Interplay of Nicotine and Social Stress Mediate Dopaminergic Neuron Firing in the Ventral Tegmental Area—Nucleus Accumbens Pathway, Contributing to Stress and Depressive Mood Disorders

Danya Adams, Nicholas Kaliss, Alexander Missner, Mary Meg Valentine
The Interplay of Nicotine and Social Stress Mediate Dopaminergic Neuron Firing in the Ventral Tegmental Area - Nucleus Accumbens Pathway, Contributing to Stress and Depressive Mood Disorders.

Danya Adams*, Nicholas Kaliss*, Alexander Missner*, Mary Meg Valentine*

1 Department of Biology, Georgetown University, Washington, DC, USA

*Indicates equal contribution

E-mail: daa112@georgetown.edu, ndk14@georgetown.edu, am3212@georgetown.edu, mmv57@georgetown.edu

Abstract

Nicotine use and social stress have a complex interplay, which has been shown to be mediated by cholinergic neurons in the ventral tegmental area (VTA). Social stress is often comorbid with nicotine consumption, and the presence of either stress or nicotine use significantly increases the risk of developing the other. In fact, it has been shown in mice that nicotine injection is sufficient to increase susceptibility to social defeat, a reliable model for stress and anxiety-like behavior. Stressful events can molecularly remodel cholinergic synapses, inducing the production of more cholinergic transporters and increasing the number of nicotinic receptor binding sites. One way stress and nicotine remodel cholinergic synapses are through long-term potentiation (LTP) in cholinergic pathways in the VTA, enhancing the experience of stress and the effects of addiction. Despite both primarily acting on the α7 subtype nicotine receptor, nicotine and stress induce LTP in vastly different ways: nicotine acts quickly via ligand-gated ion channels while stress activates a slower hormonal-induced G-protein coupled receptor pathway. These findings suggest that dopaminergic VTA neurons may be a useful therapeutic target for depression, anxiety, and other stress-related disorders. Deep brain stimulation has preliminarily shown to be a potential therapeutic treatment for untreatable depression, especially when it targets the medial forebrain bundle within the VTA-NAc pathway. Sleep patterns are also partially regulated by dopaminergic VTA neurons, and sleep deficits may contribute to social stress and other depressive symptoms. The role of nicotine dependence in stress-related mental illnesses is especially important to consider given the recent increase in adolescent nicotine use with the advent of vaping. Adolescents already have an increased risk for developing mental illnesses, and it is important that young people are made aware of the potential psychological harms of nicotine use.

Keywords: α7 subtype nicotine receptor, cholinergic synapses, long-term potentiation, nicotine, stress, nucleus accumbens, and ventral tegmental area
1. Introduction

According to the National Institute on Drug Abuse, nicotine is classified as a highly addictive substance, ranking among other drugs of abuse such as cocaine, amphetamines, and heroin. The US Department of Health and Human Services estimates some 20% of all Americans are addicted to nicotine, whether by smoking cigarettes, chewing tobacco, or vaping. While many—up to seventy percent each year—will try to quit, only around three percent will succeed. The smoking rate is doubled in individuals who have mood or stress disorders, like clinical depression, and although these individuals will attempt to quit at the same rates, their chances of success are even lower than their neurotypical counterparts. Each condition heightens the risk of developing the other: depressed individuals are more likely to begin smoking and experience more potent withdrawal symptoms when they try to stop, and smokers have a higher chance of becoming depressed at some point in their lifetimes than non-smokers. This pattern seems to follow for other drugs of abuse as well, as it has been reported in both human and animal studies that stress is sufficient enough to significantly increase the likelihood of drug self-administration and/or relapse following a period of abstinence from the drug. The difficulty that many face in trying to quit using tobacco products and the comorbidity between stress disorders and nicotine dependence can be explained in part by the biological effects nicotine and stress have on certain areas of the brain, particularly in the reward pathway.

