Differences in Nicotine Action and Dopamine Function During Nicotine Withdrawal

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Abstract

Nicotine addiction is a significant public health issue, as it greatly raises the risk of chronic health issues such as lung cancer and cardiovascular disease, with adolescents being especially susceptible to addiction. Nicotine is the main active component found in tobacco products and works by binding to nicotinic acetylcholine receptors (nAChRs). This leads to the release of dopamine, a neurotransmitter that plays a key role in reinforcing and maintaining the addictive properties of nicotine by triggering the brain's reward pathway. In this review I will be looking at differences in nicotine action and dopamine function via dopamine transporters and dopamine-metabolizing enzymes in humans and animals, which play a pivotal role in the reuptake and degradation of dopamine. These are key factors in the regulation of dopamine levels within the brain, influencing the manifestation of nicotine withdrawal symptoms upon cessation of nicotine use that draw people back towards use of the drug.

Introduction

Nicotine addiction is a major public health issue, especially among adolescents, with over 8 million (11.3%) of middle and high school students in the United States reporting that they were currently using tobacco products in 2022 [1]. This is especially concerning since tobacco smoking increases the risk of contracting tuberculosis, chronic obstructive pulmonary disease (COPD), and developing three major types of lung cancer [2, 3]. These diseases are not limited to just tobacco smoking and personal nicotine use; secondhand smoke also contributes to developing diseases and the large-scale effects. In 2019, there were over 8 million tobacco related deaths, including secondhand smoke and chewing tobacco related to tobacco smoking [4]. In addition to the large-scale health effects, there are large-scale economic effects as well, with the total global cost related to smoking tobacco is estimated to be over 1 trillion US dollars annually [5].

Nicotinic acetylcholine receptors (nAChRs) are a crucial part of nicotine's effects. These receptors are found on neurons throughout the central and peripheral nervous systems and are responsible for rapid synaptic signaling. nAChRs are pentameric structures made up of a combination of five individual subunits, including α2–α10, and β2–β4 subunits in varying organizations [6]. Being ligand gated, nAChRs require a ligand such as nicotine or acetylcholine to bind to the receptor to initiate a response. Once nicotine binds to a receptor, it allows the flow of positive ions (Na^+) into the neuron, causing it to fire [7]. Nicotine also binds to the nicotinic acetylcholine receptors present on dopaminergic neurons leading to the release of dopamine in the synapse [8, 9] .

Dopamine (DA) is an important neurotransmitter responsible for reinforcement learning and the pleasurable sensation associated with nicotine intake [8]. Along with this mild sense of euphoria, acute nicotine consumption also leads to temporary heightened cognitive function. Both are favorable symptoms which serve as positive reinforcement for the individual to continue nicotine use to maintain these symptoms [9]. However, these initial positive symptoms are not the sole cause of nicotine dependence. For instance, a 2005 study by Chaudhri et al.

found that nicotine's reinforcement properties due to positive acute symptoms were relatively weak, yet there was still prolonged use. This suggested multiple roles for nicotine and its reinforcing properties, including visual stimuli and the avoidance of withdrawal [10].

Oftentimes with nicotine addiction, people experience intense feelings of withdrawal and/or cravings for the source of the nicotine. Withdrawal refers to a collection of physical and psychological symptoms that arise after an individual stops drug use after forming an addiction to the substance. Withdrawal symptoms have been shown in both human and animal models. In a 2021 study by Chellian et al., after cessation of nicotine exposure in various forms, both mice and rats showed signs of anxiety, depression, increased appetite, attention deficits, and cognitive deficits. These symptoms were similar to many withdrawal symptoms shown in humans as well [11]. These withdrawal symptoms occurred due to the formation of an addiction to nicotine, where dopamine and acetylcholine neurotransmission has gone haywire.

