Neuroscience 282 (2014) 243–247

REVIEW

THE VENTRAL TEGMENTUM AND DOPAMINE: A NEW WAVE OF DIVERSITY

M. BARROT *

Institut des Neurosciences Cellulaires et Intégratives, Centre National de la Recherche Scientifique, Strasbourg, France

Université de Strasbourg, Strasbourg, France

Abstract—Projection systems arising from the ventral tegmental area (VTA) and the substantia nigra (SN) have a critical role in a broad range of functions, as well as in the etiology, symptoms and treatment of neurological and psychiatric diseases. Mostly studied for its dopamine neurons, the ventral tegmentum is in fact heterogeneous at cellular and functional levels. This special issue of Neuroscience gathered some experts in the field to review the connectivity of the ventral mesencephalic dopaminergic complex, its cellular heterogeneity with attention given to glutamate neurons, the D_2 autoreceptor and the cholinergic controls of dopamine activity, the influence of neurotrophins, the controls of bursting activity and the heterogeneity of neuronal activity across traits and states, the pedunculopontine tegmental and the sensory controls of dopamine activity, the sex-dependent diversity, the links between circadian and dopamine systems, the functional antero-posterior heterogeneity of the VTA and the role of its GABA tail (tVTA/rostromedial tegmental nucleus (RMTg)), the functional heterogeneity of the VTA outputs, the place of dopamine in cortico-basal ganglia circuitry, the different roles of the D_1 and D_2 striatal pathways and the role of dopamine in associative learning and memory. Recent progress also highlights the need for molecular markers of functional subpopulations within the ventral tegmentum, for deeper developmental knowledge of this region, and for a single cell level of connectomic. It also raises the question of inter-individual, sex, strain and species heterogeneity, and conversely the question of data generalization in a context of human pathology models, which warrant comparative studies and translational effort.

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

Key words: dopamine, ventral tegmental area, substantia nigra, heterogeneity.

Contents

INTRODUCTION

Dopamine systems are the most studied brain systems, ''dopamine'' retrieving close to 140,000 articles under PubMed, almost 25,000 of them published in the past 5 years. Since the description of dopamine systems in the 1960s and 1970s, accumulating evidence points to their critical role in a broad range of functions, including motor functions, motivated behavior, reward, associative learning and mood. The dopamine systems mainly arise from midbrain ventral areas harboring dopamine neuron cell bodies that project to a wide array of brain regions where they exert a modulatory influence. As a consequence of these physiological roles, dopamine systems are also implicated in the etiology, symptoms and treatment of neurological and psychiatric diseases, such as Parkinson's disease, schizophrenia, mood disorders, attention deficit hyperactivity disorder (ADHD) and drug abuse. Understanding these systems is thus critical to help understanding the physiology of adaptation as well as the brain mechanisms underlying the pathogenesis of various neurological and mental disorders.

In the past decades, major progress has been made, which is now fostering new and exciting research avenues. The functional heterogeneity of ventral tegmental neurons, including dopamine neurons, is recognized. Considering the huge amount of published data, it is important to provide critical analyses and reviews about what has been accomplished. This special issue of Neuroscience gathered some experts in the field to review advances on specific topics, highlighting the neuronal heterogeneity of midbrain areas harboring dopamine cells, the diversity of controls exerted on dopamine systems and the respective

*Address: Institut des Neurosciences Cellulaires et Intégratives, CNRS UPR3212, 5 rue Blaise Pascal, 67084 Strasbourg, France. Tel: +33-388-456-633.
E-mail address: mbarrot@inci-cnrs.unistra.fr

Abbreviations: aVTA, anterior VTA; BDNF, brain-derived neurotrophic factor; nAChRs, nicotinic acetylcholine receptors; PPTg, pedunculopontine tegmental nucleus; pVTA, posterior VTA; RMTg, rostromedial tegmental nucleus; SN, substantia nigra; SNc, substantia nigra pars compacta; tVTA, tail of the VTA; vGluT2, vesicular glutamate transporter 2; VTA, ventral tegmental area.

http://dx.doi.org/10.1016/j.neuroscience.2014.10.017

functions of the various output pathways, pointing out some key unanswered questions.

