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Involvement of Glutamatergic and GABAergic Systems in Nicotine Dependence: Implications for Novel Pharmacotherapies for Smoking Cessation

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Abstract

Tobacco smoking continues to be a major global health hazard despite significant public awareness of its harmful consequences. Although several treatment options are currently available for smoking cessation, these medications are effective in only a small subset of smokers, and relapse rates continue to be high. Therefore, a better understanding of the neurobiological mechanisms that mediate tobacco dependence is essential for the development of effective smoking cessation medications. Nicotine is the primary psychoactive component of tobacco that drives the harmful tobacco smoking habit. Nicotine binds to nicotinic acetylcholine receptors (nAChRs) in the brain, resulting in the release of a wide range of neurotransmitters, including glutamate and γ -aminobutyric acid (GABA). This review article focuses on the role of the excitatory glutamate system and inhibitory GABA system in nicotine dependence. Accumulating evidence suggests that blockade of glutamatergic transmission or facilitation of GABAergic transmission attenuates the positive reinforcing and incentive motivational aspects of nicotine, inhibits the reward-enhancing and conditioned rewarding effects of nicotine, and blocks nicotine-seeking behavior. Chronic nicotine exposure produced long-term neuroadaptations that contribute to nicotine withdrawal, but the role of GABA and glutamate transmission in nicotine withdrawal is less understood. Overall, the findings presented in this review provide strong converging evidence for the potential effectiveness of glutamatergic and GABAergic medications in nicotine dependence and potentially nicotine withdrawal.

Keywords

Nicotine; reinforcement; withdrawal; reinstatement; glutamate; γ -aminobutyric acid

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1. Introduction

Tobacco smoking is a major source of preventable morbidity and mortality worldwide. Continued tobacco smoking is driven primarily by dependence on nicotine, one of the main psychoactive ingredients of tobacco smoke (Stolerman and Jarvis, 1995). Despite the currently available smoking cessation therapies, including nicotine replacement, antidepressants (e.g., bupropion), nicotine vaccines, and nicotine receptor partial agonists (e.g., varenicline), successful quit rates remain low, and relapse rates remain high (Jorenby et al., 2006; Nides, 2008; Perkins et al., 2010). Therefore, the development of more efficacious treatments is crucial to help smokers quit and remain abstinent for the long term.

The rewarding effects of nicotine, early nicotine withdrawal and nicotine-seeking behavior after protracted abstinence play important roles in maintaining tobacco smoking behavior. The rewarding effects of nicotine drive smoking acquisition and initial maintenance (Henningfield and Goldberg, 1983). The development of nicotine dependence and aversive withdrawal effects upon abstinence from smoking drive chronic continued smoking and prevent quitting (Hughes and Hatsukami, 1986). Re-exposure to nicotine-associated cues drives nicotine seeking, resulting in high rates of relapse (Markou and Paterson, 2009). A better understanding of the neurobiological mechanisms that mediate nicotine dependence is essential for the development of novel smoking-cessation medications. This review article summarizes our current knowledge of the neural substrates of nicotine dependence, with an emphasis on the glutamate and γ -aminobutyric acid (GABA) neurotransmitter systems. Accumulating evidence suggests that pharmacological interventions directed at these systems may have therapeutic potential in the treatment of nicotine dependence.

2. Neural mechanisms of nicotine dependence

2.1. Acetylcholine-glutamate-GABA-dopamine interaction in the ventral tegmental area

The reinforcing and motivational properties of all drugs of abuse, including nicotine, are critically regulated by the mesocorticolimbic dopamine pathway that originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc), prefrontal cortex (PFC), and amygdala [for reviews see (Balfour, 2009; D'Souza and A., 2012; Koob and Volkow, 2010; Markou, 2009)]. The activity of these dopamine neurons is regulated by complex interactions among acetylcholine, glutamate, GABA and dopamine in the VTA (see Fig. 1). Nicotine can directly increase the activity of dopamine neurons in the VTA by binding to nicotinic acetylcholine receptors (nAChRs) located on these dopaminergic neurons (Champtiaux et al., 2003; Zhao-Shea et al., 2011). In addition, nicotine can indirectly facilitate the burst firing of VTA dopamine neurons by binding to excitatory nAChRs located on glutamatergic afferents and increasing glutamatergic neurotransmission in the VTA (Mansvelder et al., 2002; Schilström et al., 2000). Finally, activation of nAChRs located on inhibitory GABAergic inputs in the VTA from the NAc or interneurons within the VTA increases the release of GABA, thereby indirectly modulating the bursting activity of VTA dopamine neurons (Mansvelder et al., 2002). In the next few paragraphs, the receptors that mediate the effects of nicotine, glutamate, and GABA will be described.

2.2. Nicotinic acetylcholine receptors

Neuronal nAChRs are ligand-gated ion channels with high Ca^{2+} permeability. They are formed from combinations of five subunits (Jones et al., 1999). Heteromeric $\alpha 4\beta 2$ -containing and homomeric $\alpha 7$ nAChRs are the most abundant subtypes in the brain (Feduccia et al., 2012). Nicotine activates $\alpha 4\beta 2$ -containing nAChRs located on VTA dopamine neurons and increases dopamine release in the NAc (Picciotto et al., 1998). Importantly, nAChRs exist as heteroreceptors on glutamatergic and GABAergic neurons and modulate the release of glutamate and GABA. For example, the nicotine-induced activation

of $\alpha 7$ nAChRs located on glutamatergic terminals increases the release of glutamate in the VTA (McGehee et al., 1995; Schilstrom et al., 2000). Furthermore, nicotine activates $\alpha 4\beta 2$ -containing nAChRs located on GABAergic terminals and leads to GABA release in the VTA (Corrigall et al., 2000).