After nicotine exposure over an extended period of time, nAChRs become desensitized and have less of a response to nicotine binding, making it less likely for dopaminergic neurons to fire as a result [12]. Chronic nicotine use was also associated with a decrease in D2/D3 dopamine receptor availability. In a study conducted by Fehr et al. in 2008, nicotine dependent smokers were shown to have significantly lower amounts of D2/D3 dopamine receptors when compared to non-smokers, but the severity of dependence seemed to have no impact on receptor amount [13]. As nAChRs lose sensitivity and dopamine receptor availability decreases from chronic nicotine stimulation, this builds nicotine dependence, where cessation can cause withdrawal symptoms. These symptoms serve as additional motivation for a return to nicotine use. This was backed up in another human study by Robinson et al. in 2019, which showed that more negative withdrawal symptoms are associated with a higher likelihood of relapse [14]. There are many forms of therapy for smoking addiction, including nicotine replacement therapy, prescription drugs such as bupropion and varenicline, as well as behavioral therapy [15-18]. These forms of treatment target different areas of nicotine dependence and withdrawal to improve chances of smoking cessation. In order to improve smoking cessation treatments, it is important to understand the mechanisms behind nicotine dependence and withdrawal.

Nicotine transmission and degradation

Nicotinic interneurons are abundant and crucial regulators of neural signaling in the nucleus accumbens (NAc). The NAc is an area of the brain that regulates stimuli related to emotions and reward, using information from other parts of the emotional circuits of the brain, also known as the limbic system. The NAc is connected to many disorders related to emotion and reward such as depression and addiction, as well as being involved in motivational behaviors like eating and drinking [19]. Nicotine increases the amount of extracellular dopamine in the nucleus accumbens due to mesolimbic dopaminergic projections to the cell of the nucleus accumbens being activated [20]. This increase in dopamine could lead to increased motivation and contribute to positive reinforcing factors. In a 2022 human neuroimaging study by Kroemer et al. looking at links between depression and appetite, differences in nucleus accumbens activity were linked to differences in appetite in patients with depression [21]. This link between the NAc and appetite motivation may suggest the NAc's role in relapse, as nicotine cravings

seek positive reinforcement and avoid negative withdrawal similar to cravings for food during hunger.

All dopaminergic projections driving motivational behaviors in the NAc are based in the ventral tegmental area (VTA) [22-24] . The VTA supplies dopamine throughout the limbic circuit, driving reinforcement, and is stimulated by nAChRs on dopaminergic neurons. A 2021 study by Nguyen et al. looking at responses to nicotine injections in anesthetized mice saw different responses for DA neurons projecting to different areas of the brain. They saw inhibition of VTA DA neurons projecting to the amygdala, shown to increase anxiety. On the other hand, they saw activation of VTA DA neurons projecting to the nucleus accumbens, part of the reward pathway. These are part of two separate circuits in the brain, with each facilitating different effects on behavior [25]. This further supports the role of the NAc in nicotine addiction, as well as potentially displaying a role for the amygdala in anxiogenic symptoms apparent during withdrawal.

In addition to the NAc, the VTA also sends major dopaminergic projections to the prefrontal cortex (PFC) [26, 27]. The prefrontal cortex (PFC) is involved with attention and decision making and matures rapidly during adolescence. Because of this, looking at the effects of nicotine on the prefrontal cortex during adolescence can reveal different reasons for the susceptibility to addiction and withdrawal of nicotine in adolescents [28]. There are many nAChR expressing neurons within multiple layers of the PFC that have direct effects on transmission. Presynaptic nAChRs can augment glutamatergic signals, including input from the thalamus in layer V pyramidal neurons in the PFC, which have projections to the hypothalamus and striatum [28]. In a 2004 study by Young et al. looking at nicotine's effects on attention in normal mice, mice were given microgram doses of nicotine prior to completing the 5-choice serial reaction-time (5-CSR) task. Nicotine was shown to increase prolonged attention, and the number of correct responses. These same researchers also looked at the impact of the α7 nAChR subunit, by seeing how α7 nAChR knockout mice did in the 5-CSR task after nicotine dose. These knockout mice both had more omissions in responses and took more time to learn the task, showing the possibility that α7 nAChR subunits contribute to regulation of attention [29, 30]. This improvement in attention for the standard mice supports other human studies that show improved attention post nicotine use [31]. This may play a role in the positive reinforcement associated with nicotine use and thus contribute to nicotine dependence. However, a possibly larger impact of the PFC may be during withdrawal, as it is involved with reward processing, and may play a large role in nicotine seeking behavior.

