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Invited review

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.

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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.

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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 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 [for review, see (Balfour, 2009; D'Souza and Markou., 2012; Koob and Volkow, 2010)]. 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; Schilstrom 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 α4β2-containing and homomeric α7 nAChRs are the most abundant subtypes in the brain (Feduccia et al., 2012). Nicotine activates α4β2-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 α7 nAChRs located on glutamatergic terminals increases the release of glutamate in the VTA (McGehee et al., 1995; Schilstrom et al., 2000). Furthermore, nicotine activates α4β2-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 the 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-isoxale 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

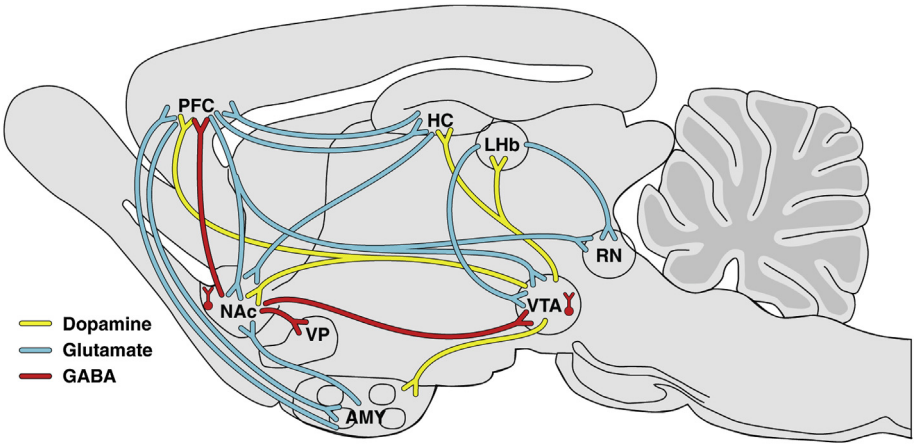

Fig. 1. Glutamate, GABA, and dopamine interactions that are involved in the development of nicotine dependence. Nicotine binds to excitatory nicotinic acetylcholine receptors (not shown in figure) that are located throughout the brain as auto- or heteroreceptors at presynaptic terminals that regulate 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 lines) 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.*

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