A $22 \pm 7\%$ decrease was measured in response to capsaicin application in the alternate eye; this was significantly larger than the saline effect (post-hoc analysis, $**p < 0.01$). Dopaminergic minima were observed 1.2 ± 0.1 minutes after capsaicin application (Table S1). The decrease in dopamine level lasted 1.9 ± 0.3 minutes (Figure S1). Application of a second capsaicin treatment to this eye caused a $5 \pm 1\%$ decrease in dopamine levels, which was not significantly different from saline (Figure 1L, post-hoc analysis, $p > 0.75$) but was significantly different from change observed after the primary capsaicin application (Figure 1L, post-hoc analysis $*p < 0.05$).

2.0 Measurement of evoked phasic dopamine levels during pain-induced hypodopaminergic states.

Having determined that a first application of capsaicin in either eye reliably produced a hypodopaminergic state of approximately 2 minutes, we next used $FSCV_{phasic}$ to determine if phasic dopaminergic levels were affected during this time period. Initial studies showed that electrical stimulation of the MFB (6 pulses, 30 Hz, 4 ms biphasic pulses, 380 μ A) evoked dopamine release (~ 5 nM) in the NAc shell and these stimulation parameters could be used repeatedly for an extended period of time without decrease in signal amplitude (Figure S3). The stimulation pattern was chosen to elicit dopamine events that mimicked transient dopamine signaling, which occurs as a result of neuronal burst firing [23] (Figure 2). Representative data demonstrate that electrically evoked dopamine release events were approximately the same magnitude as spontaneous, transient dopamine signals (Figures 2A–D).

2.1 Two consecutive saline applications to the cornea do not alter evoked phasic dopamine signals.—Experiments were designed so that electrically evoked, spontaneous-like, phasic dopamine events were recorded every two minutes (Figure 3A). Stimulations were aligned such that a phasic release event occurred one minute before and one minute after treatment with saline or capsaicin. Prior to treatment, five baseline stimulations were measured over 10 minutes. In control experiments two consecutive applications of saline were given in the same eye at 10-minute intervals, while phasic dopamine release was recorded every two minutes (Figure 3B). The average electrically evoked phasic dopamine release that occurred during the 10-minute baseline and after the two consecutive saline applications in the control experiment were not significantly different (Figure S4, one-way ANOVA, $F_{2,12} = 1.64$, $p > 0.20$).

2.2 Increased evoked phasic dopamine release is observed following application of capsaicin, but not saline, on the cornea.—Baseline stimulations made prior to saline or capsaicin treatments were stable over the course of 10 minutes (Figure 3C). Evoked phasic dopaminergic events that occurred after a corneal saline treatment were not significantly different from baseline (Figure 3C & S4, one-way ANOVA, $F_{2,12} = 8.01$, $p < 0.01$, post-hoc analysis, $p > 0.70$). Ten minutes following the saline treatment, capsaicin was applied to the same cornea. Evoked phasic dopamine release was increased one minute after the capsaicin application (Figure 3C). Additionally, the average evoked phasic release that occurred over the 10 minutes following capsaicin application was significantly higher than the average phasic dopamine release during the 10 minutes following saline application (Figure S4, $F_{2,12} = 8.010$, $**p < 0.01$). No effects were observed due to lateralization (Figure S5, unpaired t-test, $p > 0.45$). By three minutes post-capsaicin treatment evoked phasic dopamine release was no longer elevated. Similar results were observed after the first capsaicin application to the alternate cornea (Figure S6).

2.3 Capsaicin causes a significant increase in the phasic dopaminergic percent change.—The percent change in phasic dopamine release was calculated one minute after each saline or capsaicin treatment. In control experiments, the percent change in evoked dopamine release after the second saline application was not significantly different from the first (Figure 3D, Wilcoxon test, $p > 0.15$). However, in experimental (saline then capsaicin treated) animals the percent increase in phasic dopamine release post-capsaicin was significantly higher than after saline treatment (Figure 3E, Wilcoxon test, $*p < 0.05$). Phasic data for experimental animals in Figure 3 include data from 13 animals. Control data shown in Figure 3 represent eight animals.

Discussion

In this work we investigated the effects of ongoing pain on dopamine signaling in the NAc shell. We used $FSCAV_{tonic}$ and $FSCV_{phasic}$ to make tonic and phasic measurements, respectively. Importantly, $FSCAV_{tonic}$ uses the same probes, instruments, and software as $FSCV_{phasic}$, which is well established for monitoring phasic signals from neurotransmitters, especially dopamine, *in vivo* [49]. The use of these techniques allowed us to measure, for the first time, both tonic and phasic signals during periods of transient ongoing pain. Our data show that (a) consistent with previous observations, the mesolimbic dopamine circuit reliably encodes salient events such as noxious stimuli; (b) ongoing pain produces time-locked and reversible decreases in tonic dopamine levels; and (c) that an electrical stimulus mimicking spontaneous phasic signaling during a period of low tonic dopamine levels results in significantly increased phasic dopamine release.

