



Cell in focus

Dopaminergic neurons

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Received 14 July 2004; received in revised form 6 August 2004; accepted 16 September 2004

Abstract

Dopaminergic neurons of the midbrain are the main source of dopamine (DA) in the mammalian central nervous system. Their loss is associated with one of the most prominent human neurological disorders, Parkinson's disease (PD). Dopaminergic neurons are found in a 'harsh' region of the brain, the substantia nigra pars compacta, which is DA-rich and contains both redox available neuromelanin and a high iron content. Although their numbers are few, these dopaminergic neurons play an important role in the control of multiple brain functions including voluntary movement and a broad array of behavioral processes such as mood, reward, addiction, and stress. Studies into the developmental pathways which are involved in the generation of dopaminergic neurons in the brain have led to the identification of several specific transcription factors including Nurr1, Lmx1b and Pitx3, all shown to be important in the development of the mesencephalic dopaminergic system. The selective degeneration of these dopaminergic neurons in the substantia nigra pars compacta leads to PD but the exact cause for this nigral cell loss is still unknown. © 2004 Elsevier Ltd. All rights reserved.

Cell facts

- Dopaminergic neurons correspond to approximately 3–5% of total neurons in the substantia nigra.
- Dopaminergic neurons play a significant role in the cardiovascular, renal, hormonal, and central nervous systems. They are thought to control processes as diverse as movement and drug addiction.
- An excessive amount of dopamine in the brain is affiliated with schizophrenia characterized by altered behavior and delusions.
- Dopamine deficiency in the substantia nigra in aged populations results in PD which constitutes a major public health burden in westernized countries where the average life expectancy is 85 years or greater.

Keywords: Dopamine; Substantia nigra; Parkinson's disease

1. Introduction

Dopamine is one of the most intensively studied neurotransmitters in the brain due to its involvement in several mental and neurological disorders. Midbrain

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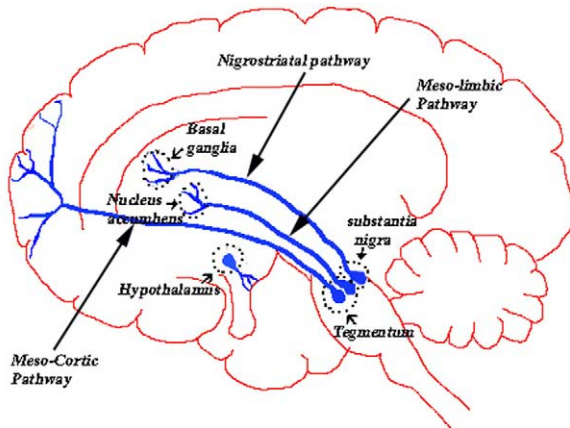


Fig. 1. Representation of dopaminergic pathway system in human brain.

dopaminergic neurons constitute the major source of dopamine in the mammalian central nervous system. Identification and localization of brain dopamine cell groups was originally performed using the Falck-Hillarp histofluorescence method (Falck et al., 1962), which is based on the visualization of fluorescent monoamines following formaldehyde treatment. Dopaminergic neurons are an anatomically and functionally heterogeneous group of cells, localized in the diencephalon, mesencephalon and the olfactory bulb (Björklund & Lindvall, *in press*). The most prominent dopaminergic cell group resides in the ventral part of mesencephalon, which contains approximately 90% of the total number of brain dopaminergic cells. The mesencephalic dopaminergic system has been subdivided into several nominal systems (Fig. 1). Probably, the best known is the nigrostriatal system, which originates in the zona compacta of the substantia nigra (SNc) and extends its fibers into the caudate-putamen (also known as the dorsal striatum). The nigrostriatal pathway plays an essential role in the control of voluntary motor movement. More medial to this pathway are the mesolimbic and mesocortical dopaminergic systems, which arise from dopaminergic cells present in the ventral tegmental area (VTA). These dopaminergic systems are involved in emotion-based behavior including motivation and reward. The cells of the VTA project most prominently into the nucleus accumbens, olfactory tubercle but also innervate the septum, amygdala and hippocampus. This subset of projections is known as the mesolimbic

