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REVIEW

DYNAMIC REGULATION OF MIDBRAIN DOPAMINE NEURON ACTIVITY: INTRINSIC, SYNAPTIC, AND PLASTICITY MECHANISMS

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Abstract—Although the roles of dopaminergic signaling in learning and behavior are well established, it is not fully understood how the activity of dopaminergic neurons is dynamically regulated under different conditions in a constantly changing environment. Dopamine neurons must integrate sensory, motor, and cognitive information online to inform the organism to pursue outcomes with the highest reward probability. In this article, we provide an overview of recent advances on the intrinsic, extrinsic (i.e., synaptic), and plasticity mechanisms controlling dopamine neuron activity, mostly focusing on mechanistic studies conducted using *ex vivo* brain slice preparations. We also hope to highlight some unresolved questions regarding information processing that takes place at dopamine neurons, thereby stimulating further investigations at different levels of analysis.

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Key words: burst, pause, firing pattern, reward prediction error, disinhibition, synaptic plasticity.

Contents

Dopamine (DA) neurons in the substantia nigra pars compacta (SNc), ventral tegmental area (VTA), and retrorubal field (RRF) are part of a network of midbrain nuclei innervated primarily by other parts of the basal ganglia, but they apparently generate one of the most important neural signals for motivated behavior found anywhere in the brain. Recording studies in non-human primates and rodents, combined with human functional imaging and computational modeling studies, have suggested that their firing pattern can encode reward prediction error, which is thought to be a critical mediator of reinforcement learning (Fig. 1; Montague et al., 1996; Schultz, 1998; Pan et al., 2005; D'Ardenne et al., 2008) [but also see (Redgrave and Gurney, 2006; Bromberg-Martin et al., 2010) for other functions of DA output]. It is likely the essential nature of this signal that links disruptions of DA function to many of the symptoms of drug addiction and a wide range of psychiatric disorders, and in the extreme case of the degeneration of these neurons, to Parkinson's disease. It is somewhat puzzling, however, that this signal should be generated by the DA neurons of the ventral midbrain, which do not seem to be in a position to directly receive all the sensory, motor, and cognitive information required to calculate the reward prediction error signal. How does the DA neuron get access to all that information? Is the cell simply a relay for a similar signal coming from elsewhere, or does it synthesize that signal from a number of independent

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Abbreviations: Ach, acetylcholine; DA, dopamine; I_h, hyperpolarization-activated cationic conductance; IP_3, inositol 1,4,5-trisphosphate; LDTg, laterodorsal tegmental nucleus; mGluRs, metabotropic glutamate receptors; NAc, nucleus accumbens; NE, norepinephrine; PPTg, pedunculopontine tegmental nucleus; RMTg, rostromedial tegmental nucleus; SC, superior colliculus; SNc, substantia nigra pars compacta; VTA, ventral tegmental area.

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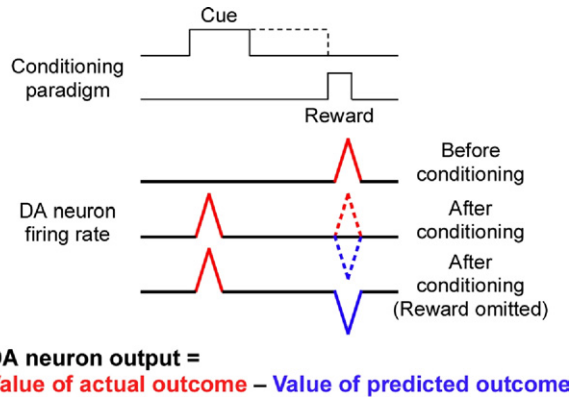

Fig. 1. Schematic diagram illustrating the encoding of reward prediction error by DA neuron firing activity. During cue-reward conditioning, the reward is delivered at the end of the cue or after a certain delay after the cue offset. After conditioning, the DA neuron burst response transfers from the time of reward delivery to the onset of the cue. Note that the depression (pause) response to the omission of expected reward after cue presentation is time-locked to the expected time of reward delivery.

inputs? As a first step toward answering these questions, it is necessary to understand the intrinsic properties that enable DA neurons to burst and pause. This will then direct future studies that will determine how DA neurons integrate their intrinsic properties with different inputs to encode reward prediction error.