The striatum is an interconnected neuron structure that makes up a significant part of the basal ganglia. The striatum plays a part in many complicated behaviors, including motor control, habit formation, reward, and emotion [32, 33]. It consists of the dorsal and ventral striatum, and the location from which dopaminergic signals arrive varies depending on the region of the striatum. For ventral striatum which includes the nucleus accumbens, dopaminergic input originates from the VTA. For dorsal striatum, there are dopaminergic projections which come from the substantia nigra pars compacta, which controls general motor movements [34]. Medium spiny projection neurons (MSNs) are found on the striatum and play a key role in striatal neurotransmission. NAChRs are not expressed on MSNs, however chronic nicotine use has been shown to modulate neurotransmission in the striatum [35]. A 2018 study by Licheri et

al. looked at the effects of nicotine on electrical signals in brain slices containing striatum prepared from juvenile male rats. In their study, they found that nicotine reduced the frequency of excitatory inputs to MSNs and decreased dorsal striatum neurotransmission. NAChR desensitization was also found to repress DA release in the striatum including the NAc shell [36].

The hippocampus is part of the limbic system and deals with the processing of memories, regulating emotions, and learning [37]. NAChRs are found throughout the hippocampus and with nicotine, are involved with synaptic plasticity in the hippocampus [38]. A 2005 study by Ge and Dani looked at slices of the hippocampus in wild-type mice to see possible associations between nAChRs and pyramidal neurons in the CA1 region of the hippocampus. They found that presynaptic nAChRs increased the release of glutamate, and that enough nAChR expression on CA1 pyramidal neurons influenced synaptic plasticity in the hippocampus [39]. Another study in 2014 by Damborsky et al. looked at the effects of neonatal nicotine exposure in rats. They observed persisting functional changes in the hippocampus and an increase in overall excitatory neuronal signaling, with no change in inhibitory signaling. Additionally, they found an overall decrease in presynaptic nAChR function on GABAergic neurons, which along with their other findings, could play a role in the behavioral changes observed after nicotine exposure in both animals and humans [40].

Degradation of nicotine transmission

In addition to nicotine transmission in various areas of the brain, the degradation of nicotine through various enzymes may also play a role in addiction and withdrawal. The majority of nicotine is metabolized in the liver, with the CYP2A6 enzyme being responsible for 90% of nicotine deactivation [41]. During the degradation process, 70-80% of nicotine metabolization leads to cotinine, a primary metabolite of nicotine. The ratio of cotinine to 3′-hydroxycotinine (another nicotine metabolite) is used as a biomarker for the activity of the CYP2A6 enzyme to observe the rate of nicotine metabolism [42]. Genetic differences in the CYP2A6 enzyme impact nicotine metabolism and smoking related behaviors, including withdrawal symptoms [41]. A 2008 study by Rubinstein et al. looked at adolescent smokers categorized into fast and slow nicotine metabolizers. Even after factoring in an increased number of cigarettes per day, faster nicotine metabolizers were shown to have more severe withdrawal symptoms compared to slower metabolizers, presenting an increased risk of addiction [43].

Acetylcholinesterase (AChE) is an important enzyme in the nervous system and is responsible for stimulating the breakdown of acetylcholine to end transmission and prevent constant nerve firing. AChE is found primarily in the central nervous system, specifically in neuromuscular junctions and cholinergic synapses [44]. To observe the effects of AChE on nicotine addiction, many studies looked at acetylcholinesterase inhibitors such as Donepezil. A 2012 study by Kimmey et al. showed that donepezil administration in rats led to reduced nicotine seeking behavior [45]. This is supported by other studies showing various other AChE inhibitors being linked to reduced nicotine seeking behavior in rats [46, 47]. Together, these results may also indicate that increased acetylcholine activity is related to reduced nicotine reinforcement.

Dopamine transmission/ degradation

A large part of nicotine reinforcement is regulated by dopamine transmission in the mesolimbic dopamine system [48]. A key part of the mesolimbic dopamine system is the ventral tegmental area (VTA), a brain structure that plays a pivotal role in motivation and the reward pathway [49]. A 2003 study by Laviolette and van der Kooy explored dopamine transmission in the VTA and its role in nicotine reward. They applied nicotine directly to the VTA in rats and looked at the effects that dopamine receptor blockades had. Their results confirmed the VTA as a vital part of regulating aversive and rewarding effects of nicotine. Blocking the DA receptors showed to reverse nicotine's effects and switch previously negative nicotine symptoms into rewarding ones [50]. Different DA receptors play varying roles, as a 2005 study by Bruijnzeel and Markou observed the role of D1 and D2 receptors in the posterior hypothalamus/anterior VTA by using D1-like and D2-like antagonists in rats. They found that blocking D1 receptors in saline treated rats increased reward thresholds to a significantly greater degree compared to nicotine treated rats. When looking at D2 receptors, reward thresholds were similar regardless of nicotine administration, indicating a larger role for D1 receptors in the effects of nicotine on reward [51].

