Mol Neurobiol (2012) 45:173–185
DOI 10.1007/s12035-011-8230-0

Contribution of Serotonergic Transmission to the Motor and Cognitive Effects of High-Frequency Stimulation of the Subthalamic Nucleus or Levodopa in Parkinson's Disease

Sylvia Navailles · Philippe De Deurwaerdère

Received: 18 October 2011 / Accepted: 20 December 2011 / Published online: 6 January 2012

Abstract Although they are effective at treating the motor impairments that are the core symptoms of Parkinson's disease, current treatments, namely L-3,4-dihydroxyphenylalanine (L-DOPA), the gold standard medication and high-frequency stimulation of the subthalamic nucleus (HFS-STN), can lead to cognitive and mood alterations. Many of these side effects, such as depression, anxiety and sleep disturbances, could be related to abnormal functioning of the serotonergic system, but much basic research remains to be done. Molecular studies in humans and animal models of the disease have reported diverse drastic changes to the serotonergic system. It has also been shown that the serotonergic system both plays a major role in the mechanism of action of the current therapies and is altered by the therapies. It has been reported that HFS-STN decreases serotonin release in several regions, mostly via inhibition of serotonergic neuron activity. The involvement of serotonergic neurons in L-DOPA treatment is even more significant. First, serotonergic neurons, able to convert exogenous L-DOPA to dopamine, are a major site to release dopamine throughout the brain. Second, the substitution of serotonin by newly synthesized dopamine in serotonin neurons leads to acute and chronic alteration of serotonin release and metabolism. Therefore, both therapeutic approaches, via distinct mechanisms, decrease serotonergic system activity and, rather than alleviating cognitive or mood disorders, tend to aggravate them. Molecular strategies targeting the serotonergic system are being developed and could be decisive in limiting L-DOPA-induced dyskinesia, as well as mood and cognitive symptoms produced by antiparkinsonian therapies.

Keywords Parkinson's disease · Serotonin release · Serotonin function · Dopamine release · L-DOPA · High-frequency stimulation of the subthalamic nucleus

S. Navailles · P. De Deurwaerdère (✉)
Unité Mixte de Recherche Centre National de la Recherche Scientifique 5293, University of Bordeaux,
146 rue Léo Saignât,
33076 Bordeaux Cedex, France
e-mail: deurwaer@u-bordeaux2.fr

Serotonergic System in Parkinson's Disease

Parkinson's disease is classically viewed as a neurological condition characterized by bradykinesia, postural instability, rigidity and tremor at rest. These motor symptoms have been associated with the destruction of the nigrostriatal dopaminergic (DA) tract, though tremor has been linked to serotonergic (5-HT) dysfunction. The 5-HT system, due to its known implication in mood and cognitive dysfunctions, is also thought to be implicated in the development of non-motor symptoms occurring in Parkinson's disease patients including depression and anxiety [1]. It has been reported that 30–50% of patients experience depression or anxiety, which is higher than age-matched controls [2, 3]. Depression has been observed before the onset of Parkinsonism [4, 5] and impairs the efficacy of antiparkinsonian treatments [6].

5-HT neurons innervating the whole encephalon are located in the dorsal (DRN) and median raphe nuclei (MRN) [7]. Postmortem neurochemical studies in Parkinson's disease patients have reported conflicting results with respect to 5-HT markers, although most studies report a decrease [8, 9]. In these studies, the levels of striatal 5-HT and its metabolite 5-hydroxyindole acetic acid (5-HIAA) are reduced by up to 50% [10–12], and the 5-HT transporter density is decreased in multiple brain regions [11, 13, 14], though in a region-dependent manner [15, 16]. The density

of 5-HT_{1A} receptors has been reported to be reduced by 27% in the DRN [17]. All these changes support a putative loss of 5-HT neurons in parkinsonian patients [8, 18–20]. It is difficult in humans to understand whether this effect is due to the progressive neurodegenerative process of the disease or to the pharmacological treatments received by the patients [8, 11].

Compared to the human situation, the alteration of the 5-HT system differs in animal models of the disease including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys and mice, the 6-hydroxydopamine (6-OHDA)-induced DA lesion in mice and rats and the genetic mice model of the disease. The 6-OHDA-lesioned rat model of Parkinson's disease is the most popular model used to assess the effect of L-3,4-dihydroxyphenylalanine (L-DOPA) since the unilateral lesion of the nigrostriatal DA pathway generates a functional asymmetry that allows testing of the anti-parkinsonian effect of L-DOPA, i.e. a rotational behaviour contralateral to the lesion [21, 22]. The motor benefit of L-DOPA has been attributed to an increase in the extracellular levels of DA that binds to hypersensitive DA receptors, thus leading to increased motor responses ([23, 24]; for review, see [25]). Furthermore, chronic treatment with L-DOPA induces dyskinesia in 6-OHDA-lesioned rats and MPTP-treated monkeys or mice, a common motor complication that also develops with long-term DA replacement therapy in Parkinson's disease patients [26, 27]. Dyskinesia is thought to emerge as a consequence of abnormal fluctuations in synaptic DA levels induced by L-DOPA treatment [28–31]. These side effects due to L-DOPA medication may, however, impair the evaluation of mood and cognitive effects in behavioural tests.

