Chapter 1

General introduction and aims of the thesis
1. General introduction

A M. Parkinson

I Introduction

James Parkinson (1755-1824) was born in Shoreditch, Middlesex (GB), where he spent his entire life. He was the oldest son of an apothecary, and in 1771 he started his apprenticeship to his father. Within 5 years he became a “dressing pupil” at the London Hospital and in 1784 he was awarded the Membership of the Company of Surgeons. During his life he made major scientific contributions in medicine, geology and palaeontology, and he also was a prominent political reformer. His first contribution to the medical literature was entitled “Some Accounts of the Effects of Lightening”, which he read at a meeting of the Medical Society in London in 1787. In 1817 his “Essay on the Shaking Palsy” was published. In 5 brief chapters, Parkinson described a previously unrecognised nervous system disorder in six human cases (of whom 3 were even not his patients: he had merely observed them during his walks in the streets), of which a “tremulous motion” seemed one of its hallmarks. Parkinson, lacking cerebral autopsy material, predicted that the lesions of his patients would be located in the cervical spinal cord. For many years the work of James Parkinson was almost forgotten. After his death in 1824 (he suffered from a stroke), the medical profession failed to recognise the disease James Parkinson had described in his essay. However, when William Gowers in 1886 published “A manual of Diseases of the Nervous System”, it contained an article on “shaking palsy” or, erroneously, “paralysis agitans”. Subsequently, it was the French neurologist Jean Martin Charcot who preferred the eponym of “Parkinson’s Disease” (PD). In the following decades successive pathological studies (e.g. Lewy, 1914) of patients with PD showed characteristic brain abnormalities, especially neuronal degeneration in the substantia nigra. It lasted until 1960s that Hornykiewicz discovered that PD patients suffered from extensive dopamine depletion in the striatum. In 1967 the “levodopa era” started when Cotzias showed that orally administered levodopa had a dramatic and sustained effect on the cardinal motor features of PD: tremor, rigidity and bradykinesia.

II Motor and non motor features

Since there is no diagnostic biological marker for PD, the clinical diagnosis is entirely based on the presence of its characteristic motor features. Thus far few attempts have been made to develop explicit diagnostic criteria, including features as proposed by the Parkinson’s Disease Society Brain Bank. These include bradykinesia (slowness of initiation of movement with progressive reduction in speed and amplitude of repeti-
tive actions), and at least one of the following motor features: rigidity, 4-6 Hz rest tremor and postural instability. Additional supportive criteria for the clinical diagnosis PD are a persistent asymmetry of motor features affecting one side most, and an excellent response to levodopa. Before the appearance of these classic motor features, there may be a prodromal period in which symptoms and signs occur but do not specifically indicate PD; these symptoms include depression, musculoskeletal pain, sensory dysfunction and autonomic disturbance. Olfactory dysfunction may also be an early symptom of PD. A recent study on odour discrimination showed that PD patients could be discriminated from healthy controls with a sensitivity of 88% and a specificity of 83%. As depression is the most common psychiatric symptom in PD, a subgroup of patients presents with a depression as the initial disease manifestation. Autonomic dysregulation is the most common non motor feature of PD. Orthostatic hypotension and gastrointestinal complaints are the most common vegetative symptoms in PD. Data on the incidence vary between 14-80% depending on the population studied and the method used. Cognitive impairment occurs in 25-40% to over 90% of patients with PD, and dementia is increasingly recognised as an important non-motor feature of PD, especially in the elderly. Mental decline in PD is often being characterised by cognitive slowing, impaired abstract thinking and difficulties with reasoning. In addition, attentional deficits, visuospatial and executive dysfunction and memory impairments can be affected even at the early stages of the disease.

III Diagnosis

The combination of asymmetry of symptom onset, the presence of a typical resting tremor, and an excellent response to levodopa best differentiates (idiopathic) PD from parkinsonism due to other, more seldom, causes. Although many signs and symptoms are present in all parkinsonian syndromes, they specifically start at different stages of the disease. These differences in the dynamics of time course become evident when comparing PD with other, more “atypical” parkinsonian syndromes (e.g. Multiple System Atrophy, Progressive Supranuclear Palsy), with the latter having a more rapid functional deterioration. In clinical practice the differential diagnosis of PD thus primarily includes other primary inherited or sporadic neurodegenerative syndromes featuring parkinsonism, parkinsonian syndromes associated with defined diseases, symptomatic parkinsonian syndromes and monogenetically inherited forms of PD (see table 1).

Despite application of explicite diagnostic criteria only 60-70% of clinical diagnosis of PD are confirmed by autopsy. Recently 800 patients with clinically PD were prospectively followed up with repeated clinical assessments; after 6 ± 1.4 years, 8.1% of patients initially diagnosed as having PD were found to have an alternate diagnosis.
Table 1  Differential diagnosis of parkinsonism

Primary neurodegenerative disorders with parkinsonism

Inherited:
1. Parkinson’s Disease (α-synuclein, Parkin, Park 3-10, NR4A2)
2. M. Alzheimer
3. M. Huntington
4. Spinocerebellar atrophies
5. Neuro-acanthocytosis
6. Dopa-responsive dystonia
7. Dentato Rubral Pallidal Luysian atrophy
8. Pantothenate kinase-associated neurodegeneration
9. Familial depression, alveolar hypoventilation and parkinsonism
10. Neuronal intranuclear inclusion disease

