Review

Biological Psychiatry

Heterogeneity in Dopamine Neuron Synaptic Actions Across the Striatum and Its Relevance for Schizophrenia

Nao Chuhma, Susana Mingote, Abigail Kalmbach, Leora Yetnikoff, and Stephen Rayport

ABSTRACT

Brain imaging has revealed alterations in dopamine uptake, release, and receptor levels in patients with schizophrenia that have been resolved on the scale of striatal subregions. However, the underlying synaptic mechanisms are on a finer scale. Dopamine neuron synaptic actions vary across the striatum, involving variations not only in dopamine release but also in dopamine neuron connectivity, cotransmission, modulation, and activity. Optogenetic studies have revealed that dopamine neurons release dopamine in a synaptic signal mode, and that the neurons also release glutamate and gamma-aminobutyric acid as cotransmitters, with striking regional variation. Fast glutamate and gamma-aminobutyric acid cotransmission convey discrete patterns of dopamine neuron activity to striatal neurons. Glutamate may function not only in a signaling role at a subset of dopamine neuron synapses, but also in mediating vesicular synergy, contributing to regional differences in loading of dopamine into synaptic vesicles. Regional differences in dopamine neuron signaling are likely to be differentially involved in the schizophrenia disease process and likely determine the subregional specificity of the action of psychostimulants that exacerbate the disorder, and antipsychotics that ameliorate the disorder. Elucidating dopamine neuron synaptic signaling offers the potential for achieving greater pharmacological specificity through intersectional pharmacological actions targeting subsets of dopamine neuron synapses.

Keywords: Corelease, Cotransmission, GABA, Glutamate, Nucleus accumbens, Optogenetics, Vesicular synergy

http://dx.doi.org/10.1016/j.biopsych.2016.07.002

Dopamine (DA) dysfunction is central to the pathophysiology of schizophrenia (1), with regional variations that likely shape schizophrenia symptoms. This idea arose with the early view that mesolimbic DA signaling mediated positive (psychotic) symptoms that could be treated with DA D_2 receptor (D_2R) antagonists, whereas blockade of nigrostriatal DA transmission accounted for extrapyramidal side effects and possible worsening of negative (deficit) symptoms. Observations made in rats (2) and extended to nonhuman primates (3) showed that propsychotic psychostimulants, such as amphetamine, elicit the greatest DA release in the limbic or ventral striatum (vStr). With the impetus of adding serotonin 2A receptor blockade to antipsychotics, atypical antipsychotics emerged (4); they appeared to have fewer side effects owing to more selective targeting of the vStr (5). However, vStr selectivity was challenged by more recent observations that DA release is increased in schizophrenia in the associative dorsal Str (dStr), where it correlates with positive symptoms, and is diminished in the vStr, where it correlates with negative symptoms (6,7). These findings—although apparently contradictory—point to heterogeneity in dopamine function across the Str and the importance of understanding regional differences in DA neuron synaptic actions. Mechanisms underlying regional differences in clinical imaging of DA release in schizophrenia can be investigated in rodents under similar baseline and pharmacological challenge conditions.

DA neurons, identified by the presence of the DA synthetic enzyme tyrosine hydroxylase (8), show significant functional heterogeneity. This heterogeneity is evident in differences in gene expression (9–11), electrophysiological properties (11,12), projection-specific functions (13,14), drug sensitivity (15), and vulnerability in neurodegenerative disorders (16,17). Such heterogeneity is likely to be fundamental to understanding differential vulnerability in schizophrenia, as well as therapeutics. Although electrochemical techniques have provided considerable insight into DA release and its variation (18), the synaptic actions of DA neurons have been harder to discern. Optogenetics has enabled selective targeting of DA neurons (19) to enable functional connectivity analyses (20,21) that have now made the synaptic actions of these neurons accessible to study. In this review, we describe multiple dimensions of heterogeneity in DA neuron synaptic signaling in the Str and functional implications.

STRIATAL CYTOARCHITECTURE

The invariant Str cytoarchitecture—with about 95% gamma-aminobutyric acidergic (GABAergic) spiny projection neurons

ISSN: 0006-3223

(SPNs), 5% GABAergic and cholinergic interneurons (ChIs), and prominent input from midbrain DA neurons and cortical and thalamic glutamatergic neurons (22–24)—engendered the early idea that the function of striatal circuits was homogenous across striatal regions. However, this view has been increasingly supplanted by findings of striatal heterogeneity.

Different striatal regions receive distinctly different excitatory inputs defining broad divisions into associative, sensorimotor, and limbic domains (25,26). The pattern of cortical inputs helps to define the correspondence between striatal regions in humans and rodents (Figure 1). The sensorimotor Str receives inputs from primary motor and premotor cortices and comprises in the primate the dorsolateral putamen and dorsolateral caudate (25,27,28), which corresponds to the lateral portion of the dStr in rodents (26,27,29). The associative Str receives inputs from association areas of the cortex (dorsolateral prefrontal cortex) and comprises in the primate large parts of the rostral putamen and most of the head, body, and tail of the caudate (25,27,28), which corresponds to the medial portion of the dStr in rodents (27,30,31). The vStr receives inputs from the hippocampus and amygdala and from the orbitofrontal and anterior cingulate cortices, comprising in the primate the nucleus accumbens (NAc) and ventral parts of the caudate and putamen (25,27,28,32). In rodents, the vStr corresponds to the NAc and the striatal component of the olfactory tubercle (OT) (27,30,33). The rodent NAc is subdivided into core and shell regions with different connectivity and function (34,35); this division is not so clear in primates, although diffusion tractography identifies putative core (lateral-rostral NAc) and shell (medial-caudal NAc) divisions (36).

