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The substantia nigra and ventral tegmental dopaminergic neurons from development to degeneration

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ABSTRACT

The pathology of Parkinson's disease (PD) is characterised by the loss of neurons in the substantia nigra parcompacta (A9), which results in the insufficient release of dopamine, and the appearance of motor symptoms. Not all neurons in the A9 subregions degenerate in PD, and the dopaminergic (DA) neurons located in the neighboring ventral tegmental area (A10) are relatively resistant to PD pathogenesis. An increasing number of quantitative studies using human tissue samples of these brain regions have revealed important biological differences. In this review, we first describe current knowledge on the multi-segmental neuromere origin of these DA neurons. We then compare the continued transcription factor and protein expression profile and morphological differences distinguishing subregions within the A9 substantia nigra, and between A9 and A10 DA neurons. We conclude that the expression of three types of factors and proteins contributes to the diversity observed in these DA neurons and potentially to their differential vulnerability to PD. In particular, the specific axonal structure of A9 neurons and the way A9 neurons maintain their DA usage makes them easily exposed to energy deficits, calcium overload and oxidative stress, all contributing to their decreased survival in PD. We highlight knowledge gaps in our understanding of the cellular biomarkers for and their different functions in DA neurons, knowledge which may assist to identify underpinning disease mechansims that could be targeted for the treatment of any subregional dysfunction and loss of these DA neurons.

1. Introduction

The cardinal neuropathological feature of Parkinson's disease (PD) is the early consistent degeneration of dopaminergic (DA) neurons within the substantia nigra (SN) (Halliday et al., 1996; Braak et al., 2004; Hornykiewicz, 2006; Davie, 2008). Unlike other parkinsonian conditions, the DA cell loss is selective in PD and most severe in the ventral tier of the substantia nigra pars compacta (SNV) compared to the other subregions of the substantia nigra pars compacta (SNC) (Fearnley and Lees, 1991; Ma et al., 1995). Moreover, the neighboring regions of the ventral tegmental area (VTA) and retrorubral field are relatively resistant to degeneration in PD (McRitchie et al., 1997). The discrepant vulnerability of these DA neurons to PD indicates that there must be biological characteristics that determine the fate of these subtypes of DA neurons.

The subgroups of SN and VTA DA neurons are developmentally, morphologically, and functionally different. Together with basic histological and pathological descriptions, quantitative assessments using either conventional single section based counting or stereological counting have provided an overview of the changes in DA neuronal number in both aging and PD. These quantitative data offer not only a better understanding on the difference between the aging process and PD-related changes, but also a picture of the different levels of cell loss in subregions of SNC and VTA. We review the biological characteristics of the subregions of SNC and VTA DA neurons and comment on potential links to their fate in PD.

Mouse models of PD have been widely used in research, and the translation of data from mouse to human PD must be based on establishing anatomical homologies between these species. As the C57BL/6J mouse is the most commonly used strain for genetic engineering and PD models, the SN and VTA structures of this strain is briefly reviewed and compared with those of humans (Zaborszky and Vadasz, 2001; Fu et al., 2012; Reyes et al., 2012).

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2. The human and mouse substantia nigra (SN) and ventral tegmental area (VTA)

Before comparing the subgroups of SN and VTA DA neurons, we must briefly recall the anatomical organization of these two structures. In the nomenclature based on the numbering of catecholamine-containing neuron systems caudal to rostral, the DA neurons in the SNC are named A9 and those in the VTA are named A10 (Smeets and González, 2000; Björklund and Dunnett, 2007). In both humans and mice, the SN and VTA are located in the floor of the adult midbrain, with the SN ventral to the VTA (for a three dimensional view of human and mouse SN and VTA (see Halliday and Tork, 1986; McRitchie et al., 1995; Fu et al., 2012). Furthermore, the same subgroups of DA neurons can be identified in the SN and VTA in both species. The SNC forms the dorsal part of the SN and comprises the dorsal tier (SND), medial cluster (SNM), lateral cluster (SNL), and SNV. SNV DA neurons are embedded in the SNR, the latter being the ventral part of the SN that is harbored in the cerebral peduncle. Compared to the mouse, the human has an enlarged cerebral peduncle and a larger volume of SNV, while the VTA is forced to extend far more dorsally (Reyes et al., 2012). It must be noted that the VTA is the collective name for a number of distinct DA neuron groups, including the laterally placed parabrachial pigmented nucleus (PBP), three intermediate structures (paranigral nucleus (PN), parapeduncular nucleus (PaP), and rostral VTA (VTAR)), and three medial structures (interfascicular nucleus (IF), rostral linear nucleus of the raphe (RLi), and caudal linear nucleus of the raphe (CLi)) (McRitchie et al., 1996).