Sporadic:
1. (idiopathic) Parkinson’s Disease
2. Parkinson “plus” syndromes
   * Progressive Supranuclear Palsy
   * Multiple System Atrophy
   * Cortical Basal Ganglionic Degeneration
   * Dementia with Lewy Bodies
   * M. Alzheimer
   * M. Pick
   * ALS-Parkinsonism-dementia of Guam
   * Hemiparkinsonism with hemiatrophy

Secondary disorders with parkinsonism

Inherited:
1. M. Wilson
2. M. Gaucher
3. GM1 gangliosidosis
4. Chediak-Higashi syndrome

Sporadic:
1. Toxic (CO, CS₂, manganese)
2. Hepatocerebral degeneration (non-Wilsonian)
3. Endocrine (hypothyroidism, hypoparathyroidism)
4. Mass lesions (AV malformations, neoplasm)
5. Vascular (vasculitis, infarction, lacunar state)
6. Trauma
7. Autoimmune or inflammatory disease
8. Lack of substrate (hypoxia, hypoglycaemia)

Others:
1. Medication induced (direct or withdrawal)
2. Normal pressure hydrocephalus
Routine imaging of the brain seems not helpful in confirming the clinical diagnosis of PD, although occasionally PD patients show an increased signal from the substantia nigra on conventional T2-weighted MRI sequences. Functional imaging techniques, like Positron Emission Tomography (PET), provides a means of assessing dopamine terminal functioning or specific cerebral glucose metabolism in vivo, and allows to detect preclinical and clinical PD. Several biochemical markers have been tested as indicators for dopamine deficiency, mostly in the cerebrospinal fluid (CSF). Overall, the sensitivity and specificity of homovanillic acid (HVA), noradrenaline and 3-methoxy-4-hydroxyphenylethylglycol in cerebrospinal fluid, and HVA in serum are too low to use as preclinical or clinical markers for PD.

IV Prevalence and incidence

PD is the commonest neurodegenerative disease after M. Alzheimer, and it is estimated that in the Netherlands approximately 40.000 people suffer from PD. However, prevalence estimates of PD in the literature vary widely, merely because of differences in diagnostic criteria and in the age distribution of the study population, and ranges from 150-300 per 100.000 population. A population-based cohort study in a general elderly population in the Netherlands showed increasing prevalence of PD with age, being 1.0 % for those over 65 to 4.3 % in those over 85 years of age. Recently the results of 7 population-based studies were examined separately and pooled to obtain estimates of PD prevalence. The overall prevalence in persons 65 to 89 years ranged from 1.8-2.6 %, being the lowest among Asians and African blacks and highest among whites. PD occurs throughout the world in all ethnic groups and affects both sexes almost equally. An overall estimated annual incidence of PD is 12 cases per 100.000.

V Etiology and pathophysiology

PD is characterised by the progressive death of selected heterogeneous populations of neurons, including dopaminergic neurons in the substantia nigra pars compacta (SNpc). The loss of dopamine-containing neurons in PD affects different parts of the nigral complex to different degrees, the most severe loss occurring in the ventrolateral part of the SNpc. Nigrostriatal degeneration leads to (severe) dopamine deficit in the striatum, and this process follows two regular characteristic inter- and subregional patterns: first the putamen loses considerably more dopamine than the caudate, and within the putamen the caudal portions are more depleted of dopamine than the rostral portions. In the caudate this rostrocaudal gradient goes in the opposite direction. It is estimated that at least 30-50 % of nigral cell loss has occurred at the onset of PD symptomatology, which percentage exceeds over 80 % in the advanced disease state.
Being a widespread degenerative illness, PD affects the central, peripheral, and enteric nervous systems. Components of the limbic system and the motor system have been shown to be particularly vulnerable to severe destruction. This damage is consistently accompanied by extranigral alterations, with predilection sites includes the entorhinal region, the second sector of the Ammon’s horn, and important subnuclei of the amygdala. In addition, the nucleus of the stria terminalis, components of the hypothalamus, all of the non-thalamic nuclei with diffuse projections to the cerebral cortex, and most of the centers regulating autonomic functions exhibit severe lesions. Afflicted neurons eventually produce Lewy bodies (neuronal cell bodies, the histological hallmark of PD) in their perikarya and Lewy neurites in their neuronal processes.

The precise mechanisms responsible for progressive cell death in PD are largely unknown. Several mechanisms have been proposed, including oxidative stress and free radical damage, mitochondrial (complex I) deficiency, glutamate excitotoxicity and inflammatory responses. Cells may die by necrosis, involving the disintegration of a cell and its organelles and subsequent removal by phagocytosis. Increasing, but controversial, evidence suggests that neuronal death may result from apoptosis, characterised by chromatin condensation, DNA fragmentation and cell shrinkage without an inflammatory response, which may be programmed or occurs in response to a toxic stimulus. Further research into the etiology of PD is likely going to show that multiple environmental and genetic factors are involved, and that PD results from the combined effect of environmental exposure, genetic susceptibility and complex genetic-environmental interactions. Most epidemiological studies support the role of pesticide exposure in PD, whereby rural living, drinking well water and farming activity may be compound risk factors. Also an inverse relationship between smoking and the risk of PD is suggested, although such an association is not confirmed in all studies. Finally, there is increasing evidence for a genetic component in the cause of PD, and the recent identification of several genes and additional loci associated with inherited forms of PD suggest that genetic factors can influence the susceptibility to the disease. By now at least 8 defined genetic loci are associated with autosomal dominant or recessive, familiar, PD, wherein thus far 5 causative mutations have been identified. The first protein implicated in familial PD was α-synuclein, a brain protein of unknown function. Since α-synuclein aggregates in Lewy bodies, and these inclusion bodies are present in sporadic and familial PD, this protein may play a substantial role in both genetic and sporadic forms of the disease. However, mutations in the gene encoding α-synuclein (which is localised on chromosome 4q21) are a very rare cause of sporadic PD. Finally these findings have led to a general hypothesis that the pathogenesis of PD involves the abnormal folding, aggregation and deposition of α-synuclein as key steps in mediating neuronal dysfunction and degeneration.

