

Disease process and drug treatments in Parkinson's disease

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1. Introduction

Parkinson's disease (PD) belongs to the neurodegenerative brain diseases. These diseases have in common that they usually start insidiously at middle age or late in life, progress relentlessly and affect multiple neuronal systems of the central nervous system. For the various groups of these diseases clinical vignettes exist if the disease has progressed sufficiently. The causes are often not known, but in recent years genetic factors have been detected to seem to play an important role. These factors create either a vulnerability to environmental influences in sporadic cases or are more prominently present in certain families. In general it is thought that disturbances of protein production or breakdown is the common mechanism in these conditions leading to a slow dysfunction and loss of the involved neurons in the brain. It is hoped that eventually a causal or protective treatment may arise from the increasing insights in pathogenetical mechanisms. To date no cure for these severe diseases exists. In some instances however important symptomatic treatment exists, particularly in PD. In that disease the dopaminergic nigrostriatal neurotransmitter system is primarily impaired leading to typical disturbances described below.

A general problem in studying brain diseases is the difficulty to obtain functional data directly from the brain tissue. A diagnostic tool which offers a window on brain tissue function in man during life is functional neuro-imaging. This chapter will describe PD and the use of functional neuro-imaging techniques like single photon emission computed tomography (SPECT) and positron emission tomography (PET) in the study of PD. Of special interest are those radiotracer methods which enable measurement of striatal dopaminergic activity.

2. Parkinson's disease

Parkinson's disease (PD) has been named after James Parkinson who for the first time described the disease in a comprehensive way in 1817 in an article entitled 'An Essay on the Shaking Palsy'. The diagnosis is made on clinical grounds solely. To date there does not exist a laboratory test to specifically confirm the cerebral pathological alterations which lie at the basis of this condition. In most cases the clinical pattern of signs and symptoms is sufficiently clear to make the diagnosis with confidence. However, a certain number of patients will pose considerable difficulties as to the correct diagnosis, particularly in early stages of their disease, even for an experienced neurologist. Overlap with diseases which are not PD, but are accompanied with some form of parkinsonian features occur frequently.

At least two of the three cardinal signs—bradykinesia, rigidity and tremor—need to be present (Levy and Cummings, 1999). The tremor is typically present when the patient is at rest. Other signs and symptoms may be present at different stages of the disease and in varying composition or intensity which understandably have far-reaching consequences for everyday life of the patient and his partner. These signs and symptoms include: impaired postural reflexes, masked face, low speech volume, swallowing difficulty, drooling, micrographia, flexed posture, small shuffling steps, movement initiation problems, freezing, painful local dystonia, loss of the sense of smell and many more. The clinical picture is often accompanied by depression. Neuropsychological impairments, mainly frontal lobe executive dysfunctions, but also others can be detected. A dementing condition may develop at later stages in 20 to 40% of the patients. The onset of PD is insidious and usually unilateral. When both body sides are affected after the disease has progressed, the asymmetries remain. The disease starts usually at middle age with increasing prevalence above the age of 50 years, but 'young onset cases' are not uncommon. Progression is in most cases slow but inexorable. The endstage of the disease is reached after many years, usually more than 10.

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The ‘idiopathic form’ of PD needs to be differentiated from other conditions resulting in parkinsonism (Levy and Cummings, 1999). Certain drugs like neuroleptics may induce parkinsonism. Typical alternative diagnoses are Progressive Supranuclear Palsy (PSP) or multiple system atrophy (MSA). If frequent falls early in the disease and a supranuclear gaze palsy are present, a PSP is more likely. An MSA is suspected if involvement of the upper motor neuron or a cerebellar syndrome is found. Often the autonomic nervous system is affected too resulting, for example, in micturition problems or orthostatic hypotension. Both PSP and MSA develop usually at a more rapid pace than PD, more symmetrically, and without much of a tremor and do not respond well to antiparkinsonian medication. Patients with early-onset or rapidly progressive dementia accompanied with visual hallucinations, not induced by medication, are more likely to have diffuse Lewy body dementia or Alzheimer’s disease.

