The pathophysiology of motor symptoms in Parkinson's disease

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Abstract

This review focuses on some of the known and hypothetical pathophysiological mechanisms underlying the motor symptoms in Parkinson's disease (PD). Current views on these mechanisms have largely been influenced by models of basal ganglia functioning and dysfunctioning. These models have allowed to explain some clinical findings and to predict a number of results of basal ganglia surgery in movement disorders. However, neurophysiological studies as well as neurochemical data have broadened our vision on basal ganglia functioning and dysfunctioning in PD. Moreover, these more fundamental insights in basal ganglia functioning allow new concepts on the development of treatment strategies, and on the prevention of motor fluctuations in PD.

Introduction : the basal ganglia

In contemporary neuro-anatomy the striatum (putamen and caudate nucleus), the pallidum (internal and external), the subthalamic nucleus and the substantia nigra (pars compacta and reticulata) are considered the nuclei of the basal ganglia. Over the last few years it has been demonstrated that these nuclei play a key role in mediating motor and non-motor behaviour, cognition and emotion. The functions of the basal ganglia have been explained in terms of anatomy and connectivity, biochemistry and electrophysiology.

Several models of the functional anatomy of the basal ganglia have been proposed. The most familiar model was introduced in the 1980's (Alexander G. E. *et al.*, 1990 ; DeLong M., 1990). This model is based on the existence of separate parallel loops, mediating motor, cognitive and emotional functions, and running through the basal ganglia in a more or less uniform fashion (Fig. 1). In this review we will focus on motor function, unless otherwise specified.

In spite of the many criticisms raised and the obvious oversimplification of basal ganglia connectivity, this model has provided a framework that allowed to predict outcomes of lesions and of surgical procedures in extrapyramidal disorders (Obeso J. A. *et al.*, 2000b). Central in the description of the model is the existence of two pathways,

a direct and an indirect pathway, connecting the input nuclei of the basal ganglia, i.e. the striatum (caudate nucleus and putamen) with the output nuclei, the internal pallidum (GPi) and substantia nigra pars reticulata (SNr). These two pathways have opposite effects on the output of the basal ganglia : the direct pathway has a net positive effect on the basal ganglia output, while the indirect pathway has a negative effect. Dopamine released from striatal terminals of substantia nigra pars compacta (SNc) neurons has opposite effects on both pathways, resulting in a net release of thalamic output to cortical motor areas. In this way a release of motor programs and inhibition of unwanted movements can be balanced to result in finely tuned motor behaviour.

Both direct and indirect pathways originate in the matrix compartment of the striatum. Recently it was suggested that a third pathway, originating in the striosomal compartment of the striatum also exerts control over movement by means of its connections to the substantia nigra. This pathway might therefore control dopamine release according to variables such as experience and evaluation (Graybiel A. M. *et al.*, 2000). It is a well-known that dopamine release is dependent on the prediction of reward of an action (Walters J. R. *et al.*, 2000).

Apart from dopamine, several other neurotransmitters have been implicated in basal ganglia function (Fig. 1), the most important being glutamate and GABA. Finally, the electrophysiological properties of basal ganglia nuclei are complicated and differ substantially from one nucleus to another one. Tonic discharges can be interrupted by phasic alterations which are related to initiation or performance of movements.

