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Potential Substrates for Nicotine and Alcohol Interactions: a Focus on the Mesocorticolimbic Dopamine System

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Abstract

Epidemiological studies consistently find correlations between nicotine and alcohol use, yet the neural mechanisms underlying their interaction remain largely unknown. Nicotine and alcohol (i.e., ethanol) share many common molecular and cellular targets that provide potential substrates for nicotine-alcohol interactions. These targets for interaction often converge upon the mesocorticolimbic dopamine system, where the link to drug self-administration and reinforcement is well documented. Both nicotine and alcohol activate the mesocorticolimbic dopamine system, producing downstream dopamine signals that promote the drug reinforcement process. While nicotine primarily acts via nicotinic acetylcholine receptors, alcohol acts upon a wider range of receptors and molecular substrates. The complex pharmacological profile of these two drugs generates overlapping responses that ultimately intersect within the mesocorticolimbic dopamine system to promote drug use. Here we will examine overlapping targets between nicotine and alcohol and provide evidence for their interaction. Based on the existing literature, we will also propose some potential targets that have yet to be directly tested. Mechanistic studies that examine nicotine-alcohol interactions would ultimately improve our understanding of the factors that contribute to the associations between nicotine and alcohol use.

Keywords

Nicotine; Alcohol; Dopamine; drug abuse; stress

1. Introduction

Tobacco and alcohol use is a worldwide health problem, accounting for more than 7 million deaths per year combined [1, 2]. Epidemiological studies demonstrate a shared vulnerability to tobacco and alcohol abuse, in which one substance influences the use of the other [3–6]. Estimates indicate that over 83% of alcoholics also smoke, with alcoholism approximately 10 times more prevalent in smokers than in non-smokers [7–9]. Adolescent and college-age smoking increases the risk of developing alcohol use disorders [10, 11]. Similarly, binge patterns of alcohol drinking occur more often in regular or occasional smokers compared to non-smokers [4, 6].

Rodent models often show that exposure to nicotine can increase alcohol self-administration [12–14]. Rats exposed to nicotine during adolescence show significantly higher alcohol

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intake as adults upon re-exposure to nicotine [15]. Some studies have reported other effects of nicotine on alcohol intake [16], which possibly arise from methodological differences in the self-administration procedures. There is also evidence for the converse relationship (i.e., the influence of alcohol on nicotine self-administration). Alcohol consumption potently increases ad-lib smoking behavior in humans [17, 18]. Alcohol also enhances the craving to smoke and the positive feelings associated with smoking [19–21].

Thus, there is a potent and complex interaction between tobacco and alcohol reinforcement. Many factors contribute to this interaction, including psychosocial and genetic influences, as well as the widespread availability of tobacco and alcohol [22, 23]. Accumulating evidence suggests that nicotine and alcohol also interact through neurobiological mechanisms [24]. In rodents and humans, chronic nicotine administration is associated with a reduced sensitivity to the pharmacological effects of ethanol, a phenomenon known as cross-tolerance [25, 26]. Behavioral studies that have examined nicotine and alcohol interactions suggest the involvement of the cerebellum, hippocampus, hypothalamus, and striatum [27–29]. Although the mesocorticolimbic dopamine (DA) system has a central role in the development of drug reinforcement and addiction [30], there is little mechanistic information on how nicotine and alcohol interact within this system. Other brain systems contribute significantly to drug-seeking behavior, but we have limited the scope of our discussion mainly to nicotine and alcohol interactions that implicate the DA system and its afferent connections. To identify common targets of action, we will describe the separate actions of nicotine and alcohol within the context of the DA system. The review will highlight relevant functional interactions when appropriate and will examine potential mechanistic interactions that largely await future investigations.

2. The Mesocorticolimbic DA System

The mesocorticolimbic DA system regulates mood, emotional responses, and incentive-based behavior [31, 32], and dysregulation of this system is a hallmark of the drug-addicted state [30, 33, 34]. Neurons in the ventral tegmental area (VTA) are the primary source of the mesocorticolimbic DA system. Those neurons project to many cortical and forebrain limbic structures, including the nucleus accumbens (NAc), ventral pallidum, amygdala, and the medial prefrontal cortex (mPFC). A simplified summary of the mesocorticolimbic pathway is shown in Fig. 1 (darkened symbols). DA neurons represent an abundant cell type in the VTA, but the exact percentage of DA neurons varies between subregions [35–37]. The VTA also contains glutamate neurons and GABA neurons that project to the forebrain and can form local synapses with other VTA neurons [37–41]. A fourth cell type synthesizes both DA and glutamate, and there are potentially other mixed transmitter neurons in this area [42, 43].

