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BioNB 2220: Introduction to Neuroscience

There is more to Parkinson's disease than motor dysfunctions: A review on both motor and non-motor symptoms

Abstract

Although Parkinson's disease (PD) is considered a motor system disorder caused by the degeneration of dopaminergic neurons in the substantia nigra, it is also associated with a wide range of nonmotor symptoms. Some of these symptoms include sensory dysfunction, depression, and dementia. Because the exact biochemical pathways for these nonmotor symptoms are not yet completely understood, current treatment options for PD focus primarily on relieving motor symptoms of the disease and leave the nonmotor symptoms inadequately treated. It is important to better understand nonmotor symptoms because not only are these symptoms associated with the rapid progression of PD, many of these symptoms often precede the more obvious motor symptoms such as bradykinesia, tremors, and rigidity, and could thus be used for early diagnosis of PD.

Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disease that affects approximately 2.0% of adults over the age of 65 (Lieberman 2006), and 1 in 300 in the general population (Schapira et al. 2006). PD is most commonly linked with a degeneration of the dopamine synthesizing neurons in the midbrain substantia nigra that project to the striatum, which causes an overall loss in motor function, as presented by tremors and rigidity in movement

(Dauer and Przedborski 2003, Lieberman 2006, McGeer and McGeer 2004, Mendez et al. 2008, Poewe 2008, Richardson et al. 1997, Schapira et al. 2006, Shahed and Jankovic 2007). Recent data pointed to the possibility of chronic inflammation and sustained immune responses in the brain in causing dopaminergic cell death in PD (McGeer and McGeer 2004). However, PD affects more than the dopaminergic systems, including areas of the brain that are not directly related to motor control, such as the amygdala and peripheral autonomic nervous system (Lieberman 2006, Poewe 2008). Defects in these areas lead to the nonmotor symptoms that affect many PD patients, such as pain, cognitive and sensory dysfunction (Poewe 2008), as well as depression and other mood disorders as seen in 20 – 40% of PD patients (Lieberman 2006). Thus, the aim of this review is to examine both the motor and nonmotor PD symptoms and review the current understanding of the associated biochemical pathways.

Motor Symptoms

Parkinson's disease (PD) is often associated with overt motor symptoms that include the asymmetric onset of bradykinesia, tremors, and rigidity due to the degeneration of dopaminergic nigrostriatal neurons of the basal ganglia (Dauer and Przedborski 2003, Lieberman 2006, McGeer and McGeer 2004, Mendez et al. 2008, Poewe 2008, Richardson et al. 1997, Schapira et al. 2006, Shahed and Jankovic 2007). Bradykinesia, or a slowness of movement, is a trademark of basal ganglia disorders and is a clearly identifiable symptom of PD (Shahed and Jankovic 2007). With this symptom, PD patients experience a decrease in dexterity and fine motor control. Of all the motor symptoms, the rest tremor is the most well known and is the classic motor dysfunction associated with PD. This type of tremor occurs at rest but decreases with

voluntary movement (Dauer and Przedborski 2003). Tremors can be observed in the hands, lip, chin, jaw and legs, but almost never involves the neck-head regions or the voice (Shahed and Jankovic 2007). Although the tremors usually remain asymmetric, it may manifest into bilateral tremors as PD progresses (Shahed and Jankovic 2007). The pathophysiology of the rest tremors are not fully understood, but it has been generally accepted to be caused by atypical synchronous oscillating neuronal activity within the basal ganglia (Shahed and Jankovic 2007). Tremors often accompany rigidity, or the resistance seen in the passive movement of a limb (Shahed and Jankovic 2007). Rigidity may also play a role in the recurrent pain afflicting PD patients. An early diagnosis of PD can be greatly supported when rigidity increases with reinforcing movements and is seen ipsilateral to the rest tremor (Shahed and Jankovic 2007). At later stages of PD, postural instability develops and can become one of the major devastating symptoms and a main cause of falls in PD patients (Shahed and Jankovic 2007). Postural instability contributes to gait abnormalities seen in patients with PD, who often shuffle with slow, narrow steps in a characteristically stooped posture (Shahed and Jankovic 2007).

Neuronal Mechanisms Governing Motor Symptoms

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Smooth, well coordinated muscle movement is determined by the direct and indirect output pathways of the basal ganglia to the globus pallidus and the substantia nigra (Richardson et al. 1997). While the direct pathways disinhibit the thalamocortical neurons, the indirect pathways inhibit these neurons (Richardson et al. 1997). These neurons are influenced by excitatory inputs from the cortex and thalamus and by regulatory control by dopamine release from the nigrostriatal neurons (Richardson et al. 1997). As seen in Figure 1, in PD, dopamine denervation occurs with the death of nigrostriatal neurons. Dopamine denervation causes an imbalance in the activity of the two basal ganglion pathways, which is thought to correlate with the motor symptoms seen in PD (Richardson et al. 1997, Schapira et al. 2006).