The nucleus accumbens also plays a large role in dopamine transmission, and DA transmission in nucleus accumbens directly regulates aversive and rewarding effects of nicotine [52]. The nucleus accumbens is composed of its shell and core, with the shell of the nucleus accumbens being the most sensitive to dopamine transmission after acute nicotine use [53]. A 2000 study by Cadoni and Di Chiara studied the effects of behavioral sensitization to nicotine in dopamine transmission in the shell and core of the nucleus accumbens in rats. They observed a lower dopamine response in the shell of the nucleus accumbens, while seeing the opposite, an increased response, in the core. This suggests differing roles and responses for the core and shell of the nucleus accumbens [54]. Not only do different regions of the nucleus accumbens play different roles, the nucleus accumbens may also play a role in sex differences for nicotine withdrawal. A 2017 study by Carcoba et al. used rats to investigate whether sex differences in nicotine's aversive withdrawal symptoms was regulated by the nucleus accumbens. They found that male rats experienced lower amounts of dopamine during nicotine withdrawal compared to females, possibly explaining part of the variation in withdrawal symptoms based on sex [55].

The prefrontal cortex makes up a major part of the brain and is responsible for decision making and executive control. However, during drug addiction, its capacity to provide responses and execute decisions is greatly reduced. Simultaneously, the prefrontal cortex becomes hyperactive in response to drug seeking stimuli based on the predictability of a reward being obtained [56]. The prefrontal cortex's response to nicotine varies in some ways compared to other parts of the brain such as the nucleus accumbens. Depending on the type of stimuli, levels of dopamine transmission can be higher or lower in the prefrontal cortex when compared to the nucleus accumbens [57]. A 2013 study conducted by Gozen et al. analyzed whether nicotine exposure influenced D1 receptor expression in various areas of the brain including the prefrontal cortex. After administering nicotine in rats, they found significantly higher D1 receptor expression in nicotine treated rats in comparison to the control group. This increase was seen in all three of the brain areas observed, the prefrontal cortex, VTA, and STR [58]. This higher expression of D1 receptors likely corresponds to increased activity in these brain areas to reward and cues related to nicotine. Thus, dopamine transmission in these brain areas may

increase when presented with nicotine associated cues, leading to further nicotine seeking and craving during withdrawal.

As previously mentioned, the striatum also plays an important role in dopamine release and the reward pathway. In the striatum, reward signaling is primarily conveyed through the release of dopamine in rapid bursts, rather than through individual spikes and sustained activity [59]. Different dopamine receptors in the striatum also have been shown to have varying effects on nicotine response. A 2006 study by Tammimäki et al. explored the effects of chronic nicotine administration on dopamine transmission in dorsal striatum in mice. They found that during nicotine administration, both overall dopamine transmission and extracellular dopamine levels were elevated in the dorsal striatum. Quinpirole, a D2/D3 agonist that generally reduces locomotor activity was given to mice, and mice treated with nicotine were slightly less affected by quinpirole. This may mean that D2/D3 receptors play a minor role in dopamine transmission differences in nicotine addiction [60]. As many of these studies were observed in rats and mice, striatal dopamine release after smoking has been analyzed in humans as well. A 2013 study by Le Foll et al. used neuroimaging technology to look at dopamine levels in humans after smoking, especially in striatal regions with abundant D2 and D3 receptors. After smoking, subjects had significantly decreased withdrawal symptoms and cravings, and motivation to smoke corresponded with the amount of dopamine released in the striatum. D3 areas had increased dopamine release after smoking compared to other areas, indicating a possible role for D3 receptors in cravings and withdrawal symptoms [61].

The dorsal hippocampus is involved with feelings of anxiety, and therefore D1 and D2 receptors in the hippocampus may play a role in anxiety produced by nicotine [62]. A 2010 study by Zarrindast et al. looked at the role of ventral hippocampal dopamine receptors on nicotine's anxiogenic effects in rats. They found that D1 receptor antagonist SCH23390 and D2 receptor antagonist sulpiride both decreased anxiety-like symptoms due to nicotine use. This may suggest that blocking D1 and D2 receptors reduces the anxiogenic response caused by nicotine induced dopamine release [63].