Numerous afferent inputs regulate the activity of DA and non-DA neurons in the VTA. Major excitatory inputs arise from the laterodorsal and pedunculopontine tegmentum, the lateral hypothalamus, the bed nucleus of the stria terminalis, and the prefrontal cortex [44–47]. The major GABAergic inhibitory inputs to the VTA arise from the rostromedial tegmental nucleus, the ventral pallidum, the laterodorsal tegmentum, and the nucleus accumbens (NAc) [48–50]. The serotonergic (5-HT) neurons of the dorsal raphe nucleus constitute another important afferent projection, which transmits mainly excitatory signals to the VTA [51]. Fig. 1 summarizes these different afferent inputs to the VTA, including their relevant neurotransmitters. Some inputs target specific subsets of VTA neurons. The excitatory inputs from the laterodorsal tegmentum, for example, mainly target VTA DA neurons that project to the nucleus accumbens [44], whereas the inhibitory inputs from the nucleus accumbens were shown to target non-dopaminergic VTA neurons [49].

2.1. VTA Neuron Properties

DA neurons are the most well studied class of cells in the VTA. The classic DA neurons (found mainly in the lateral VTA and in the substantia nigra compacta) display various modes of firing activity in vivo, including tonic and phasic activation [52, 53]. Tonic activity involves slow irregular patterns of single action potentials, whereas phasic activity involves short-latency bursts of action potentials (typically 2–4 action potentials, each separated by less than 80 ms). DA neurons in brain slices do not display normal burst activity [54], indicating that burst firing depends on afferent synaptic input, which is altered and disrupted in brain slices. The tonic firing frequency of DA neurons in freely moving animals is approximately 2–10 Hz. However, within a single burst of action potentials the average firing frequency increases to approximately 15–28 Hz [53, 55]. The transition from tonic to phasic firing activity is hypothesized to be a key mechanism for transmitting behaviorally relevant information [31]. Molecular substrates, including the DA transporters and DA autoreceptors, further filter the information encoded by DA neurons to regulate DA release. Owing to regional differences in these molecular substrates, phasic DA signals lead to greater extracellular DA levels in the ventral striatum compared to the dorsal striatum [56–58].

In addition to DA neurons, VTA GABAergic and glutamatergic neurons provide input to the mesocorticolimbic target areas (Fig. 1). A high firing frequency (typically above 20 Hz) and relatively short action potential duration characterize a well-studied subset of GABAergic neurons [39, 55, 59]. Recent studies indicate that VTA GABA neurons make selective synaptic connections with cholinergic interneurons in the NAc that influence local DA transmission and contribute to associative learning [60, 61]. Glutamatergic VTA neurons also innervate the nucleus accumbens and other structures, and their properties and their regulation continue to be studied [37, 42, 43, 62].

3. Nicotine and Alcohol Regulate DA Function

Rodents will learn to press a lever to obtain nicotine or alcohol, suggesting that nicotine and alcohol are reinforcing. The development of nicotine and alcohol reinforcement involves the DA system [33, 63]. In contrast to the many and diverse molecular targets of alcohol, nicotine initially acts upon the DA system via nicotinic acetylcholine receptors (nAChRs). Targeted manipulation of nAChRs in the VTA has determined a critical role for these receptors in mediating the reinforcing properties of nicotine [64–68]. Blockade of nAChRs in the VTA or upon afferents to the VTA consistently reduces operant self-administration of nicotine.

As for nicotine and other addictive drugs, alcohol self-administration coincides with an increase in DA levels in the NAc [69–71], and with learning, this DA signal may arise from the initial sensory cues of the alcohol solution [72, 73]. Local infusion of DA receptor antagonists into the VTA and the NAc reduces subsequent operant responses for alcohol [74–76], and neurotoxic lesions of the DA system decrease alcohol intake [77, 78]. The lesions only appear to alter alcohol intake when applied prior to the acquisition of drinking behavior (i.e., prior to training), and not after self-administration behavior becomes established, suggesting that DA signaling is particularly critical during the acquisition and development of alcohol reinforcement. Many of these features of alcohol self-administration are shared by other addictive drugs.