The neurotoxin MPTP has been shown to decrease 5-HT tissue brain concentrations in addition to a drastic lesion of catecholaminergic neurons [32–34]. Modification of basal 5-HT release in the striatum of MPTP-treated monkeys depends on the functional territories considered and the status of the animal [35]. In MPTP-treated mice, changes in 5-HT concentrations are less consistent regarding the brain region examined and the MPTP treatment protocol and survival periods used [36–39]. Sprouting in 5-HT afferents into the striatum has been observed in adult MPTP-treated mice [40]. Several studies have shown that the unilateral destruction of DA neurons in adult rats using 6-OHDA does not alter 5-HT tissue levels [41–43]. Changes of 5-HT system activity consequent to the destruction of the nigrostriatal tract have been reported, but the data are controversial. Some studies have shown an overall hyperactivity of the 5-HT system with a hyperinnervation of forebrain 5-HT fibres in the striatum [44], elevated brain tissue levels of 5-HT [45] and hyperactivity of DRN and MRN 5-HT neurons [46–50]. However, some studies have reported a significant reduction in 5-HT innervation in the striatum [51] and a decreased activity of DRN 5-HT neurons [52].

High-Frequency Stimulation of the Subthalamic Nucleus Decreases the Activity of Serotonergic Neurons

HFS-STN is the best surgical approach to Parkinson's disease, and its efficacy against the core and motor symptoms of the disease is even better than classical medication. As with pharmacological treatment, however, HFS-STN is associated with some side effects that could be related to impairment of 5-HT transmission including depression [53–57], mania [58], attempted suicide [56, 59, 60] and cognitive dysfunctions such as speed of mental processing, working memory, phonemic fluency, encoding of visuospatial material and long-term consolidation of verbal material [61].

In the 6-OHDA rat model of Parkinson's disease, HFS-STN induced a "depressive-like" behaviour in the forced swimming test [47]. The increased immobility time, representative of the depressive-like behaviour, was reversed by pre-treatment with the selective 5-HT reuptake inhibitor (SSRI) citalopram. In line with a putative impaired 5-HT tone, HFS-STN decreased the firing rate of 5-HT neurons in the DRN during the stimulation. However, this effect was not blocked by pre-treatment with SSRI [47]. Moreover, HFS-STN reduced the release of 5-HT in the prefrontal cortex (PFC), the hippocampus (HIPP) and the striatum ([56, 62]; Fig. 1). The decrease in 5-HT release occurs in intact and 6-OHDA-lesioned rats like the inhibition of DRN neurons. The effect was also seen whether the rats were anaesthetized with isoflurane or chloral hydrate or were freely moving. This decrease in 5-HT neuron firing induced by HFS-STN could contribute to the decrease in 5-HT release. Indeed, the inhibitory effect of HFS-STN on 5-HT release is not additive to that induced by 8-OHDPAT, a 5-HT_{1A} agonist known to inhibit 5-HT release via a decrease in 5-HT neuron firing [62], suggesting that both treatments share the inhibition of 5-HT neuron firing in their ability to decrease 5-HT release. It is noteworthy that the inhibition of 5-HT neuron firing is almost immediate and continues after the period of stimulation whereas the inhibitory effect on 5-HT release is not immediate, as it appears 40–60 min after the end of the HFS-STN. Thus, although the decrease in 5-HT neuron firing probably contributes in the effect of HFS-STN, we and others have reported small differences in 5-HT release between sampled brain regions (magnitude of effect, delay of appearance, anaesthesia, sensitivity to the 6-OHDA lesion, interaction with L-DOPA, see point IV and Fig. 1) suggesting that other factors may also play a part. This idea is further supported by extracellular levels of the 5-HT metabolite 5-HIAA. HFS-STN did not alter 5-HIAA extracellular level in the PFC or the striatum [62, 63] but decreased it in the HIPP (Fig. 1). 5-HT neurons projections are not uniform in terms of molecular determinant, regulatory mechanisms or raphe nuclei of origin [64–67]. This feature