Dopamine Transporter (DAT) and Dopamine Reuptake

Dopamine transporters (DAT) are crucial to dopamine function, since they are responsible for facilitating dopamine reuptake, moving extracellular dopamine back into the neuron. DAT is especially present in clearing dopamine in the striatum, where 80% of the dopamine is transmitted [64]. Differences in DNA methylation for the DAT gene has been linked to varying levels of nicotine dependence, supporting other evidence for the link between DAT and the effects of nicotine [65]. In addition to differences in DNA methylation, genetic differences also play a role in the link between DAT and nicotine. The SLC6A3 gene is responsible for the DAT protein, and the 10r/10r genotype of this gene could decrease SLC6A3 expression in humans. Those who are homozygous for the 10r allele have less DAT proteins and therefore an increased amount of extracellular dopamine and are less likely to be nicotine dependent compared to people with the minor allele [66]. Both looking at DNA methylation and genetic differences can open doors to treatments targeting the DAT protein in reducing withdrawal symptoms.

On top of genetic differences, nicotine use has been shown to impact DAT protein activity in many areas of the brain. A study by Hadjiconstantinou et al. in 2010 looked at the DAT protein structure and function in rat striatum during nicotine withdrawal. They observed increased DAT activity, meaning faster DA clearance which contributes to lower DA levels observed during withdrawal. After later using DAT inhibitors, DA level increased and reached similar levels to rats not treated with nicotine, which further confirms DAT's role in reduced extracellular DA during nicotine withdrawal [67]. Other studies have had similar results, showing unregulated DAT levels after chronic nicotine exposure contributing to reduced extracellular dopamine levels [68]. The relationship between nicotine and DAT does not appear to be strictly linear, however. A 2016 study by Kambeitz et al. looked at the interaction of DAT and nicotine in humans in decision making based on reward. Interestingly, they found that performance on decision making tests were dependent on an individual's DAT binding potential. For those with low DAT binding potential, nicotine negatively affected their learning rate and consistency on test performance. However, for those with higher DAT binding potential, these effects were not observed [69]. This presents another avenue to explore nicotine-DAT protein interactions, based on DAT binding potential.

Monoamine Oxidase (MAO) and Dopamine Degradation

Monoamine Oxidase (MAO) is an enzyme responsible for the breakdown of dopamine. There are two types of Monoamine Oxidase, MAO-A and MAO-B. In the brain, 80% of MAO is MAO-B, with presynaptic MAO metabolizing dopamine, and MAO-B metabolizing dopamine in glial cells and the synaptic cleft [70]. Tobacco smokers are shown to have reduced MAO-B activity, and smoking reduces overall MAO activity in the brain and other tissues. During withdrawal, these reduced MAO levels and activity in the brain slowly return to normal. This means decreased extracellular dopamine, which contributes to the depressive symptoms experienced during withdrawal [71]. However, MAO seems to have differing effects on somatic withdrawal symptoms compared to depression. A 2013 study by Malin et al. looked at the effect of inhibiting MAO on somatic nicotine withdrawal symptoms in rats. They observed that when inhibiting both MAO A and B, somatic withdrawal symptoms were significantly increased in nicotine treated rats. When inhibiting only MAO A, similar increases were observed. However, when solely inhibiting MAO B, somatic withdrawal symptoms were reduced. This suggests differences in MAO A and B in terms of nicotine interaction and the intensity of withdrawal symptoms [72].

COMT and Dopamine Degradation

Catechol-O-methyltransferase (COMT) is an enzyme involved with the breakdown of neurotransmitters including dopamine. While DAT is primarily responsible for dopamine breakdown in brain areas such as the nucleus accumbens and striatum, COMT breaks down dopamine in areas with low levels of DAT, such as the prefrontal cortex. COMT is only found on postsynaptic neurons and glial cells, and accounts for about 50% of dopamine elimination in the prefrontal cortex [73]. Polymorphisms in the COMT gene have been shown to impact nicotine withdrawal. A 2013 study by Herman et al. analyzed the impact of the COMT Val158Met polymorphism on nicotine effects in humans. They found that the Val/Val genotype was associated with more severe withdrawal symptoms and worse subjective feeling in people [74].