dopaminergic system. Cells in the medial VTA project to the prefrontal, cingulate and perirhinal cortex. This pathway is known as the mesocortical dopaminergic system. There is considerable overlap between the VTA cells that project to these various targets. Because of the overlap between the mesocortical and mesolimbic dopaminergic neurons, the two systems are often collectively referred to as the mesocortico-limbic system (Wise, 2004). The various clusters of dopaminergic neurons in the central nervous system therefore, have different anatomical positions and projections and play crucial roles in different cellular functions. In principle they may be considered as totally unrelated neurons having in common only the synthesis of the neurotransmitter dopamine.

Considerable differences exist in the numbers of midbrain dopaminergic cell bodies in various mammals ranging from about 45,000 in the rat, 165,000 in the macaca monkey, to 590,000 in human beings (German & Manaye, 1993). This latter number applies to humans in their fourth decade of life but drops to an average of about 350,000 during the sixth decade of life (Bogerts, Hantsch, & Herzer, 1983). Such an age-dependent decrease in the numbers of midbrain dopaminergic cells has also been reported for nonhuman primates however not for rodents such as mice or rats perhaps due to their short life spans.

2. Cell origin and plasticity

The development of midbrain dopaminergic neurons follows a number of stages marked by distinct events. Most of the dopamine-containing cells develop from a single embryological cell group that originates at the mesencephalic–diencephalic junction and projects to various forebrain targets. Developmental studies of the pathways involved, have led to the identification of several factors that influence the final formation of midbrain dopaminergic neurons in the adult animal. The identity of early proliferating dopaminergic progenitor cells are specified by the existence of two secreted signaling proteins, sonic hedgehog (Shh) and fibroblast growth factor 8 (Fgf8), derived from the floor plate of the ventral midline and the mid/hindbrain border, respectively. While transcription factors that are specifically expressed in the proliferating dopaminergic progenitor cells have yet to be

identified, others important for post-mitotic dopaminergic cell development have already been characterized. These include Nurr1, Lmx1b, Pitx3, and En1/En2. Nurr1 appears to be strictly coupled to neurotransmitter synthesis (Zetterstrom et al., 1997), where as Lmx1b is necessary for the expression of Pitx3 (Smidt et al., 2000). Pitx3 is expressed exclusively in mesencephalic dopaminergic neurons and involved in development and/or maintenance of these neurons (Nunes, Tovmasian, Silva, Burke, & Goff, 2003). Studies analyzing the functions of these transcription factors has not only increased the understanding of how dopaminergic neurons are generated in vivo, but also allowed the development of new strategies in stem cells for engineering dopaminergic neurons in vitro. These results may be significant in terms of the development of future therapies for PD patients (Wallen & Perlmann, 2003).

3. Functions

Although dopaminergic neurons correspond to less than 1% of the total number of brain neurons, they play an important role in regulating several aspects of basic brain function. They are necessary for tasks specific to the brain regions that they innervate including motor behavior, motivation and working memory. Regulation of dopamine therefore plays a crucial role in both our mental and physical health. Dopaminergic neurons, for example, play a crucial role in the reward system that controls the learning of many specific behaviors. Unpredicted rewards in monkeys increase firing of the dopamine neurons while the absence of an expected reward has an inhibitory effect. This has led to the proposal that dopamine neurons function as detectors of reward prediction errors (Schultz, 1997).

4. Dopamine and associated pathologies

Dopaminergic neurons are believed to be particularly prone to oxidative stress due to their high rate of oxygen metabolism, low levels of antioxidants, and high iron content. Dopamine is thought to be capable of generating toxic reactive oxygen species (ROS) via both its enzymatic and non-enzymatic catabolism (Halliwell, 1992). Specifically, dopamine oxidation can occur either spontaneously in the presence of transition metal ions or via an enzyme-catalyzed re-

action involving monoamine oxidase (MAO). Oxidation of dopamine via MAO generates a spectrum of toxic species including H₂O₂, oxygen radicals, semiquinones, and quinones (Graham, Tiffany, Bell, & Gutknecht, 1978). Conditions that increase brain concentration and/or turnover of dopamine could potentially increase the formation of reactive metabolites especially under conditions in which the ratio of available dopamine to antioxidant capacity is high (Hastings & Zigmond, 1994).

