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Review

# Molecular heterogeneity of midbrain dopaminergic neurons – Moving toward single cell resolution

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ABSTRACT

**Since their discovery, midbrain dopamine (DA) neurons have been researched extensively, in part because of their diverse functions and involvement in various neuropsychiatric disorders. Over the last few decades, reports have emerged that midbrain DA neurons were not a homogeneous group, but that DA neurons located in distinct anatomical locations within the midbrain had distinctive properties in terms of physiology, function, and vulnerability. Accordingly, several studies focused on identifying heterogeneous gene expression across DA neuron clusters. Here we review the importance of understanding DA neuron heterogeneity at the molecular level, previous studies detailing heterogeneous gene expression in DA neurons, and finally recent work which brings together previous heterogeneous gene expression profiles in a coordinated manner, at single cell resolution.**

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## 1. Introduction

Roughly half a century ago, dopamine (DA) neurons in the ventral midbrain were first identified and categorized into three anatomically defined groups, which are commonly called the retrorubral area (RR, A8), the substantia nigra pars compacta (SNc, A9) and the ventral tegmental area (VTA, A10) [1–3]. These neurons share the enzymes tyrosine hydroxylase (TH) and dopa decarboxylase (DDC; also known as aromatic L-amino acid decarboxylase), involved in the synthesis of DA, but lack enzymes needed to generate adrenaline or noradrenaline (Fig. 1). DA neurons have since been prolifically studied due to their underlying role in voluntary movement, a variety of behaviors, and several devastating neuropsychiatric disorders including Parkinson's disease (PD), schizophrenia, attention deficit disorder, emotional/mood disorders and drug addiction [4]. Yet, it remains to be understood whether intrinsic differences in these neurons, which share a neurotransmitter phenotype, could in part, underlie such a spectrum of functions.

Of the traditionally defined midbrain DA groups, the SNc and VTA contain the vast majority of DA neurons. Thus, a simplistic subdivision of DA neurons into two separate groups often facilitated their subsequent study. An overwhelming amount of the literature, including work on DA axonal projections, function, physiological properties, molecular profiles in the developing and adult brain, and vulnerability in disease are presented within this framework. This anatomically based approach has both enabled the description of common DA neuron characteristics, and the elucidation of several aspects in which DA neurons in the SNc differ from DA neurons located in the VTA. Recent studies, however, make it increasingly clear that the neurons within these two anatomically defined clusters are not necessarily homogenous (reviewed in [5–9]). In fact, there are likely multiple distinct DA neuron subtypes within and possibly across anatomical boundaries. Thus, there is an urgent need to purposefully characterize and reclassify these neurons to gain a deeper understanding of the dopaminergic system and to develop more effective treatments for the various diseases associated with it.

In this review, we will focus on the molecular heterogeneity of midbrain DA neurons. We will discuss, (1) the importance of understanding molecular heterogeneity of DA neurons, (2) the expression of individual molecules histochemically demonstrated to have non-uniform expression patterns in DA neurons in vivo, (3) recent large scale gene expression profiling studies, which provide a plausible point to begin addressing DA neuron heterogeneity in a systematic fashion. For space reasons, we will not address the developmental basis for DA neuron diversity, nor the functional consequences of molecular heterogeneity. Our goal is to provide a resource of known markers and their distributions for those researchers aiming to identify DA neuron subtypes in the normal brain, in various pathological settings, or in DA neurons derived from stem cells. In doing so, we hope to complement other excellent reviews on the heterogeneous properties of midbrain DA neurons [5–11].