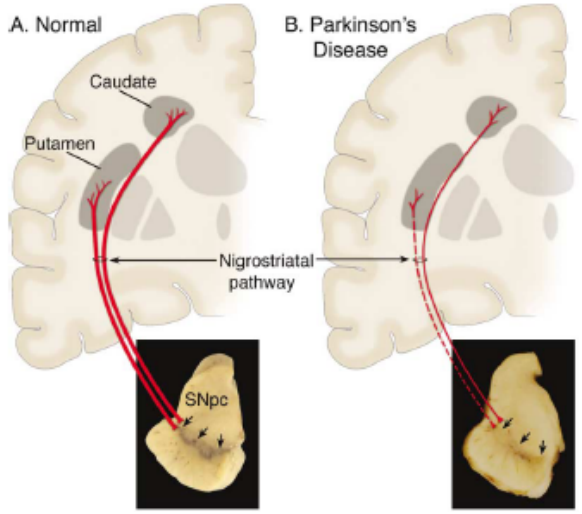

Figure 1. Neuropathology of Parkinson's Disease
A. Schematic representation of the normal nigrostriatal pathway in the coronal plane. The black arrows in the photograph point to the dopaminergic neurons located in the substantia nigra (SNpc). This area is darkened due to normal pigmentation by neuromelanin within the dopaminergic neurons. As shown by the thick red arrows, these neurons project to the basal ganglia of the brain and synapse in the striatum.
B. Schematic representation of the diseased nigrostriatal pathway. The black arrows in the photograph point to the loss of dopaminergic neurons in PD, indicated by the loss of neuromelanin. The dashed red line and thinner red line projecting from the substantia nigra to the striatum illustrates the decrease in dopaminergic neurons projecting to these areas.

(Dauer and Przedborski, 2003)

Neuronal loss observed in brains of PD patients may be due to the presence of Lewy bodies, or a mass of fine fibers, as illustrated in Figure 2. Lewy bodies serve as defining histological characteristics of PD and have been

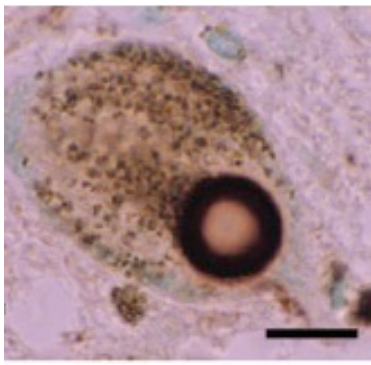

Figure 2. A typical Lewy Body found in the substantia nigra. Bar, 10 μm.

(Wakabayashi et al. 2007)

found in various areas of the central and peripheral nervous systems in PD patients (Wakabayashi et al. 2007). The extensive distribution of these Lewy bodies may also be linked to the wide range of motor and non-motor symptoms seen in PD patients (Wakabayashi et al. 2007).

In PD, Lewy bodies are mainly comprised of a presynaptic nerve terminal protein known as α-synuclein (Wakabayashi et al. 2007). In a healthy brain, α-synuclein is found in presynaptic terminals and is absent in the neuronal cytoplasm. In the normal aging process, the protein, α-synuclein, non-pathologically accumulates in the substantia nigra, but not in other dopamine neuronal nuclei (Mendez et al. 2008). However, in PD, α-synuclein develops inside nerve cells as pale and diffuse cytoplamsic inclusions and displaces other components of the cell (Mendez et al. 2008, Schapira et al. 2006). The molecular components of α-synuclein are cytotoxic and as long as these toxins are made, Lewy bodies expand. This causes an excessive build-up of protein aggregates in the host cell and leads to cell death.

Early Non-motor Symptoms

Non-motor symptoms afflicting patients with PD often precede the more obvious motor symptoms associated with the disease. One recent hypothesis suggests that the Lewy body pathology develops only after the olfactory system and lower brainstem areas have become affected (Poewe 2007). Recent data have been found to show a relationship between the decreased sensitivity to odors and an increased risk of developing PD (Chaudhuri et al. 2006). Olfactory dysfunction eventually effects up to 90% of patients with PD (Poewe 2007, Chaudhuri

et al. 2006). Another common early symptom seen in PD patients is constipation (Chaudhuri et al. 2006). This may be one of the earliest symptoms of Lewy body degeneration as seen in PD. Lewy bodies found to effect the peripheral autonomic nervous system also affect the colonic sympathetic denervation which has been associated with a prolonged intestinal passage time leading to constipation (Poewe 2007). Constipation has been reported as one of the main complaints preceding the classic motor symptoms in about half of PD patients (Poewe 2007). In one longitudinal study following the bowel habits of 7000 men over the course of 24 years, those with initial constipation were three times more likely of developing PD over a mean time period of 10 years (Chaudhuri et al. 2006). Therefore, the identification of early non-motor symptoms, such as the decrease in function of the olfactory system and the onset of constipation, could lead to an earlier diagnosis of PD.