Another study added to the link between the Val158Met polymorphism and nicotine dependence, and added that on the other hand, the Met/Met genotype has been linked to higher quitting success rates with nicotine replacement therapy [75].

Role of Nicotine in Withdrawal and Relapse

During nicotine withdrawal, people experience a variety of symptoms known as withdrawal symptoms after cessation of drug use. These symptoms include both somatic and cognitive symptoms and play a large role in drug relapse. These symptoms include depression, appetite changes, anxiety, irritability, and other negative symptoms [11, 76]. Acute nicotine use has been found to increase nAChR activity, however over longer periods of nicotine use, nAChRs experience desensitization, where they become less receptive to neurotransmitters over time [77]. Since nicotine desensitizes nAChRs over time, chronic nicotine use plays a role in altering mesolimbic dopamine neuron function. Desensitization over chronic use may play a large role in nicotine withdrawal symptoms as it influences nicotine dependence [78]. A 2009 study examined saturation of α4β2 nAChRs in tobacco-dependent smokers. They found for these tobacco-dependent smokers, 96% to 98% of α4β2 nAChRs were occupied during the day, and that around 50% of these nAChRs were desensitized. They also found that almost all of the α4β2 nAChRs needed to be occupied to satiate nicotine cravings, as smoking a quarter of a cigarette occupied around 75% but had little effect on reducing cravings [79]. These results may indicate that keeping nAChRs occupied is a motivation for nicotine cravings and that activation of non-desensitized α4β2 nAChRs provides positive reinforcement contributing to addiction. Furthermore, this may indicate a link to the prefrontal cortex, where keeping nAChRs occupied serves as motivation for nicotine seeking during withdrawal.

There is evidence showing that nAChR desensitization is directly related to its upregulation, as more nAChRs may be required to achieve similar responses after desensitization [79, 80]. NAChRs upregulation plays a significant role in the manifestation of withdrawal symptoms, especially after chronic nicotine use. After chronic nicotine administration, smokers experience an increase in the number of nicotine binding sites, or nAChRs [81, 82]. The upregulation of nAChRs has been shown in vitro for both human and animal cells, and may depend on multiple underlying processes, of which many are currently unknown [83, 84]. A study conducted by Trauth et al. in 1999 looked at nAChR upregulation in adolescent and adult rat brains in response to nicotine use. They found upregulation of nAChRs in both adolescent and adult rats, however they varied depending on brain areas. Adolescent rats showed mostly uniform upregulation throughout brain areas with nAChRs, while adult rats displayed significantly less upregulation in the midbrain in relation to the cerebral cortex and hippocampus. Thus, midbrain nAChR upregulation was significantly higher in adolescent rats compared to adults [85]. Upregulation of nAChRs has also been shown to be dependent on nAChR subtype. A 2007 study by Mao et al. looked at nAChRs in adult rat brains to see the effects of nicotine use on nAChR upregulation. They observed that α4β2 receptors containing the α5 subunit were resistant to upregulation, while those without the α5 were consistently prone to upregulation after chronic nicotine use. This may suggest a regulatory role for the α5 subunit in nAChR upregulation [86]. Considering these variables, both nAChR desensitization and upregulation play significant roles in nicotine withdrawal, especially nicotine cravings leading to relapse.

Dopamine in Withdrawal and Relapse

Dopamine also plays a significant role in withdrawal as there are unusually high DA levels following nicotine use, and chronic nicotine administration leads to adaptations in dopaminergic neurons and DA reuptake [87]. Alongside high DA levels, increased DA reuptake is present following nicotine administration. During withdrawal, there is a significant drop in extracellular DA levels, due to both decrease in DA release and increased DA reuptake [88]. A 2013 study by Zhang et al. tested DA levels in mice during nicotine withdrawal and observed decreased basal DA concentration in the nucleus accumbens. Re-exposing the mice to nicotine temporarily increased the DA concentration and reversed the previously low dopamine levels [89]. This return to normal DA levels may serve as positive reinforcement for nicotine cravings during withdrawal. The prolonged hypodopaminergic state during withdrawal may also explain depression-like withdrawal symptoms, as well as others like anxiety.