2.3. Glutamate receptors

The actions of excitatory neurotransmitter glutamate are mediated by ionotropic (iGluR) and metabotropic (mGluR) glutamate receptors (Kew and Kemp, 2005). iGluRs, such as *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors, are involved in fast excitatory glutamate neurotransmission. In contrast, mGluRs are slow-acting and modulate glutamate transmission (Schoepp, 2001). Group I receptors (mGluR1 and mGluR5) are primarily located postsynaptically where they positively regulate the excitatory effects of glutamate on NMDA receptors (Awad et al., 2000). Group II receptors (mGluR2 and mGluR3) are predominantly located presynaptically and function as inhibitory autoreceptors that regulate glutamate release or heteroreceptors that control the release of neurotransmitters other than glutamate (Schoepp, 2001). Group III receptors (mGluR4, mGluR6, mGluR7, and mGluR8) are largely presynaptic and inhibit the release of neurotransmitters, including glutamate (Ferraguti and Shigemoto, 2006). In summary, glutamatergic transmission can be attenuated either by blockade of postsynaptic mGluRs (mGluR1 and mGluR5) or activation of presynaptic inhibitory mGluRs such as mGluR2/3.

2.4. GABA receptors

The actions of the inhibitory neurotransmitter GABA are mediated through ionotropic GABA_A and GABA_C receptors and metabotropic GABA_B receptors (Bormann, 1988; Bowery, 1989). The activation of GABA_A receptors opens ligand-gated ion channels and induces the rapid component of inhibitory postsynaptic potentials. In contrast, GABA_B receptors are G-protein-coupled receptors that mediate the slow and prolonged component of synaptic inhibition (Bormann, 1988). Accumulating evidence suggests a critical role for GABA_B receptors in the regulation of different aspects of nicotine dependence (Amantea and Bowery, 2004; Vlachou and Markou, 2010). Thus, this article mainly focuses on the role of GABA_B receptors in nicotine dependence.

3. Nicotine reward and incentive motivation: conditioned effects of nicotine and nicotine-induced reward enhancement

In humans, the positive reinforcing effects of tobacco smoking, such as mild euphoria, increased arousal, decreased fatigue, and relaxation, drive the acquisition and maintenance of tobacco use (Henningfield et al., 1985). In the laboratory, the intravenous nicotine self-administration procedure provides a reliable animal model that has good construct validity for drug-taking behaviors in humans (Markou et al., 1993; O'Brien and Gardner, 2005). In the intravenous nicotine self-administration procedure, the fixed-ratio (FR) schedule of reinforcement and the progressive-ratio (PR) schedule of reinforcement are used to assess the primary reinforcing and incentive motivational effects of nicotine, respectively (Markou et al., 1993; O'Brien and Gardner, 2005). In addition, a widely used animal model for the assessment of the conditioned rewarding effects of nicotine is the conditioned place preference (CPP) paradigm. In this procedure, the reinforcing effect of nicotine is measured by pairing the administration of a drug, such as nicotine, with a specific environment while pairing vehicle administration with a different environment. When the animal is subsequently given access to both environments in a drug-free state, it will typically spend more time in the nicotine-paired environment than the environment paired with vehicle (Le Foll and Goldberg, 2005). Furthermore, the reward-enhancing effects of nicotine may

account for its intrinsic rewarding properties and explain how nicotine increases the sensitivity to nondrug rewarding environmental stimuli (Caggiula et al., 2001; Chaudhri et al., 2006; Harrison et al., 2002). The intracranial self-stimulation (ICSS) procedure provides an objective and quantitative assessment of brain reward function in rodents reflected in brain reward thresholds (Markou and Koob, 1992; Stoker and Markou, 2011; Vlachou and Markou, 2011). Brain reward thresholds are lowered by nicotine administration, reflecting the reward-enhancing properties of the drug (Harrison et al., 2002).

3.1. Neural substrates of nicotine reward

A large body of electrophysiological, microdialysis, and voltammetric evidence indicates that both acute non-contingent nicotine administration and contingent nicotine self-administration increases the firing frequency of VTA dopamine neurons, leading to increased extracellular dopamine levels in the NAc (Corrigall et al., 1994; Dani et al., 2001; Lecca et al., 2006; Nisell et al., 1994; Picciotto et al., 1998; Zhang et al., 2009). As described in Section 2.1, nicotine-induced increase of NAc dopamine is mediated by nAChRs located on dopaminergic neurons in the VTA, as well as nAChRs located on glutamatergic and GABAergic afferents, which indirectly regulate the activity of VTA dopaminergic neurons (see Fig. 1). This review is focused on the role of glutamate and GABA in nicotine dependence. The role of nAChRs and dopamine in nicotine dependence is well described in other reviews (Balfour, 2009; Fowler et al., 2008; Markou, 2008; Stoker and Markou, 2013).

3.2. Glutamate system and nicotine reward

3.2.1. Glutamate receptors and nicotine self-administration—The blockade of glutamate transmission with iGluR antagonists attenuated both nicotine-induced increases in NAc dopamine and nicotine self-administration. Specifically, systemic administration of the NMDA receptor antagonists (*E*)-(±)-2-amino-4-methyl-5-phosphono-3-pentenoic acid ethyl ester (CGP39551) and dizocilpine (MK-801) and the AMPA receptor antagonist ([3,4-dihydro-7-(4-morpholinyl)-2,3-dioxo-6-(trifluoromethyl)-1(2*H*)-quinoxaliny]methyl)phosphonic acid (ZK200775) inhibited nicotine-induced increases in NAc dopamine in nicotine-naïve animals (Kosowski et al., 2004; Shoaib et al., 1997). Similar inhibitory effects on nicotine-enhanced dopamine release were observed with intra-VTA administration of the NMDA receptor antagonist 2-amino-5-phosphonopentanoic acid (AP-5) and *cis*-4-[phosphomethyl]-piperidine-2-carboxylic acid (CGS19755) (Fu et al., 2000; Schilstrom et al., 1998). Furthermore, systemic and intra-VTA administration of the competitive NMDA receptor antagonist (3*S*)-[3 α ,4 α ,6 β ,8 α]-decahydro-6-(phosphonomethyl)-3-isoquinolinecarboxylic acid (LY235959) attenuated nicotine self-administration (Kenny et al., 2009). Altogether, these data suggest that excitatory glutamatergic neurotransmission through the activation of iGluRs in the mesolimbic system partially mediates the reinforcing effects of nicotine.