VI The basal ganglia: a pathophysiologic PD model

The basal ganglia (striatum, pallidum, subthalamic nucleus and substantia nigra) are crucial to function in the motor and cognitive domains, and are usually regarded as
components of several largely segregated basal ganglia-thalamo-cortical circuits serving motor, oculomotor and cognitive functions. In models of basal ganglia function in PD (see figure 1), loss of dopamine leads to a shift of balance within these circuits: in the “motor circuit” modulation via dopamine D1 and D2 receptors within the striatum (putamen) leads to overactivity of the subthalamic nucleus (STN) and finally results in decreased activity of thalamocortical projection neurons. It is postulated that this results in decreased facilitation of cortical motor areas and subsequent development of akinesia and bradykinesia in PD. However, these models do not account for a variety of anatomical, physiological, experimental and clinical findings.

Figure 1  Influence of dopamine on striatal output pathways

Acb = nucleus accumbens; Caud = nucleus caudatus; GPe = external pallidum; GPi = internal pallidum; MC = primary motor cortex; MD = nucleus mediodorsalis; MEA = midbrain extrapyramidal area; O = occipital cortex; P = parietal cortex; PFC = prefrontal cortex; Put = putamen; sc = sulcus centralis; SNC = substantia nigra pars compacta; SNR = substantia nigra pars reticulata; STN = nucleus subthalamicus; T = temporal cortex; VA = nucleus ventralis anterior; VL = nucleus ventralis lateralis; VP = ventral pallidum; VTA = ventral tegmental area

B Treatment of M. Parkinson

I Introduction

Current strategies on treatment of PD are basically focussed on control of motor symptoms of the disease and prevention or treatment of the complications of symptomatic agents. Symptomatic treatment of PD mainly includes replacement or mimicking of dopamine (dopaminergic therapy) and functional (stereotactic) neurosurgery. However, since PD progresses over time a major therapeutic aim nowadays is the limiting or halting of the disease process. Neuroprotective therapies in PD can be defined as those medical or surgical interventions that favourable alter the underlying etiology or pathogenesis and thus delay the onset or slow dopaminergic decline. Neuroregeneration, the salvage of dying dopaminergic neurons, may be part of the process of neuroprotection. Finally, neurorestauration is the process of increasing the numbers of dopaminergic neurons by cell implantation or the use of nerve growth factors.

II Dopaminergic therapy

Current drug therapy in PD is symptomatic and primarily aimed at restoring dopaminergic function in the striatum. Levodopa, in combination with a peripheral decarboxylase inhibitor, is the single most effective drug for the symptomatic treatment of PD and its use is associated with decreased morbidity and mortality. Levodopa is most successful during the first years of treatment, and this period is known as the levodopa “honeymoon”. Although usually well tolerated initially, the chronic administration of oral levodopa is often associated with significant motor complications like response fluctuations. Major subtypes of these fluctuations include “wearing off” (shrinkage of duration of levodopa dose-induced benefit), “on-off” (sudden, unpredictable loss of levodopa effect) and “on-dyskinesia” (chorea at peak dose of dopamine concentration). The prevalence of these motor features increases with the duration of exposure to levodopa, occurring in approximately 50% of PD patients who received levodopa for more than 5 years. It is believed that these motor phenomena may be caused by a complex combination of central pharmacodynamic (loss of dopamine storage sites as PD progresses) and peripheral pharmacokinetic (delayed absorption of levodopa in the duodenum and pulsatile levodopa administrations) mechanisms. Prescribing controlled-release levodopa has shown to be associated with a lower incidence of motor fluctuations and dyskinesia. Despite major advantages, levodopa has no impact on several motor features, including speech, gait, posture and balance, and tends to aggravate non motor features like hallucinations, cognitive impairment and orthostatic hypotension.
Dopamine agonists exert their antiparkinsonian effects by acting directly on postsynaptic dopamine receptors and mimic the endogenous neurotransmitter. Apomorphine was the first dopaminergic agonist synthesised in the 19th century, and in 1951 Schwab noted that apomorphine injections caused marked improvement in PD patients. In 1974 Calne et al. reported the beneficial effects of bromocriptine, an ergot derivative, as add-on therapy to levodopa in PD, and in 1982 pergolide, also an ergot derivative, proved to be effective as levodopa adjunct in PD patients with motor complications. In 1997 another 2, non ergot, dopamine agonists were introduced in Europe as potent antiparkinsonian drugs: pramipexole and ropinirole. Nowadays dopamine agonists are basically used as monotherapy (especially in de novo patients) and as adjunct to levodopa. For PD patients requiring initiation of symptomatic therapy, either levodopa or a agonist can be used, although levodopa provides superior motor benefit but seems associated with a higher risk of dyskinesia.

Despite the initial outstanding benefit, long-term levodopa and dopamine agonist therapies do not solve all the problems faced by PD patients. Especially in advanced disease not all parkinsonian motor features can adequately be controlled with dopaminergic medication. Furthermore, PD is not just a motor disorder. Dysfunction of autonomic, cognitive and psychiatric systems frequently accompany PD and these non motor features tend to be poorly responsive to dopaminometica or may even be worsened by antiparkinsonian medication.

