The progressive loss of substantia nigra pars compacta neurons that characterizes Parkinson’s disease pathology leads to impaired levels of dopamine in several key structures of the basal ganglia neuronal circuit and subsequent alteration of the finely regulated balance between activities of the output nuclei—the internal segment of the globus pallidus and the substantia nigra pars reticulata—that is considered essential for normal function of the circuit (Fig. 1A).

Although many advances have been made in the field of Parkinson’s disease research, the precise mechanisms leading to symptom onset are still far from being unravelled. An impairment of the ability of neurons in the basal ganglia circuit to undergo synaptic plasticity is a key component of several current theories explaining neuronal network abnormalities during this neurodegenerative disease (Calabresi et al., 2006). Synaptic plasticity, in the form of long-term depression (LTD) and long-term potentiation (LTP), is one of the most fascinating properties of the brain and is represented by the ability to encode and retain memories via the activity-dependent functional and morphological remodelling of synapses (Di Filippo et al., 2008).

Interestingly, biochemical and electrophysiological studies carried out in experimental models have demonstrated that dopamine plays a crucial role within the basal ganglia in regulating long-lasting changes in synaptic strength (Calabresi et al., 2007). Since the striatum represents the main input station of the basal ganglia, the large majority of experimental electrophysiology studies on basal ganglia neuroplasticity have focused on this neural structure. The crucial role played by dopamine in the modulation of synaptic plasticity in the basal ganglia has been evident since the first description of striatal LTD and LTP (Calabresi et al., 1992; Calabresi et al., 2007). The role of dopamine was then confirmed by further studies on genetic models lacking the D2 dopamine receptors and DARPP32 (the dopamine and cAMP-regulated phosphoprotein 32 kDa) (Calabresi et al., 2007). Studies on experimental models of Parkinson’s disease have confirmed the link between substantia nigra pars compacta neurons degeneration and loss of the main forms of neuroplasticity (Calabresi et al., 2007). In particular, by utilizing both toxic and genetic models of Parkinson’s disease, it was shown that impairment in LTD and LTP induction paralleled dopamine depletion and onset of the characteristic symptoms of the disease (Calabresi et al., 1992; Goldberg et al., 2005). The discovery of dopamine deficiency in Parkinson’s disease led to the introduction of replacement therapy with the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA). Interestingly, treatment with L-DOPA was demonstrated to be able to restore LTP expression in the 6-OHDA experimental model of Parkinson’s disease (Picconi et al., 2003) indicating that treatment with a drug able to ameliorate disease symptoms is associated with the recovery of a selective form of synaptic plasticity.

Another form of synaptic plasticity, named ‘depotentiation’, which results from the reversal of established LTP by a low-frequency stimulation protocol, was also found to be dependent on dopaminergic signalling and, interestingly, to be lost selectively in an experimental model of L-DOPA-induced dyskinesia (Picconi et al., 2003), a very disabling hyperkinetic long-term side effect of the therapy with L-DOPA. The hypothesis of a link between LTP alterations and Parkinson’s disease has also been directly investigated in patients suffering from the disease. The presence of an aberrant motor cortex plasticity in Parkinson’s disease and the ability of L-DOPA of restoring physiological plasticity in non-dyskinetic but not in dyskinetic patients has been demonstrated by utilizing transcranial magnetic and median nerve stimulation (paired associative stimulation protocol) (Morgante et al., 2006).

Nevertheless, to date, direct electrophysiological proof of the inter-relation between basal ganglia synaptic plasticity, dopamine and Parkinson’s disease in human patients has been lacking.

In this issue, Prescott et al. (2009) provide this lacking evidence by studying synaptic plasticity in the substantia nigra pars reticulata of 18 Parkinson’s disease patients undergoing therapeutic implantation of deep brain stimulating electrodes in the subthalamic nucleus. In particular, the authors recorded evoked field potentials from one electrode while stimulating with single pulses from a second electrode; and they utilized, as an LTP-inducing protocol, a high-frequency stimulation given during both OFF and ON dopaminergic medication states. By utilizing this experimental approach, the authors show that high-frequency stimulation did not induce a lasting change in field potential amplitude in Parkinson’s disease patients recorded in the OFF state and that, interestingly, patients with a higher Unified Parkinson’s Disease