This special issue more particularly addresses the connectivity of the ventral mesencephalic dopaminergic complex (Yetnikoff et al., 2014), and its cellular heterogeneity with attention given to glutamate neurons within the midbrain dopamine regions (Morales and Root, 2014). It also summarizes present knowledge on the D_2 autoreceptor (Ford, 2014) and the cholinergic (Faure et al., 2014) controls of dopamine activity, on the influence of neurotrophins on dopamine systems (Nikulina et al., 2014; Walsh and Han, 2014), and more largely on the controls of bursting activity (Paladini and Roeper, 2014) and on the heterogeneity of dopamine neuron activity across traits and states (Marinelli and McCutcheon, 2014). The pedunculopontine tegmental (Hong and Hikosaka, 2014) and the sensory (Overton et al., 2014) controls of dopamine activity, the sex-dependent diversity in dopamine systems (Gillies et al., 2014) and the links between circadian systems and dopamine systems (Mendoza and Challet, 2014) are reviewed. The functional antero-posterior heterogeneity of the ventral tegmental area (VTA) and the role of its GABA tail (tVTA) (Sanchez-Catalan et al., 2014), the functional heterogeneity of the VTA outputs (Walsh and Han, 2014), the different roles of the D_1 and D_2 pathways (Keeler et al., 2014; Nakanishi et al., 2014), the place of dopamine in cortico-basal ganglia circuitry (Haber, 2014) and its role in associative learning and memory (Puig et al., 2014), are also addressed.

OVERVIEW OF THE CONTRIBUTIONS TO THIS SPECIAL ISSUE

The midbrain dopaminergic complex includes the VTA, the substantia nigra (SN) and the retrorubral field. The inputs and outputs of these brain regions are reviewed by Yetnikoff et al. (2014). After presenting the general organization of these regions, including the cellular diversity, the authors are detailing the afferent and efferent connections based on anatomo-functional categories. Species differences are discussed, as well as the complexity of the intrinsic organization and the network organization of this midbrain complex (Yetnikoff et al., 2014).

Most of the research on the ventral tegmental neurons focused on dopamine cells, but the ventral tegmental neurons display at least three main neurochemical phenotypes, dopamine, GABA and glutamate, which may in part be identified based on pharmacological and electrophysiological properties ex vivo (Morales and Root, 2014). The review from Morales and Root concerns the glutamate neurons, as identified by the vesicular glutamate transporter 2 (vGluT2). These glutamate neurons were recently observed in all midbrain dopamine nuclei, but they display a molecular diversity, including the presence of vGluT2-TH neurons, as well as heterogeneity of location within the ventral tegmental subregions and heterogeneity of output projections, which suggests a potential variety of roles that are still to identify (Morales and Root, 2014).

The key roles of dopamine D_2 autoreceptors in regulating dopamine neuron activity, as well as dopamine production and release at terminals, are reviewed by Ford. He discusses the respective roles of the short and long isoforms of the D_2 receptors, supporting an implication of both isoforms as autoreceptors (Ford, 2014). The review highlights the variety of D_2 mechanisms regulating dopamine release and dopamine cell activity, discusses the differential expression of D_2 autoreceptors depending on anatomical output pathways, the species differences in the regulation of somatodendritic dopamine release, and the role of local versus volume dopamine transmissions in recruiting extrasynaptic D_2 autoreceptors. The physiological relevance of the ''high-affinity'' state of the D_2 receptors is questioned; and the potential role of the D_2 autoreceptors in inter-individual differences, including vulnerability to drugs of abuse and related plasticity, is detailed (Ford, 2014).

Nicotinic acetylcholine receptors (nAChRs) are among the key modulators of dopamine neurons (Faure et al., 2014). Faure et al. present the diversity of pentameric nAChRs on ventral tegmental cells and on their afferents, emphasizing the role of subunit composition and the dysregulation of cholinergic controls following exposure to nicotine. The authors more specifically focused on the influence of somatic nAChRs on the burst firing of dopamine neurons in mice, reviewing evidence associating the diverse expression of nAChRs subtypes to the diverse bursting/firing properties of the dopamine neurons, and discussing the possible role for nAChRs in synchronizing or in decorrelating dopamine cell subpopulations (Faure et al., 2014). The functional influence of ventral tegmental nAChRs on locomotion and exploratory behaviors is detailed. The authors also discuss recent evidence questioning the *in vivo* relevance of the disinhibition model of nicotine action, and review the role and the antero-posterior heterogeneity of the ventral tegmental nAChRs in the reinforcing effects of nicotine (Faure et al., 2014).

Electrical activity of midbrain dopamine neurons *in vivo* includes bursts and pauses. Paladini and Roeper review the functional studies on the bursting signal of these neurons in awake primates and rodents, from the seminal reward prediction error theory to recent evidence revealing a more complex reality and the functional diversity of dopamine neuron responses (Paladini and Roeper, 2014). This heterogeneity implies dopamine neurons with partly different location within midbrain dopamine nuclei, and concerns the response to aversive/rewarding stimuli and their conditioned cues, working memory cues, salient events, the timing of action sequences, and can be modulated by context. Heterogeneity and complexity is also present in the temporal response displayed by the dopamine neurons. The authors then detail at circuitry level the diversity of excitatory and inhibitory afferent inputs controlling burst activity and pauses and at cellular level the implicated membrane, channel and intracellular mechanisms (Paladini and Roeper, 2014).

The activity of dopamine neurons varies across traits and states (Marinelli and McCutcheon, 2014). After