3.1. Nicotine and Alcohol Increase Dopamine Excitability

The behavioral responses to nicotine and alcohol arise from their cellular and molecular actions in the brain, including those acting directly and indirectly upon the mesocorticolimbic DA system. Although alcohol targets a wider range of molecular targets

and neural substrates than nicotine, both drugs potently act and converge upon the mesocorticolimbic DA system to increase DA transmission. In vivo administration of either nicotine or alcohol increases the action potential firing rate of DA neurons and the phasic burst activity of DA neurons [79–82]. Concomitant with this activation, nicotine increases the correlated firing activity among subsets of VTA DA neurons [55], which would amplify and synchronize the output of the DA signal to the target areas. Nicotine enhances the firing rate and burst activity of DA neurons, in part, by activating cholinergic and glutamatergic inputs from the laterodorsal and pedunculopontine tegmentum [44, 83–85], and via a direct activation of nAChRs within the VTA [79, 86]. NMDA glutamate receptors also participate in nicotine-induced burst firing of DA neurons [87]. A recent study provides evidence that nicotine increases burst firing through the co-activation of VTA GABA neurons [68]. Alcohol-induced activation of the DA system may also involve cholinergic and glutamatergic inputs from the laterodorsal and pedunculopontine tegmentum, but support for this hypothesis is limited at this point [88–90].

3.2. Nicotine and Alcohol Increase DA Release

The DA neuron activity induced by nicotine and alcohol correlates with increased DA release at target areas, including the NAc, ventral pallidum, and mPFC [91–98]. In target areas in the dorsal and ventral striatum, nAChRs located on DA terminals (and/or axons), as well as on cholinergic interneurons, regulate DA release [58, 86, 99, 100]. Different regulatory mechanisms involving nAChRs allow initial nicotine administrations to increase extracellular DA levels largely in the ventral striatum compared to the dorsal striatum [101]. Nicotine also increases the DA input to the hippocampus to modulate perforant pathway long-term potentiation and conditioned behavior [102, 103]. Nicotine and alcohol administered simultaneously produce an additive increase in DA release in the NAc compared to each drug alone [104]. However, pretreatment with nicotine has been shown to decrease subsequent alcohol-induced DA release [105, 106]. Therefore, the DA system represents a prime target for functional interactions between nicotine and alcohol.

4. Cellular and Molecular Actions of Nicotine

The following sections summarize some of the cellular and molecular actions of nicotine associated with the DA system, but we do not mean to imply that the DA system is the primary system through which nicotine acts. Nicotinic AChRs mediate the effects of nicotine throughout the brain, and non-dopaminergic effects are essential to nicotine reinforcement [65]. We simply wish to convey how nicotine targets specific substrates within the DA system that are also critical for the responses to alcohol.

The nAChR is a pentameric ligand-gated ion channel formed by different combinations of subunits (α 2- β 10 and α 2- β 4) [107, 108]. Much of the work with nAChR subunit combinations has been done in rodents. The most common nAChRs in the rodent VTA are the high affinity α 2-containing subtype (often in combination with β 4 and/or β 6) and the lower affinity α 7-containing subtype [109–111]. DA and GABA VTA neurons, as well as the afferent GABAergic inputs to VTA neurons, express the high affinity α 2-containing nAChR [109, 110, 112]. The α 7-containing nAChR is located predominately on presynaptic glutamatergic inputs and to a lesser extent on VTA GABA neurons [109, 111].

4.1. Acute Nicotine Action in the VTA

The low brain concentrations of nicotine obtained from tobacco (~20–100 nM) activate the α 2-containing nAChRs [113–115]. Within minutes of exposure, nicotine begins to desensitize mainly the high affinity nAChRs [110, 114]. This process leads to a decrease particularly in GABA inhibition of VTA DA neurons [112, 116]. Due to differences in

agonist affinity, these low concentrations of nicotine do not readily desensitize $\alpha 7$ -containing nAChRs [110, 116]. This distinction may allow $\alpha 7$ -containing nAChRs to exert a prolonged excitatory effect over glutamatergic afferents onto DA neurons, favoring the induction of long-term synaptic potentiation [112, 116]. However, the $\alpha 2$ -containing, and not the $\alpha 7$ -containing, nAChRs are of greater importance during the initiation of nicotine self-administration [115, 117]. During those initial exposures, a single administration of nicotine is sufficient to induce long-term synaptic potentiation of glutamatergic afferents onto DA neurons, as indicated by an increase in the AMPA/NMDA receptor ratio and an increase in the probability of glutamate release [89, 118, 119]. These kinds of synaptic changes underlie learning and memory. Working throughout the brain, this “drug associated learning” may link the drug use to environmental cues [33].

4.2. Chronic Nicotine Action in the VTA

In addition to any acute effects, chronic repeated exposure to nicotine causes a persistent upregulation of some nAChRs subtypes, meaning that nicotine increases the number of nAChRs available for binding [120, 121]. Upregulation of nAChRs varies between nAChR subtypes, between brain regions, and even between local cell types [120, 122–124]. Various cellular mechanisms may account for upregulation, including increased receptor assembly and trafficking to the plasma membrane, increased nAChR function, and decreased rate of nAChR turnover [125–129]. Behavioral studies also indicate that nicotine self-administration upregulates AMPA receptors in the VTA [130]. These neuroadaptations and others could contribute to changes in the long-term sensitivity to nicotine and alcohol [10, 131, 132].