III Surgical treatments

History and targets

Surgical treatments as possible therapy for PD have been performed since the beginning of the 20th century. The first neurosurgical operation for relief of parkinsonism was performed by the Frenchman Leriche in 1912. By performing a bilateral posterior rhizotomy of lower cervical radices moderate tremor suppression was achieved. Since an unwanted but associated loss of voluntary motor function accompanied this treatment, it soon was abandoned. After Bucy and Case in 1939 extirpated the Brodmann’s areas 4 and 6 in a patient with posttraumatic rest and intention tremor, neurosurgeons started to perform cortical ablations. Meyers became the first to perform an operation in the basal ganglia in 1939 by extirpating the almost entire head of the caudate nucleus in a postencephalitic parkinsonian patient. In addition he placed lesions in other extrapyramidal structures like the pallidofugal fibers, which relieved tremor and rigidity in 60 % of PD patients. The development of stereotactic instruments, which already had been designed initially by Clarke and Horsley in 1906, and stereotaxis atlases, first introduced by Spiegel and Wycis in 1952, permitted more accurate target localisation and fewer side effects and subsequently the application for stereotactic surgery increased. Were initially the inner segment of the globus pallidus...
and the ansa lenticularis the main targets for surgery, several groups (e.g. Leksell) preferred attacking the posteroverentral pallidum. Since Cooper in 1958 noted that lesions placed within the thalamus provided similar effects and less side effects, thalamotomy became the favourite surgical procedure in relieving PD tremor in the late 1950s and 1960s.

With the introduction of levodopa in 1969 the demand for surgery declined. In the 1970s and 1980s surgical procedures were rarely performed, but because of insufficient relief of tremor by levodopa, thalamotomy regained popularity as surgical target.

Advancements in understanding of the pathophysiology of PD, based on models of basal ganglia function, led to renewed surgical procedures in the 1990s. In 1992 Laitinen described 38 PD patients in whom he had performed a lesion of the posteroverentral region of the internal part of the pallidum (GPi), following the original concept of Leksell. Based on these results several groups began to perform posteroverentral GPI pallidotomy in PD. The most consisted finding in these studies has been the dramatic improvement in contralateral dyskinesia, while results with respect to parkinsonism were less striking. In addition, side-effects of bilateral pallidotomy largely restricted surgery to unilateral procedures, and long term results of pallidotomy on persistent benefit are variable.

Deep Brain Stimulation (DBS), introduced by Heath et al in 1950, was based on the common effect of tremor suppression during high-frequency testing of the target site during ablative surgery with the electrode to confirm proper placement. DBS as a treatment for PD was introduced by Benabid et al in 1987 and was first tested in the ventral intermediate (VIM) nucleus of the thalamus in patients with tremor dominant disease. Although DBS of the VIM has now been shown to dramatically ameliorate contralateral tremor, most studies have not found significant benefit in other PD symptoms. The major advantages to DBS is that, unlike ablative surgery, it permits a bilateral procedure, its side-effects associated with stimulation are reversible, and adjustment of stimulation parameters maximises benefits and minimises adverse events. Because clinical efficacy of thalamus-DBS in PD was limited to tremor suppression only, interest in the late 1990s shifted to DBS of the GPI and the subthalamic nucleus (STN). Based on extensive electrophysiological and metabolic studies indicating overactivity of GPI and STN in animal PD models and PD patients, DBS of these structures offered an opportunity to functionally inhibit their overactivity without making a destructive lesion. In addition, high-frequent stimulation of the STN in an animal model of PD, the MPTP-lesioned monkey, decreased tremor, rigidity and akinesia successfully. Since then several studies on bilateral GPI-DBS showed alleviation of all PD motor symptomatology. Limousin et al (1995) were the first to describe the beneficial efficacy of STN-DBS in 3 PD patients with advanced disease. Like GPI-DBS, STN-DBS improved all cardinal motor features of PD, but no randomised, blinded clinical trial has shown superiority of one target over the other yet.
By now, the precise mechanism as to how DBS exactly works is not known\textsuperscript{73}. It is believed that DBS suppresses the neuronal firing pattern in the target area either directly or by inducing the release of inhibitory transmitters; other possibilities include back firing, “jamming” and depolarisation blockage\textsuperscript{80}.

**Chronic stimulation of the subthalamic nucleus**

A. The subthalamic nucleus

The subthalamic nucleus (STN) was “discovered” by the French investigator Jules Bernard Luys\textsuperscript{81}, and subsequently he published his knowledge in his book “Studies on the structure, functions and diseases of the nervous system” in 1865. The STN is a small biconvex-shaped structure surrounded by dense bundles of myelinated fibers (see figure 2). Its anterior and lateral borders are adjacent to the internal capsule and rostromedially the STN lies adjacent to the Fields of Forel. Posteromedial it is adjacent to the red nucleus and its ventral limits are the cerebral peduncle and the ventrolateral substantia nigra\textsuperscript{82}. Dorsally the STN is limited by the fasciculus lenticularis and zona incerta. The volume of the STN is approximately 175\textsuperscript{3} in humans (Levesque, 2005).

![Figure 2 Coronal brain section representing the major anatomical structures and fibre tracts associated with the subthalamic nucleus](image-url)

AL = ansa lenticularis; CP = cerebral peduncle; FF = Fields of Forel; GPe = globus pallidus externus; GPi = globus pallidus internus; H1 = H1 Field of Forel (thalamic fasciculus); IC = internal capsule; LF = lenticular fasciculus (H2); PPN = pedunculopontine nucleus; Put = putamen; SN = substantia nigra; STN = subthalamic nucleus; Thal = thalamus; ZI = zona incerta.