Phasic mesolimbic dopamine signaling is associated with salient events including relief of pain aversiveness [35]. However, human studies have reported variable influences of pain on phasic dopamine signals in the NAc [10]. PET imaging studies, also in humans, have demonstrated that a pain stimulus increases NAc dopamine release in healthy subjects but surprisingly, not in patients with chronic pain [68]. Additionally, a noxious, but not non-noxious, thermal stimulus applied to the hand caused decreased fMRI activations in the NAc [1]. fMRI studies have also demonstrated a negative NAc signal change in response to the

application of a noxious thermal stimulus and positive signal change upon the termination of the stimulus, suggestive of the saliency of pain onset and pain relief though this approach could not identify the relevant transmitters [8,9]. Dopamine signals are altered in burning mouth syndrome [28] and atypical facial pain [27] in the human striatum. Application of a noxious stimulus showed an increase in fMRI BOLD signal at stimulus onset and a decrease at offset in patients with chronic pain [6], a finding suggestive of the relative relieving effects of acute pain on a background of chronic pain. Such observations are supportive of an interaction between phasic and tonic dopamine signaling in humans, but interpretation is complicated by many factors including, for example, the continued use of medications that likely altered the expression of receptors and neurotransmitters.

Preclinical investigations have yet to clarify the role of dopamine signaling in the NAc response to persistent pain states despite significant efforts. This is due, in part, to the use of multiple models that likely differ in their mechanistic responses following: transient trauma, inflammatory injuries, or persistent neuropathic pain. An acute noxious stimulus (tail-pinch) in rodents increased dopamine release in the NAc core, which lasted for the duration of the three-second stimulus [15]. Additionally, this study found that dopamine release in the NAc shell was increased for a similar length of time following termination of the tail-pinch. When intraperitoneal lactic acid was given to rodents a decrease in dopaminergic tone was measured using microdialysis, which reached significance approximately 60 minutes post-injection, likely reflecting persistent visceral pain [37]. Electrophysiological studies revealed a decrease in VTA cell firing five days after peripheral nerve injury in the rat [52]. Consistent with this, a decrease in dopamine levels in the rodent NAc was reported using microdialysis in response to neuropathic pain [52]. However, other reports found no changes in NAc dopamine levels following peripheral nerve injury using microdialysis [69] and indeed some reports have shown increased NAc shell dopamine levels in rats with neuropathic pain [56]. Previous work from our laboratory and others used microdialysis to show increased NAc dopamine levels following relief of neuropathic and incisional pain in rats [33,69] consistent with the conclusion that pain decreases dopamine in the NAc and that dopamine signals increase when pain is relieved.

The present experiments directly measured tonic and phasic NAc dopamine signals following induction of a period of ongoing pain that persists for approximately 2 minutes. Behavioral studies have shown that capsaicin produces a vigorous eye-wiping response in awake rats that resolves within five minutes presumably due to desensitization of the TRPV1 channel [12]. The capsaicin-cornea model was chosen here largely for its known pain duration and the translational relevance of the pain state. Additionally, the pain stimulus induced by capsaicin lasted long enough to capture both a tonic and phasic response. Notably, animals in this study were lightly anesthetized and the depth of anesthesia was standardized to a behavioral response (tail flick), which is an additional control not included in previous studies. FSCAV_{tonic} measurements revealed that application of capsaicin to the cornea significantly decreased tonic dopamine levels in the NAc shell. As dopaminergic tone is believed to be largely regulated by overall population activity of dopaminergic VTA neurons [23], this observation is consistent with data demonstrating inhibition of VTA dopaminergic cell firing in rodents during application of an acute noxious stimuli [14,63]. Consistent with behavioral data, the observed decrease in tonic dopamine levels was

significant but recovered within approximately two minutes. A second application of capsaicin to the same eye, however, elicited a smaller or absent dopaminergic response. This is likely explained by the well-known phenomenon of desensitization of the TRPV1 channel that mediates the capsaicin-induced activation of corneal afferents and is consistent with the time-related decrease in eye-wiping response following application of capsaicin to the cornea of awake animals [57]. The correlation of electrophysiological, neurochemical, and behavioral observations thus provide strong support for the conclusion that mesolimbic dopamine signals encode salient stimuli regardless of conscious state of the animal. This conclusion is strengthened by the observation of a diminished effect on dopamine neurotransmission following desensitization of TRPV1 channels after a second capsaicin treatment on a previously tested cornea, but a prominent dopaminergic response to the first capsaicin treatment in the alternate (untested) eye.