Two important characteristics of basal ganglia function included in this classical model are convergence and segregation. Convergence refers to the fact that along the circuits the number of neurons decreases by each step, thus converging information following each relay. Segregation not only implies separation of the individual circuits along their path through the basal ganglia, but also the separation of information flow for motor functions
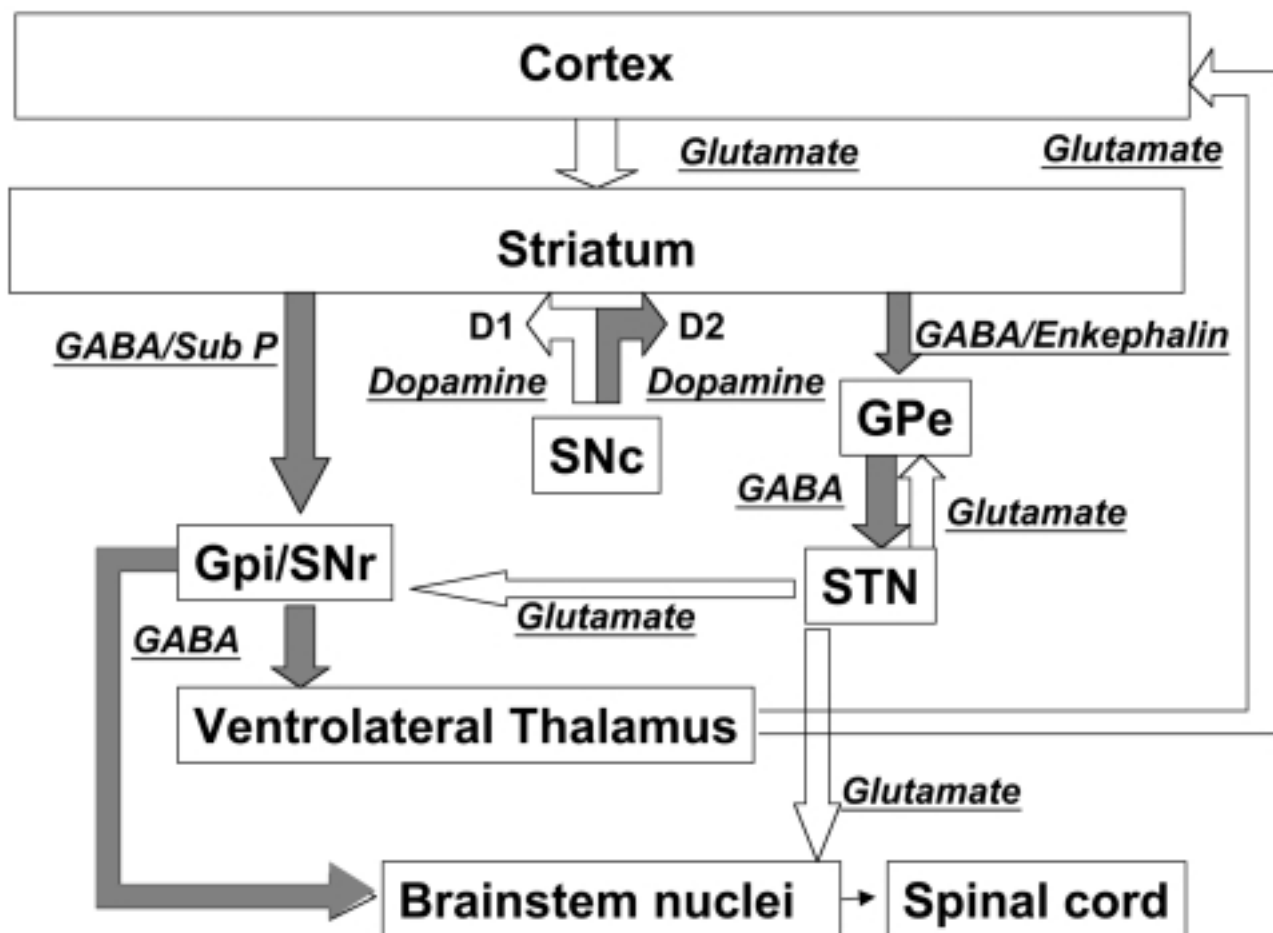
Fig. 1. — The model of basal ganglia functional anatomy as proposed by Alexander and DeLong. White arrows indicate an excitatory connection, dark arrows indicate an inhibitory connection. Neurotransmitters involved in these connections are indicated in italics. The existence of two pathways, a direct and indirect one, is indicated.

of individual parts of the body. The "focussing" hypothesis of basal ganglia function in movement is based on this segregation. According to this hypothesis the release of motor programs is focussed to a specific body part, while movements of surrounding body parts are inhibited by means of the indirect pathway.

An important consideration is the fact that basal ganglia output ultimately results in changes of cortical output. Electrophysiological studies have demonstrated that basal ganglia modulate spatiotemporal organisation of cortical activity implicated in the selection and propagation of adequate movement (Brown P. *et al.*, 1998). It appears that basal ganglia are implicated in coherence of muscle and cortical activity at higher frequency ranges (Salenius S. *et al.*, 2002). This leads to fusion of motor unit activities sufficient to sustain adequate force and speed of movement onset (Pfann K. D. *et al.*, 2001) ("scaling" – see below).

