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ACh/Dopamine Crosstalk in Motor Control and Reward: A Crucial Role for α6-Containing Nicotinic Receptors?

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The midbrain dopaminergic system is a key element in the control of motor activity, cognition, and the motivational effects of drugs of abuse, including nicotine. In this issue of *Neuron*, Drenan et al. find that α6-containing nicotinic acetylcholine receptors might selectively activate mesolimbic and mesostriatal dopaminergic neurons, enhancing striatal dopamine release and its behavioral consequences.

Nicotine, the primary psychoactive component of tobacco smoke, exerts its actions by acting on endogenous nicotinic acetylcholine receptors (nAChRs), pentameric complexes formed from a portfolio of α and β subunits (α2–α10 and β2–β4) that show unique functional and structural properties depending on the differential association between subunits. nAChRs are ubiquitously expressed throughout the central nervous system at both presynaptic and postsynaptic sites where they cooperate with other neurotransmitter systems to modulate synaptic transmission and plasticity (Dajas-Bailador and Wonnacott, 2004). Bidirectional crosstalk between the cholinergic and the dopaminergic signaling systems is thought to be crucial for the physiological function of neuronal networks in several neural structures. In particular, in the striatum, the main input station of the basal ganglia neural circuit, interaction between dopaminergic and cholinergic signaling mediates cognitive processes (Calabresi et al., 2006), motor responses selection, and reward-related information (Cragg, 2006).

It is generally accepted that the striatum is composed of a dorsal sensorimotor region (dorsal striatum) and a ventral portion that processes limbic information (ventral striatum or nucleus accumbens [NAc]). Although these regions are very similar with respect to neural cytoarchitecture, their functional roles and dopaminergic projections vary. The dorsal striatum is mainly innervated by associative and sensorimotor areas of the cortex and receives dopaminergic inputs from the substantia nigra pars compacta (SNc) through the so-called "mesostriatal" dopaminergic pathway. Conversely, the NAc primarily receives afferents from limbic structures and dopaminergic innervation from the ventral tegmental area (VTA), constituting a primary component of the "mesolimbic" pathway. While the dorsal striatum seems to be involved in movement generation and learning, mesolimbic dopaminergic neurons of the VTA play a crucial role in mediating the reinforcing effects of natural rewards and the motivational effects of a wide variety of addictive drugs, including nicotine (Laviolette and van der Kooy, 2004). Both the VTA and the SNc contain dopaminergic and GABAergic neurons (Lacey et al., 1989; Laviolette and van der Kooy, 2004) and express nAChRs, although their subunit composition profiles seem to substantially differ (Keath et al., 2007).

Nicotine can activate midbrain dopaminergic neurons and presynaptic dopaminergic terminals in the striatum (Calabresi et al., 1989; Picciotto et al., 1998; Pidoplichko et al., 1997; Zhou et al., 2001), leading to dopamine (DA) release and thus exerting a major role in modulating the dopaminergic control of both motor activity and reward. The original description of the direct nicotinic action on VTA neurons suggested that endogenous acetylcholine (ACh) is able to activate postsynaptic receptors located on midbrain dopaminergic neurons (Calabresi et al., 1989). However, VTA and SNc dopaminergic neurons seem to be differentially modulated by nicotine, leading to more profound effects in VTA than SNc (Keath et al., 2007), supporting the observation that in vivo nicotine administration elicits stronger DA release in the NAc than in the dorsal striatum (Di Chiara and Imperato, 1988).

In the VTA, GABAergic neurons express $\alpha4\beta2$ nAChRs, while glutamatergic terminals express $\alpha7$-containing nAChRs that show less desensitization (Keath et al., 2007). Accordingly, it has been hypothesized that exposure to nicotine might initially result in increased firing of VTA GABAergic neurons through the activation of $\alpha7$-containing nAChRs, followed by their desensitization, leading to the disinhibition and firing of DA neurons. This latter event might be also enabled by the more prolonged activation of $\alpha7$-containing nAChRs expressed on glutamatergic terminals (Keath et al., 2007).