In addition to iGluRs, mGluRs also partially mediate the reinforcing effects of nicotine. The blockade of postsynaptic mGluR5 or activation of presynaptic mGluR2/3 attenuated nicotine-induced neurochemical and behavioral effects. Specifically, the mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) and mGluR2/3 agonist (1*R*,4*R*,5*S*,6*R*)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268) attenuated nicotine-induced increases in NAc dopamine levels in both nicotine-naïve and nicotine-experienced animals (D'Souza et al., 2011; Tronci and Balfour, 2011). Furthermore, systemic administration of MPEP selectively attenuated nicotine self-administration without affecting food self-administration (Liechti and Markou, 2007a; Palmatier et al., 2008; Paterson and Markou, 2005; Paterson et al., 2003), suggesting that MPEP selectively inhibits the reinforcing and motivational effects of nicotine but not a food reinforcer. Additionally,

central injection of MPEP into the VTA or the NAc shell decreased nicotine self-administration (D'Souza and Markou, 2011a), suggesting that mGluR5 in the VTA and the NAc shell partially mediate the reinforcing effects of nicotine. Systemic, intra-VTA, or intra-NAc administration of the mGluR2/3 agonist LY379268 decreased nicotine self-administration, but only systemic administration of the highest dose of LY379268 affected food self-administration (Liechti et al., 2007). However, chronic administration of LY379268 selectively attenuated nicotine self-administration compared with food self-administration (Liechti et al., 2007). Furthermore, selective activation of the mGluR2 subtype with a positive allosteric modulator (i.e., a benzothiazolone derivative) attenuated nicotine self-administration (Sidique et al., 2012b). Altogether, these results highlight the important modulatory role of mGluRs in the mesolimbic pathway in the reinforcing effects of nicotine.

Glutamatergic neurotransmission can be modulated by compounds acting on the glutamate transporters. Administration of *N*-acetylcysteine attenuated nicotine self-administration without affecting food self-administration in rats (Ramirez-Nino et al., 2013). The precise mechanism by which *N*-acetylcysteine attenuated the reinforcing effects of nicotine is not completely understood. *N*-acetylcysteine binds to the cystine-glutamate exchanger and increases extrasynaptic levels of glutamate by exchanging cysteine for intracellular glutamate. This increase in extracellular glutamate is hypothesized to increase mGluR2/3 signaling (Moussawi and Kalivas, 2010) and reverse downregulation of mGluR2/3 seen after repeated nicotine self-administration (Liechti et al., 2007). Consistent with this hypothesized mechanism, the mGluR2/3 agonist LY379268 decreased nicotine self-administration (Liechti et al., 2007). *N*-acetylcysteine is also a precursor for glutathione (Meister et al., 1986). *N*-acetylcysteine-induced increases in glutathione levels are hypothesized to potentiate NMDA receptor activity (Choi and Lipton, 2000; Javitt and Zukin, 1991; Sucher and Lipton, 1991). However, considering that NMDA receptor blockade attenuated nicotine self-administration (Kenny et al., 2009), it is unlikely that the increase in NMDA receptor activity mediated the effects of *N*-acetylcysteine on nicotine self-administration.

Finally, nicotine increases glutamatergic transmission by acting on excitatory $\alpha 7$ nAChRs located on glutamatergic afferents in the VTA and the NAc (McGehee et al., 1995). Consistent with findings showing that blockade of glutamatergic neurotransmission decreased the reinforcing effects of nicotine, systemic administration of the $\alpha 7$ nAChR antagonist methylcoconitine (MLA) attenuated nicotine self-administration (Markou and Paterson, 2001). In contrast, motivation to self-administer nicotine under the PR schedule of reinforcement was increased after local infusion of the $\alpha 7$ nAChR antagonist α -conotoxin ArIB into the NAc shell and decreased after infusion of the $\alpha 7$ nAChR agonist PNU282987 into the NAc shell (Brunzell and McIntosh, 2012). Differences in selectivity of the $\alpha 7$ nAChR antagonist used (MLA vs. α -conotoxin ArIB), mode of administration of the $\alpha 7$ nAChR antagonist (systemic vs. localized injections in the NAcc shell) and schedule of nicotine self-administration (FR vs. PR) likely contributed to the contradictory results in the two studies. Altogether, the data described above suggest that nicotine reinforcement is associated with increased glutamate transmission and compounds that decrease glutamate transmission block the primary reinforcing and motivational effects of nicotine.

3.2.2. Glutamate receptors and nicotine-induced reward enhancement—In addition to the reinforcing and motivational effects of nicotine, the blockade of glutamatergic transmission attenuated nicotine-induced reward enhancement, reflected by lowered brain reward thresholds. Specifically, the NMDA receptor antagonist LY235959 blocked the nicotine-induced lowering of ICSS thresholds but had no effect on ICSS thresholds when administered alone (Kenny et al., 2009), suggesting an important role for

NMDA receptors in the reward-enhancing effects of nicotine. Similarly, the mGluR5 antagonist MPEP and mGluR2/3 agonist LY314582 attenuated the nicotine-induced lowering of brain reward thresholds (Harrison et al., 2002; Kenny et al., 2009). However, MPEP or LY314582 alone also elevated ICSS thresholds, indicating that MPEP and LY314582 may have intrinsic aversive effects that are additive and negate nicotine-induced reward facilitation rather than directly block or reverse the reward-enhancing effects of nicotine.

3.2.3. Glutamate receptors and nicotine-induced conditioned place preference

—The decrease of glutamate transmission by 1-aminocyclopropanecarboxylic acid (ACPC), an NMDA antagonist, attenuated the acquisition and expression of nicotine-induced CPP (Papp et al., 2002). The VTA appears to be critically involved in this action because conditional knockout of NMDA receptors on VTA dopamine neurons prevented the acquisition of nicotine-induced CPP (Wang et al., 2010). Taken together these findings suggest an important role for NMDA receptors, particularly in the VTA, in the conditioned rewarding effects of nicotine. The role of mGluRs in nicotine-induced CPP has not yet been investigated extensively and studies were limited to the mGluR5. In nicotine-induced CPP, the administration of MPEP produced conflicting results ranging from inhibition (Yarabasi et al., 2010) to no effect (McGeehan and Olive, 2003) or potentiation (Rutten et al., 2011). Differences in species, strains, and experimental protocols likely contributed to the contradictory results with regard to the role of mGluR5 in nicotine-induced CPP.