The demonstration that capsaicin reliably produced a transient hypodopaminergic state allowed for direct investigation of the hypothesis that the magnitude of phasic signals may be inversely related to tonic levels (Figure 4A). Independent regulation of cellular signals that underlie phasic and tonic dopamine levels in rats has been demonstrated [23]. As such, relatively low tonic dopamine levels might allow phasic signals to be increased as a consequence of decreased D2 autoreceptor feedback inhibition [24,26,42]. Previous work has demonstrated that D2 antagonism increases phasic release. In the presence of a D2 antagonist, D2 autoreceptor feedback inhibition is ineffective and thus the antagonist abolishes changes observed in response to consecutive electrical stimulation events [45]. As such, testing the effects of D2 regulation on tonically altered changes in phasic dopamine release is not possible using this paradigm. Whether this inverse relationship occurs in conditions that reflect clinical states of pain has not previously been determined.

We found that evoked phasic dopamine release was increased and time-locked to the hypodopaminergic period (Figure 4B). When stimulations were applied following the resolution of the capsaicin-induced hypodopaminergic period, the phasic signals returned to baseline. These data directly demonstrate the inverse relationship of tonic and phasic dopamine release in conditions of ongoing pain. Two limitations of this study are the use of only male rats as well as the assessment of dopamine levels in anesthetized, as opposed to awake, animals. We note, however, that the depth of anesthesia was standardized by the latency to a pain-induced behavioral reflex allowing comparisons to be made across animals. Future studies should include evaluations in female animals. Nevertheless, the implications of these findings are significant as phasic dopamine release is believed to underlie impulsivity [19], reward response [58], and decision making [54]. Therefore disordered dopamine signaling could underlie comorbidities associated with chronic pain, such as the reward-related major depressive disorder, from which many chronic pain patients suffer [5,36]. Cognitive deficits in decision making tasks are seen in chronic pain patients using the Iowa Gambling Task [2] and replicated in animal models of pain using the Rodent Gambling Task [48]. Furthermore cognitive flexibility, wherein responses are adapted to favor the most advantageous outcome, is impaired in chronic pain patients [64] and in rodent pain models [38]. This disordered habit-like responding has been associated with addiction [60], another comorbidity with chronic pain [51].

It is notable that preclinical investigations show that pain symptoms can be treated with triple reuptake inhibitors, which increase tonic dopamine levels [43]. Whether these drugs improve cognitive disorders in addition to improving pain remains to be determined. Further investigation of phasic and tonic interactions could also aid treatment of other dopaminergic disorders such as Parkinson's disease, which has decreased NAc dopamine levels, as well as increased pain [11], impaired cognition [50], and increased impulsivity [32]. Also, schizophrenia and psychosis, which are associated with decreased pain perception [21] and impaired emotional responsivity [40], are often treated with dopaminergic antagonists [59]. Thus, the dynamic relationship that we have confirmed between tonic and phasic dopamine signaling resulting from ongoing pain, may underlie the cognitive pathology observed in multiple clinical states.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Ongoing pain (capsaicin) causes a transient decrease in NAc shell tonic dopamine levels. (A) Experimental protocol: FSCAV_{tonic} was used to measure tonic dopamine concentrations every twenty seconds. Baseline tonic dopamine measurements were made for 10 minutes. Subsequently, saline (Saline, Cornea I) was applied (one drop from a syringe, ~15 μ L) to the first cornea, randomized ipsilateral or contralateral relative to recording electrode hemisphere. Ten minutes after the saline control application, a first (or primary) treatment of capsaicin to the same cornea was given (Capsaicin I, Cornea I). Next, a second drop of capsaicin was applied to the same cornea (Capsaicin II, Cornea I). This process was then repeated in the alternate eye. (B) Schematic of corneal capsaicin (or saline) application. A single drop was applied to the animal's cornea for each treatment. (C) Schematic of FSCAV_{tonic} demonstrates how tonic dopamine measurements are made at CFMEs once every 20 seconds. During a ten-second holding period, dopamine is allowed to adsorb to the electrode surface until an equilibrium is reached. After the adsorption period, a dopaminergic measurement is made that is representative of the equilibrium state (or tonic level). Reproduced from Ref. [4] with permission from the Royal Society of Chemistry. (D) Baseline tonic dopamine measurements in the NAc shell show no change in tonic dopamine levels. (E-G) Abscissa, time; ordinate, normalized tonic dopamine (DA_{tonic}). Vertical dotted lines represent the application of saline or capsaicin to the cornea. (E) Saline application to the first cornea. (F) The first (or primary) capsaicin application to the first cornea reduced