The brain’s reward pathway - the dopaminergic mesolimbic system - typically functions to reinforce survival-promoting behaviors, such as eating, or positive social interactions, producing positive feelings, and serving to motivate such behavior. Drugs of addiction, however, act on the same pathways to produce their characteristic “high” and reinforce drug seeking-behaviors and dependence. Nicotine, for example, is an agonist of the endogenous neuronal nicotinic acetylcholine receptor (nAChR), an ionotropic receptor type found widely dispersed throughout the CNS. nAChRs have been found to be critical in the modulation of dopaminergic activity throughout the mesolimbic system. Several brain regions have been linked to the encoding of reward-related behaviors, including the nucleus accumbens (NAc), ventral tegmental area (VTA), amygdala, and hypothalamus, with a particular emphasis on the dopaminergic projections from the VTA to NAc. The VTA and NAc are strongly implicated in both nicotine addiction and many stress and mood disorders. The variety of inputs that both the VTA and NAc receive - glutamatergic, cholinergic, peptidergic, and serotonergic - function to modulate dopaminergic neuron firing between the VTA and NAc (Figure 1). At the core of encoding reward-related behaviors in these two regions are the distinct modes of the firing of the VTA dopaminergic neurons innervating the NAc: tonic and phasic. Tonic firing is low-frequency and regular, whereas the phasic mode is characterized by high-frequency bursts of firing. Cholinergic signaling - especially as mediated by nAChRs - is critical in facilitating the switch between VTA neurons’ tonic and phasic modes and, therefore, in encoding reward-related information and behaviors. Further, both stress and drug addiction have been reliably shown to be key in determining the basal firing rate for dopaminergic neurons. Combined, this evidence points toward an important connection between stress, addiction, and cholinergic signaling in the dopaminergic mesolimbic system.
Figure 1. A variety of complex neural inputs modulate dopaminergic signaling from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). The illustration above shows a simplified summary of several well-established circuits that influence mood and have been implicated in the dysregulation of mood. Glutamatergic areas include the prefrontal cortex (PFC), hippocampus (HP), and amygdala (Amy), where the dorsal raphe/locus coeruleus (DR/LC) mainly transmit serotonin and norepinephrine (5HT, NE). The hypothalamus (Hypo) also influences the VTA and NAc with peptidergic inputs. (Figure taken from Nestler and Carlezon, 2006).

Like all complex neural systems, the ability of the mesolimbic system to encode nuanced information relies on the amount and type of afferent input it receives. nAChR subtypes are differentially expressed on different types of neurons throughout the VTA and NAc; depending on the subunit composition of the receptor, its affinity for endogenous or pharmacological agonists varies. These receptors’ unique expression patterns lend each region the ability to integrate a variety of signals and encode complex behaviors and are differentially implicated in the pathology of both nicotine dependence and stress. This paper explores these cholinergic influences in the mesolimbic system and the convergence and divergence of the pathologies of nicotine and stress, implicating mechanisms of long-term potentiation (LTP) and exploring potential therapeutic targets.

2. Nicotinic Receptors and Social Stress’ Role on the VTA

Interestingly, mood disorders and social stress have also been shown to affect dopaminergic signaling in the same pathways. Several studies have found that the effects of nicotine use and stress can exacerbate each other, independent of the withdrawal effects common in nicotine addiction. Morel et al., 2018 found that this bidirectional relationship between nicotine and stress is likely mediated by dopaminergic (DA) VTA neurons. Because the etiologies of stress-related and depressive symptoms are often quite varied and complex, studying these in animal models can pose a difficult challenge.

Both nicotine exposure and social stress have been shown to increase the frequency and bursting activity of VTA DA neuron firing. Interestingly, this study found that the effects of stress seem to depend upon the same nAChRs that nicotine acts on. Specifically, both nicotine and stress interact with the $\alpha_7$ homomeric and $\beta_2$-containing heteromeric nAChRs, the two primary nAChRs in the brain. $\alpha_7/\beta_2$ double knockout mice who experienced the social defeat (SD) paradigm did not show the same increased VTA DA neuron firing as wild type mice who experienced SD.
Additionally, knockout mice did not exhibit social aversion, contrasting the typical results of SD on wild type mice (Figure 2). Corroborating this information suggests that nAChRs in the brain are key to both the cellular and the behavioral effects of stress. Unsurprisingly, nicotine injection also failed to induce increased VTA DA neuron firing in knockout mice, confirming that stress and nicotine interact with the same nAChRs.