The consequences of dopaminergic deficit in Parkinson's disease

Following degeneration of the SNc dopaminergic neurons projecting to the striatum, several bio-

chemical and electrophysiologic changes can be predicted from the model. Many of these predictions have been confirmed by in vitro and in vivo findings in animal models and humans. A characteristic increase in firing rate of the GPi and STN has been found in MPTP-treated animals (Obeso J. A. *et al.*, 2000b). The consequence of this increased firing rate is an excessive activation of basal ganglia output nuclei, leading to inhibition of the thalamo-cortical and brainstem motor systems. This increase is reversed by administration of dopaminergic agents. Moreover pallidotomy and deep brain stimulation of the STN or GPi can induce clinical improvement in patients with PD (Obeso J. A. *et al.*, 2000b).

Electrophysiological studies in animal models have suggested that oscillatory activity may appear within the basal ganglia nuclei following dopaminergic depletion in the striatum. Studies of the electrical activity of neighbouring neurons have shown that coherence increases, which suggests a loss of segregation within the basal ganglia (Bergman H. *et al.*, 2002 ; Brown P., 2003).

From a biochemical point of view dopaminergic denervation of the striatum increases expression of preproenkephalin and D2 receptor mRNA in
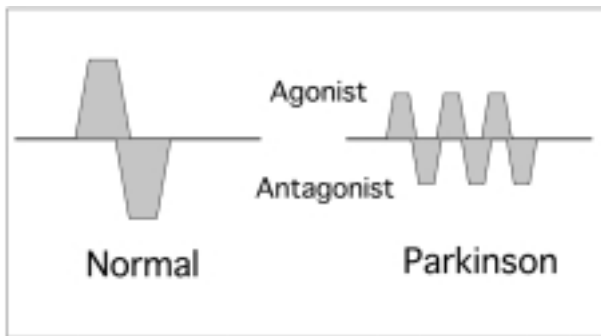
F<small>IG</small>. 2. — Schematic representation of EMG bursts in agonist and antagonist muscles during a reaching movement in normal controls and in PD. In normal controls the goal is reached by single agonist-antagonist mechanisms. In PD, agonist bursts are hypometric, requiring multiple bursts to reach the target (scaling).

neurons of the indirect pathway. Conversely in neurons of the direct pathway the expression of mRNA for the D1 receptor, substance P and dynorphin is decreased (Obeso J. A. *et al.*, 2000b).

Bradykinesia and hypokinesia

These cardinal features of parkinsonism point to a number of different alterations of movement. They refer to slowness of movement, reduced movement amplitude, disturbances of movement initiation, and decrease of spontaneous or associated movements (Berardelli A. *et al.*, 2001).

Bradykinesia and hypokinesia are commonly explained by the changes occurring in the basal ganglia as explained above. It is frequently quoted in this sense that PD patients are "driving while stepping on the brakes". Of course this is an oversimplification, which becomes more clear when these features of parkinsonism are analyzed in greater detail. It has been demonstrated manifold that PD patients have longer latency times before movement occurs, that they take longer before reaching appropriate forces to perform voluntary movements, and that movements are more frequently broken down in small steps, requiring multiple EMG bursts to reach a target (Berardelli A. *et al.*, 2001) (Fig. 2).

These changes can be explained in part by the results of studies of alterations in cortical activity in PD patients performing isometric contractions. It has been shown that coherence between cortical activity and muscular activity is decreasing in the higher frequency ranges (Salenius S. *et al.*, 2002). This leads to a defective fusion of motor units resulting in a slower recruitment of force, and an inappropriate generation of muscular force to reach a target. This might be implicated in the under-scaling of movement (hypometria), which is to be corrected by multiple bursts of muscular activity (Pfann K. D. *et al.*, 2001) (Fig. 2). Furthermore this might explain a well-known phenomenon, which is

the occurrence of an isometric tremor in PD patients, characteristically evoked by squeezing the fingers of the examiner. Indeed, if fusion of motor units does not occur appropriately when stronger forces are to be generated, this might lead to interruptions of motor activity, and hence isometric tremor. The frequency of this tremor is not correlated to the frequency of the resting tremor which may be present in the same patient (De Letter M. *et al.*, 2003 ; Salenius S. *et al.*, 2002).

Finally, alterations in sensory processing have been suggested to contribute to bradykinesia and hypokinesia. This suggestion is supported by the reduced amplitude of the frontal component of the somatosensory evoked potentials in PD (Abbruzzese G. *et al.*, 2003).

Tremor

Although text books teach us that the classical tremor of PD is a resting tremor, a variety of tremors can be found in PD (Deuschl G. *et al.*, 1998). Most frequently, a rest tremor and postural or kinetic tremor with equal frequency ranging from 4-7 Hz is found (classical parkinsonian tremor) although in the early stages and in severe akinetic-rigid symptoms higher frequencies may occur (Deuschl G. *et al.*, 2000).