dopaminergic tone for 2.0 ± 0.3 minutes. (G) The second application of capsaicin to the first cornea. (H) Calculated percent change resultant from saline or capsaicin application in the first cornea. The first application of capsaicin to the cornea induced a significant decrease in dopaminergic tone when compared to a previous saline application in the same eye (one-way ANOVA, $F_{3, 27} = 5.18$, $p < 0.01$, post-hoc Tukey's multiple comparisons test, $*p < 0.05$). (I-K) Abscissa, time; ordinate, normalized DA_{tonic} . Vertical dotted lines represent the application of saline or capsaicin to the cornea. (I) Saline application to the alternate cornea. (J) A subsequent capsaicin application to the alternate eye produced a decrease in dopaminergic tone that lasted 1.9 ± 0.3 minutes. (K) A secondary application of capsaicin in the alternate cornea. (L) Calculated percent change resultant from saline or capsaicin application in the alternate cornea. The primary application of capsaicin to the alternate cornea induced a significant decrease in dopaminergic tone when compared to a previous saline application in the same cornea (one-way ANOVA, $F_{3, 27} = 7.14$, $p < 0.01$, post-hoc Tukey's multiple comparisons test, $*p < 0.05$, $**p < 0.01$). In all cases data are represented as mean $\pm$ SEM, $n = 10$ rats.

Figure 2.

Electrically evoked phasic dopamine release mimics spontaneous NAc shell dopamine release. (A) Concentration versus time trace and false color representation (color plot) of electrochemical activity for a representative spontaneous transient dopamine event in the NAc shell. The current versus time trace is taken from the dopamine oxidation potential, indicated by the horizontal dashed line in the color plot. The purple color indicates dopamine release. (B) Cyclic voltammogram of a dopamine signal taken from the vertical dashed line in the color plot in Panel A. (C) Representative concentration versus time trace (taken from the horizontal line in color plot) of electrically evoked dopamine release and the corresponding color plot. Electrical stimulation (6 pulses, 30 Hz, 4 ms biphasic pulses, 380 μ A) of the MFB is indicated by the red arrow. (D) Cyclic voltammogram of an electrically evoked phasic dopamine signal taken from the vertical dashed line in Panel C; this shows the similar magnitude of the evoked phasic dopamine and the spontaneous event in Panel B.

Figure 3.

Electrically evoked phasic dopamine release is increased in response to transient ongoing pain (capsaicin). (A) Experimental protocol, FSCV_{phasic} was used to measure electrically evoked phasic dopamine release throughout the experiment. First, five consecutive baseline electrical stimulations of the medial forebrain bundle (MFB) were given at two-minute intervals. Next, saline was applied to the cornea (randomized ipsi- or contralateral to the recoding electrode hemisphere); five subsequent stimulations were applied to the MFB with the first stimulation occurring one minute after saline application. Finally, capsaicin (or saline in control animals) was applied again to the same, previously tested, cornea with stimulations every two minutes; the first of the five stimulations occurred exactly one minute after corneal treatment. (B) Control experiment. Abscissa, time; ordinate, normalized phasic dopamine (DA_{phasic}). Data are normalized to the average stimulated release from the baseline, $n = 8$ rats. Saline was applied twice consecutively (vertical dotted lines) to the same eye. (C) Ongoing pain experiment. Abscissa, time; ordinate, normalized DA_{phasic}. The first vertical dotted line represents the saline application, and the second dotted line represents capsaicin application, $n = 12$ rats. (D) Calculated percent change after saline applications in control animals from Panel B. The first application of saline caused a $5 \pm 5\%$ decrease; the second application in the same cornea caused a $4 \pm 8\%$ increase. No significant differences were observed between primary and secondary corneal saline treatments in control animals (Wilcoxon test, $p = 0.20$). (E) Calculated percent change after saline and capsaicin applications from Panel C. The application of saline caused an $8 \pm 11\%$ increase. Capsaicin application caused a significant increase ($57 \pm 18\%$) in evoked phasic dopamine release when compared to saline application in the same cornea (Wilcoxon test, $p < 0.05$). In all cases data are represented as mean $\pm$ SEM.

Figure 4.

The interplay of tonic and phasic dopamine neurotransmission. (A) Hypothesized tonic / phasic dopamine relationship. Tonic dopamine levels (black line) regulate phasic dopamine release (red spikes) via D2 receptor feedback inhibition. (*i.e.* Hypo-dopaminergic tone augments phasic dopamine release and hyper-dopaminergic tone attenuates phasic dopamine release). (B) Schematic representation of the relationship between tonic and phasic dopamine neurotransmission during ongoing pain tested directly in this work. Corneal capsaicin (transient ongoing chemical pain) induces a hypodopaminergic state, which corresponds with an increase in evoked phasic dopamine release. These data show directly the inverse and dynamic relationship of tonic and phasic dopamine signaling during pain.