Functionally the STN is subdivided into a limbic and associative part (the medial portion of the rostral two-thirds) and a portion related to motor circuits (dorsal part of the lateral portion of the rostral two-thirds) within the basal ganglia. Most of the cortical afferents to the STN arise from the primary motor cortex, (pre-) supplementary motor area and the dorsal and ventral pre-motor cortices and predominately innervate the dorsal part. The ventromedial portion of the STN receives afferents from the frontal eye field (area 8) and the supplementary frontal eye field. However, its major afferents comprises the projection from the external pallidum, and, to a lesser extent, thalamus (parafascicular and centromedian nuclei) and brainstem (substantia nigra, pedunculopontine nucleus, tegmental nuclei, dorsal raphe nucleus). The major efferent projections from the STN are mainly directed to both segments of the globus pallidus, substantia nigra and striatum. The STN innervates both components of the substantia nigra: although most fibers innervate the SNpr, some ascend and reach the SNpc, comprising one mechanism responsible for the regulation of dopamine release.

The main excitatory drive to the STN is provided by excitatory amino acids, and NMDA and AMPA receptors have been described in STN neurons. It is believed that these multiple glutamate receptor subtypes mediate a complex signalling pathway in the STN. GABAergic activity also has a major role in aspects of STN physiology by modulating its firing rate and pattern of neuronal activity. The impact of GABA on the STN is related to the initial membrane potential of the cells, which is strongly dictated by pallidal afferents. It is estimated that in vivo 55-65% of the STN neurons fire irregularly, whereas 15-25% fire regularly and 15-50% present bursting activity in non-human primates, and the average firing rate of STN neurons is 18-25 Hz. 30-50% of STN neurons are related to movement, and most of them are localised in the dorsal half of the nucleus and are activated by passive or active movement of contralateral joints. In addition, 20% of the neurons are responsive to eye fixation or visual stimuli, and these are primarily found in the ventral STN. The STN is currently thought to play a prominent role in the pathophysiology of PD. Metabolic, electrophysiological and behavioural studies performed mainly in the MPTP monkey model of PD revealed an increase in neuronal activity of the STN and its main output basal ganglia nuclei. In the current model of the basal ganglia in PD, STN hyperactivity has been attributed to the underactivation of the globus pallidus externus (GPe) due to abnormalities in the indirect pathway elicited by dopamine depletion in the striatum. However, recent studies suggest that other brain regions, e.g. the cerebral cortex and thalamus, may also be responsible for increased STN activity in PD. The pathological STN drive thereby modifies the overall activity in output structures like SNr, Gpi, GPe and PPN, and disrupts the normal physiology of the basal ganglia. In the SNpc, STN glutamatergic overactivity is predicted to enhance bursting activity and increases the release of dopamine. Although this has been considered an initial compensatory mechanism after dopamine depletion, this excessive glutamate release may lead to excitotoxic damage within the SNpc and could promote a further loss of dopaminergic neurons.
B. Chronic bilateral STN-DBS

Limousin et al were the first to describe the clinical efficacy of bilateral STN-DBS in 3 advanced PD patients, suffering from unpredictable motor fluctuations. At 3 months follow up, the UPDRS motor subscore (part III) in off-medication condition had improved by 84%, 75% and 42% respectively. The individual levodopa dosage could be reduced by 50% and 40% in the first 2 patients, and was withdrawn in the third in the following months postoperatively. They subsequently extended their data set and in 1998 published the results of bilateral STN-DBS in 24 patients with advanced PD, suffering from disabling motor fluctuations. After 1 year of STN-DBS the motor scores (as examined by the UPDRS part III in off-medication condition) improved by 60%, including subscores on akinesia, tremor, rigidity and gait. The mean dosage of dopaminergic drugs was reduced by half, and, consequently, levodopa induced dyskinesia significantly diminished. On average, neuropsychological assessment showed no change after surgery, despite worsening of cognitive impairment in 1 patient. The most serious adverse event was an intracerebral hematoma (1 patient) and a subcutaneous infection developed at the site of the extension lead in 1 patient. In 8 patients transient adverse effects on mental status (hallucinations, confusion) developed after surgery, which lasted for a maximum of 2 weeks.

Since then several institutions published their beneficial results on bilateral STN-DBS in PD, of which the main results are emphasised in table 2. It can be concluded that bilateral STN-DBS substantially improves all levodopa responsive PD motor features significantly up to (at least) 5 years after surgery. Since STN-DBS mimicks the effect of levodopa, it allows dopaminergic therapy to be (partially) discontinued postsurgically. All studies have shown a significant improvement of time spent with disabling dyskinesia or diminishing of severity of dyskinesia. In addition, the improvement in on-period dyskinesia might be mainly due to this decrease in levodopa daily dose, although a specific effect of stimulation on motor fluctuations itself is also argued. Since DBS is an elective procedure, the disability of the patient must be profound to justify the risk of surgery (permanent morbidity and mortality of STN-DBS: 1-3%) . Most important side effects of the STN-DBS procedure are mild and transient, and consist of direct surgical complications (e.g. asymptomatic intracerebral bleeding detected on MRI, wound healing problems) or postoperative confusion. Persistent body weight gain has consistently been reported after STN-DBS, and in some patients the procedure can induce cognitive decline or behavioural changes. The latter is probably caused by direct stimulation effects of DBS on the STN or its adjacent structures, which have strong connections with limbic structures. As a result, demented patients and patients suffering from depression or levodopa-induced psychosis are considered not to be suitable candidates for STN-DBS, although clear-cut studies are lacking.
Finally, there is much debate about as to how STN-DBS exerts its efficacy. The immediate reduction of patients’ rigor and rest tremor is believed to result from a depolarization block of the neurons surrounding the electrode tip or from a disruption of pathologically synchronised neural firing pattern by additional high-frequent stimuli (neural jamming). In contrast, the amelioration of akinesia and the induction of dyskinesia by STN-DBS takes minutes up to hours or even weeks to occur. This observation, as well as the clinical experience that motor improvement achieved by STN-DBS resembles those achieved after levodopa, raised questions about a delayed increase of striatal dopaminergic transmission following DBS. In addition, the area encompassing the dorsal STN and the axons dorsal to the STN seems the most effective target for the amelioration of PD symptoms after successful STN-DBS. Since the nigrostriatal tract

