Axonal control of striatal dopamine transmission: Direct drivers and diverse gates

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Introduction

Striatal dopamine (DA) transmission regulates motivation and action selection through the basal ganglia. Disruptions to DA signaling underlie a variety of common psychomotor disorders, including addiction disorders and Parkinson’s disease. However, we require a better knowledge of the mechanisms that govern striatal DA transmission if we are to understand DA function and dysfunction fully. Activity in DA neurons has long been assumed to be the principal driver of striatal DA release, and for DA neurons this activity spans a broad range of firing frequencies, from tonic low frequencies to phasic bursts at higher frequencies. Current hypotheses suggest that phasic DA neuron activity encodes reward predictions, learning and/or salience. But how distinct modes of activity are reported to the striatum will depend on how DA axons and their presynaptic zones translate this, or other activity, into DA release.

The extensive axonal arbours formed by DA neurons are endowed with a large variety of activity-dependent conductances and neuromodulatory receptors. We have shown previously that presynaptic nicotinic acetylcholine receptors (nAChRs) in particular play a powerful role in gating DA transmission. Striatal nAChRs gate whether DA release reflects frequency of activity in DA neurons, through receptor subtypes that vary with striatal region [1-4]. Furthermore, we have now explored the consequences on DA transmission of discretely activating striatal cholinergic interneurons. We have identified that single action potentials in a small population of these interneurons drives DA transmission directly by transiently activating presynaptic nAChRs, bypassing activity in DA neurons [5]. These new findings shed new light on the function of presynaptic nAChRs, and suggest that the control of DA transmission by local axonal mechanisms extends beyond gating, to driving neurotransmission directly. Here I present and review these and other studies of the mechanisms that regulate striatal DA release probability, with and without the influence of striatal ACh.

Methods

In mouse acute striatal slices we have combined detection of DA using fast-scan cyclic voltammetry at carbon-fibre microelectrodes with whole cell patch clamp recordings of cholinergic interneurons (ChIs), and used an optogenetic strategy to light-activate striatal ChIs or other inputs that express channelrhodopsin2 (ChR2) after AAV delivery to Cre-driver lines.
Results and Discussion

Striatal DA release was evoked by light stimuli that evoked single action potentials in a small population of striatal ChIs, producing DA levels equivalent to those produced by local electrical stimulation. Release evoked by this approach is TTX-sensitive, and dependent on Ca$^{2+}$ and nAChRs but not receptors for glutamate, GABA or mAChRs. We show that synchronization of activity among ChIs is required to drive DA release, but that DA release does not vary with frequency of action potentials. We reproduced this observation by light-activating thalamic inputs to ChIs. Furthermore, the concurrence of activity in ChIs and DA axons prevents DA release from reporting variable activity in DA axons. These data reveal that endogenous ACh released by single action potentials coordinated among ChIs directly activates presynaptic nAChRs on DA axons to drive DA transmission.

These data revise several existing concepts. They suggest that presynaptic nAChRs can act to short circuit, or override, activity ascending from parent neurons, by generating ectopic excitability that evokes neurotransmission directly. This requires us to revise our pre-existing assumptions that presynaptic neuromodulatory receptors might play only limited roles as gates, but not drivers. This finding also suggests that neural circuits besides those that input to DA neurons will participate in DA function, indicating additional functions for DA beyond those identified from changes in DA neuron activity. Namely, inputs to ChIs e.g. thalamostratial inputs that promote firing across the ChI network in response to salient unpredicted stimuli, might have previously unrecognized roles in driving DA transmission.

We also show here that other neuromodulatory influences on DA transmission depend on the state of the ChI network. We show that the regulation of short-term plasticity in DA transmission varies with the state of this ChI network, and shows diversity between different striatal territories.

References