Neuroscience 282 (2014) 248–257

REVIEW

THE PLACE OF DOPAMINE IN THE CORTICO-BASAL GANGLIA CIRCUIT

S. N. HABER *

Department of Pharmacology and Physiology, University of Rochester School of Medicine, 601 Elmwood Avenue, Rochester, NY 14642, United States

Abstract—The midbrain dopamine (DA) neurons play a central role in developing appropriate goal-directed behaviors, including the motivation and cognition to develop appropriate actions to obtain a specific outcome. Indeed, subpopulations of DA neurons have been associated with these different functions: the mesolimbic, mesocortical, and nigrostriatal pathways. The mesolimbic and nigrostriatal pathways are an integral part of the basal ganglia through its reciprocal connections to the ventral and dorsal striatum respectively. This chapter reviews the connections of the midbrain DA cells and their role in integrating information across limbic, cognitive and motor functions. Emphasis is placed on the interface between these functional domains within the striatum through corticostriatal connections, through the striato-nigro-striatal connection, and through the lateral habenula projection to the midbrain.

This article is part of a Special Issue entitled: Ventral Tegmentum & Dopamine.

Key words: functional integration, prefrontal cortex, lateral habenula, striatum, substantia nigra, ventral tegmental area.

Contents

*Tel: +1-585-275-0948; fax: +1-585-273-2652.
E-mail address: suzanne_haber@urmc.rochester.edu

Abbreviations: ACC, anterior cingulate cortex; BG, basal ganglia; CaBP, calbindin-positive; DA, dopamine; dPFC, dorsal prefrontal cortex; GPe, globus pallidus, external segment; GPi, globus pallidus, internal segment; LHb, lateral habenula; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; Pu, putamen; PD, Parkinson's disease; RMTg, rostromedial tegmental nucleus; SN, substantia nigra; SNc, substantia nigra, pars compacta; VP, ventral pallidum; VS, ventral striatum; VTA, ventral tegmental area.

http://dx.doi.org/10.1016/j.neuroscience.2014.10.008

INTRODUCTION

A key component in developing appropriate goal-directed behaviors is the ability to first correctly evaluate different aspects of reward, including value versus risk and predictability, and inhibit maladaptive choices, based on previous experience. These calculations rely on integration of different aspects of motivation and cognition to develop and execute appropriate action plans. The midbrain dopamine (DA) neurons play a central role in these behaviors including reward, cognition, and motor control. Indeed, subpopulations of DA neurons have been associated with these different functions: the mesolimbic, mesocortical, and nigrostriatal pathways, respectively (Wullner et al., 1994; Sawaguchi, 1995; Goldman-Rakic, 1998; Wise, 2004). Recently, all DA cell groups have been associated with the development of reward-based learning, leading to goal-directed behaviors (Schultz, 2002).

The substantia nigra (SN) was first recognized in 1786 with the description of brain neuromelanin distribution (Vicq D'Azyr, 1786). The link to the motor system came much later with its association with Parkinson's disease (PD) (Brissaud, 1895; Bremer, 1920; Hassler, 1939). Collectively the work of several investigators then demonstrated that the cells contained DA, that DA was a neurotransmitter, and that these cells were depleted in PD (Ehringer and Hornykiewicz, 1960; Hornykiewicz, 1966; Bazelton et al., 1967). Around the same time DA was also linked to psychoses and subsequently addiction, and behavioral disorders, see (Baldessarini, 1985). With the visualization of DA neurons and the advances in connectivity and lesion methods in the 1960s, the subpopulations of DA neurons were associated with reward, cognition, or motor control: the mesolimbic (ventral tegmental area-VTA), mesocortical (VTA-retrorubral), and nigrostriatal (substantia nigra, pars compacta-SNc) pathways, respectively. Collectively these discoveries

demonstrated that the DA cells are an integral part of the basal ganglia (BG). The VTA and SNc send a massive output to the striatum, the main input structure of the BG. Moreover, this is a bidirectional pathway, with the DA cells receiving a major input from the striatum.