Neuropsychiatric Dysfunctions

PD patients are not only affected by somatic nonmotor symptoms but also neuropsychiatric nonmotor symptoms, ranging from depression, anxiety, and apathy. Studies have indicated that depression, characterized by guilt, lack of confidence, sadness, and remorse (Chaudhuri et al. 2006), often occurs with anxiety in PD patients (Lieberman 2006). Depression or panic attacks have been seen to antedate the onset of motor symptoms in up to 30% of patients with PD (Poewe 2007). Separate from the depression that is usually seen in PD patients, apathy has also been recognized as a unique symptom of PD (Chaudhuri et al. 2006). Apathy is defined as the presence of reduced motivation that is not related to a decrease in conscious state or emotional distress (Lieberman. 2006) and could be caused by the neuronal degeneration in the

reward centers of the brain, such as the dopaminergic projections between the ventral tegmentum and nucleus accumbens (Chaudhuri et al. 2006). Anxiety and apathy are both commonly seen early on in PD (Poewe 2007) and can be preclinical risk factors (Chaudhuri et al. 2006).

Neuronal Mechanisms Governing Depression as seen in PD

Damage to the limbic noradrenergic and dopaminergic mechanisms and to the serotoninergic neurotransmission as seen in PD patients may link depression to a more biological cause than to a reaction to the disease itself (Chauduri et al. 2006). Neurons in the ventral mesencephalon, located near the substantia nigra, project to limbic and cortical structures that control cognition, emotions, and reward-seeking behavior (Lieberman 2006). There is a greater degeneration of dopaminergic neurons in this area in PD patients who have depression than those who do not (Lieberman 2006). Depression associated with PD is also associated with a decrease in serotonin in the dorsal raphe nucleus and norepinephrine in the locus coeruleus (Lieberman 2006). The locus coeruleus projects to the anterior cingulated gyrus, the hippocampus, the ventral striatum, and the amygdala (Lieberman 2006). The amygdala, a region of the brain closely associated with motivation and emotional behavior, is atrophied and consists of Lewy bodies in PD patients with depression, which may link PD to depression (Lieberman 2006). Therefore, the relatively weak correlation between depression and the severity of PD suggests that depression is not a psychological reaction to PD but part of PD itself (Lieberman 2006).

Cognitive Impairment

Some hypotheses propose that depression antecedes dementia (Lieberman 2006). Dementia, another nonmotor symptom, is seen in up to 40% of PD patients – a rate that is about six times greater than that of healthy individuals (Chaudhuri et al. 2006, Poewe 2007). Dementia advances gradually but is associated with a rapid progression of disability, which often puts many PD patients at risk of nursing home placement. Dementia is clinically characterized by impairment to visuospatial abilities, memory, and the executive attention in the control of thoughts and emotions (Chaudhuri et al. 2006, Poewe 2008). Personality disorders, hallucinosis, and psychosis are also seen in PD patients afflicted with dementia (Poewe 2008).

Neuronal Mechanisms Governing Dementia as seen in PD

The underlying mechanisms of dementia in PD are not yet fully understood. There have been hypotheses that Lewy body degeneration is a main driving factor for the development of dementia in PD (Poewe 2008). There have been studies linking the presence of Alzheimer-type changes in the brain, such as senile plaques, with the α-synuclein of Lewy bodies (Caballol et al. 2007). A decrease in hippocampal volume has also been seen in PD patients with dementia that is comparable in extent to the decrease seen in individuals afflicted with Alzheimer's disease (Chaudhuri et al. 2006). Connections have also been made between the severity of motor symptoms and intellectual impairment (Huber et al. 1988). Using the Mini-Mental State examination to assess intellectual status, Huber et al. found a significant negative correlation between intellectual impairment and the severity of both rigidity and bradykinesia. This seemed to suggest that these motor symptoms were related to the increased intellectual impairment seen in patients with PD.

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Discussion

PD, a disease that is usually categorized as a motor system disorder, also has many nonmotor symptoms. Neurodegeneration in PD affects the central nervous system as well as the peripheral nervous system, leading to a wide range of classic motor symptoms, such as bradykinesia, tremors, and rigidity (Lieberman 2006, McGeer and McGeer 2004, Mendez et al. 2008, Poewe 2008, Richardson et al. 1997, Schapira et al. 2006, Shahed and Jankovic 2007), in addition to nonmotor symptoms. Many non-motor symptoms, such as sensory dysfunction and depression, often precede the more obvious motor symptoms. Therefore, it is important to pay attention and correctly identify early non-motor symptoms, as they could lead to an earlier diagnosis of PD.

Although many drugs are currently prescribed to relieve the classic motor system malfunctions seen in PD patients, these drugs often worsen nonmotor symptoms and decrease the quality of life (Poewe 2007, Richardson et al. 1997, Schapira et al. 2006). While newer treatments are beginning to treat both motor and nonmotor symptoms, there are currently no medications that stop the degeneration of dopaminergic neurons (Dauer and Przedborski 2003). Thus, future studies that aim to gain a better understanding of the relationship between the biochemical pathways of PD and the motor and nonmotor symptoms are warranted. Furthermore, being able to pinpoint the neurons that are most susceptible to neurodegeneration could lead to more effective treatment options for relieving both motor and nonmotor symptoms in PD.

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