DA neurons project from the ventral midbrain to the Str topographically (Figure 2). Medial DA neurons in the ventral tegmental area (VTA) project predominantly to vStr. More lateral DA neurons in the substantia nigra (SN) project predominantly to associative and sensorimotor dStr domains (33,37–39). Individual DA neurons target compact striatal domains that may subtend as much as 5% of the total striatal volume (40). The density of dopaminergic input to the striatal subregions is highest in the dStr and lowest in the NAc shell region of the vStr (41). Str SPNs project back to the ventral midbrain in a matching topology, predominantly targeting GABAergic neurons (21,42), but also making connections to DA neurons (43,44), with the exception of DA neurons projecting to the posterior Str that receive a wider range of inputs, from the globus pallidus, subthalamic nucleus, and zona incerta (45).

SYNAPTIC DOPAMINE SIGNALING IN THE STRIATUM

DA signaling in the Str is mainly mediated by diffusion of DA to extrasynaptic G-protein coupled DA receptors, that is, by volume transmission (46,47), engendering a range of modulatory effects, including the regulation of the excitability of SPNs and interneurons, and presynaptic regulation of excitatory input (46,48–51). Modulatory actions of DA mediate longer time-scale control of motivational salience, vigor, and social behavior (52–54). However, DA neurons mediate faster, discrete DA synaptic responses, in addition to volume transmission.

In ventral midbrain slices, DA neurons produce subsecond D_2R-mediated dendrodendritic inhibitory postsynaptic responses in neighboring DA neurons (55). Optogenetic studies have revealed subsecond DA synaptic responses in dStr brain slices (56) seen as a pause in the firing of ChIs and associated with a subsecond hyperpolarization (56,57), mediated by a D_2R coupling to G-protein coupled inward rectifier K^+ channels (56). D_2R-mediated inhibitory postsynaptic currents (IPSCs) in Str ChIs have a latency of about 8 ms (56). Considering that the latency involves the time for channelrhodopsin 2 (ChR2) mediated depolarization (58), the activation of transmitter release machinery, and G-protein coupled receptor transduction (slower than that of ionotropic receptors), the D2-IPSC is mediated monosynaptically. Although a D2-IPSC has not been reported in D2-SPNs, with G-protein coupled inward rectifier K^+ channels 2 transfection D2-IPSCs become detectable (59), indicating that DA neurons can elicit synaptic DA signals in projection areas, so long as D_2Rs are proximate to DA release sites.

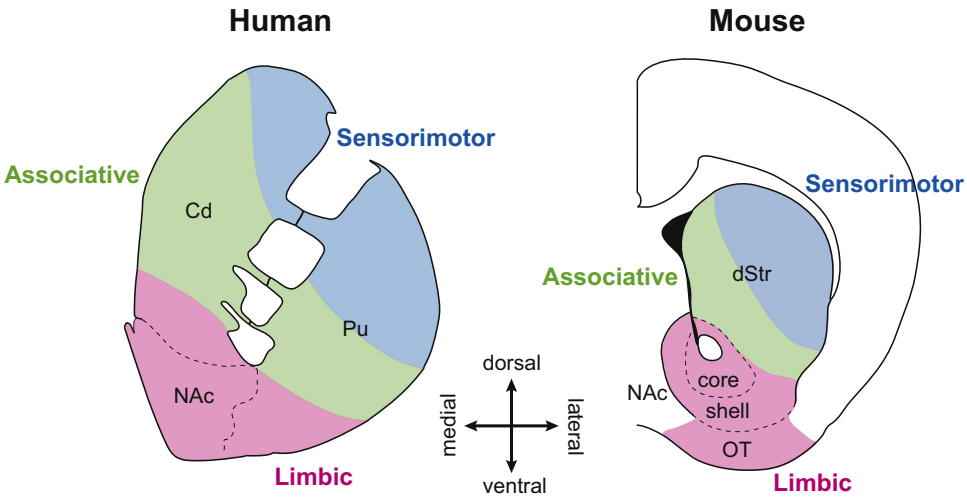

Figure 1. Functional subdivisions of the striatum (Str) in humans and rodents. Functionally, the Str can be divided into corresponding limbic (magenta), associative (green), and sensorimotor (blue) regions, in both human (left) and rodent (right), determined by cortical inputs mediating each function. The schematics shown are midway along the anterior-posterior axis; there are substantial phylogenetic differences both anteriorly and posteriorly (25,74). The nucleus accumbens (NAc), which makes up the ventral Str, is indicated by the dashed lines. In mouse, a second dashed line indicates the border between the accumbens core and shell. Orientation of sections is indicated by arrows. Striatal outlines are modified from atlases (136,137). Cd, caudate; dStr, dorsal striatum; OT, olfactory tubercle; Pu, putamen.