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* in months
# reduction in % (in off-medication on-stimulation condition) of pre-operative score
+ reduction in % of pre-operative dopaminergic therapy
runs in close apposition to this dorsal surface of the STN, it also is subject to the effects of DBS. It is hypothesized that one possible effect of DBS could be the activation of those nigrostriatal axons arising from the SNpc, with the release of endogenous dopamine in the striatum. However, recent Positron Emission Studies successively failed to show a substantial increase of striatal dopamine release after STN-DBS in PD.

IV Neuroprotective, neurorestaurative and neuroregenerative therapy

In the absence of an identified biological marker in sporadic PD, prevention of dopaminergic cell decline is aimed at slowing, stopping or reversing neuronal death. It is obvious that any neuroprotective therapy for PD should ideally be introduced before the onset of clinical manifestation, or at least as soon as possible when clinical features of PD become manifest.

The first drugs to be studied in PD were antioxidants. In 1993 the DATATOP study evaluated the antioxidant vitamin E and the MAO-B inhibitor deprenyl as putative neuroprotective therapy in PD. While no beneficial effect of vitamin E was detected, deprenyl seemed to slow disease progression. However, since deprenyl also exerted symptomatic efficacy, interpretation of the study results seemed confounded; subsequently, an additional study on deprenyl versus placebo showed confounding results too. In a double-blind placebo-controlled pilot study coenzyme Q10 (an enhancer of ATP production and antioxidant) was studied as a putative neuroprotective agent in PD in 2002. Although a reduced rate of deterioration of patients’ motor function during the study course was noticed, again an unexpected symptomatic effect of the drug confounded study interpretation. Dopamine agonists also exhibit neuroprotective potency as antioxidants, and in addition decrease dopamine turnover and thereby reduce the generation of free radicals. In laboratory studies dopamine agonists protected dopaminergic and nondopaminergic neurons from toxins in PD models. Thus far 2 neuroimaging studies (CALM-PD and REAL-PET) on 2 dopamine agonists (pramipexole and ropinirole) have been performed testing the capacity of these agonists to modify disease progression in PD. Both studies demonstrated that dopamine agonists were associated with a significant delay in the rate of tracer uptake decline, but, however, neither study showed a corresponding clinical benefit. Also pharmacological differences in the capacity of these drugs to regulate neuroimaging tracer dynamics have made the interpretation of study results controversial.

The first promising attempt to treat PD patients by use of cell transplantation in 1985 involved striatal infusion of autologous adrenal medullary cells. However, later studies showed poor results with no improvement in patients’ motor disability. Following several unblinded but promising case series of human foetal cell transplantation, in 2001 Freed published results on fetal nigral cell transplantation versus sham surgery in 40 PD patients. Again, no significant improvement was established, although younger patients showed a small benefit. A double-blind controlled trial of
bilateral fetal nigral transplantation in PD by Olanow in 2003 showed similar disappointing results. A small, unblinded study using xenogenic neural transplants of embryonic porcine ventral mesencephalic cells in PD showed small motor benefit in study patients. Controlled trials with larger graft doses are needed to assess this procedure's efficacy in the future. Studies on embryonic-stem-cell transplantation are in the early stages of development.

The use of neural trophic factors has been proposed as a method of promoting the restoration and maintenance of degenerating dopaminergic cells. A large double-blind, placebo controlled trial of intraventricular infusion of glial-cell-derived neurotrophic factor showed no benefit at 8 months follow-up. However, since autopsy results suggested that the neurotrophic factor had not reached the target area in this study, direct infusion of glial-cell-derived neurotrophic factor into the putamen showed indeed a modest motor benefit in patients in another study. Recently a randomised, double blind, placebo-controlled phase II study has been stopped because of lack of efficacy (Amgen Inc, 2004).

