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Glutamatergic mechanisms in the dyskinesias induced by pharmacological dopamine replacement and deep brain stimulation for the treatment of Parkinson's disease

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ABSTRACT

Dyskinesias represent a major complication of dopamine replacement therapy in Parkinson's disease (PD) and have prompted a search for alternative treatments. The most radical advances in this field have been provided by surgical manipulations of the deep basal ganglia nuclei, and particularly by deep brain stimulation (DBS) of the subthalamic nucleus (STN). Although being very effective, high-frequency stimulation (HFS) of the STN is a poorly understood treatment. Besides its anti-akinetic activity, it can be pro-dyskinetic above a certain stimulation intensity. Accumulating evidence indicates that dyskinesias induced by STN-HFS and dopamine replacement therapy are linked to dysregulation of glutamate transmission in the basal ganglia. In rat models of PD, both types of dyskinesia are associated with increased concentrations of extracellular glutamate and altered expression of glutamate transporters in the substantia nigra pars reticulata and the striatum. Furthermore, a vast and ever growing literature has revealed changes in the expression, phosphorylation state, and/or subcellular distribution of specific subtypes of glutamate receptors in these dyskinetic conditions. Both types of dyskinesias are linked to an increased phosphorylation of NR2B-containing NMDA receptors in critical basal ganglia circuits. We conclude that disruption of glutamate homeostasis and activation of perisynaptic and extra-synaptic glutamate receptors are an important pathophysiological component of these treatment-induced dyskinesias in PD. These findings lay the ground for therapeutic development initiatives targeting dysfunctional components of glutamate transmission in the basal ganglia.

Contents

Abbreviations: 6-OHDA, 6-hydroxydopamine; AIMs, abnormal involuntary movements; AMPARs, AMPA receptors; DA, dopamine; DBS, deep brain stimulation; EP, entopeduncular nucleus; GPe, external segment of the globus pallidus; GLT1, glial glutamate/aspartate transporter 1; GPi, internal segment of the globus pallidus; HFS, high-frequency stimulation; iGluRs, Ionotropic glutamate receptors; L-DOPA, L-3,4-dihydroxyphenylalanine; LFP, local field potentials; LFS, low-frequency stimulation; LID, L-DOPA-induced dyskinesia; LTD, long-term depression; LTP, long-term potentiation; mGluRs, metabotropic glutamatergic receptors; mGluR5, metabotropic glutamate receptor type 5; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NHP, non-human primates; NMDARs, NMDA receptors; NR2B/NMDARs, NR2B-containing NMDA receptors; PD, Parkinson's disease; PET, positron emission tomography; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Thal, thalamus; VGLUT, vesicular glutamate transporter.

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1. The basal ganglia and generation of dyskinesias

The basal ganglia are interconnected nuclei interposed between the cerebral cortex, the thalamus, and premotor centres in the brain stem (Fig. 1). They play a central role in behavior through the control of movement and cognitive/motivational processes leading to action (Alexander, 1994; Middleton and Strick, 2000; Graybiel, 2005). Their main input structure, the striatum (subdivided into caudate nucleus and putamen in higher mammalian species) receives abundant glutamatergic afferents from the entire cerebral cortex and from certain thalamic nuclei (mainly the centromedian-parafascicular complex; Smith et al., 2004). The output nuclei of the basal ganglia consist of the internal pallidal segment (GPi) (corresponding to the entopeduncular nucleus, EP, in rodents) and the substantia nigra pars reticulata (SNr). These nuclei comprise GABAergic projection neurons that maintain a high level of tonic inhibition onto their thalamic and brain stem targets. Such inhibition needs to be lifted in a spatiotemporally precise manner for a fluid execution of movement sequences (Mink, 1996). Neuronal activities in the GPi/SNr are controlled by two main extrinsic sources: the striatum and the subthalamic nucleus (STN). The STN is a key node in the basal ganglia network. This nucleus mainly consists of glutamatergic efferent neurons receiving a direct cortical input (“hyperdirect pathway”) and providing a diffuse, extensive innervation to the GPi/SNr. Such a pathway is attributed a critical role in interrupting all ongoing, irrelevant activities in preparation to the next specific movement in a sequence (Mink, 1996; Nambu, 2004). Importantly, the STN is strongly interconnected with inhibitory neurons in the external segment of the globus pallidus (GPe) (Parent and Hazrati, 1995). These strong reciprocal connections would make the STN and GPe