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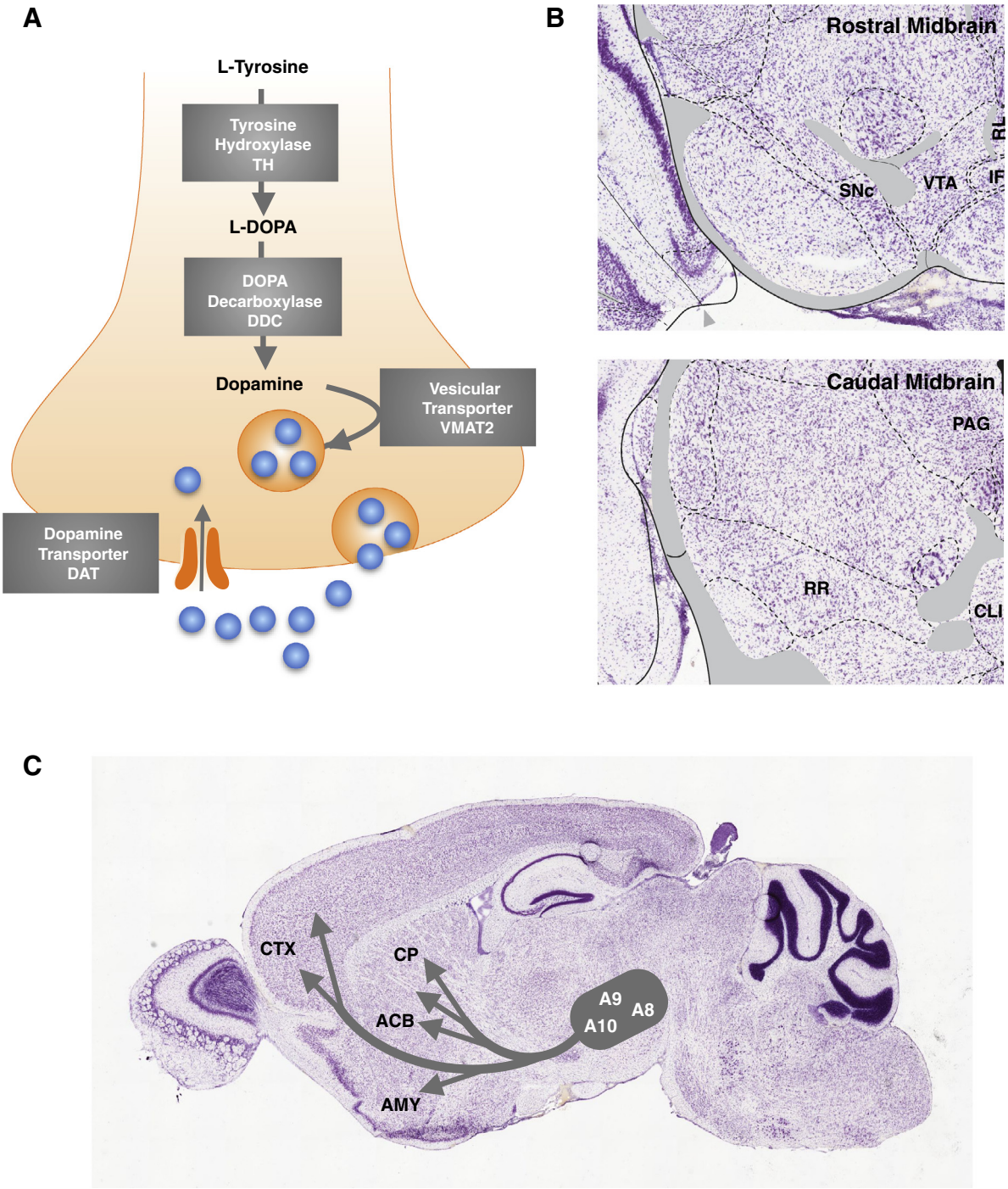


**Fig. 1.** Overview of the midbrain DA system. (A) Schematic of the pathway of DA production and reuptake. (B) Rostral and caudal coronal sections from the Allen Reference Atlas, depicting key DA neuron containing regions in the midbrain. (C) Sagittal section, depicting the midbrain DA neuron clusters A8–10, and their key projections to the amygdala (AMY), caudate putamen (CP), accumbens (ACB) and cortex (CTX).

## 2. Importance of understanding molecular heterogeneity of DA neurons

DA related diseases impose an enormous socioeconomic burden, making this one of the most clinically relevant neurotransmitter systems. A detailed understanding of this system and its constituent components is therefore imperative. We highlight four key reasons for further understanding DA neuron diversity.

### *2.1. Differential DA neuron vulnerability in PD*

PD is a neurodegenerative disorder typified by motor symptoms that result from the progressive loss of midbrain DA neurons. Several post-mortem studies on control and PD brains have now demonstrated differential vulnerability of DA neurons [12–16]. Most studies point to a preferential loss of SNc neurons, which are the main component of the mesostriatal pathway, compared to VTA neurons, which largely comprise the mesolimbic and

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