Only two human conditions with resting tremor are known : PD and Holmes' tremor. Both conditions share the common factor of dopaminergic deficiency in the striatum (Brooks D. *et al.*, 1992). This would suggest that lesions of the SNc are indispensible for the occurrence of resting tremor. Many observations support this hypothesis, but the question is if dopamine deficiency is enough. Indeed, in primate models resting tremor can only be evoked by combined lesions in the SNc, the red nucleus and the cerebello-thalamic fibers (Deuschl G. *et al.*, 2000). PET studies have suggested the influence of serotonergic denervation in the origin of rest tremor (Doder M. *et al.*, 2003). Other PET studies of cerebral metabolism have pointed to cerebellar hypermetabolism in tremor, which was reverted by thalamic stimulation leading to tremor arrest (Deiber M. P. *et al.*, 1993). This suggests a mechanism originating in the cerebellum or its connecting systems, such as the oliva inferior.

In a clinical context, it is well known that dopaminergic suppletion is not always able to control parkinsonian tremor (Elble R. J., 2002). Moreover it has been argued that patients displaying tremor have a better prognosis as far as motor progression and development of mental deterioration is concerned (Deuschl G. *et al.*, 2000). Recent findings however have shed doubt on these dogmatically accepted statements (Vingerhoets G. *et al.*, 2003).

The pathophysiology of parkinsonian tremor remains a matter of debate. Peripheral influences, if

ever present, are minor and all available evidence points towards a central mechanism involved in the generation of the tremor in PD.

So-called tremor cells, displaying rhythmic activity linked to the tremor frequency have been found in several basal ganglia nuclei. Tremor cells are more frequently found in ventrolateral thalamic nuclei than in the internal pallidum and subthalamic nucleus. Rare tremor cells have been described in the external pallidum and none were detected in the striatum (Deuschl G. *et al.*, 2000). This suggests that convergence may be implicated in the generation and enhancement of tremor activity along the basal ganglia-thalamic pathways.

Another observation linking clinical and electrophysiological data is that although frequency of parkinsonian tremor may be very similar in different body parts, tremor activity is almost never coherent between limbs, which suggests that the basic rhythm might be an inherent characteristic of a patient's disturbed basal ganglia system, but the generators of the tremor might be different from one body part to another one (Deuschl G. *et al.*, 2000).

It has been suggested manifold that the thalamic motor nuclei are at the origin of parkinsonian tremor. A putative mechanism involves specific voltage-dependent calcium channels that are able to generate a spontaneous rhytmicity of neurons in conditions of hyperpolarization. Indeed, in PD, thalamic nuclei are inhibited and hence hyperpolarized by enhanced GABA-ergic neurotransmission (Jahnsen H. *et al.*, 1984 ; Magnin M. *et al.*, 2000). However the electrophysiological characteristics of the spikes generated by these calcium currents do not fit the tremor-linked activity of thalamic neurons.

Another very interesting putative mechanism is the STN-GPe pacemaker. When neurons from these two nuclei are isolated in vitro, they develop rhytmic activity (Plenz D. *et al.*, 1999). The frequencies of these rhythms are lower than tremor frequencies in PD. However it cannot be excluded that filtering through downstream nuclei somehow modifies tremor frequencies, perhaps under the influence of dopaminergic deficiency.

Finally loss of segregation, as mentioned above, might be at the origin of the coherence of neighbouring neurons, leading to the development of functional units propagating tremor activity along the cortico-subcortico-cortical pathways. These functional units may display coherence between their neurons, but not with neurons belonging to other neighbouring functional units. In this way different tremor generators may develop for different parts of the body (Deuschl G. *et al.*, 2000).

Rigidity

The pathophysiology of rigidity in PD remains a matter of debate. The traditional view holds that long-loop reflexes originating in muscle spindles and running through cortical relays are at the basis of increased muscle tone. This view is based on an increase of M2-responses after arrest of a voluntary movement. However, this finding has not been accepted universally and several aspects of rigidity in PD do not fit the hypothesis of long-loop reflexes (Delwaide P. *et al.*, 1990). Most compelling is the equal distribution of rigidity in distal and proximal as well as axial musculature. Another clinical finding which is hard to reconcile with this theory is the increase of rigidity by contralateral movement (Froment's sign). Therefore other mechanisms must be involved.