3.3. GABA system and nicotine reward

3.3.1. GABA_B receptors and nicotine self-administration—Accumulating evidence indicates that enhancement of GABAergic neurotransmission in the VTA by activation of metabotropic GABA_B receptors attenuated both nicotine-induced increases in mesolimbic dopamine levels and the reinforcing effects of nicotine. For example, the GABA_B receptor agonist baclofen significantly decreased nicotine-induced increases in dopamine in the NAc (Fadda et al., 2003) and nicotine self-administration in rats (Paterson et al., 2004). Furthermore, systemic administration or microinjection of the GABA_B receptor agonist (3-amino-2[S]-hydroxy-propyl)-methylphosphinic acid (CGP44532) into the NAc shell or the VTA inhibited nicotine self-administration (Corrigall et al., 2000; Paterson et al., 2004). Consistent with the findings with agonists, administration of the indirect agonist γ -vinyl-GABA (GVG), which increases extracellular GABA levels by inhibiting GABA transaminase (i.e., the enzyme that breaks down GABA), also significantly inhibited nicotine self-administration (Paterson and Markou, 2002). Altogether, these data support an important role for mesolimbic GABA neurotransmission and GABA_B receptors in the regulation of the reinforcing effects of nicotine. However, both baclofen and CGP44532 also inhibited food self-administration, and tolerance to the inhibitory effects on nicotine self-administration developed after repeated administration (Filip et al., 2007; Paterson et al., 2005b), indicating the limited potential of full GABA_B agonists for medication development.

Positive allosteric modulators (PAMs) of GABA_B receptors bind to allosteric sites on the GABA_B receptors that are distinct from the orthosteric binding sites where GABA_B receptor agonists bind. GABA_B receptor PAMs are devoid of substantial intrinsic agonist activity and potentiate the efficacy of full receptor agonists (Christopoulos, 2002; Jensen and Spalding, 2004). Administration of the GABA_B receptor PAM *N,N'*-dicyclopentyl-2-(methylthio)-5-nitro-4,6-pyrimidinediamine (GS39783) combined with a subthreshold dose of the GABA_B receptor agonist CGP44532 selectively decreased nicotine self-administration, with no effect on food-maintained responding (Paterson et al., 2008). Moreover, GABA_B receptor PAMs, such as 3,5-*bis*(1,1-dimethylethyl)-4-hydroxy- β , β -dimethyl-benzenepropanol (CGP7930),

GS39783, and *N*-([1 *R*,2*R*,4*S*]-bicyclo[2.2.1]hept-2-yl)-2-methyl-5-(4-[trifluoromethyl]phenyl)-4-pyrimidinamine (BHF177), decreased nicotine self-administration in rats at doses that did not affect behaviors reinforced by food (Paterson et al., 2008). Furthermore, repeated administration of BHF177 for 14 days selectively attenuated nicotine self-administration compared with food-maintained responding (Vlachou et al., 2011a). Finally, GABA_B receptor PAMs have less sedation, less tolerance, and minimal effects on food reward, compared with agonists. Altogether, these data suggest that GABA_B receptor PAMs may be more promising than full agonists as treatments for nicotine dependence.

3.3.2. GABA_B receptors and nicotine-induced reward enhancement—The activation of GABA_B receptors was shown to block the reward-enhancing effects of nicotine. Specifically, the GABA_B receptor agonist CGP44532 attenuated the acute nicotine-induced lowering of brain reward thresholds at the highest dose that also significantly impaired brain reward function when administered alone (Paterson et al., 2008). However, the PAM BHF177 blocked the threshold-lowering effects of nicotine at intermediate and high doses, whereas only the highest doses of BHF177 significantly elevated brain reward thresholds when administered alone (Paterson et al., 2008). Overall, these data suggest that activation of GABA_B receptors results in an additive rather than interactive effect on the reward-enhancing effects of nicotine, but PAMs may still have less aversive effects on brain reward function compared with full receptor agonists.

3.3.3. GABA_B receptors and nicotine-induced conditioned place preference—Compounds, such as GVG and 1*R*,4*S*-4-amino-cyclopent-2-ene-carboxylic acid (ACC), that increase extracellular GABA levels by inhibiting GABA transaminase, attenuated the expression of nicotine-induced CPP in rats (Ashby et al., 2002; Dewey et al., 1999). Consistent with this finding, the activation of GABA_B receptors by the agonist baclofen attenuated the expression of nicotine-induced CPP in rats (Le Foll et al., 2008). Similarly, the GABA_B receptor PAM GS39783 attenuated the acquisition but not expression of nicotine-induced CPP (Mombereau et al., 2007). This decrease in nicotine-induced CPP by GS39783 was correlated with the inhibitory action of this compound on the nicotine-induced accumulation of Δ FosB (Mombereau et al., 2007), an effect that is seen with most drugs of abuse (McClung et al., 2004). These data support a role for GABA_B receptors in nicotine-induced reward and conditioned behavioral responses.

4. Nicotine withdrawal

Nicotine withdrawal is associated with negative affective symptoms in humans, including anhedonia, depressed mood, irritability, craving, and anxiety (American Psychiatric Association, 1994). In rodents, affective signs observed during nicotine withdrawal include “anhedonia” and anxiety-like behavior (Stoker et al., 2008). Physical or somatic aspects of nicotine withdrawal are observed in both humans and rodents (American Psychiatric Association, 1994; Epping-Jordan et al., 1998; Malin et al., 1992). This aversive abstinence syndrome, consisting of both affective and somatic signs, is hypothesized to contribute to the persistence of nicotine intake and relapse to smoking even after a period of abstinence (Kenny and Markou, 2004; Koob, 2009; Reichel and Bevins, 2009). Therefore, amelioration of the signs of early nicotine withdrawal using medications may prevent relapse to tobacco smoking when the urge to reinitiate nicotine use is the strongest (Abrantes et al., 2008; Brown et al., 2009; Shiffman et al., 2007).