Furthermore, mice given acute nicotine along with subthreshold SD (SubSD) exhibited much higher VTA DA neuron excitability compared to control mice who experienced SubSD with no nicotine administration. This demonstrated a clear remodeling of nicotinic synapses on the VTA. Mice who underwent SD also had a greater number of cholinergic transporters and nAChR-binding sites, indicating a comprehensive effect of stress on nicotinic pathways in the VTA.

Morel et al., 2018 employed PNU, an \(\alpha_7\) nAChR positive allosteric modulator, to explore subtype-specific effects. PNU-treated mice who experienced SubSD exhibited DA VTA firing increases equivalent to that found in mice experiencing the full SD paradigm. Additionally, these mice exhibited social aversion quite similar to those undergoing the full SD paradigm. Mice who underwent SubSD and were pre-treated with NS9238, a \(\beta_2\) nAChR positive allosteric modulator, exhibited DA VTA firing and behavioral changes similar to WT mice who underwent SubSD. Thus, it seems that activation of the heteromeric \(\beta_2\) nAChR does not significantly modulate the effects of stress. Both PNU and nicotine administered via a cannula led to increased social aversion when paired with SubSD, confirming that this stress-nicotinic relationship was occurring specifically in the VTA.
These results implicate $\alpha_7$ nAChRs as the primary receptor upon which stress has its synaptic effects in the cholinergic VTA system. $\alpha_7$ nAChRs can therefore be considered as possible therapeutic targets for stress and mood disorders going forward.

Interestingly, stress and nicotine both seem to have a significant effect on long-term potentiation (LTP) of synapses on DA VTA neurons. Mice who underwent SD were found to have an increased AMPAR/NMDAR ratio for their DA VTA neurons, signifying LTP occurring at these synapses. AMPAR/NMDAR ratio serves as a marker of LTP, as the insertion of AMPARs, and thus an increase in AMPAR/NMDAR ratio, is the primary biomarker of LTP. LTP at these synapses helps to complete the picture of the cholinergic-stress-VTA pathway as it likely contributes to greater firing rates and bursting activity in DA VTA neurons for mice under stress. Mice treated with PNU also experienced increased LTP on DA VTA neurons (Figure 3).

Changes in LTP may be the main way in which stress and nicotine remodel VTA DA synapses. They both initiate molecular changes which result in AMPAR insertion into VTA DA neurons, leading to an increase in the firing rate of their neurons and likely mediate the behavioral changes associated with stress. Being that these neurons are highly implicated in addiction, LTP at these neurons may also increase the susceptibility of an individual to addiction, nicotine or otherwise. This implicates stress as a risk factor for addiction and also implicates nicotine use as a risk factor for increases in stress response and potentially mood dysregulation.

3. Synaptic Mechanisms: Role of LTP in the Reward Pathway

Morel et al., 2018 found that dopamine firing is likely modulated through LTP as a response to nicotine and/or stress. Here, the mechanisms of modulated dopamine firing through LTP are examined. Through this mechanism, LTP amplifies the reward associated with dopamine release in the mesolimbic pathway. Both stress and nicotine affect the signaling strength of excitatory and inhibitory synapses on dopamine neurons in the VTA through NMDAR-dependent LTP and GABA$_A$R-dependent LTP, respectively.$^{12, 13}$ The mechanisms by which stress and nicotine alter these pathways are very different, but these same pathways play a large role in addiction and reward association.