Lester and colleagues showed that chronic nicotine exposure tends to upregulate high affinity nAChRs on VTA GABA neurons, which was related to an increase in GABAergic inhibition of DA neurons [124]. Increased GABAergic inhibition could contribute to withdrawal by causing a reduction in tonic DA levels in the nucleus accumbens [133, 134]. A stronger inhibition of the tonic DA response after nicotine withdrawal increases the ratio between tonic and phasic DA signaling [134]. Therefore, during the withdrawal period, re-exposure to nicotine or alcohol may induce DA signals that increase the vulnerability to the drug abuse. Relapse to smoking often occurs within two weeks of abstinence, suggesting that early withdrawal from nicotine is a critical period for relapse [135].

Lastly, evidence also suggests that some actions of nicotine within the DA system occur through non-nicotinic receptor mechanisms. Prolonged exposure to nicotine can inhibit ubiquitin-related proteasomal activity, which was shown to regulate $\alpha 7$ -containing nAChRs as well as several ionotropic and metabotropic glutamate receptors [136]. These responses were only partially blocked by a nAChR antagonist, indicating that nicotine activation of nAChRs does not completely account for the results. Therefore, nicotine influences a diverse array of molecular substrates and systems (including the cholinergic, glutamatergic, and GABAergic systems), and these substrates represent known targets of alcohol.

5. Alcohol Regulation of Dopamine and Behavior

Alcohol is an allosteric modulator of many ligand-gated ion channels, giving alcohol broad access to the DA system and to the brain as a whole. Alcohol potentiates the function of GABA_A, nACh, and 5-HT₃ receptors, and can inhibit the function of glutamatergic receptors [137]. Although not comprehensive, the following section will review evidence of how alcohol can modulate these and other neurotransmitter systems, including upstream and downstream effects, to influence the DA system and behavior. This will provide a basis for understanding potential interactions between nicotine and alcohol.

5.1. Direct Action on Dopamine Neurons

At concentrations achieved during intoxication (20–100 mM), alcohol moderately excites VTA DA neurons in brain slices, as well as in acutely dissociated DA neurons lacking synaptic inputs, indicating a direct alcohol action on DA neurons [138–140]. Alcohol reduces the amplitude of the after-hyperpolarization phase of the DA action potential and influences other ionic conductances and metabotropic signals, which may increase DA neuron excitability [140–144]. In addition to these direct actions, the *in vivo* effects of alcohol on DA neurons arise from a complex interplay between alcohol and many neurotransmitter systems that converge on the local circuits of the VTA.

5.2. Alcohol and GABA

Substantial evidence indicates a role of GABA signaling in alcohol self-administration [145, 146]. Local blockade of GABA_A receptors in the VTA and the ventral pallidum and knockout of GABA_A receptors in the NAc decreases alcohol self-administration [147–149]. At the molecular level, alcohol binds to specific amino acid residues on the GABA_A receptor, which enhances inward chloride conductance and inhibition [150–152]. Alcohol also modulates GABA_A receptors indirectly via the activation of neuroactive steroids [153], which we discuss further below.

Application of alcohol to VTA brain slices increases presynaptic GABA release onto DA neurons [154, 155], and evidence suggests that *in vivo* alcohol exposure induces a long lasting (at least 24 h to 1 week) potentiation of GABA inhibition in the VTA [156]. The precise mechanism by which ethanol enhances presynaptic GABA release is not understood, but could involve 5-HT transmission and stress signaling pathways [155, 157]. Evidence from the hippocampus also suggests that nicotinic receptors mediate varying degrees of GABAergic inhibition in target cells [158]. If these mechanisms extend to the VTA, local circuit interactions involving alcohol-induced activation of the cholinergic system (see section 5.4) could potentially influence GABAergic activity in the VTA. *In vivo* recordings from putative VTA GABA neurons indicate that GABAergic responses to alcohol can vary substantially between cells, and single cells can even show transient excitation and inhibition during a single recording [159, 160]. The dose of ethanol and the timing between injections are factors that likely contribute to different GABAergic responses [159, 161].

Withdrawal from chronic alcohol exposure is associated with decreases in GABA_A function [162]. Prolonged exposure to alcohol can decrease GABA_A synaptic transmission and decrease GABA_A receptor levels in the VTA and elsewhere [163, 164]. During abstinence, alcoholics show a reduced sensitivity to GABA_A receptor ligands, such as benzodiazepines [165], which is consistent with blunted GABA_A receptor function. Interestingly, nicotine and alcohol interactions during withdrawal may involve changes in GABA_A responses [166]. Smoking appears to attenuate some of the deficits in GABA_A function that occur during withdrawal [167].