In laboratory animals, nicotine withdrawal induces a deficit in brain reward function, measured by elevations of ICSS thresholds (Epping-Jordan et al., 1998). Such elevations of brain reward thresholds are an operational measure of “diminished interest or pleasure” in

rewarding stimuli (i.e., anhedonia). Interestingly, the somatic aspects of nicotine withdrawal are dissociated from the depression-like anhedonic aspects of nicotine withdrawal because different mechanisms appear to underlie these phenomena (Epping-Jordan et al., 1998; Stoker et al., 2012b; Watkins et al., 2000a; Watkins et al., 2000b). Moreover somatic signs appear to be primarily peripherally mediated, whereas affective signs are mediated by the central nervous system (Watkins et al., 2000b). Therefore, assessing the effects of treatments on both the affective and somatic aspects of drug withdrawal is important, although the affective aspects of drug withdrawal are hypothesized to be more critically involved in drug dependence than the somatic signs of withdrawal (Koob, 2009; Koob et al., 1993).

In addition to depression-like anhedonia, anxiety is another affective symptom of nicotine withdrawal that predicts the inability to abstain from tobacco smoking (Pomerleau et al., 2005; Weinberger et al., 2010; Zvolensky et al., 2009). Different experimental procedures that measure anxiety, including fear-potentiated startle (FPS) and light-potentiated startle (LPS), have predictive validity for standard anxiolytic compounds (Davis et al., 1993) and reveal anxiety-like responses during nicotine withdrawal in humans and rats (Engelmann et al., 2009; George et al., 2007; Hogle et al., 2010; Jonkman et al., 2008). Therefore, behavioral procedures that assess anxiety-like behaviors could provide important information about how the modulation of GABA and glutamate systems may alter anxiety-like responses during nicotine withdrawal.

4.1. Chronic nicotine-induced neuroadaptations in glutamate and GABA systems and their relevance to nicotine withdrawal

Chronic exposure to nicotine modulates dopamine transmission by directly activating dopamine neurons in the VTA or indirectly by modulating excitatory glutamate or inhibitory GABA transmission as described above. Studies have shown a significant decrease in dopamine during nicotine withdrawal in the striatum (Fung et al., 1996; Varani et al., 2011), cortex (Hildebrand et al., 1998; Varani et al., 2011); but see (Carboni et al., 2000), and NAc (Zhang et al., 2012) and decreased 5-hydroxytryptamine (5-HT) transmission in the striatum (Slotkin and Seidler, 2007; Varani et al., 2011) but not cortex or hippocampus (Varani et al., 2011). The majority of the aforementioned studies investigated the neurochemical changes that occur during precipitated nicotine withdrawal (i.e., after administration of the nAChR antagonist mecamylamine). Additional *in vivo* microdialysis studies are needed to determine the directional changes in various transmitter systems that occur during spontaneous nicotine withdrawal. These studies will be of great importance, especially when considering findings that suggest the differential effects of similar drug treatments on spontaneous and antagonist-precipitated nicotine withdrawal (Bruijnzeel et al., 2007).

Chronic nicotine exposure induces adaptive changes in the glutamate system and is hypothesized to lead to decreased glutamatergic transmission (Liechti and Markou, 2008; Markou, 2008). This hypothesis is based on findings that chronic nicotine self-administration upregulated NMDA and AMPA receptor subunit expression in the VTA and amygdala (Kenny et al., 2009). Decreased expression of the NR2A, NR2B, and Glu2 subunits was observed in the PFC during early withdrawal from prolonged nicotine self-administration (Wang et al., 2007). Altered expression of iGluR subunits may reflect compensatory changes in glutamate transmission that develop to counteract the effects of decreased glutamate transmission during nicotine withdrawal.

The role of mGluRs in nicotine dependence and withdrawal has been investigated extensively in recent years (D'Souza and Markou, 2011b; Liechti and Markou, 2008). Downregulation of mGluR2/3 function in the NAc shell, hypothalamus, and hippocampus was observed during early withdrawal from nicotine self-administration (Liechti et al., 2007). Thus, compounds that decrease glutamatergic transmission may be expected to

worsen nicotine withdrawal, and compounds that increase glutamate release may be expected to improve nicotine withdrawal.

Investigations of the role of the GABA system in nicotine withdrawal have not been as extensive as investigations of the glutamate system (Vlachou and Markou, 2010). Recent findings showed that decreased levels of dopamine and 5-HT neurotransmission in the cortex and striatum during mecamylamine-precipitated nicotine withdrawal were prevented by an acute injection of the GABA_B receptor agonist baclofen (Varani et al., 2011). However, chronic nicotine administration did not alter GABA_B receptor function. The GABA_B receptor regulation of brain reward function was unchanged in rats chronically exposed to nicotine compared with saline (Paterson et al., 2005a). Thus, chronic nicotine exposure may not induce neuroadaptations in GABA_B receptor function or GABA neurotransmission, but further studies are needed to investigate this issue.

4.2. Glutamate system and nicotine withdrawal

Direct blockade of postsynaptic iGluRs with the AMPA/kainate receptor antagonist 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide (NBQX) precipitated elevations of brain reward thresholds in nicotine-dependent but not control rats, suggesting that decreased glutamate transmission is associated with the anhedonic-like signs of nicotine withdrawal (Kenny et al., 2009). Furthermore, the mGluR5 antagonist MPEP significantly elevated brain reward thresholds and increased somatic withdrawal signs associated with spontaneous nicotine withdrawal (Liechti and Markou, 2007a), but it did so equally in control rats (Harrison et al., 2002; Kenny et al., 2003b), indicating that MPEP nonspecifically decreased brain reward function and increased the number of somatic signs. Interestingly, mGluR5 knockout mice exhibited an attenuation of threshold elevations during nicotine withdrawal, with no increases in somatic withdrawal signs (Stoker et al., 2012a). These findings suggest that the lack of mGluR5 in knockout mice may have prevented the development of nicotine dependence, whereas the presence of this receptor during nicotine exposure in rats rendered these receptors more sensitive to blockade with an mGluR5 antagonist.