3. Heterogeneity of dopaminergic (DA) neurons in SN and VTA

3.1. Multi-segmental neuromeric origin

While the midbrain location of DA neurons in the developing SN and VTA is well known, it is often not recognised these DA neurons are also located in the diencephalon and the isthmus (Marin et al., 2005; Puelles et al., 2007, 2013; Hebsgaard et al., 2009). Using the traditional biomarker tyrosine hydroxylase (TH, the rate-limiting enzyme for DA synthesis that catalyses the synthesis of L-3,4,-dihydroxyphenylalanine (L-DOPA)), Aubert et al. (1997) described a series of development events of the SN and VTA DA neurons in human fetuses: (1) TH-immunoreactive signal first appears in mesencephalon at fetal week 12; (2) after this stage, TH-immunoreactive precursors are still migrating from the ventricle; (3) SN is anatomically visible but the main subgroups of SN DA neurons become distinguishable at fetal week 16; (4) the SN displays an organisation resembling that of the adult SN at fetal week 19; and (5) also at this stage, neurons with morphology of those in the future VTA are visible. In a later study, Hebsgaard et al. (2009) confirmed that the DA neuron determinant, LMX1a, is expressed in the diencephalic and mesencephalic DA neuron domains during human development and that the progenitor cells are located in the ventricular zone of the floor plate region.

In the chick the caudal SN arises from the isthmus (the most rostral segment of the hindbrain) instead of the mesencephalon, and the caudal VTA originates from rhombomere 1 of the hindbrain (Puelles et al., 2007). In the embryonic mouse, SNC and VTA DA neurons are located in the basal plate rostrocaudally from diencephalic prosomere 3 to the isthmus region (see review in Ang, 2006). Although the isthmus forms a complete segment of the brainstem between the mesencephalon and the rhombomeres of the hindbrain, it has been a region largely ignored when the origin of neuronal clusters has been considered (Puelles et al., 2013). The origin of DA neurons in the human isthmus has still to be confirmed by gene expression studies, but study of mice of a cre *fgf8* lineage (fgf8 is the main organising molecule in the developing isthmus (Martinez, 2001) and fate mapping could be used to examine isthmus-born DA neurons in mammals (Watson, 2010). If the avian multi-segmental neuromeric origin of the SN and VTA DA neurons is also true of humans, it may have implications for the pathogenesis of PD. It should be noted that there are rostrocaudal morphological differences in SN DA neurons in the mouse (Fu et al., 2012) which may have relevance to the increased rostrocaudal gradient of cell loss in PD patients (Damier et al., 1999). Anatomical landmarks revealing the developmental location of the DA cell groups should be considered in future pathological assessments. For instance, the medial terminal nucleus of the accessory optic tract is an exclusively diencephalic structure, the oculomotor nerve exits exclusively from the mesencephalon, and the rostal SN and VTA DA neurons are located in prosomeres 1, 2, and 3 of the diencephalon (Puelles et al., 2007).

3.2. Transcription factors for SN and VTA DA neurons

Clearly, most studies to date have not considered the isthmic and diencephalic origin of many A9 and A10 neurons. However, DA neurons receive region-specific signals that lead them to develop into specific subsets distinguishable by their molecular and physiological parameters (Smidt and Burbach, 2007; Hegarty et al., 2013; Blaess and Ang, 2015). At embryonic stages, the SN and VTA DA precursor cells are under the regulation of different transcription factors (for recent reviews on molecular mechanisms that direct DA subset specification in development (see Hegarty et al., 2013; Veenvliet and Smidt, 2014; Blaess and Ang, 2015). Some of these transcription factors persist in their expression into adulthood, although remarkably little is known about their late functions in mature DA neurons. It is possible that some of these developmentally acting transcription factors are required throughout adulthood as key regulators of the axonal energy balance for different types of DA neurons (Doucet-Beaupré and Lévesque, 2013). This may contribute to their different vulnerability in PD, particularly through differences in mitochondrial dynamics (Zaltieri et al., 2015). PD-associated genes also directly or indirectly impinge on mitochondrial integrity, therefore linking the developmental regulation of DA neurons and the pathophysiological alterations observed in sporadic PD (see review in Winklhofer and Haass, 2010). Here we review reports on two types of such transcription factors. Most of their late functions have been revealed in mice, and these functions need to be confirmed in humans (Fig. 1): (1) transcription factors that differentiate SN and VTA DA progenitors and preserve a regional specific expression pattern into adulthood; (2) transcription factors that are expressed by DA progenitors and neurons in both embryonic and adult stages and function in cell survival and maintenance, but have no regional specific expression in the SN and VTA.

3.2.1. Transcription factors differentiating SN and VTA DA neurons

Orthodenticle homeobox 2 (Otx2) is expressed in the midbrain as far caudal as the midbrain–hindbrain boundary and so identifies mesencephalic-derived DA neurons in developing mouse brain (Omodei et al., 2008; Di Giovanni et al., 2009). Otx2 targets genes that are nuclear-encoded mitochondrial mRNAs (Spatazza et al., 2013). It is known that neurons with high levels of glycosylated dopamine transporter have efficient dopamine reuptake and pronounced vulnerability to PD-related degeneration (Di Salvio et al., 2010a). Interestingly, Otx2 can suppress the expression of the glycosylated dopamine transporter (Di Salvio et al., 2010a), indicating its protective role. In adult mice, Otx2 controls the identity of subtypes of neurons by antagonizing molecular and functional features of the dorsal-lateral VTA, such as G-protein-coupled inwardly rectifying potassium channel subunit (GIRK2) and dopamine transporter (DAT) (Simeone et al., 2011).

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