Although significant advances have been made in understanding nAChR-mediated control of dopaminergic transmission, a number of questions still remain unanswered and the complex issue of interpreting the role of the large portfolio of different nAChR subtypes expressed by VTA and SNc neurons is far from being solved. In this issue of *Neuron*, Drenan and colleagues provide new insights into the complex mechanisms underlying the ACh-mediated control of dopaminergic signaling (Drenan et al., 2008). In particular, the authors generated mice with gain-of-function $\alpha6$-containing nAChRs in order to selectively amplify and characterize the cholinergic control of DA release mediated by these receptors. Although mutant mice exhibited normal levels and localization of neuronal nAChRs, the results obtained by the authors with behavioral, electrophysiological, and molecular biology techniques suggest that $\alpha6$-containing nAChRs might play a specific and crucial role in regulating DA release and its behavioral consequences.

Mutant mice were markedly hyperactive in comparison to WT mice and did not show habituation when placed in a novel environment. Nicotine administration resulted in a strong activation of locomotion in mutant mice without having any effect in WT animals, and interestingly, this effect on locomotor behavior was not changed after repeated nicotine injections.

After separating tissue samples of the mesostriatal and mesolimbic pathways, the authors measured nicotine-stimulated DA release from striatal synaptosomes of mutant and WT mice and showed that the selective activation of $\alpha6$-containing nAChRs is capable of stimulating DA release. Interestingly, the authors uncovered no difference in GABA release, suggesting that striatal GABA release could be independent from the stimulation of $\alpha6$-containing nAChRs.

With electrophysiological recordings from VTA/SNc dopaminergic neurons, the authors then demonstrated that neurons from mutant mice are markedly hypersensitive to nicotine, showing larger inward currents after nicotine puffs. Interestingly, the authors noticed greater fluctuations in the holding current in mutant VTA/SNc neurons, which was absent after $\alpha6$ blockade, suggesting its dependence on the tonic activation of some $\alpha6$-containing channels. The authors then more selectively investigated the electrophysiology of midbrain dopaminergic versus GABAergic neurons, leading to one of their central discoveries. Indeed, the hypersensitive nicotinic responses were found to be present in dopaminergic neurons, but not GABAergic neurons, suggesting that functional $\alpha6$-containing nAChRs, in contrast to $\alpha4$-containing nAChRs, might be restricted to dopaminergic neurons in the midbrain.

It is difficult to understand whether the observed effects of low-dose nicotine on locomotor behavior are preferentially based on a "motivational" effect caused by the stimulation of the mesolimbic pathway or on a more selective "motor" effect consequent to the activation of the mesostriatal pathway. This issue, unfortunately, has not been directly addressed with behavioral experiments. Nevertheless, the direct comparison of the results of DA release with the electrophysiological experiments seems to suggest that the mesolimbic pathway is more influenced by $\alpha6$-containing nAChR stimulation than the mesostriatal pathway is.

The experimental and clinical implications of this research are considerable, and they might suggest future research directions. Indeed, pathological conditions ranging from Parkinson's disease to drug addiction might benefit from a drug able to modulate the dopaminergic system in an indirect manner. In particular, the possibility of selectively influencing, either positively or negatively, dopaminergic transmission via the manipulation of $\alpha6$-containing nAChRs opens the way to the development of new pharmacological compounds for the treatment of neuropsychiatric diseases characterized by an altered dopaminergic signaling. The potential usefulness of $\alpha6$-containing nAChR manipulation as an effective therapeutic strategy seems to be also supported by the interesting observation that, at least in the presented experimental model, the repeated activation of these receptors produced neither tolerance nor sensitization, suggesting potentially reduced risks of drug abuse.

Although the interesting results obtained by Drenan and colleagues shed light on the mechanisms underlying the ACh-mediated control of dopaminergic transmission, the provided data also raise several crucial and yet unanswered questions.

Compelling evidence suggests that the interaction between the cholinergic and the dopaminergic systems is not unidirectional, but mutual. Indeed, in different neuronal structures, but particularly in the striatum, a bidirectional crosstalk occurs between these two neurotransmitters to physiologically modulate synaptic transmission and, notably, synaptic plasticity (Calabresi et al., 2006). Moreover, this DA/ACh interaction is not only based on the activation of nAChRs, but also on the stimulation of muscarinic ACh receptors (Calabresi et al., 2006). These latter observations provide several interesting points of discussion. What is the net effect of the complex mechanisms by which the

