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Review article

# Expanding the repertoire of L-DOPA's actions: A comprehensive review of its functional neurochemistry

Philippe De Deurwaerdère[a,*], Giuseppe Di Giovanni[b,c], Mark J. Millan[d]

[a] CNRS (Centre National de la Recherche Scientifique), Institut des Maladies Neurodégénératives, UMR CNRS 5293, F-33000 Bordeaux, France
[b] Neuroscience Division, School of Biosciences, Cardiff University, Cardiff, UK
[c] Department of Physiology & Biochemistry, Faculty of Medicine and Surgery, University of Malta, Malta
[d] Institut de Recherche Servier, Pole for Therapeutic Innovation in Neuropsychiatry, 78290 Croissy/Seine,Paris, France

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ABSTRACT

Though a multi-facetted disorder, Parkinson's disease is prototypically characterized by neurodegeneration of nigrostriatal dopaminergic neurons of the substantia nigra pars compacta, leading to a severe disruption of motor function. Accordingly, L-DOPA, the metabolic precursor of dopamine (DA), is well-established as a treatment for the motor deficits of Parkinson's disease despite long-term complications such as dyskinesia and psychiatric side-effects. Paradoxically, however, despite the traditional assumption that L-DOPA is transformed in residual striatal dopaminergic neurons into DA, the mechanism of action of L-DOPA is neither simple nor entirely clear. Herein, focussing on its influence upon extracellular DA and other neuromodulators in intact animals and experimental models of Parkinson's disease, we highlight effects *other* than striatal generation of DA in the functional profile of L-DOPA. While not excluding a minor role for glial cells, L-DOPA is principally transformed into DA in neurons yet, interestingly, with a more important role for *serotonergic* than dopaminergic projections. Moreover, in addition to the striatum, L-DOPA evokes marked increases in extracellular DA in frontal cortex, nucleus accumbens, the subthalamic nucleus and additional extra-striatal regions. In considering its functional profile, it is also important to bear in mind the marked (probably indirect) influence of L-DOPA upon cholinergic, GABAergic and glutamatergic neurons in the basal ganglia and/or cortex, while anomalous serotonergic transmission is incriminated in the emergence of L-DOPA elicited dyskinesia and psychosis. Finally, L-DOPA may exert intrinsic receptor-mediated actions independently of DA neurotransmission and can be processed into bioactive metabolites. In conclusion, L-DOPA exerts a surprisingly complex pattern of neurochemical effects of much greater scope that mere striatal transformation into DA in spared dopaminergic neurons. Their further experimental and clinical clarification should help improve both L-DOPA-based and novel strategies for controlling the motor and other symptoms of Parkinson's disease.



*Abbreviations:* AADC, aromatic L amino acid decarboxylase; COMT, catechol-O-methyl-transferase; CSF, cerebrospinal fluid; 6-OHDA, 6-hydroxydopamine; DBH, dopamine β-hydroxylase; DOPAC, 3,4-dihydroxyphenylacetic acid; 3-MT, 3-methoxytyramine; DA, dopamine; DAT, dopamine transporter; DRN, dorsal raphe nucleus; DSP-4, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine; MRN, median raphe nucleus; GP, globus pallidus; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; EPN, entopeduncular nucleus; HVA, homovanillic acid; HDC, histidine decarboxylase; HFS-STN, high frequency stimulation of the subthalamic nucleus; L-DOPA, levodopa 3,4-dihydroxy-L-phenylalanine; MAOA, monoamine oxidase A; MAOB, monoamine oxidase B; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; PET, positron emission tomography; 5-HIAA, 5-hydroxyindolacetic acid; 5-HT, serotonin or 5-hydroxytryptamine; 5-HTP, 5-hydroxytryptophan; NA, noradrenaline; SERT, serotonin transporter; NET, noradrenaline transporter; OCT, organic cation transporter; SN, substantia nigra; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; STN, subthalamic nucleus; SSRI, selective serotonin reuptake inhibitor; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; TTX, tetrodotoxin; VMAT2, vesicular monoamine transporter 2.

* Corresponding author.
*E-mail address:* deurwaer@u-bordeaux.fr (P. De Deurwaerdère).

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**Contents**



## 1. Introduction: Parkinson's disease and its management by L-DOPA, an overview and aims of the eview

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the cardinal motor deficits of bradykinesia, rigidity, postural instability and tremor at rest, together with a suite of other symptoms like anosmia, depressed mood, psychosis, sensory disturbances and pain, disruption of sleep and cognitive dysfunction (Hirao et al., 2015; Olanow et al., 2009). Despite several familial forms of PD linked to specific genetic mutations, most patients suffer from idiopathic PD.

It is important not to ignore a widespread and progressive pattern of anomalies in cortico-subcortical circuits and a broad-based disruption of cerebral plasticity, yet the most striking and common feature of PD is the age-related and gradual degeneration of nigrostriatal dopaminergic pathways innervating the striatum: loss of these neurons is closely linked to the above-mentioned cluster of motor symptoms leading to the diagnosis of PD (Burke and O'Malley, 2013; Hornykiewicz, 2006; Olanow et al., 2009).

L-DOPA acquired its status as a core antiparkinsonian treatment soon after the biochemical demonstration that levels of the neurotransmitter dopamine (DA) are greatly reduced in the caudate nucleus and putamen of PD patients (see Lees et al., 2015). This decrease is, as remarked above, a consequence of the loss of DA neurons in the substantia nigra pars compacta (SNpc), which project to the basal ganglia (Hornykiewicz, 1973), a group of subcortical structures interlinked with the cortex, thalamus and hippocampus and critically involved in the control of motor behavior – as well as cognition, social behavior, reward and mood (Esposito et al., 2007; Obeso et al., 2008a; Pauli et al., 2016). L-