5.3. Alcohol and Glutamate

In contrast to its effects on other ligand-gated receptors, alcohol primarily inhibits the function of NMDA-type glutamate receptors [168, 169]. However, prior activation of DA receptors (and DARPP-32 signaling) was shown to attenuate alcohol-induced inhibition of NMDA receptors in the NAc [170], suggesting that DA signaling may circumvent this inhibition. In addition, alcohol can inhibit non-NMDA (AMPA/kainate) receptors [169, 171, 172], particularly in the amygdala, but results can vary depending on the brain region and the age of the subject [168, 173]. The inhibition of the metabotropic glutamate receptor (mGluR) by alcohol [174] is of additional interest due to the influence of these receptors on alcohol self-administration. Several studies demonstrate that inhibitors of the mGluR5

subtype decrease alcohol self-administration and reinforcement [175–177], which is intriguing because mGluR5 inhibitors were also shown to decrease nicotine self-administration and reinstatement [178, 179].

Regarding its presynaptic action, acute application of alcohol to VTA brain slices enhances glutamatergic transmission onto DA neurons [180], but glutamatergic transmission can differ in other brain regions [169, 172, 173]. Increased extracellular glutamate levels have also been reported in the NAc as measured by in vivo microdialysis [181]. Lastly, long-term exposure to alcohol upregulates glutamatergic receptors in the VTA, amygdala, and elsewhere [182–185]. There is little information on functional interactions between alcohol and nicotine involving glutamatergic transmission. However, one study has shown that co-abuse of alcohol and nicotine regulates the expression of the vesicular glutamate transporter differently from nicotine abuse alone [186].

5.4. Alcohol and ACh

There is a direct interaction between alcohol and the nicotinic cholinergic system via the nAChRs. Low concentrations of alcohol increase the affinity of acetylcholine for neuronal nAChRs and potentiate the nicotinic currents produced by acetylcholine [187, 188]. Heterologously expressed recombinant nAChRs that contain the $\alpha 2$ or $\alpha 4$ subunit are particularly sensitive to activation by alcohol [189, 190]. Evidence indicates that alcohol potentiates receptor function by stabilizing the open state of the $\alpha 4$ -containing nAChR [191], but prolonged exposure to alcohol may increase nAChR desensitization [192]. In contrast, alcohol seems to inhibit the nicotinic responses of some $\alpha 7$ -containing nAChRs, but the results can vary depending on the expression system or the duration of the bath alcohol application [189, 193]. Interestingly, chronic exposure to alcohol was shown to upregulate high affinity nAChRs in the thalamus and hypothalamus [194], similar to chronic nicotine exposure. Whether alcohol induces similar nAChR upregulation within the DA system remains to be tested.

In addition to any direct actions on nAChR function, alcohol may influence the DA system via activation of afferent cholinergic inputs. Alcohol self-administration elevates extracellular acetylcholine levels in the VTA [88], and a single dose of alcohol activates cholinergic interneurons in the nucleus accumbens, as measured by Fos expression [195]. Substantial evidence indicates an involvement of distinct nAChRs in alcohol-induced DA release and self-administration. Intra-VTA or systemic blockade of nAChRs antagonists with mecamylamine (a general nAChR antagonist) reduces alcohol consumption and alcohol-induced DA release in the NAc [12, 196, 197]. Mecamylamine was also shown to reduce the subjective rewarding effects of alcohol in humans [198]. One caveat is that mecamylamine acts as an antagonist at the NMDA glutamate receptor [199], which raises the issue of specificity.

Using antagonists that are more selective than mecamylamine, several studies have indicated a contribution of different nAChR subtypes to alcohol responses. Blocking $\alpha 3 \beta 2$ -containing nAChRs (and/or $\alpha 3 \beta 4$ nAChRs) with α -conotoxin MII prevents alcohol-induced DA release and alcohol self-administration [200–202]. Pharmacological studies have not provided reliable evidence for the involvement of other high affinity nAChRs, nor for $\alpha 7$ -containing nAChRs, in these responses [201–203]. However, using a novel nAChR ligand, one study has suggested that $\alpha 4 \beta 2$ -containing nAChRs participate in self-administration of both nicotine and alcohol [204]. Likewise, recent work using $\alpha 4$ nAChR knockout models demonstrates that alcohol-induced DA responses and alcohol conditioned place preference require $\alpha 4$ -containing nAChRs [205]. Knockout studies also suggest a role for the $\alpha 7$ -containing nAChRs in alcohol consumption [206]. Other alcohol-induced behaviors, such as sedation, anxiolytic responses, and motor activity/coordination involve high affinity

nAChRs and the lower affinity $\alpha 7$ -containing nAChRs [207–209]. Interestingly, varenicline, an anti-smoking agent and a partial agonist at several nAChR subtypes, effectively reduces alcohol consumption in rodents and in humans [210, 211]. Varenicline administration also appears to decrease DA release induced by alcohol [212]. Although the role of specific nAChR subtypes remains unclear, the facts suggest that nAChRs mediate many actions of alcohol.

