Shifting pharmacology of nicotine use and withdrawal: Breaking the cycle of drug abuse

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Smoking is the leading preventable cause of death, responsible for over 400,000 premature deaths every year in the United States and weighing heavily on an economy with a nearly $200 billion combined cost of health care and lost productivity (1). Despite the deleterious immediate and long-term effects of smoking, only 3% of smokers successfully quit, although 70% of all smokers express the desire to do so (2). Nicotine is the main addictive psychoactive ingredient present in tobacco smoke (3). Chronic exposure to nicotine initiates neuroadaptation; these alterations, in turn, promote continued tobacco use. When a smoker attempts cessation, this new equilibrium maintained by nicotine exposure is disrupted, leading to the withdrawal state. Withdrawal is a series of affective and somatic symptoms that emerge a few hours after nicotine abstinence, reflecting neurochemical imbalance (4); however, the precise nature of this imbalance has remained elusive. Nicotine, as is the case with many other drugs of abuse, is known to have an impact on the dopamine (DA) system (5). Grieder et al. (6) perform a series of elegant experiments using pharmacology and electrophysiology in parallel with genetic and behavioral approaches to examine how the dopaminergic system may be involved in this process. An important aspect of their work is that it highlights the double dissociation of dopaminergic system involvement between acute exposure to nicotine and the chronic withdrawn state with respect to DA neuron activation in the ventral tegmental area (VTA) and the DA receptors that mediate conditioned place aversion (Fig. 1).

It has been known (7) that DA neuron activity can exist in two states: a tonic baseline firing mode and an activated state known as burst firing (8, 9); the latter state is typically associated with phasic reward-related events (10). Furthermore, these activity states are known to have an impact on different DA receptors, with tonic DA transmission affecting primarily D2 receptors (D2Rs) and phasic bursting stimulating D1 receptors (D1Rs) (11). Nicotine binds to nicotinic AChRs that are activated by the endogenous neurotransmitter ACh (12). The cholinergic system exerts a profound effect on dopaminergic activity; when this drug is delivered to the VTA, it promotes a transition of DA neuron activity from tonic firing to phasic bursts that signal reward and salience (13, 14). Recording VTA DA neuron activity during nicotine acute exposure, chronic exposure, and withdrawal, the authors report evidence for dissociation in DA neuron activity patterns between these different stages. Acute exposure increases signaling mediated via phasic bursts, whereas chronic exposure and withdrawal induces no change in burst activity but causes lower tonic firing rates. Burst firing produces a large, transient release of DA that activates D1Rs, whereas tonic DA neuron firing releases a steady but lower amount of DA, which activates the higher affinity D2Rs (11, 15). Therefore, the results support the model whereby nicotine exposure first activates the reward-related phasic DA release, which, on continued use and withdrawal, is replaced by the lower tonic DA neuron firing. This suggests that dependent human smokers have decreased DA activity during withdrawal, potentially drawing them into the abuse cycle to restore DA tone.

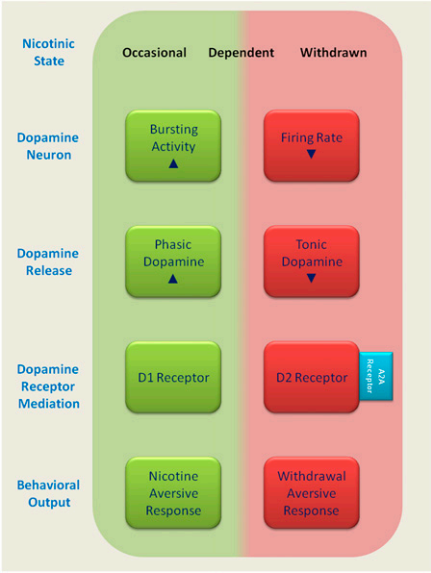

Fig. 1. Schematic summary of the double dissociation between acute nicotine exposure and the dependent/withdrawn state. Nicotine signaling during acute exposure increases phasic burst firing in DA neurons, which may lead to an increase in D1R stimulation and expression of aversive behavior. A key mechanism signaling nicotine withdrawal is decreased tonic activity of the VTA DA neurons, which may act through D2Rs, and indirectly through A2ARs, to signal an aversive motivational state, leading to reinstatement of nicotine abuse.

DA signaling has been implicated both in positive and aversive motivational responses to nicotine during various stages of exposure and withdrawal (16, 17). By pharmacological manipulation and use of genetic KO mice, Grieder et al. (6) report a second dissociation between acute exposure and nicotine withdrawal. They first show that phasic burst activity is necessary for the immediate aversive behavioral response to nicotine and that disruption of DA receptor activity blocks chronic withdrawal aversion. They then demonstrate that the D1R is not only necessary to mediate the aversive motivational response during acute exposure but that any alteration of D1 stimulation disrupts this response. In contrast, D2Rs are essential for the nicotine withdrawal aversion response, and, similarly, any alteration of D2 signaling circumvents this behavioral expression. These results provide unique and important information in the understanding of the neural basis of withdrawal and suggest that long-term exposure to nicotine causes the system to enter a new allostatic state (18, 19). As a consequence, an abrupt cessation of nicotine or other drugs of abuse selectively alters DA system activity, reinforcing the addiction cycle (20–23).

Because of the potential negative consequences of directly manipulating the DA system, Grieder et al. (6) also investigate the possibility that nicotine dependence may be altered by manipulating non-DA receptors. For this, the authors focused on the adenosine 2A receptors (A2ARs). These receptors are known to form heteromers with D2Rs in the striatum (an important target of the VTA and a reward-related site of the basal ganglia) and negatively modulate D2R signaling (24, 25). Pharmacological modulation of the A2AR (positive or negative) blocked aversion to withdrawal from chronic nicotine.

In summary, Grieder et al. (6) demonstrate through an elegant set of electrophysiological and behavioral studies using pharmacological manipulations and a KO model that there is a shift in DA signaling

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during the nicotine use cycle, from a reward/acute aversive condition mediated by phasic DA stimulation of D1Rs to a long-term withdrawal-associated aversive state that is dependent on decreased tonic DA activation of D2Rs. This specific withdrawal-associated steady-state balance may predispose an individual to further nicotine use (6). What is unique is the finding that the neurobiological changes go beyond a simple up- or down-regulation of the DA system but show that a new equilibrium is established; as a consequence, a nicotine replacement strategy can only go so far to palliate the full range of negative symptoms associated with withdrawal. Bupropion (an atypical antidepressant) has produced encouraging long-term results in smoking cessation, although serious adverse effects have been reported (26, 27). A2ARs may present as a unique and potentially viable target for future therapeutic development that targets the stressful effect of abrupt nicotine cessation.

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