NMDAR-dependent LTP is crucial for increasing the strength of excitatory synapses. Glutamate signaling on dopaminergic neurons in the VTA drives this process through the reinforcement of excitatory synapses via insertion
of AMPARs postsynaptically.\textsuperscript{14} This LTP pathway involves both AMPAR subtype GluR1 and NMDARs (Figure 4). When glutamate is released from the presynaptic terminal, it binds to GluR1 receptors on the postsynaptic terminal. The binding of glutamate onto GluR1 allows the influx of sodium (Na\textsuperscript{+}) and potassium (K\textsuperscript{+}), which depolarizes the postsynaptic cell. Once the membrane is depolarized, the magnesium (Mg\textsuperscript{2+}) voltage-dependent block on NMDA receptors is released and glutamate binds to these receptors with the help of a glycine or serine cofactor. Once glutamate binds to NMDA, there is an intracellular influx of calcium (Ca\textsuperscript{2+}), which activates Ca\textsuperscript{2+}/calmodulin-dependent protein kinase (CaMKII) through Ca\textsuperscript{2+}-dependent autophosphorylation. Following this, CaMKII phosphorylates GluR1 to increase conductance and targets stargazin-like transmembrane AMPAR regulatory protein in order for AMPA localization and clustering to occur, leading to an increase in AMPARs.

Figure 4. NMDAR-mediated LTP pathway.\textsuperscript{15, 16} (Adapted from Dr. Mann.)

The way nicotine and stress contribute to this LTP pathway differs. In the VTA, some nAChRs are located on the presynaptic terminals of glutamatergic neurons.\textsuperscript{17} Once nicotine binds to nAChRs on the presynaptic terminal, it allows for the influx of Na\textsuperscript{+} and Ca\textsuperscript{2+}, which depolarizes the presynaptic neuron. Depolarization causes further Ca\textsuperscript{2+} influx, which mediates the docking and release of glutamate. Following its release, glutamate binds to AMPARs on the postsynaptic membrane of dopaminergic neurons, leading to NMDAR-mediated LTP as described previously.\textsuperscript{18}

For stress-induced NMDAR-mediated LTP, G-protein coupled (GPCRs) glucocorticoid receptor (GR) signaling is crucial.\textsuperscript{19} Exposure to acute stress leads to a sympathetic nervous system response in which adrenaline is released from the adrenal medulla.\textsuperscript{20} Following this, there is an increase in noradrenaline (NA) in the CNS. With the increase of NA in the brain, corticotropin-releasing factor (CRF) neurons in the hypothalamus are stimulated, which stimulates the anterior pituitary, and adrenocorticotropic is released. This activity in the hypothalamic-pituitary-adrenal (HPA) axis elicits the release of corticosteroids from the adrenal cortex into the bloodstream. These corticosteroids can pass through the blood-brain barrier, and once in the brain, they bind to GRs. GRs in dopaminergic neurons of the nucleus accumbens (NAc) communicate with dopaminergic neurons in the VTA through glutamatergic interneurons.\textsuperscript{21} When the corticoids bind to these GRs on dopaminergic neurons, glutamate release through this positive feedback pathway excites the dopaminergic neurons in the VTA, which when stimulated leads to LTP. While nicotine and stress both increase DA VTA firing, nicotine acts quickly through an ionotropic receptor while stress acts slower on a metabotropic receptor that requires many different neuroendocrine pathways.

Conversely, both nicotine and stress inhibit GABA\textsubscript{A}R-mediated LTP, which leads to decreased inhibition of dopaminergic neurons in the VTA (Figure 5). This form of LTP is characterized by an enhancement of inhibitory postsynaptic potentials (IPSP) via increased
GABA release. When GABAergic neurons release GABA from their presynaptic terminals, GABA binds to GABA_{A}Rs on the postsynaptic terminals of dopaminergic neurons in the VTA, hyperpolarizing these neurons via an influx of intracellular chloride (Cl{\textsuperscript{-}}). Following numerous IPSPs, there is a rebound depolarization of the membrane, and, subsequently, voltage-gated Ca{\textsuperscript{2+}} channels (VGCC) on the dendrite are activated. With the activation of VGCCs, there is an influx of Ca{\textsuperscript{2+}}. Furthermore, when glutamate activates NMDARs, GABA_{A}Rs in neighboring synapses may be potentiated. The influx of Ca{\textsuperscript{2+}} is crucial for the mechanism of LTP. It is suspected that this increase of intracellular Ca{\textsuperscript{2+}} leads to the release of nitric oxide (NO), a retrograde messenger. NO activates presynaptic soluble guanylate cyclase, which produces cyclic guanosine monophosphate (cGMP). cGMP activates the cGMP-dependent protein kinase, which increases GABA release from the presynaptic neuron. When this type of LTP is inhibited, GABA release decreases, resulting in less inhibition on DA neurons in the VTA. Research shows that there is an impairment of this form of LTP following the injection of nicotine and acute stress.