5.5. Alcohol and 5-HT

Another mechanism by which alcohol influences the DA system is through 5-HT signaling. Alcohol concentrations achieved during intoxication potentiate the function of the 5-HT₃ ligand-gated receptor [213, 214]. Similar to its action on nAChRs, alcohol appears to stabilize the open state of the 5-HT₃ receptor and may slow the rate of receptor desensitization [215]. Substantial evidence indicates that 5-HT receptors contribute to the many systemic and behavioral effects of alcohol. Alcohol administration increases serotonin release in the VTA and the NAc, and blockade of 5-HT₃ receptors prevents this increase in serotonin [216–218].

Activation of 5-HT₃ receptors also contributes to alcohol reinforcement. Systemic or intra-VTA administration of 5-HT₃ receptor antagonists attenuates operant alcohol self-administration [219, 220]. Moreover, intra-VTA self-administration of alcohol is prevented by locally blocking 5-HT₃ receptors during training [221]. There are many metabotropic 5-HT receptors (5-HT_{1A-F}, 5-HT_{2A-C}, 5-HT₄, 5-HT₅, 5-HT₆, and 5-HT₇), but alcohol does not appear to interact with them directly. Instead, these receptors appear to modulate alcohol-induced responses. Blockade of 5-HT_{2A} receptors, for example, decreases ethanol drinking in several rodent lines [222]. The 5-HT_{2C} receptor modulates specific actions of alcohol within the VTA. Blockade of 5-HT_{2C} receptors blocks alcohol-induced GABAergic inhibition onto DA neurons, suggesting that alcohol induces GABA release via 5-HT transmission [155]. 5-HT_{2C} receptors have also been shown to modulate nicotine reinforcement [223]. Furthermore, recent studies show that a 5-HT₆ receptor antagonist was effective at reducing both nicotine and ethanol reinstatement [224].

5.6. Alcohol and Endocannabinoids

Although endocannabinoid (eCB) receptors are not direct targets of alcohol and nicotine, substantial evidence suggests that certain aspects of alcohol and nicotine reinforcement involve eCB signaling [225]. Endogenous cannabinoid pathways modify the central nervous system and immune responses through CB1 and CB2 receptors, respectively [226]. DA neurons appear to release eCBs, which act in a retrograde manner to bind CB1 receptors on glutamatergic and GABAergic inputs [227]. CB1 antagonists reduce alcohol self-administration and alcohol conditioned place preference [228–230]. CB1 receptor antagonists also reduce nicotine self-administration as well as nicotine-induced DA release in the NAc [231, 232]. Local blockade of CB1 receptors in the VTA and the NAc reduces alcohol consumption, suggesting a critical role of eCB signaling in the mesoaccumbens pathway [233]. Pretreatment with a CB1 receptor agonist or with nicotine blocked alcohol-induced DA release, suggesting that these agents may interact with alcohol through a common mechanism [105]. In addition, alcohol increases conditioned place preference induced by nicotine, and this effect is prevented by blocking eCB receptors [234]. Repeated nicotine or alcohol exposure correlates with an increase in eCB levels across different brain regions [235]. Furthermore, clinical trials evaluating CB1 antagonist rimonabant as an aid for smoking cessation report a doubling in abstinence rates [236]. Rimonabant may therefore be useful in the treatment of alcohol use disorders.

6. Potential Interactions via Neuroendocrine Pathways

In addition to the acute effects of nicotine and alcohol, nicotine influences the long-term use of alcohol, suggesting that neuroadaptative mechanisms involving gene transcription and protein synthesis contribute to this interaction. One way that nicotine and alcohol could interact is through neuroendocrine pathways associated with the hypothalamic-pituitary-adrenal (HPA) axis. Stressful or arousing events activate the HPA axis to induce long-term adaptive changes in the brain and in behavior [237]; and drugs of abuse activate these pathways [238]. The stress response is governed by neurons in the paraventricular nucleus (PVN) of the hypothalamus that release corticotropin-releasing factor (CRF) into the hypophyseal portal system. CRF then activates corticotrophs in the pituitary that release adrenocorticotrophic hormone (ACTH) into the bloodstream. ACTH stimulates the secretion of stress hormones, such as glucocorticoids, from the adrenal cortex [239], which influence neuronal activity via both genomic and non-genomic mechanisms [240]. Other HPA-related hormones, such as progesterone and its metabolites, also participate in stress responses [241, 242].