A very interesting and attractive hypothesis is the involvement of reticulospinal tracts. In fact, electrophysiological studies have demonstrated that the activity of inhibitory interneurons at spinal levels are differentially altered in PD. The activity of IA spinal inhibitory interneurons is increased, while the activity of IB interneurons seems to be decreased. This may lead to tonic facilitation of alpha motor neurons. These processes can be reversed by administration of L-DOPA. The only descending tract able to differentially influence these interneurons is the reticulospinal tract (Delwaide P. *et al.*, 1993). Reticular nuclei in the brainstem, such as the nucleus reticularis gigantocellularis and the nucleus pontis caudalis receive afferents from the pedunculopontine nucleus, which is connected to the basal ganglia as shown in the original model (Pahapill P. A. *et al.*, 2000). The activity of these reticular nuclei can be tested electrophysiologically by means of the startle reflex and the audiospinal augmentation of the H-reflex (Delwaide P. *et al.*, 1993).

The pathophysiology of motor fluctuations

Motor fluctuations are a serious burden in advancing PD. It has been suggested that 50% of patients treated with L-DOPA for 5 years suffer from motor fluctuations (Marsden C. D. *et al.*, 1977). Several types of fluctuations have been described, the most notable ones being end-of-dose and on-off fluctuations and dyskinesia. Advanced disease, therapy duration and half-life of the dopaminergic agent used to initiate therapy have consistently been correlated with the development of motor fluctuations (Fahn S., 2000). Progressive degeneration of nigral neurons leads to loss of buffer capacity for L-DOPA and hence a deterioration of the long-duration response. The remaining short-duration response may not be sufficient to sustain motor function continuously and subsequently off-episodes develop before a new dose of L-DOPA is taken.

Current knowledge considers the development of on-off fluctuations and dyskinesias a consequence of plasticity in the basal ganglia induced by

chronic intermittent stimulation with short-acting dopaminergic agents (Obeso J. A. *et al.*, 2000a). Indeed, compared to long-acting dopaminergic agents, an increase in Immediate Early genes (IEG) in the Fos family and in mRNA for prepro-enkephalin is found in MPTP animals treated with short-acting dopaminergic treatments. This means that the mechanisms involved in the development of motor fluctuations and dyskinesias are essentially controlled by altered transcription of genes (Bedard P. J. *et al.*, 1999). However, it is unknown how these changes develop in the context of dopaminergic treatment with short-acting agents. Some have suggested that this may depend on changes in the state of phosphorylation of NMDA-receptors, located in the vicinity of dopamine receptors, and responsible for the control of long-term potentiation and depression (LTP and LTD, respectively). This could lead to a form of abnormal learning and memory with subsequent dyskinesia and shortened motor responses (Obeso J. A. *et al.*, 2000a). In the three pathway-model suggested above, dyskinesias would follow striosome-predominant activation of IEG medially due to LTD in the input from associative cortex, combined with matrix-predominant activation in the sensori-motor striatum, located more laterally, as a consequence of sensorimotor cortico-striatal LTP (Graybiel A. M. *et al.*, 2000). An interesting observation is the potential role of adenosine 2A (A2A) receptor antagonists in the treatment of PD. A2A receptors are involved in phosphorylation of glutamate receptors and antagonists seem to confer benefit in animal models of PD, as well as in human PD. This underscores the role of glutamate-mediated mechanisms following dopaminergic denervation and intermittent receptor stimulation (Bara-Jimenez W. *et al.*, 2003).

Conclusion

Many aspects of the pathophysiology of symptoms in PD remain to be unraveled. It is at present unclear why some patients develop symptoms that do not occur in others. This suggests the presence of subgroups of PD, perhaps related to difference in progression rate and prognosis. The view on the pathophysiology of PD symptoms is evolving into a modified one, in which different aspects of connectivity, plasticity, neurophysiology and molecular biology are to be integrated. Present evidence suggests that basal ganglia are important in the spatiotemporal organisation of motor cortex output. Dopamine deficiency causes electrophysiological changes in the basal ganglia and leads to biochemical alterations that ultimately result in altered gene transcription, further modified by pharmacological therapy. An important characteristic of dopamine deficiency in the basal ganglia is the

loss of segregation, causing increased coherence of neurons that are normally acting independently.

Further pathophysiological studies on coherence within basal ganglia and coherence with cortical and muscular activity might enhance our knowledge of bradykinesia and tremor.

Finally, brainstem reticular nuclei seem to be involved in the generation of rigidity and axial symptomatology. These nuclei are awaiting further exploration to define their exact pathophysiological role in PD.

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