The mechanism by which nicotine and stress lead to inhibition of GABA_{A}R-mediated LTP is not completely known. α7-containing nAChRs are localized on the presynaptic terminals of GABAergic neurons in the VTA. When nicotine binds to these nAChRs, the GABAergic presynaptic terminals desensitize quickly. This leads to less release of GABA, which inhibits the LTP pathway on postsynaptic terminals of DA neurons in the VTA. For acute stress, the glucocorticoid pathway described in NMDAR-mediated LTP contributes to reduced GABA firing. The initial response to this acute stress is an increase in GABA firing mediated through the NO-cGMP-PKG pathway, but the long-term effect of this acute stress is an inhibition in this form of LTP. After sustained hyperpolarization, there is a shift in Cl{\textsuperscript{-}} reversal potential, making GABA become excitatory rather than inhibitory. Although more research needs to be performed to elucidate the specific pathway, both nicotine and stress affect this LTP pathway.

These two LTP neural mechanisms play a key role in how nicotine and stress increase DA VTA release on a synaptic level. By increasing excitatory input on dopaminergic neurons via NMDA-receptor mediated LTP and decreasing inhibitory input on dopaminergic neurons via GABA-mediated LTP, there is an increase in excitatory postsynaptic potentials (EPSP) on the dopaminergic neurons, leading to enhanced dopamine firing. With greater DA firing, the reward association increases as the mesolimbic pathway of reward is more active. Since nicotine and stress have similar results on DA VTA firing via different pathways involving nAChRs and GRs, respectively, showing that nicotine and stress exacerbate each other. With nicotine and stress's underlying LTP mechanisms, which modulate the firing rates of DA VTA neurons, long-term nicotine use and stress can both have detrimental effects on the excitation of DA neurons and transmitter release; in this way, increased

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Figure 5. GABA_{A}R-mediated LTP pathway. (Adapted from Govindpani et al.)
dopamine signaling underlies the neural mechanism for addiction. Furthermore, with LTP changing neural connections, this can lead to effects such as depression during withdrawal of nicotine due to not enough stimulation of dopamine pathways in the brain.

4. Future Directions: Decreasing Dopamine Firing as a Potential Therapy

Morel et al. 2018 demonstrate that social defeat triggers increases in VTA DA neuron spontaneous activity. This is exacerbated by nicotinic binding to the $\alpha_7$ nAChR in the VTA. Both the frequency and burst activity increases significantly in mice exposed to SD and nicotine. This novel finding demonstrates that local VTA exposure to nicotine and SubSD is sufficient to trigger social aversion. Given that activation of nAChRs has an effect on DA VTA signaling, DA signaling is implicated. Altogether, this data suggests that dopamine signaling is necessary for the behavioral manifestations of social stress. Preventing this increased dopamine firing could, therefore, be a potential therapy for social aversion, which has been established to be a symptom in depression.

To test how dopamine modulation directly impacts the VTA, Chaudhury, et al. 2013 selectively altered levels of dopamine in the VTA using optogenetics to test social avoidance in order to evaluate depression-like symptoms in mice. While Morel et al. found that nicotinic binding leads to alterations in DA signaling, it did not directly establish that modifying DA signaling changes social aversion-like symptoms. This is why optogenetic inhibition of dopamine in the VTA is a powerful tool to investigate the potential therapeutic opportunities for altering dopamine signaling.