One of the major neurodegenerative disorders associated with dopaminergic cell loss is PD. PD, first described by James Parkinson in 1817, is a neurodegenerative disorder associated with specific neuropathological lesions (Parkinson, 1817). The main pathological hallmark of PD is a progressive loss of neuromelanin-containing dopaminergic neurons in the SNpc of the ventral midbrain. Dopaminergic cell loss is associated with the presence of eosinophilic intraneuronal inclusions, called Lewy bodies, composed of alpha-synuclein, neurofilaments, and ubiquitin (Goldman, Yen, Chiu, & Peress, 1983). In PD, the loss of nigral neurons follows a specific pattern with the more susceptible area being located laterally in the ventral part of the SNpc. This results in severe dopamine depletion in the striatum, responsible for the motor symptoms associated with PD, especially bradykinesia (slowness of movement), tremor, rigidity and loss of postural control. Other less severe lesions, such as degeneration of the dopaminergic VTA, the noradrenergic locus ceruleus and the ascending cholinergic pathway from the Meynert basalis nucleus are also observed (Candy, Perry, Perry, Irving, Blessed, & Fairbairn, 1983) These non-nigral lesions lead to cognitive and psychological impairments such as dementia, which is estimated to occur in around 30% of all PD cases (Aarsland, Tandberg, Larsen, & Cummings, 1996). Although the pathological changes and motor dysfunction that characterize the disease are well documented, the mechanism(s) responsible for the death of dopaminergic neurons has yet to be clearly established. Therefore, most of the current treatment for the disease is largely symptomatic rather than preventative. The most commonly prescribed drug for PD is L-dopa. L-Dopa is the natural precursor for the metabolism of dopamine (Cotzias, Van Woert, & Schiffer, 1967). It is used as a treatment for PD patients to replace lost midbrain dopamine as, unlike dopamine

itself, which is charged, it can cross the blood-brain barrier. While intake of L-dopa reduces the severity of Parkinsonian symptoms suggesting that it is effectively transformed into dopamine within the SNpc, it also causes severe side effects such as nausea, vomiting, and altered blood pressure. Unfortunately, L-dopa and other Parkinsonian drugs are only able to control the symptoms of the disease but not on-going cell death and eventually become ineffective once sufficient dopaminergic neurons are lost. Despite the failure of L-dopa to prevent continued neurodegeneration it is still one of the major prescribed treatments for the disease. Dopamine agonists are also used therapeutically to replace dopamine function in the affected brain. However, so far none appears to work as efficiently as L-dopa. Before L-dopa was discovered, surgery was used to treat PD. Recently, there has been resurgence in the use of surgical techniques such as pallidotomy and thalamotomy in which lesions are made in the patient's globus pallidus or thalamus, respectively. While these surgical treatments appear to relieve the symptoms in certain PD patients, they are not effective in all cases. Experimental methods used at this time include deep brain stimulation, where electrodes are placed in the brain, which stimulate the thalamus and the implantation of stem cells. Transplantation of neural stem cells from fetal tissue into the PD striatum seems to be the most promising approach, as the fetal tissue not only appears to survive in the host, but also to replace the function of the damaged dopaminergic neurons (Storch, Sabolek, Milosevic, Schwarz, & Schwarz, 2004). However, a recent clinical trial examining transplantation of fetal stem cell tissue into older Parkinsonian patients unfortunately showed no more efficacy than sham surgery based on patient self-report (Freed et al., 2001). In addition, this technique carries with it a host of ethical issues. Scientists hope that eventually techniques will be refined to enable stem cells from the patient's own body to be coaxed into dopaminergic SNpc neurons, which can then be used for the replacement of the midbrain dopaminergic neurons lost during the disease process.

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