Even though a patient with parkinsonism can usually be classified correctly during life, a definitive diagnosis of PD can only be made by autopsy. Typically a loss of dopamine neurons in parts of the substantia nigra pars compacta in the brainstem is found. During life, neuroimaging studies applying the radiotracers described below can demonstrate the presence at the striatal level of a presynaptic dopaminergic defect in the nigrostriatal neuronal system, but this does generally not differentiate between the various forms of parkinsonism. However, if various tracers are combined (including energy metabolism tracers), typical patterns of alterations in brain metabolism can be determined suggesting the presence of one of the brain diseases mentioned above and thus assisting in making a correct diagnosis at an early stage of the disease.

3. Basal ganglia circuits

The cerebral stations which prepare and execute movements constitute a complex system of neuronal networks. Motor plans are activated by many parietal and frontal cortical regions. In addition, two major ‘subcortical’ systems interact with the cortex to make movements possible. The cerebellum is necessary, for example, for obtaining accuracy and context-shaping of multi-joint movements. The basal ganglia (mainly the striatum, pallidum, subthalamic nucleus, as well as part of the thalamus) have a role in learning automated skilled movements, but their role is much more difficult to formulate in physiological terms. They have a role in temporal and spatial discrimination. A system of integrated influence, either activating or inhibiting, has been proposed for the basal ganglia to explain the function of the loops connecting the cortex with the subcortical systems. A central role is played by the dopaminergic nigrostriatal projection, which modifies in various ways the transmission of the cortico-striatal signals and thus the function of the neuro-

nal loops further downstream. Since the dopaminergic neuronal system is primarily impaired in PD, the basal ganglia circuits are therefore in disarray (Bergman et al., 1998). Ultimately this results in an altered firing pattern of the internal part of the globus pallidus to which the basal ganglia massively converge as major output station. The segregation between firing pallidal neurons is lost, leading to oscillatory activity of the pallidum which is normally not present (Raz et al., 2001). The pallidum has, in turn, an enormous divergent connection with the cortex through the thalamus. It therefore is understandable that a pathologically altered firing pattern of a globus pallidus neuron has a vastly disturbing influence on the cortical functions. The major projection of the basal ganglia is to the supplementary cortex, which is an important motor area: initiation of movements, organization of sequential movements, and others are prepared in this region.

4. PET and SPECT

Computerised tomography (CT) and magnetic resonance imaging (MRI) give insight into the normal and pathological anatomy of the cerebrum, but radiotracer-based imaging allows in vivo determination of three-dimensional brain biochemistry and physiology. These imaging techniques are either positron emission tomography (PET) or single photon emission computerised tomography (SPECT). Both make use of radiopharmaceuticals, but with different energy levels. SPECT uses single photon emitters such as ^{99m}Tc with 141 keV gamma rays and views the activity distribution at a limited number of angles at a time. PET uses radiopharmaceuticals which after positron emission emit two opposing 511 keV gamma rays whose distribution can be measured at all angles simultaneously.

5. Striatal dopamine system: dopa-decarboxylase and dopamine re-uptake

At the striatal level the dopaminergic status of the presynaptic nerve terminals projecting from the substantia nigra pars compacta to the striatum is nowadays usually assessed in vivo using two classes of radiotracers.

- (A) 6-[^{18}F]-fluoro-L-dopa (FDOPA) is an analogue of levodopa and measures decarboxylation capacity of levodopa to dopamine and storage of F-dopamine in the striatal nerve terminals (Firnau et al., 1987; Hoshi et al., 1993). The metabolism of FDOPA is practically identical compared to endogenous levodopa (Melega et al., 1990a,b, 1991). FDOPA is transported across the blood–brain barrier like all large neutral amino acids (Leenders et al., 1986a). Specific FDOPA conversion into FDA relates directly to the total

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