Induction of phasic firing in VTA neurons in the VTA–NAc pathway in mice that were undergoing SD induced a susceptible depressive phenotype with increased social avoidance. Mice that were resistant to social avoidance, after being exposed to SD, became depressed when DA phasic firing was optogenetically induced. Stimulation of phasic dopamine firing corresponded to a rapid onset of the susceptible phenotype after stress exposure. The fact that social stress was a precursor to dopamine alteration in rendering a depressed phenotype shows the context-dependent alterations that occur. This finding emphasizes that dopamine is being directly acted on, which confirms that VTA DA neurons serve in stress-response modulation, contributing to a depressive-like phenotype.

Deep brain stimulation (DBS) therapies to the VTA could be an effective way to reduce dopamine firing and mediate anti-depressive effects. The circuit and context-specific nature of this pathway make it a prime therapeutic target. If dopamine activity is restored to tonic firing following stress, social defeat scores decrease. In DBS surgery, an electrode is stereotactically implanted into specific neuroanatomical regions, and electrical stimulation is provided via a pacemaker-like stimulator. DBS is used in movement disorders such as Parkinson’s disease. Recently, DBS has been studied for neuropsychiatric disorders.

Open-label studies have convincing data that suggest that DBS is effective in mediating antidepressant effects in individuals who do not respond to conventional treatments for depression. Data from clinical studies of the neurophysiological effects of DBS suggest that electrical stimulation leads to both short-term and long-term effects on firing rates and patterns. Although the direct mechanism of action by which DBS works is unknown, it has been proposed that DBS inhibits neurons being stimulated, potentially by modulating the electrical activity of potassium and sodium channels. Another
The proposed mechanism of DBS is that it disrupts neuronal signals and activity from being propagated in neural pathways.

Recently, a review was published that investigated DBS for treatment-resistant depression. The review highlights clinical trials where DBS was used to treat depression in different brain regions. The results from this review emphasize the importance of the medial forebrain bundle (MFB)—a pathway between the VTA and lateral hypothalamus—as a potential therapeutic target for DBS in the VTA-NAc pathway (Figure 6).

Figure 6. The medial forebrain bundle (MFB) connects the VTA and lateral hypothalamus. The VTA is connected to subcortical and cortical prefrontal regions. The mesolimbic reward pathway is contained within the MFB, composed of dopaminergic axons that project from the VTA to NAc. (Figure taken from McGill University)

The nerve fibers of the reward circuit are located in this pathway, which is composed of dopaminergic neuron axon projections that go from the VTA to the NAc. Even though this pathway involves brain regions beyond the VTA - NAc connection that Morel et al. focus on, it is useful to evaluate DBS as a potential therapy.

Despite being limited to 11 patients, findings indicate that DBS of the MFB could induce antidepressant effects. Short-term bilateral stimulation of the MFB led to a rapid reduction of depressive symptoms in 6 out of 7 patients in one study. In other studies, the antidepressant effects were also consistent, with no evidence of cognitive impairment following months of stimulation. The hypothesized mechanism of action for these encouraging results is that DBS activates the mesocorticolimbic by modulating system dopaminergic glutamatergic and neurotransmission. The circuit that achieves this neurotransmission may be that DBS alters the firing of glutamatergic fibers from the mPFC to the VTA, which indirectly modulates dopaminergic firing at the VTA. Even though the mechanism has yet to be fully elucidated, the results show that DBS reduces antidepressant-like symptoms without yielding severe or common side effects.

DBS is a promising future direction given that phasic dopamine firing in the VTA – NAc pathway leads to depressive features in mice, which optogenetic alterations reduce. The study cited makes evident that DBS is surgically viable and potentially modulates the VTA – NAc projection. If DBS can alter dopamine in the VTA, as proposed, then this therapy is especially promising.