6.1. Complexity of the Stress Pathways

Although stress is a known risk factor for nicotine and alcohol abuse, the mechanisms by which HPA axis contributes to drug interactions have only been hypothesized. The complexity of the HPA system has limited our ability to identify stress-mediated adaptations that promote subsequent nicotine or alcohol use. First, glucocorticoids and other stress hormones act throughout the brain and can serve different functions [243]. Within the PVN of the hypothalamus, for example, glucocorticoids act as a negative feedback signal to inhibit CRF activity [244]. However, in extra-hypothalamic regions, such as the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST), glucocorticoids deliver a positive feedback signal to potentiate CRF activity [245]. CRF activity in extra-hypothalamic regions, including the DA system, contributes to different aspects of drug abuse [243]. Second, stress hormones can induce fast, non-genomic interactions at the cell membrane (seconds to minutes) as well as slow, transcription-dependent effects via intracellular receptors (15 minutes to hours or days) [240, 246]. Finally, stress hormones can serve as precursors for the production of neuroactive steroids, which exert rapid effects on neural transmission and regulate neuroendocrine responses [247, 248]. More specifically, progesterone and other structurally related molecules can act as potent allosteric modulators of nACh, GABA_A, and NMDA receptors [249–252]. Therefore, stress hormones and neuroactive steroids may act in concert through multiple mechanisms to influence the responses to drugs of abuse.

6.2. Stress Pathways and Drug Abuse

Several studies support the hypothesis that activation of the HPA axis contributes to the motivational properties of nicotine and alcohol. Animals will learn to self-administer glucocorticoids intravenously, suggesting that glucocorticoids are reinforcing [253]. Nicotine and alcohol separately activate stress pathways to elicit glucocorticoid release [254, 255]. Glucocorticoids and other stress-related hormones act directly on the DA system to modulate DA transmission and behavior [256, 257]. Adrenalectomized rodents show reduced dopamine responses to nicotine and reduced alcohol self-administration [258, 259]. Conversely, local activation of glucocorticoid receptors in the ventral striatum has been shown to increase alcohol intake [260], and the development of alcohol dependence may involve the activation of glucocorticoid receptors in the DA system [261]. Consistent with these findings, studies in humans suggest that low glucocorticoid levels among alcoholic patients are a risk factor for early relapse [262]. In terms of interactions between nicotine

and alcohol, it is essential to determine how glucocorticoids acting during nicotine exposure influence the responses to alcohol and vice versa.

The tolerance associated with repeated exposure to nicotine or alcohol involves stress hormones and their neuroactive metabolites [263–265]. Whether neuroendocrine systems undergo cross-tolerance to the effects of nicotine and alcohol is an intriguing question but remains to be determined. Inhibition of nAChRs by stress hormones may contribute to nicotine tolerance [266]. Because alcohol also targets nAChRs, stress-mediated alterations in nAChR function induced by nicotine could potentially influence subsequent sensitivity to alcohol.

Chronic drug exposure and persistent HPA activation may sensitize extra-hypothalamic CRF systems during drug withdrawal [245, 267]. The abrupt cessation of nicotine or alcohol intake after chronic exposure initiates a withdrawal syndrome characterized by negative affect, deficits in reward function, and a propensity for relapse [268, 269]. Elevated CRF signaling in the extended amygdala is hypothesized to mediate these symptoms, as CRF antagonists block their expression [270–272]. Even during protracted abstinence when withdrawal symptoms have subsided, the CRF circuitry remains sensitized to stress responses and increases the vulnerability to relapse [273].

6.3. Neuroactive Steroids

Another possible mechanism that could contribute to drug sensitivity is the modulation of GABA_A receptors by neuroactive steroids. Initially, nicotine or alcohol exposure increases the levels of the allopregnanolone [255, 274], a progesterone-derived steroid that acts as a positive allosteric modulator of GABA_A receptors. Like glucocorticoids, allopregnanolone has reinforcing properties, causes dopamine release, and induces conditioned place preference [275–277]. In addition, allopregnanolone contributes to the pharmacological action of alcohol [278, 279]. Evidence suggests that allopregnanolone-sensitive receptors mediate the discriminative stimulus effects of alcohol [280], promote alcohol consumption [281, 282], and contribute to alcohol tolerance [283]. Allopregnanolone also acts within the VTA, influencing alcohol-induced withdrawal behaviors [284]. Interestingly, nicotine dose-dependently increases allopregnanolone levels [255, 285], suggesting that nicotine could alter the responses to alcohol via allopregnanolone signaling.