Additionally, mGluR2/3 plays an important role in nicotine withdrawal. The mGluR2/3 antagonist (2*S*)-2-amino-2-([1*S*,2*S*]-2-carboxycycloprop-1-yl)-3-(xanth-9-yl) propanoic acid (LY341495) reversed the affective aspects of nicotine withdrawal (Kenny et al., 2003a). Systemic or intra-VTA administration of the relatively selective mGluR2/3 agonist 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY314582; a racemic mixture of [1*S*,2*S*,5*R*,6*S*]-2-aminobicyclo[3.1.0] hexane-2,6-dicarboxylic acid [LY354740]) produced withdrawal-like elevations of brain reward thresholds in nicotine-dependent but not control rats (Kenny et al., 2003a). In later work, however, administration of the selective mGluR2/3 agonist LY379268 only tended to aggravate nicotine withdrawal-induced reward deficits, but it produced mild reward deficits in control rats (Liechti and Markou, 2007b). Thus, mGluR2/3 agonists do not appear to worsen the affective anhedonic-like aspects of nicotine withdrawal as one may have expected from studies that used mGluR5 antagonists. This finding is important when considering that mGluR2/3 agonists decreased nicotine reinforcement (see above) and nicotine seeking (see below), suggesting that mGluR2/3 agonists may be good candidates as smoking cessation medications.

Interestingly, attenuation of the depression-like reward deficits of nicotine withdrawal with the mGluR2/3 antagonist LY341495 (Kenny et al., 2003a) is consistent with the antidepressant-like effects of LY341495 and the mGluR2/3 antagonist (1*R*,2*R*,3*R*,5*R*,6*R*)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluorobicyclo[3.1.0] hexane-2,6-dicarboxylic acid (MGS0039) in the forced swim test and learned helplessness test in rats and tail suspension test in mice (Chaki et al., 2004; Karasawa et al., 2006). Importantly, these findings are consistent

with findings that demonstrated that reward deficits associated with psychostimulant withdrawal were reversed after administration of various clinically used antidepressant treatments, indicating that the elevations of brain reward thresholds during withdrawal from psychostimulants including nicotine have predictive validity as an animal model of anhedonia (Barr and Markou, 2005; Barr et al., 2002; Cryan et al., 2002; Paterson and Markou, 2007).

Finally, nicotine withdrawal is also associated with increased anxiety in nicotine-abstinent humans compared with non-smokers, measured in the fear-potentiated startle procedure (Grillon et al., 2007; Hogle et al., 2010). Fear-potentiated startle was shown to be sensitive to the anxiolytic-like effects of the mGluR2/3 agonist LY354740 and its pro-drug (1*S*,2*S*,5*R*,6*S*)-2-([2'*S*]-[2'-amino]-propionyl)amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride (LY544344) in humans (Grillon et al., 2003). Additionally, LY354740 and LY544344 reduced generalized anxiety disorder symptoms in humans (Dunayevich et al., 2008). However, how mGluR2/3 agonists alter anxiety-like behavior during nicotine withdrawal is not fully understood. Recent findings showed that administration of ceftriaxone, a β -lactam antibiotic, reversed anxiety-like behavior and somatic signs associated with nicotine withdrawal in mice (Alajaji et al., 2013). It is hypothesized that ceftriaxone reversed nicotine withdrawal-induced decreases in glutamate transmission via upregulation of the glutamate transporter-1 and/or cystine-glutamate exchanger (Knackstedt et al., 2010; Lewerenz et al., 2009; Rothstein et al., 2005).

4.3. GABA system and nicotine withdrawal

Systemic administration of low doses of the indirect GABA_B receptor agonist GVG and GABA_B receptor agonist CGP44532 did not affect brain reward thresholds in the ICSS procedure in chronically saline- or nicotine-treated rats, whereas the highest dose of each drug elevated thresholds in both groups of animals (Paterson et al., 2005a; Vlachou et al., 2011b). Microinjection of CGP44532 into the VTA elevated thresholds equally in both the saline- and nicotine-treated groups, indicating that prolonged nicotine exposure did not alter the GABA_B receptor-mediated regulation of brain reward function (Paterson et al., 2005a). Surprisingly, GABA_B receptor blockade, similar to GABA_B receptor activation, also elevated brain reward thresholds in all groups, resulting in the exacerbation of the effects of nicotine withdrawal in the nicotine-treated groups (Vlachou et al., 2011b). These similar effects of GABA_B receptor activation and blockade on the anhedonic-like aspects of nicotine withdrawal possibly reflect the differential efficacy of these compounds at presynaptic GABA_B hetero- and autoreceptors and postsynaptic GABA_B receptors. Based on these findings, changes in GABA_B receptor activity do not appear to play a role in brain reward deficits associated with spontaneous nicotine withdrawal. In contrast to the anhedonic-like aspects of nicotine withdrawal, administration of baclofen attenuated the somatic signs associated with precipitated nicotine withdrawal induced by the nAChR antagonist mecamylamine (Varani et al., 2011). Furthermore, the somatic signs of nicotine withdrawal were absent in GABA_{B1} knockout mice (Varani et al., 2012).

The GABA_B receptor PAMs GS39783 and CGP7930, which have distinct chemical structures, resulted in a broad anxiolytic-like profile in rodents (Cryan et al., 2004; Jacobson and Cryan, 2008; Mombereau et al., 2004a). Studies in mice that lacked specific subunits of the GABA_B receptor corroborated pharmacological findings by showing that both GABA_{B1} and GABA_{B2} receptor subunit knockout mice exhibited more anxiety-like behaviors than their wildtype counterparts in several tests of anxiety and showed diminished responsiveness to benzodiazepine anxiolytics (Cryan et al., 2004; Jacobson et al., 2007; Mombereau et al., 2005; Mombereau et al., 2004b). Recent work demonstrated that the anxiolytic-like effects of acute nicotine were abolished in GABA_{B1} knockout mice (Varani et al., 2012). Thus,

future research on the effects of GABA_B compounds on the anxiety-like aspects of nicotine withdrawal is warranted.

5. Reinstatement of nicotine-seeking behavior

Relapse to cigarette smoking in abstinent smokers is a major hurdle in the promotion of smoking cessation (Agboola et al., 2010; Hughes et al., 2004). Clinical reports suggest that several factors, including exposure to environmental stimuli previously associated with smoking, stressful life events, and cigarette smoking itself, can lead to relapse in smokers (Ferguson and Shiffman, 2009; Shiffman et al., 1985). The extinction-reinstatement procedure in experimental animals is a putative model of relapse in humans (Shaham et al., 2003). In this model, animals are first allowed to self-administer nicotine for an extended period of time. Subsequently, the animals undergo extinction training, during which they have no access to nicotine, thus resulting in a decrease in their nicotine-seeking responses. After nicotine seeking is extinguished, the animals are re-exposed to one of the factors known to induce relapse in humans (i.e., cues/contexts associated with nicotine, stressful stimuli, or nicotine itself). Exposure to one of the aforementioned factors was shown to reinstate extinguished nicotine seeking (Bruijnzeel et al., 2009; Dravolina et al., 2007; Paterson et al., 2005b). The extinction-reinstatement procedure has been extensively used to improve our understanding of the neurobiology of relapse to nicotine-seeking behavior in humans.