5. Sleep Disorders: Contribution of Dopamine in the VTA - NAc Pathway

It has been shown that nicotine users experience decreased sleep quality. Since Morel et al. focus on how nAChRs mediate the combined effect of stress and nicotine by altering the activity of DA neurons in the VTA, this activity may also affect sleep disorders. In addition to the stress and depression effects of altered DA signaling in the
VTA, DA regulates motivational processes via this pathway. DA neurons project from the VTA to many brain regions (Figure 6). To study how the VTA—NAc pathway specifically alters sleep, researchers used chemogenetic and optogenetic manipulations with polysomnographic recordings. These recordings are a diagnostic test used in sleep medicine to comprehensively record physiological changes during sleep. Chemogenetics is similar to optogenetics but uses chemically engineered molecules and ligands instead of light and light-sensitive channels (opsins). These methods provide incredible techniques to study the relationship between neuronal activity and behavior.

VTA dopamine neurons have been found to undergo changes in firing in rapid eye movement (REM) sleep and non-REM (NREM) sleep, making them interesting candidates to further examine. Through complex analysis of DA neuron activity in VTA projections, researchers found that these neurons are altered by different arousal states: in NREM sleep their activity is reduced, and when active they maintain long-term wakefulness. Overall, dopamine neurons that project from VTA – NAc promote wakefulness and suppress sleep. Selectively optogenetically activating the neurons maintained wakefulness and suppressed nest-building behavior, which is where mice sleep. Inhibiting the activity of these neurons promotes sleep-related nesting behavior. Even though this study examined the VTA projections to the NAc, prefrontal cortex, amygdala, and dorsolateral striatum, the NAc was the only projection that stimulated arousal. The NAc increased wakefulness and decreased NREM and REM sleep. While other pathways such as the prefrontal cortex have a larger effect on REM duration, NAc was still significant in modulating arousal.

These findings are important because they implicate VTA dopamine in mediating stress and sleep-like behaviors. Nicotine, as established by Morel et al., increases the activity of these DA neurons, which induces stress-like behavior as a symptom of depression. It is also possible that the same mechanism leads to heightened arousal-like states, hurting the ability to sleep. A recent survey-based study found that college students who use electronic cigarettes report significantly higher difficulty sleeping compared to non-users. Interestingly, electronic cigarette users also report more difficulty sleeping compared to traditional cigarette users, suggesting that electronic cigarettes may be more potent for nicotine than traditional cigarettes and thus may pose an increased risk for the side effects of nicotine. Taken together, nicotine's effect on DA firing has extensive implications, which likely contribute to sleep difficulty.

Conclusion

The combination of social stress and nicotine binding to acetylcholine receptors in the VTA modulates DA firing through various synaptic mechanisms. Modulations in DA firing in the VTA have broad implications related to several mood and sleep disorders. This social stress-nicotine bidirectional interplay supports and partially explains the strong association between behavioral disorders and nicotine addiction. The data presented in this paper thus demonstrate a comorbidity between social stress and nicotine dependence: a pattern wherein both pathologies enhance the other. Elucidating the synaptic link between the disorders has therapeutic implications as well, where modulation of dopamine activity via DBS or antagonistic binding to acetylcholine receptors may reduce the stress and depressive symptoms that these mechanisms are sufficient to induce. The complexity of these mood-responses
are mediated by diverse neural, endocrine, and physiological pathways, which leaves a lot of mechanisms and connections unknown. Further investigating the connections between drugs and the environment, and the effects they have on synapses, will uncover more of the mechanisms by which a broad range of mood disorders arise.

The importance of understanding these neural processes is especially important today, as nicotine vaping rates have been rapidly increasing in the United States. In 2018, a steep increase in vaping was observed, with 37% of high school seniors reported vaping activity.\(^3\) In 2019, 10.5% of middle schoolers and 27.5% of high school students reported vaping, an alarming increase from past years.\(^3\) In many cases, these students do not know that nicotine is contained in their electronic cigarettes, or do not think that nicotine alone is harmful. Discovering these synaptic mechanisms will demonstrate to uninformed teens how nicotine is detrimental and can be a risk factor for mood and sleep disorders, especially when stressors are involved. It is imperative that information on these dangers of nicotine becomes more widespread so that society will have a comprehensive understanding of how consuming nicotine can put people at risk for adverse behavioral disorders, independent from addiction.

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