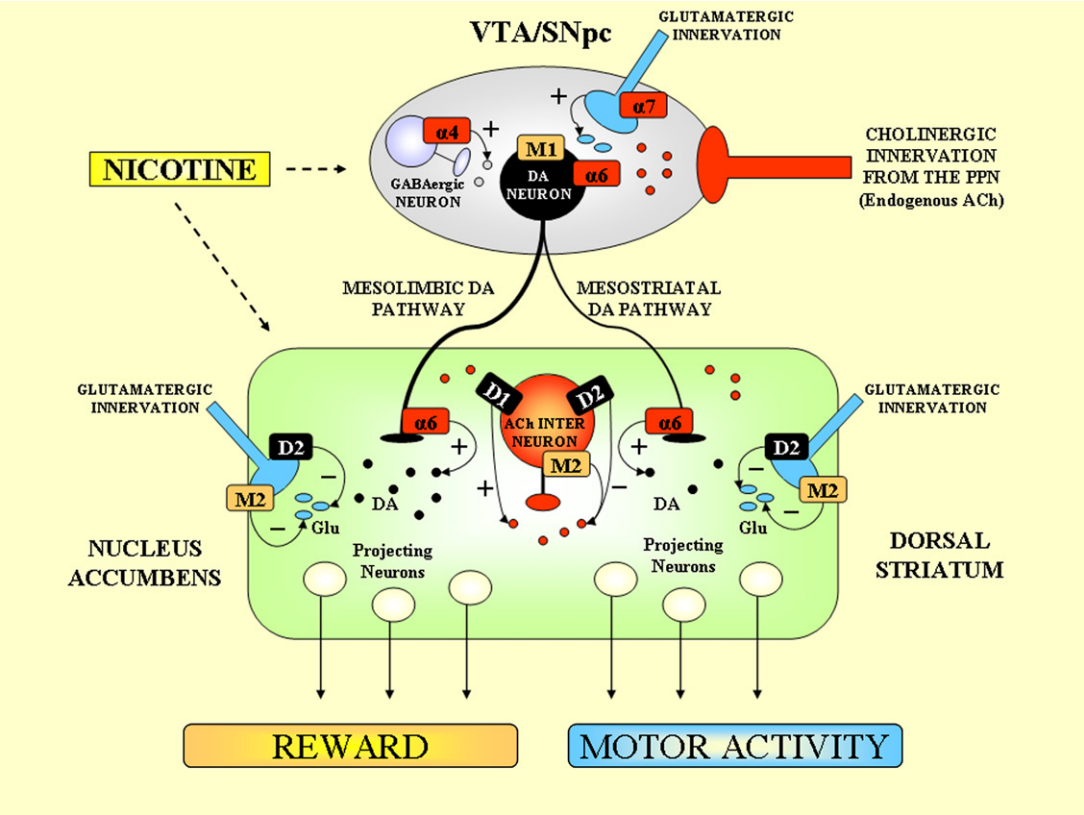

Figure 1. ACh/Dopamine Crosstalk in the Mesolimbic and Mesostriatal Pathways
Simplified representative scheme of the complex interactions occurring between the dopaminergic and the cholinergic signaling systems regulating reward and motor activity. The selective presence of α6-containing nicotinic ACh receptors on dopaminergic neurons influences DA release both in the ventral and in the dorsal striatum. ACh also exerts a modulatory role in the basal ganglia via M1-like (M1) and M2-like (M2) muscarinic ACh receptors. At the same time, striatal DA regulates ACh release via D1-like (D1) and D2-like (D2) DA receptors. Abbreviation: PPN, pedunculopontine nucleus.

dopaminergic and the cholinergic systems influence each other in the striatum? For example, striatal cholinergic interneurons express both D1-like and D2-like DA receptors and can be either excited or inhibited by DA (Calabresi et al., 2006), further complicating the issue of the intrastriatal DA/ACh interactions. What is the relative role played by muscarinic ACh receptors in the ACh-mediated depolarization of SNc and VTA neurons in physiological conditions? ACh has indeed been demonstrated to depolarize SNc and VTA neurons through muscarinic M1-like receptors (Lacey et al., 1990), suggesting that in the absence of nAChR stimulation by exogenous nicotine, the effects of ACh might also be crucially dependent on its effects on muscarinic receptors (Figure 1).