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Rating Scale score underwent less change in field potential amplitude following high-frequency stimulation. Conversely, the authors report that the same high-frequency stimulation protocol, given following administration of L-DOPA, potentiated the field potential amplitudes (LTP), suggesting that a widely used anti-parkinsonian drug is able to mediate the induction/restoration of a form of neuroplasticity in the human substantia nigra pars reticulata. This latter, interesting, result provides human data to support the theory of the central role of dopamine in the modulation of synaptic plasticity within the basal ganglia and in particular during Parkinson’s disease. The evidence that neurons from substantia nigra pars reticulata are able to express a form of extracellularly recorded synaptic plasticity after the administration of L-DOPA represents a novel and appealing result but, as with any interesting discovery, raises more questions than answers. It is obvious that the study of synaptic plasticity in humans by utilizing electrodes for deep brain stimulation represents an invasive procedure and it is thus not applicable to patients not undergoing a deep brain stimulation procedure for therapeutic purposes. For this reason, due to the absence of control conditions, it is impossible to know if neurons of human substantia nigra pars reticulata are actually able to undergo LTP in physiological conditions and thus to know if L-DOPA is really able to restore an impaired form of neuroplasticity during Parkinson’s disease or per se induces potentiation of the field potential amplitudes.

The fact that the data have been obtained in one of the output nuclei of the basal ganglia is of particular interest. In the substantia nigra pars reticulata, striatal GABAergic inputs, subthalamic nucleus glutamatergic inputs and dopaminergic inputs from the substantia nigra pars compacta converge and the output signal...
is thought directly to modulate activity of thalamic neurons that, in turn, activate cortical motor programmes. A crucial question then arises: Where and how does L-DOPA exert its action? The effect observed in the substantia nigra pars reticulata might indeed represent the indirect downstream effect of modulating the nucleus striatum or the subthalamic nucleus rather than representing a direct effect of L-DOPA on the substantia nigra pars reticulata. It is also worth considering that the mechanisms by which L-DOPA might potentially modulate the described form of synaptic plasticity remain unclear. Indeed, L-DOPA exerts its effects after transformation to dopamine (by dopamine- and non-dopamine-containing cells) and to noradrenaline (by noradrenaline-containing cells) (Mercuri and Bernardi, 2005). Thus, the described effects might not only depend on the activation of D1- and D2-like dopamine receptors but also result from stimulation, in the substantia nigra pars reticulata, of α- and β-adrenoceptors or of unconventional dopaminergic sites (Mercuri and Bernardi, 2005).

Another crucial point deals with the potential interpretation, in terms of relevance for the circuit dynamics, of the observed field potential potentiation that followed the administration of L-DOPA in this study. As already mentioned, GABAergic and glutamatergic signals converge in the substantia nigra pars reticulata. The authors’ hypothesis is that the field potentials described are GABAergic in nature. During Parkinson’s disease, activity of the GABAergic neurons of the output nuclei is thought to be enhanced and to cause excessive inhibition of the thalamic neurons. This inhibition of thalamic activity might thus act as a ‘brake’ on activity of the supplementary motor cortex resulting in the onset of the parkinsonian syndrome (Bezard et al., 2001) (Fig. 1B). If this is the case, potentiation of GABAergic signals onto substantia nigra pars reticulata, by lowering neurons firing rate, could (at least in part) mediate the beneficial symptomatic effects of L-DOPA (Fig. 1C). Another crucial question then arises: ‘is it possible that neuroplasticity also mediates the long-term complications of L-DOPA therapy and, in particular, dyskinesias?’ It is well accepted that, in order to avoid neuronal network destabilization, the mechanisms underlying synaptic plasticity need to be finely regulated and, in experimental models of the disease, one crucial form of homeostatic synaptic plasticity, depotentiation, is selectively lost during dyskinesias (Picconi et al., 2003). Thus, it remains possible that L-DOPA, via the continuous and uncontrolled increase of the strength of GABAergic synapses onto output nuclei neurons may lead to progressive destabilization of postsynaptic firing rates, virtually reducing these to zero and thus leading to pathological disinhibition of thalamic nuclei and the onset of abnormal involuntary movements (Fig. 1D).

Although these and other questions might be inspired by the work of Prescott et al., the results of the study published in the current issue certainly open the way to a new experimental approach in the field of Parkinson’s disease research, strengthening the view of Parkinson’s disease as a ‘synaptopathy’ that can be rapidly counteracted by the manipulation of a neurotransmitter system. The hope is that, in the future, the study of human synaptic plasticity might shed light on the complex mechanisms underlying symptoms of the disease and the disabling long-term side effects of treatment with L-DOPA.

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