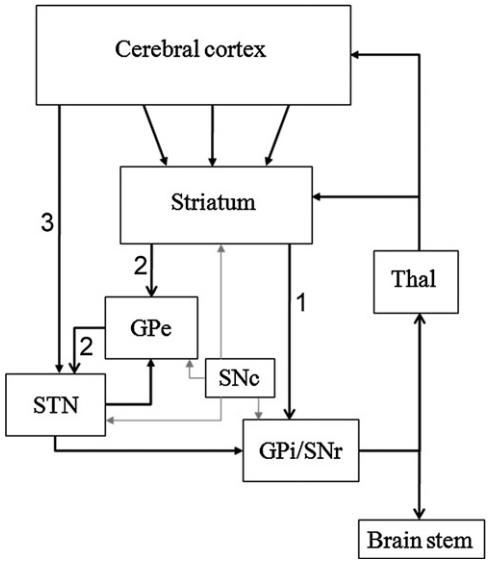

Fig. 1. Scheme representing the anatomo-functional organization of the basal ganglia (BG), showing the direct (1), indirect (2) and hyperdirect (3) pathways. Arrows represent the synaptic connections between the different structures and nuclei. Black arrows with closed or opened arrowheads represent glutamatergic or GABAergic connections, respectively. Grey arrows represent dopaminergic connections.

capable of generating persistent oscillatory activities (Wilson and Bevan, 2011). The striatum regulates the basal ganglia output layer via two GABAergic pathways: a direct projection (“direct pathway”) and an indirect projection that is relayed at the level of the GPe and the STN (“indirect pathway”) (Albin et al., 1989; Alexander and Crutcher, 1990; DeLong, 1990) (Fig. 1). Striatal efferent neurons giving rise to the direct and indirect pathways have opposite functional roles, facilitating or inhibiting movement, respectively. Nigrostriatal dopaminergic projections oppositely modulate activities in the direct and indirect pathways because of the preferential expression of D1 and D2 receptors, respectively, on the corresponding populations of striatal efferent neurons (Gerfen et al., 1990).

Abnormal patterns of neuronal activity in the STN, globus pallidus (GP), and SNr are associated with a spectrum of movement disorders characterized either by deficits in movement initiation/slowness of movement (akinesia/bradykinesia) or by excessive, uncontrollable movements (Wichmann and DeLong, 1996; Bezard et al., 2001; Obeso et al., 2002). The term dyskinesia applies to a broad range of involuntary movements that are caused by lesion or dysfunction of cortico-basal ganglionic-thalamocortical networks. Some types of dyskinetic movements are more frequently associated with certain disease conditions (Table 1). An imbalance between GABAergic and glutamatergic activities within the STN-GPe-GPi/SNr network seems to be crucial for generating dyskinesia and the associated patterns of oscillatory neural activities (Bevan et al., 2002; Hammond et al., 2007; Weinberger et al., 2009; Zaidel et al., 2009). This contention is supported by a vast literature showing that lesions and pharmacological or electrical stimulations targeting the deep basal ganglia nuclei can release different types of abnormal movements in drug untreated animals (Table 2). A large number of experimental studies in different animal species have focused on the STN following the observation that infarction of the STN in humans induces hemiballism (Martin, 1927). Hemiballism is defined as unilateral involuntary hyperkinesias of the extremities with a sudden development. These movements have wide amplitudes of motion and occur in the absence of axial dyskinesia, which distinguishes hemiballism from hemichorea. Experimental studies in naïve monkeys have shown that electrolytic (Whittier and Mettler, 1949; Carpenter et al., 1950) or excitotoxic lesions (Hammond et al., 1979; Hamada and DeLong, 1992) restricted to the STN result in dyskinesias that are similar to those in humans with hemiballism. Also the application of $GABA_A$ receptor antagonists, such as picrotoxin (Crossman et al., 1980) or bicuculline (Crossman et al., 1984; Karachi et al., 2009), to the monkey STN can induce dyskinetic movements of the contralateral limbs that, when severe, resemble hemiballism. A similar injection in the monkey zona incerta (just above the STN) induces torticollis and rotational behavior, alone or in addition to contralateral limb dyskinesia (Crossman et al., 1984). Unilateral STN lesion also triggers contralateral hemiballism in DA-depleted monkeys (Bergman et al., 1990; Aziz et al., 1991; Wichmann et al., 1994; Guridi et al., 1994, 1996). In rats, unilateral excitotoxic lesions of STN have been shown to produce postural asymmetry with the head and tail turned towards the intact side, as well as immediate contraversive turning (Kafetzopoulos and Papadopoulos, 1983; Piallat et al., 1996). After a few hours, the rats exhibited postural asymmetry towards the lesioned side and spontaneous ipsiversive turning which continued for 4–8 days at decreasing intensity