As previously mentioned, the dopamine transporter (DAT) is responsible for a large part of DA reuptake, and therefore plays a role in the hypo-dopaminergic state during withdrawal. A study conducted in 2010 by Hadjiconstantinou et al. examined DAT function in male mice during withdrawal and found increased DAT function and upregulation of DAT soon after cessation of nicotine [67]. This supports the theory that increased dopamine reuptake plays a role in the reduced DA levels during withdrawal.

Treatment of Nicotine Addiction

Nicotine patches are one of the most popular options for treating smoking addiction and are a form of nicotine replacement therapy through a patch attached to the skin using an adhesive [15]. Responses to nicotine patches can vary, but the nicotine metabolite ratio used to determine nicotine metabolism can also be used to anticipate response to nicotine patches. Those with a lower nicotine metabolite ratio are fast nicotine metabolizers and have greater success with these nicotine patches [90]. A 2019 study by Walker et al. looked at nicotine patches in combination with e-cigarettes and saw improvements in smoking cessation results [91].

Nicotine gum is another popular form of nicotine replacement therapy for smoking cessation. It is administered through chewing, and produces similar nicotine levels to smoking tobacco, however it has slower absorption compared to smoking [92]. Results for nicotine gum as an aid for smoking cessation are varied, as one study in 2019 by Shiffman et al. showed little to no improvement in smokers trying gum as a method for treatment [93]. Other forms of nicotine replacement therapy exist, including lozenges and nasal sprays. A 2019 study by Lindson et al. found that combining multiple forms of NRT had more success compared to only using one form. They also found that higher dosage, 4mg gum was more successful than 2mg gum. When looking at dosage for nicotine patches, results were varied and did not show a pattern with high certainty [94].

Bupropion is an antidepressant and smoking cessation treatment that has been shown to have success in smoking cessation [16]. Bupropion was shown to have a 52% to 77% higher likelihood that an individual will effectively quit smoking. However, the use of bupropion has also been associated with adverse side effects which are unwanted, but is not associated with

severe or lethal effects [95]. A 2021 study by Kranzler et al. looked at the effectiveness of bupropion in pregnant women. They found that in pregnant women, bupropion was ineffective for improving chances of smoking cessation. However, they did find that there were no pregnancy complications associated with bupropion [96].

Varenicline is another prescription smoking cessation therapy and works as a partial agonist for α4β2 nAChRs. Since it is a partial agonist, it mediates DA release and reduces the reinforcement of smoking, while also mitigating withdrawal symptoms by activating these nAChRs [97]. Varenicline is administered orally, and has fewer adverse effects compared to bupropion while also having significant effect on improving chances for smoking cessation [17]. A 2016 study by Ebbert et al. looked at Varenicline in light smokers and saw that it was both safe and effective in increasing cessation in light smokers [98]. In comparison to other smoking cessation treatments, Varenicline has been shown to be the most effective. A 2022 study by Cinciripini et al. compared Varenicline to Bupropion, nicotine patch and placebo, and found Varenicline to be the best option [99]. For those looking for the most effective prescription nicotine treatment option with minimal side effects, Varenicline seems to be the best option currently.

In addition to NRT and prescription solutions for nicotine dependence, behavioral intervention is another popular treatment for smoking cessation. When studying its effectiveness, a 2015 study by Thrul et al. looked at the extent of participation in behavioral intervention in relation to other smoking factors. They found that a previous attempt at quitting, strong nicotine dependence, and a high motivation to quit were all factors associated with increased participation in behavioral intervention programs [18]. Behavioral intervention has been observed in combination with various other nicotine treatments. In a 2010 study by Ebbert et al. they looked at behavioral intervention in addition to nicotine lozenges. Their results showed that both increased chances of smoking cessation, and that behavioral intervention on its own may also improve results [100]. Thus, behavioral intervention, especially in combination with other treatment methods is an effective method for improving chances of smoking cessation.

Conclusion

Both nicotine and dopamine play significant roles in the development of nicotine addiction and the manifestation of withdrawal symptoms. Looking at factors such as differences in nAChRs, nicotine degradation, and dopamine reuptake can reveal possible solutions for the development of addiction treatments. Although a lot is known about nAChRs and dopamine, we can look further at their role in nicotine seeking behavior in relation to different areas of the brain for the advancement of treatment methods targeted at these areas.

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