DOPAMINE NEURON POPULATIONS

The most widely studied populations of DA neurons are (1) those in SNc that project to the dorsal striatum, giving rise to the nigrostriatal system; and (2) those in the VTA that project to limbic structures, mainly the ventral striatum [i.e., the nucleus accumbens (NAc)], and the prefrontal cortex, giving rise to mesolimbic and mesocortical pathways. Historically, the nigrostriatal system has been largely implicated in volitional control of movement, while the mesocorticolimbic system is thought to be more critical for reward-based learning and motivation. However, accumulating evidence indicates that this type of dichotomous (or trichotomous) distinction is oversimplified and that it can rather be described as a lateral-to-medial gradient, in which significant intermixing of DA neuron populations, having different projection targets, is observed (Björklund and Dunnett, 2007; Ikemoto, 2007; Wise, 2009). Furthermore, different parts of the VTA/SNc complex may have functional interactions, either through local connections (Ferreira et al., 2008) or through long-range feedback loops (Haber et al., 1990, 2000; Heimer et al., 1991; Paladini et al., 2003). In the latter case, there appears to be a cascading spiral of projections between the VTA/SNc and the NAc/striatum. Here, DA neurons in the medial part of the VTA innervate medium spiny projection neurons in the ventral striatum, which then project back to more lateral parts of the VTA/SNc complex that in turn send projections to more dorsal parts of the striatum. It has been suggested that this type of anatomical organization might underlie the transition from a goal-directed action to a stimulus-response habit during the progression of reward-based behavioral conditioning (e.g., drug addiction), in which more lateral parts of the VTA/SNc complex, together with more dorsal parts of the striatum, are gradually recruited (Everitt and Robbins, 2005; Belin and Everitt, 2008).

In line with the anatomical and functional heterogeneity of DA neurons in intact animals, studies using *ex vivo* brain slice preparations have described different electrophysiological and neurochemical properties of DA neurons depending on their location, for example, lateral-to-medial gradients in the expression levels of certain ion channels (Wolfart et al., 2001; Neuhoff et al., 2002). It should also be noted that the definition of the SNc and VTA is somewhat arbitrary with different laboratories using different slice planes (e.g., horizontal vs. coronal). More recent studies have investigated electrophysiological and pharmacological profiles of DA neurons based on their projection targets (Ford et al., 2006; Margolis et al., 2006, 2008; Lammel et al., 2008, 2011). However, only a few laboratories have conducted this type of analysis that involves recording of DA neurons labeled with retrograde tracers, followed by post hoc tyrosine hydroxylase immunohistochemistry, and some conflicting results have been reported. This may be partly due to differences in the species/strain/age of animals examined, together with some difference in the site and volume used for retrograde tracer injection; and even differences in internal solution used for whole-cell recordings, which tends to dialyze the intracellular contents of the recorded cell (Margolis et al., 2010; Zhang et al., 2010). It is also possible that even DA neurons sharing the same projection target might be heterogeneous in terms of their intrinsic properties, or in terms of their specific inputs. Therefore, full characterization of different subpopulations of DA neurons still requires more time and effort to reach consensus in the field, hopefully with the aid of genetically engineered animals having different DA neuron subpopulations fluorescently labeled.

In the present article, we provide up-to-date knowledge regarding (1) the ionic mechanisms underlying intrinsic properties of DA neurons, (2) influences of neurotransmitter inputs on DA neuron activity, and (3) plasticity of these neurotransmitter inputs, mostly focusing on studies conducted *ex vivo*. We will frequently refer to DA neurons as "SNc DA neurons" or "VTA DA neurons," with the understanding that this simple distinction may become obsolete in the future. Furthermore, identification of DA neurons in the vast majority of recording studies (both *in vivo* and *ex vivo*) has been based solely on electrophysiological criteria (e.g., action potential width, hyperpolarization-activated cationic conductance termed I_h, D2 DA receptor-mediated inhibition), and those neurons remain to be putative DA neurons without unequivocal confirmation of their neurochemical identify, especially in the medial VTA (Ungless et al., 2004; Lammel et al., 2008, 2011; Margolis et al., 2008; Zhang et al., 2010).