C STN-mediated excitotoxicity in PD: a target for neuroprotection

I Introduction

Essential to the concept that the STN might contribute to neurodegeneration in PD is the existence of a glutamatergic pathway between the STN and the SNpc. Anatomical studies clearly demonstrated these glutamatergic projection in several animal models of PD. In addition, electrophysiologic studies confirm that the STN exerts an excitatory effect on dopamine neurons in the SNpc, which is mediated by glutamate acting on NMDA receptors. Theoretically, increased STN activity in PD may result from reduced inhibition, increased excitation or both. It is believed that a loss of inhibitory drive of the external pallidum (GPe), secondary to dopamine depletion, to the STN is the major mechanism responsible for excess firing of the STN in PD. Because STN neurons use glutamate as a neurotransmitter, there is reason for concern that excess neuronal firing in the STN might lead to excitotoxic damage in its target structures, especially the SNpc. Although the precise molecular mechanisms involved in this process are unresolved, excitotoxicity primarily involves an NMDA-mediated rise in intracellular Ca. In normal neurons there is an ATP-dependent Mg blockade of NMDA channels. As a result, physiologic concentrations of glutamate do not excessively activate NMDA receptors or promote calcium influx. However, in PD the release of high concentrations of glutamate could overcome this blockade and stimulate NMDA receptors inducing an alteration in calcium influx. In addition, a bioenergetic cellular defect due to primary mitochondrial (complex I) dysfunction in PD results in a loss of the voltage dependent Mg blockade of NMDA receptors and permits even physiologic concentrations of glutamate to induce excitotoxicity. Finally, lesions of
the STN have shown to be neuroprotective in several experimental models of PD. Pallett et al (1996) showed that chemical ablation of the STN prevented dopaminergic nigral degeneration in 6-OHDA lesioned rats\textsuperscript{128}. In their study the number of tyrosine hydroxylase-immunoreactive cells in the SNpc was not significantly different on the STN-lesioned side compared to the control side. In 1999, Nakao et al showed an attenuated progressive loss of nigral TH-positive neurons after chemical STN ablation in 3- nitropropionic lesioned rats\textsuperscript{129}.

II The excitotoxic hypothesis in PD

Rodriguez et al speculated that the STN plays a major role in the pathogenesis of PD according to the following sequence of events\textsuperscript{124}:

1. An inherited or acquired mitochondrial defect and / or oxidant stress make dopaminergic SNpc neurons susceptible to noxious stimuli and vulnerable to degeneration or even apoptosis; as a result a small portion of these cell actually degenerate
2. The loss of dopaminergic neurons causes a reduction in striatal dopamine, which results in a reduced dopaminergic inhibition of D2 striatal neurons, increased inhibition of the GPe, and finally disinhibition of the STN, with increased activity in excitatory STN neurons
3. Enhanced STN neuronal firing produces excessive glutamate release in the SNpc
4. Increased glutamate release in the SNpc leads to a further loss of dopaminergic neurons and reduction in striatal dopamine
5. Increased degeneration of SNpc neurons and dopamine depletion induces further disinhibition of the STN
6. Finally, a vicious cycle is created in which dopamine neuronal degeneration in the SNpc leads to further STN disinhibition, and STN overactivity leads to excitotoxic damage in remaining SNpc neurons
7. When degeneration of SNpc neurons and loss of striatal dopamine reach a critical level, the signs and symptoms of PD emerge

This hypothetic model illustrates how disinhibition of the STN and resultant excitotoxicity could contribute to the neurodegenerative process in PD, regardless of the specific, and yet unknown, etiology. A consequence of this hypothesis is the aim of providing a neuroprotective therapy in PD that slows the rate of disease progression by reducing STN overactivity. Since it is estimated that approximately 30-50 % of dopamine neurons already have degenerated by the time the first signs and symptoms of PD appear\textsuperscript{130}, any “protective” treatment should be introduced as early as possible in the course of the disease. Theoretically, such a treatment could involve dopamine agonists (by restoring dopaminergic tone), agents that inhibit glutamate release, selective NMDA receptor antagonists (to block glutamate release) and surgical interventions that inhibit neuronal firing of the STN.
Since all pharmacological therapies thus far have failed to show a neuroprotective effect in PD in vivo, surgical treatments that inhibit STN firing represent an additional and promising option to attenuate progressive dopaminergic cell decline. In addition, the clinical introduction of DBS of the STN in PD has yet provided an opportunity to functionally inhibit the STN.

FDOPA-PET and M. Parkinson

I Positron Emission Tomography

Positron Emission Tomography (PET) is an imaging method used to track the regional distribution and kinetics of chemical compounds labelled with short-lived-positron-emitting isotopes in the living body\textsuperscript{131}. Positron imaging was initially suggested by Wrenn et al in 1951\textsuperscript{132}. At that time, cyclotrons became available for the production of short-lived radioisotopes and initial studies with carbon-11 (\textsuperscript{11}C), nitrogen-13 (\textsuperscript{13}N) and fluorine-18 (\textsuperscript{18}F) were performed. PET studies are carried out by administering a tracer labelled with a positron-emitting isotope with a short half-life generated by a cyclotron. The tomographic image in PET is formed by recording of two 511 keV photons emitted in positron decay with a circumferential array of radiation detectors. Since these photons are simultaneously emitted 180° apart, a special coincidence technique is used to define the origin of emission. These data are processed through a conventional reconstruction algorithm to form the tomographic images of the tracer concentration in tissue. While the first PET scanner (PETT II) provided a single tomographic image plane with restricted spatial resolution, modern scanners have multiple rings of detectors to allow the simultaneous collection of multiple planes of imaging\textsuperscript{133}. In addition to conventional datasets of regional tracer uptake collected in two-dimensional (2-D) mode, nowadays software is available allowing PET data to be acquired in a 3-D mode, which have led to a further increase in spatial resolution\textsuperscript{134}. The integrity of the presynaptic nigrostriatal dopaminergic projection can be studied in vivo with radiotracers whose striatal uptake reflects a measure of structural as well as the biochemical integrity of the dopaminergic nerve terminals (FDOPA) or dopamine transporter density (FP-CIT, \(\beta\)-CIT)\textsuperscript{135}.