5.1. Neural substrates of nicotine seeking

Chronic drug (including nicotine)-induced neuroadaptations in glutamate neurotransmission are hypothesized to play an important role in the reinstatement of drug seeking (Knackstedt and Kalivas, 2009; Liechti and Markou, 2008). Drug-associated cues have been shown to increase glutamate levels in the NAc core, and this cue-induced increase in glutamate levels plays an important role in the reinstatement of drug seeking (LaLumiere and Kalivas, 2008). Furthermore, blockade of glutamate transmission in the NAc core attenuated the reinstatement of drug seeking (Backstrom and Hyttia, 2006; Cornish et al., 1999; Xie et al., 2012). In addition to the NAc core, blockade of glutamate transmission in the VTA, dorsal hippocampus, and basolateral nucleus of the amygdala attenuated the reinstatement of drug seeking (Lu et al., 2012; Sinclair et al., 2012; Xie et al., 2010). These studies highlight an important role for glutamate in the reinstatement of drug seeking.

5.2. Glutamate system and nicotine seeking

Systemic administration of *N*-acetylcysteine attenuated the cue-induced reinstatement of nicotine seeking (Ramirez-Nino et al., 2013), possibly by increasing glutamatergic tone at presynaptic mGlu2/3 receptors (Kupchik et al., 2012). In addition to *N*-acetylcysteine mGluR2/3 activation by the agonist LY379268 attenuated the cue-induced reinstatement of nicotine seeking in rats (Liechti et al., 2007). Further, blockade of glutamatergic neurotransmission by the mGluR5 antagonist MPEP attenuated cue-induced nicotine seeking (Bespalov et al., 2005). Moreover, blockade of mGluR1 attenuated both the cue- and nicotine-induced reinstatement of nicotine seeking (Dravolina et al., 2007).

However, administration of either *N*-acetylcysteine or LY379268 also attenuated reinstatement of food seeking (Liechti et al., 2007; Ramirez-Nino et al., 2013), suggesting that the effects of these compounds are not specific to the reinstatement of nicotine seeking. Smokers who abstain from smoking often experience extreme food cravings that result in undesirable weight gain (Friedman and Siegel, 1980). Therefore, the blockade of cue-induced food seeking may be considered a desirable effect in the case of medications developed to prevent relapse in smokers. Furthermore, the data from Liechti and colleagues

suggest that glutamate-dependent mechanisms may be involved in conditioned behavioral responses, regardless of the reinforcer.

5.3. GABA system and reinstatement of nicotine seeking

Findings have indicated that GABA neurotransmission may also be involved in the cue-induced reinstatement of nicotine seeking. The GABA_B receptor agonists baclofen and CGP44532 attenuated the cue-induced reinstatement of nicotine seeking but not food seeking (Paterson et al., 2005b). Baclofen also attenuated the nicotine-induced reinstatement of extinguished nicotine seeking (Fattore et al., 2009). The GABA_B receptor PAM BHF177 attenuated cue-induced nicotine seeking without affecting food seeking (Vlachou et al., 2011a). Altogether, these data suggest that the effects of GABA_B receptor activation are specific to nicotine-associated conditioned motivational behavioral responses and that GABA_B receptors may be a promising target for attenuating relapse to nicotine seeking in abstinent human smokers.

6. Role of glutamate and GABA neurotransmission in nicotine dependence: Evidence from studies in humans

Studies in nicotine dependent smokers have evaluated medications targeting glutamate and GABA neurotransmission on the subjective effects of smoking and the aversive effects associated with smoking cessation. The subjective effects of nicotine were attenuated by decreases in glutamatergic transmission after administration of memantine, a NMDA receptor antagonist, (Jackson et al., 2009) and low dose of *D*-cycloserine, a partial agonist at the glycine site of the NMDA receptor which has antagonist properties at low doses (Nesic et al., 2011). Further, a small double-blind study in humans showed that repeated *N*-acetylcysteine administration reduced the number of cigarettes smoked daily over a period of four weeks when alcohol consumption was taken into consideration (Knackstedt et al., 2009). More recently, a small double-blind placebo controlled study reported decreased rewarding effects for the first cigarette after a period of abstinence in smokers treated with *N*-acetylcysteine compared to placebo (Schmaal et al., 2011) suggesting that *N*-acetylcysteine may be a potential treatment option for smoking cessation.

Reduced GABA levels have been observed in the dorsal anterior cingulate cortex of abstinent smokers (Janes et al., 2013). Administration of a single acute dose of baclofen, a GABA_B receptor agonist, had no effect on the number of cigarettes smoked (Cousins et al., 2001). However, chronic baclofen administration significantly decreased the number of cigarettes smoked per day (Franklin et al., 2009). Furthermore, pregabalin, a GABA analogue, attenuated symptoms of nicotine withdrawal, such as irritability and anxiety, in abstinent smokers (Herman et al., 2012).

Several genetic studies, including human genome wide association studies, suggest involvement of the glutamate and GABA systems in nicotine dependence. Nicotine dependence has been associated with genes coding for the NMDA and kainate receptors (Ma et al., 2010; Vink et al., 2009), mGluR5 (Bierut et al., 2004) and the glutamate uptake transporters (dos Santos et al., 2012; Flatscher-Bader et al., 2008). In addition, a genome wide association study linked nicotine dependence to the neurexin gene family (Bierut et al., 2007). Neurexins code for a number of cell surface proteins that regulate neurotransmitter release and play an important role in GABAergic and glutamatergic synapse genesis. Finally, several studies report a strong link of genes coding for the GABA_A receptors to nicotine dependence (Agrawal et al., 2009; Agrawal et al., 2008; Saccone et al., 2007).