A third question regards the potential downstream effects exerted by α6-containing nAChRs in the regulation of neuroplasticity. Indeed, a very important role seems to be played by long-term synaptic plasticity both in the striatum and in dopaminergic midbrain during both physiological learning and pathological conditions such as Parkinson's disease or drug addiction. A considerable amount of research is aimed at investigating the substrate of synaptic plasticity alterations occurring during these pathological conditions.

In this context, the work presented here might provide a new basis for the development of pharmacological compounds able to restore synaptic plasticity in these pathological scenarios.

The authors' finding that α6-containing nAChRs play a selective role in the modulation of DA release in both the NAc and in the dorsal striatum might open new neuropharmacological horizons, allowing an indirect but extremely selective control of the dopaminergic signaling system. Further experimental investigations are necessary to prove the validity of these hypotheses.

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Walk This Way

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The neural mechanisms that decide when and where to walk are not well understood. In this issue of *Neuron*, Felsen and Mainen use an olfactory-guided orienting task to show that the superior colliculus is necessary in rodents for the normal execution of spatial locomotor choices.

The superior colliculus (SC), also called the optic tectum in many vertebrate species, plays a central but only partly understood role in sensory-motor processing and decision-making (Wurtz and Albano, 1980). Perhaps the most distinctive feature of the SC is that it holds its sensory and motor signals in the form of neatly organized spatial maps that provide a topographic representation of the world. The maps are often dominated by vision, but they can also represent auditory, somatosensory, vibratory, and even infrared or electrical signals, depending on the sensory capabilities of the animal. In most vertebrates, the SC is the premier brain center for integrating sensory inputs from multiple modalities and for governing how the animal orients and interacts with its environment (Holmes and Spence, 2005). In primates, the SC is best known for its role in the motor control of saccadic eye movements, but recent work shows that the primate SC in fact participates in a broad range of functions, including the control of head movements, smooth pursuit, target selection, and perhaps even spatial attention (Krauzlis et al., 2004). The range of functions touched on by the SC is striking, and it also makes it more difficult to pinpoint the particular neural computations that are accomplished by this structure.

In this issue of *Neuron*, Felsen and Mainen (2008) employ an olfactory discrimination task that they have pioneered over the past several years (Uchida and Mainen, 2003) in a novel attempt to address these issues. In their task, rats first sampled an odor or odors presented at a central port and then moved to an adjacent port on either the left or right side to receive a potential water reward. The job of the rats was to identify which of two odors was presented at the central port and then move to the appropriate reward port. In some sessions, Felsen and Mainen recorded neural activity from the SC of the freely moving rats using tetrodes, and in other sessions they made focal and reversible lesions in order to establish causal relationships between SC activity and choice. Their findings show that the SC plays a surprisingly important role in generating locomotor choices.

A majority of the neurons recorded by Felsen and Mainen (2008) in the deeper layers of the rat SC exhibited directional selectivity during specific phases of the task. Some showed selectivity while the rats were still standing at the central odor port, whereas others showed selectivity as the rats walked to the left or right port to claim their potential reward. Still others retained their directional selectivity even after the movement was completed and the rat lingered at the reward port. Although a few other studies have studied SC activity in freely moving rats (e.g., Pond et al., 1977; Weldon et al., 2007), this is the first time in the rat that SC activity has been studied in a discrimination choice task.

More significantly, the authors also show that reversible inactivation of the SC on one side causes a spatial bias in the choices made during the task. For these experiments, the rats were presented with mixtures of two odors at the central port. Each odor was associated with a reward port, and the rat chose the port corresponding to the odorant with the greater concentration. Task difficulty was modulated by manipulating the relative ratio of the two odors. Just before the behavioral session, the SC on one side was infused with muscimol, which decreases neuronal activity by binding to the inhibitory $GABA_A$ receptor. Consistent with the spatial organization of the SC (e.g., the left SC represents the right side of space), inactivation biased choices away from whichever odor was associated with the inactivated side. Moreover, when rats did choose with the inactivated side, their reaction times for those responses were longer. These results provide strong evidence that SC is necessary for spatial locomotor choices in the rat.

Nevertheless, it remains unknown which aspects of task performance were impaired by lesion of the SC. Successful completion of the task presumably requires a variety of separate processes including perception of the odorants,