II FDOPA-PET

PET was the first technology that enabled direct measurement of components of the dopamine system in the living human brain\textsuperscript{131}. In 1983 Garnett et al reported on the successful application of 6-\textsuperscript{18}F\textsuperscript{]-fluoro-L-3, 4-dihydroxyphenylalanine (FDOPA) for PET studies of nigrostriatal dopaminergic neurons in living man\textsuperscript{136}, while in 1986 Leenders et al administered FDOPA in trace amounts to healthy controls and PD patients\textsuperscript{137}.
Since then FDOPA-PET has provided an objective means of assessing the functional integrity of the presynaptic nigrostriatal dopaminergic projections in vivo. It estimates the rate of enzymatic decarboxylation of FDOPA to F-dopamine as well as its storage in dopaminergic nerve terminals. Although striatal FDOPA uptake is not a measurement of endogenous dopamine synthesis, it is highly correlated with dopamine cell counts measured in post mortem specimens. FDOPA-PET can sensitively discriminate PD from normal populations, and several studies reported a marked decrement of striatal FDOPA uptake in PD, which is specifically more pronounced in the putamen than in the caudate. Various studies have demonstrated that specific FDOPA uptake in the putamen of PD patients is on average 40% of control values and in caudate 60%. In early PD these values can be considerably higher and for caudate will often be normal. At very late stages of the disease a 60-70% or more drop in striatal uptake in PD may be observed, caudate being less severely affected than putamen with however a significant uptake decrement in advanced stages of the disease. Initially, FDOPA-PET has also been used to differentiate among parkinsonian syndromes (e.g. Multi System Atrophy, Progressive Supranuclear Palsy). Subsequent studies have shown that differences on the presynaptic dopaminergic level are not sufficiently precise to categorise individual cases of disease.

III FDOPA-PET studies on the rate of PD progression

FDOPA-PET provides a potential means of objectively monitoring disease progression in PD. The first reported PET study was by Bhatt (1991) who measured striatal FDOPA uptake on 2 occasions over 3 years in groups of 9 PD patients and 7 normal subjects. The mean interval between the scans was 3.3 years for the group with idiopathic parkinsonism and 3.9 years for the control subjects. Both groups showed a statistically significant 5% reduction of striatal FDOPA uptake over the study interval and the rate of decrease was almost identical in each group. They inferred that the usual rate of loss of integrity of the dopaminergic nigrostriatal pathway in PD patients was slow and the rate of change between the two groups was comparable. A follow-up study was performed by Vingerhoets et al. They performed FDOPA-PET on two occasions, 7 years apart, on 16 patients with PD (mean age 51 years, mean disease duration 4.5 years) and 10 normal controls (mean age 54 years). Their PET index ((striatal-occipital)/occipital ratio) dropped by 1.7% per year versus the normals’ ratio 0.3%, and in addition the ratios in the PD group progressed significantly faster than the controls. However, one problem with the interpretation of study results was that large whole striatal Regions Of Interest were employed to analyse disease progression whereas the PD pathology primarily targets dopamine storage in the putamen only. Morrish et al, using an FDOPA influx constant (K), studied PD disease progression in a group of 10 patients with recent onset PD (mean age 53.7 years, mean disease duration 18 months), and a group of seven patients with established PD (mean age 60 years,
mean disease duration 71 months), using both clinical assessment and FDOPA-PET\(^{144}\). Results were compared with those of a group of 10 normal subjects (mean age 66 years). The mean annual rate of reduction in mean putamen $K_i$ in the PD patients was 12.5\% per annum, whereas the control group showed no significant change in $K_i$ over a mean of 32 months follow up. The rate of progression was more rapid in the recent onset compared with the established disease group but this did not reach statistical significance. Assuming a linear progression for the entire group they additionally estimated PD symptom onset with a mean preclinical period of 3.1 years. They successively extended their study in 1998 on 32 PD patients with PD (mean age 58 years, mean disease duration 39 months) using graphical ($K_i$) and ratio methods of analysis\(^{145}\). The mean annual rate of deterioration in specific putamen FDOPA uptake was 9\% from baseline scan (or 4.7\% of normal mean). Extrapolation of these data suggested that symptom onset occurred after a 30\% loss of dopaminergic terminal function and the estimated preclinical window was estimated to be 6 ± 3 years.

Finally, in 2001 Nurmi et al investigated the rate of progression in PD using FDOPA-PET in 21 PD patients\(^{146}\). FDOPA-PET was carried out twice at an approximately 5-year interval. The FDOPA uptake declined by the time of the second PET scan and the calculated annual rate of decline was 8.3\% of the baseline mean in the anterior putamen, and 10.3\% in the posterior putamen. In the caudate nucleus, FDOPA uptake decreased by 5.9\% of the baseline mean per year. They successively estimated the preclinical PD period being longest for the posterior putamen (6.5 years). In healthy controls no significant decline in FDOPA uptake in any striatal subregion was established.
Aims of the thesis

Since glutamate-mediated excitotoxicity is suggested to contribute to nigrostriatal degeneration in PD, the clinical introduction of STN-DBS in PD provided an opportunity to functionally inhibit STN activity and therefore decrease disease progression. The primary aim of this thesis was to prospectively determine disease progression in a population of PD patients after STN-DBS by means of repetitive FDOPA-PET. Is STN-DBS really “neuroprotective” in PD? In addition, we studied the clinical efficacy of STN-DBS on motor features in PD. Does STN-DBS “work” in our own PD study population? We also investigated the nature of the relationship between striatal dopamine depletion and cognitive functioning in PD. Does FDOPA-PET reveal the nature of basal ganglia dysfunction in patients’ cognitive impairment? Finally, we sought to determine the predictive value of the patients’ presurgical nigrostriatal status on motor efficacy of STN-DBS in PD using FDOPA-PET. Is the nigrostriatal dopaminergic deficit in PD related to surgical outcome?
References


Chapter 1


General introduction and aims of the thesis


General introduction and aims of the thesis