Overall, the BG was best known for its relevance to motor functions, due to its role in movement control diseases. This concept dramatically changed in the last 35+ years to a more complex set of functions that mediate the full range of goal-directed behaviors, including emotions, motivation, and cognition. In the late 1970s, Heimer discovered that the nucleus accumbens (NAcc), (a basal forebrain region associated with limbic function), and the surrounding area were actually part of the striatum and termed this the ventral striatum (VS). Moreover, he identified the cells that were located ventral to the anterior commissure as pallidal in nature and showed that they received inputs from the VS. These cells are referred to as the ventral pallidum (VP) (Heimer, 1978). Subsequently he and others showed that the VP projected to the medial dorsal (MD) thalamus and back to non-motor cortex, thus identifying a separate functional loop of the BG (Young III et al., 1984; Haber et al., 1985). The concept of several functional, yet separate cortical loops through BG was then expanded in primates (Alexander et al., 1990). While the notion that these circuits are anatomically segregated remains prominent in the field, the idea of a motivation-to-movement interface, rather than separate loops through BG circuits was developed soon after the discovery of the VS/VP circuit. Researchers interested in how motivation impacts learning and the development of habits, recognized that integration between functional circuits was necessary to carry out goal-directed behaviors (Mogenson et al., 1980; Percheron and Filion, 1991; Dickinson and Balleine, 1994; Haber et al., 2000; Belin and Everitt, 2008; Leung and Balleine, 2013). Thus, the BG is now recognized to mediate the full range of behaviors leading to the development and execution of action plans, including the emotions, motivation, and cognition that drive them.

OVERVIEW OF THE BG CIRCUITRY

The striatum is the main input structure of the BG. Its afferent projections are derived from three major sources: (1) it receives a massive and topographic input from all of the cerebral cortex; (2) the second largest input is derived from the thalamus; and (3) the third main input is from the brainstem, the largest from the midbrain DA cells. Striatal functional domains are derived from the topography of its cortical inputs. Thus, we briefly review the topography of those inputs here. In general, the cortical afferent projections terminate in a patchy and interdigitated manner (Künzle, 1975; Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1985; Kunishio and Haber, 1994; Chikama et al., 1997; Haber et al., 1995a; Yeterian and Pandya, 1998). Overall, cortical regions associated with reward and motivation, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) project primarily to

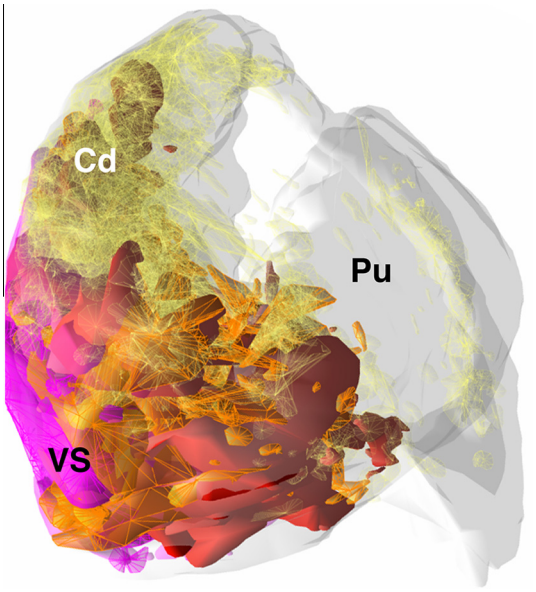

Fig. 1. Medio-frontal view of a 3-D striatal reconstruction illustrating convergence of inputs from PFC. Red, inputs from ventromedial prefrontal cortex; dark orange, inputs from orbitofrontal cortex; light orange, inputs from dorsal anterior cingulate cortex; yellow, inputs form dorsal prefrontal cortex. Cd, caudate nucleus; Pu, putamen; VS, ventral striatum. Figure adapted from Haber and Behrens (2014).

the ventral and medial parts of the rostral striatum, including the medial wall of the caudate nucleus (Cd) and the medial putamen (Pu). In addition, the amygdala projects to VS (Fudge et al., 2002). Dorsal prefrontal cortical (dPFC) areas project to the central striatum, and motor regions project to the dorsal and lateral parts of the striatum, primarily caudal to the anterior commissure. However, despite this general topographic organization, embedded within these striatal territories are subregions containing convergent terminals between different reward-processing cortical areas, between these projections and those from the dPFC, and between the dPFC and rostral motor control areas (Haber et al., 2006; Calzavara et al., 2007) (Fig. 1). In other words, projections from different functional regions of the cortex are not completely separated. Rather there are key areas within the striatum that receive these multiple inputs that may be particularly sensitive to synchronizing information across functional areas to impact on long-term strategic planning, and habit formation (Averbeck et al., 2014). Indeed, cells in the dorsal striatum are progressively recruited during different types of learning, from simple motor tasks to drug self-administration (Porrino et al., 2004; Graybiel, 2005; Volkow et al., 2006).

The striatum, in turn, projects topographically to the pallidal complex, the VTA and SN (Haber, 2012). The outputs from the globus pallidus, internal segment (GPi)/SN then projects back to the cortex via the thalamus, completing the basic cortico-BG circuit. This is known as the direct pathway. The side loop, from the striatum via the globus pallidus, external segment (GPe) passes through the subthalamic nucleus to the GPi, and is referred to as the indirect pathway (Fig. 2). In addition, there are other projections of the striatum including those to the brainstem (Haber, 2012).