In summary, stress hormones may act through multiple mechanisms to promote drug reinforcement, tolerance, and withdrawal. Because stress hormones and drugs of abuse target similar brain regions, adaptations mediated by neuroendocrine pathways are centrally linked to the development of nicotine and alcohol abuse. Therefore, detailed studies of the mechanisms by which stress hormones influence nicotine and alcohol interactions would advance this field.

7. Potential Interactions via Neuroimmune Pathways

Nicotine and alcohol could also interact through neuroimmune signaling pathways. The neuroimmune system consists of neurons that regulate immune responses, as well as the inflammatory signals that feedback to modulate neural function. During an immune response, foreign stimuli activate macrophages (peripheral) and microglia (central) of the innate immune system to elicit the release of inflammatory cytokines [286]. Importantly, the activation of immune signals is implicated in the actions of drugs of abuse [287].

Immune responses could mediate nicotine-alcohol interactions through direct and indirect mechanisms. In terms of a direct mechanism, 7 nAChRs are expressed on macrophages and microglia of the innate immune system [288]. These receptors mediate cholinergic anti-

inflammatory pathways within the immune system [289]. Interestingly, alcohol can inhibit the function of $\alpha 7$ nAChRs [290], a receptor that mediates the responses to both nicotine and alcohol. To our knowledge, no experiments have examined the contribution of $\alpha 7$ nAChRs to alcohol's inflammatory profile, but such work would be relevant to the neuroimmune hypothesis of alcohol abuse [291].

Repeated drug exposure potentially leads to complex interactions between nicotine, alcohol, and the immune system. During chronic nicotine exposure, for example, the activation of some proinflammatory pathways, such as IL-1 β -mediated signaling, are required for nicotine's immunosuppressive effects [292]. These same proinflammatory pathways can directly modulate alcohol intake [293, 294]. In fact, evidence now suggests that immune signaling in the VTA and amygdala is a factor in alcohol abuse [295, 296]. Stress hormones could mediate additional indirect interactions between nicotine, alcohol, and the immune system. Glucocorticoids potentially interact with the inflammatory pathways [297–299] and modify the immune responses to nicotine and alcohol [297, 300]. Taken together, these findings warrant further research to explore the contribution of immune signaling to the development of nicotine and alcohol co-abuse.

8. Summary and Conclusions

Nicotine can influence the use of alcohol and vice versa. This multifaceted interaction arises from a combination of genetic, psychosocial, and neurobiological factors. Because of its central role in drug reinforcement, the mesolimbic DA system may represent an important locus for mechanistic interactions between nicotine and alcohol. Nicotine and alcohol share many common targets that directly and indirectly impinge on the mesolimbic DA system. Nicotine and alcohol influence GABAergic, glutamatergic, cholinergic, serotonergic, endocannabinoid, stress, and immune signaling pathways that regulate the DA system. These common pathways provide neural targets for nicotine and alcohol interactions. The complexity of the responses arises from the diverse actions of these drugs, which can differ between cell types and brain regions. Alcohol and nicotine modulate the function of numerous membrane-bound proteins, as well as neuroendocrine effectors, to influence inhibitory and excitatory transmission. Because of this inherent complexity, multiple mechanisms likely contribute to nicotine-alcohol interactions within and outside of the DA system.

The concurrent use of nicotine and alcohol may involve the modulation of nAChR transmission in concert with other acute mechanisms. Concurrent administration of nicotine and alcohol produces an additive increase in DA release in the NAc compared to each drug alone, suggesting that nicotine and alcohol in combination are more reinforcing. However, the fact that early age smoking is a risk factor for future alcohol abuse suggests that the interaction is multidimensional and involves long-term adaptive processes. Long-term adaptations in the DA and neuroendocrine systems may represent one important process. These systems could undergo a cross-tolerance to the effects of nicotine and alcohol, in which one drug alters the sensitivity to the other [25]. However, the cellular and system level events contributing to cross-tolerance remain unclear. To advance our understanding of these different interactions, future studies involving nicotine and alcohol should examine the functional relationships between these many signaling pathways.

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Figure 1.

A simplified schematic of the mesocorticolimbic DA system (darkened symbols) and its afferent inputs. The ventral tegmental area (VTA) is the primary source of the mesocorticolimbic DA system, which projects to several limbic and cortical structures. Numerous excitatory (+) and inhibitory (-) inputs, as well as neuromodulatory signals (e.g., CRF), regulate the output of the VTA. N. = nucleus, GLUT = glutamate, ACH = acetylcholine.