7. Glutamate and GABA-based novel pharmacotherapies for smoking cessation: Opportunities, challenges and concluding remarks

Medications promoting smoking cessation should ideally target multiple aspects of nicotine dependence. That is, such medications should attenuate the reinforcing effects of nicotine, alleviate multiple symptoms associated with nicotine withdrawal and/or prevent relapse amongst abstinent smokers (Harmey et al., 2012; Markou et al., 2008). Compounds that decrease glutamate transmission by blocking postsynaptic glutamate receptors (NMDA, AMPA, mGlu5), activating presynaptic inhibitory mGluR2/3 or increase inhibitory GABAergic transmission by activating GABA_B receptors attenuated the positive reinforcing and incentive motivational effects of nicotine, inhibited the reward-enhancing and conditioned rewarding effects of nicotine, and/or blocked reinstatement of nicotine seeking in animal models. Thus, medications targeting these receptors may attenuate the reinforcing effects of nicotine and prevent relapse to smoking in humans.

The aversive aspects of nicotine withdrawal are hypothesized to be partially mediated by decreased glutamatergic and GABAergic transmission. An increase in glutamate transmission resulting from blockade of inhibitory presynaptic mGluR2/3s reversed the reward deficits associated with nicotine withdrawal; while a decrease in glutamate transmission by blocking postsynaptic iGluRs or mGluR5 worsened anhedonic aspects of nicotine withdrawal. Activation of mGluR2/3 or GABA_B receptors did not appear to aggravate reward deficits associated with nicotine withdrawal. Increased anxiety and somatic signs of nicotine withdrawal were attenuated by an increase in glutamate transmission via upregulation of the glutamate transporter-1, the cystine-glutamate exchanger or GABA_B receptor activation. Thus, medications that decrease mGluR2/3-mediated glutamatergic transmission, reverse nicotine-induced downregulation of glutamate transporters or increase GABA_B receptor activity may attenuate the affective and somatic aspects of nicotine withdrawal in abstinent smokers.

Slow acting G-protein coupled glutamate and GABA receptors appear to be better targets than fast-acting ionotropic receptors for smoking cessation medications. Blockade of NMDA/AMPA receptors is associated with undesirable effects, including neurotoxicity and psychotogenicity (Bisaga et al., 2000; Kornhuber and Weller, 1997). In contrast, mGluR ligands subtly modulate glutamate neurotransmission, and thus are likely to have improved pharmacological profiles than iGluRs, and may be more suitable targets for smoking cessation medications. Similarly, G-protein coupled GABA_B receptors appear to be better targets compared to ionotropic GABA_A receptors.

Furthermore, positive allosteric modulators (PAMs) are preferred ligands for medication development compared with full receptor agonists because PAMs act at sites that are distinct from the orthosteric binding site and are devoid of substantial intrinsic agonist activity. Recent studies suggest that compared with GABA_B receptor agonists, GABA_B PAMs induce less sedation, less tolerance and minimally affect responding for food rewards (Li et al., 2013; Paterson et al., 2005b; Vlachou et al., 2011a). The anxiolytic properties of GABA_B receptor PAMs would also be beneficial for smoking cessation because GABA_B receptor PAMs may diminish the increased anxiety associated with nicotine withdrawal. Similar to GABA_B receptor PAMs, mGluR2 PAMs blocked nicotine (Sidique et al., 2012a) and cocaine (Jin et al., 2010) self-administration at doses that did not affect responding for food compared to mGluR2/3 agonists (Jin et al., 2010). The improved pharmacological and side-effect profile of GABA_B receptor and mGluR2 PAMs, and potentially mGluR5 negative allosteric modulators (NAMs) that have not been investigated much in nicotine dependence models, makes these compounds promising candidates for the development of smoking cessation medications.

Finally, it should be acknowledged that the role of the different glutamate and GABA receptors in nicotine dependence has been investigated using relatively selective pharmacological compounds that may have off-target effects. In addition, the role of the various glutamate and GABA receptors in specific brain sites that are involved in different aspects of nicotine dependence needs further investigation. Thus, future studies that use receptor-selective compounds and more targeted molecular approaches, such as viral-mediated overexpression or suppression of specific glutamate and GABA receptors in specific brain sites, are warranted.

In conclusion, significant progress has been made in understanding the role of glutamate and GABA neurotransmission in different aspects of nicotine dependence. Compelling evidence from studies in humans and animals suggests that glutamate and GABA transmission appear to be highly interesting targets in the search for smoking cessation medications with novel mechanisms of actions that differ from those of currently Food and Drug Administration (FDA)-approved smoking cessation pharmacotherapies.

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Highlights

- blockade of glutamatergic transmission inhibited nicotine reward
- facilitation of GABAergic transmission inhibited nicotine reward
- blockade of glutamatergic transmission inhibited nicotine-seeking behavior
- facilitation of GABAergic transmission inhibited nicotine-seeking behavior
- glutamatergic and GABAergic medications may be promising for smoking cessation

Figure 1.

Glutamate, GABA and dopamine interactions that are involved in the development of nicotine dependence. Nicotine binds to excitatory nicotinic acetylcholine receptors (not shown in figure) that are located throughout the brain as auto- or heteroreceptors at presynaptic terminals that regulate the release of several neurotransmitters, including dopamine, glutamate and γ -aminobutyric acid (GABA). The mesolimbic dopaminergic neurons (depicted as yellow lines) mediate the reinforcing effects of several drugs of abuse including nicotine. These dopaminergic neurons originate in the ventral tegmental area and project to several limbic and cortical regions, including the nucleus accumbens, prefrontal cortex, amygdala, hippocampus, and habenula. The activity of these dopaminergic neurons is regulated by reciprocal glutamatergic (excitatory; depicted as blue) and GABAergic (inhibitory; depicted as red lines) projections that originate from the aforementioned cortical and limbic brain regions. AMY, amygdala; LHb, lateral habenula; HC, hippocampus; NAc, nucleus accumbens; PFC, prefrontal cortex; RN, raphe nucleus; VP, ventral pallidum; VTA, ventral tegmental area. Taken with permission from D'Souza MS and Markou A (2012) *The "Stop" & "Go" of Nicotine Dependence: Role of GABA and glutamate*. In: *Addiction: A neurobiological perspective*. Pierce, R.C., Kenny, P.J. (eds.). © Cold Spring Harbor Laboratory Press, New York.