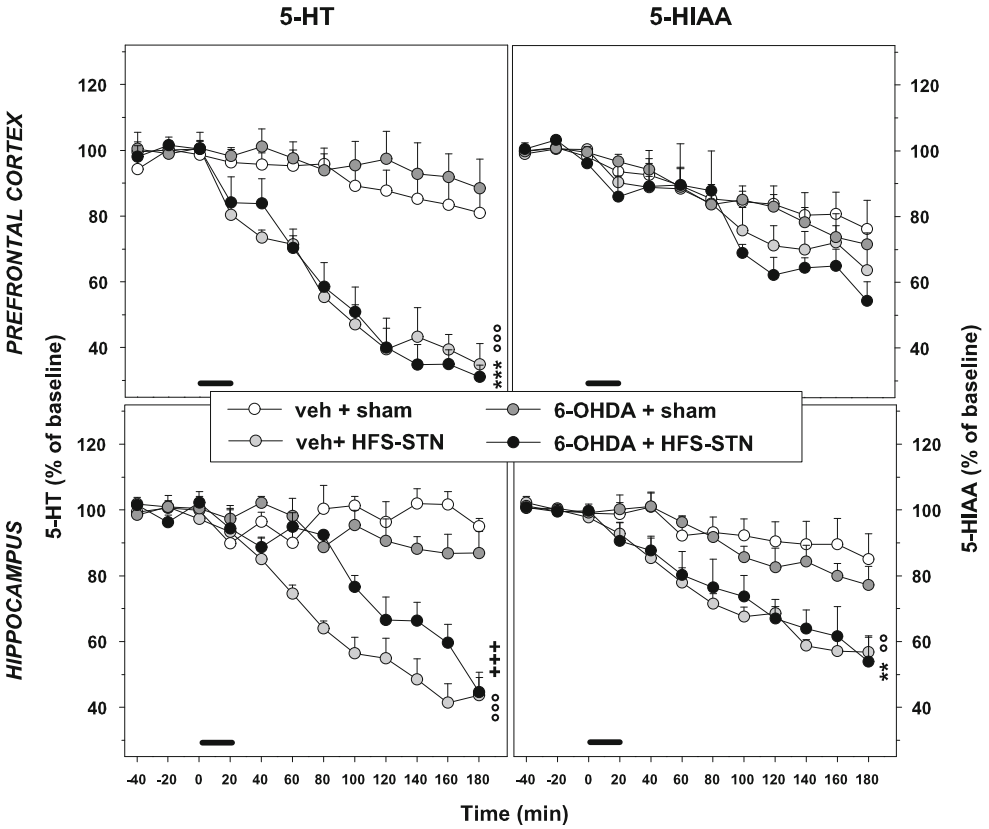

Fig. 1 Effect of high-frequency stimulation of the subthalamic nucleus (HFS-STN) on 5-HT and 5-HIAA extracellular levels in the prefrontal cortex and hippocampus of sham-lesioned and 6-OHDA-lesioned rats. Dialysis experiments were performed 21–28 days after the injection of 6-OHDA or its vehicle (*veh*) in the median forebrain bundle. HFS-STN (130 Hz, 30 μA) or sham stimulation (sham) was applied for a 20-min period as indicated by the *horizontal bar*. Data represent the mean± SEM (standard error mean) percentages of baseline in each sample (n= 4–5 rats/group) along the time course of the study. °°p<0.01; °°°p< 0.001 for veh+HFS-STN group versus veh+sham group and **p<0.01, ***p<0.001 for 6-OHDA+HFS-STN versus 6-OHDA+sham group (Fisher's PLSD test after a significant one-way ANOVA); ^{+++}p<0.001 for the 6-OHDA+HFS-STN group versus the veh+HFS-STN group (Fisher's PLSD test after a significant two-way ANOVA). Figure adapted from Navailles et al. [62]

of 5-HT transmission may well play a role in the distinct regional sensitivity of 5-HT terminals to HFS-STN.

The mechanism involved in the inhibitory influence of HFS-STN on 5-HT function is not clear. Part of this effect could be related to antidromic activation of DRN induced by HFS-STN [68]. However, deep brain stimulation of the nucleus accumbens shell enhances 5-HT content in the shell, making less likely the hypothesis that antidromic activation of 5-HT fibres leads to decreased 5-HT output [69]. Alternatively, this inhibitory effect could be related to outputs from the STN influencing the activity of 5-HT neurons. It has been suggested that STN could activate inhibitory interneurons in the raphe, indirectly inhibiting the activity of 5-HT cells [70]. The activation of raphé interneurons by HFS-STN could possibly occur via the medial prefrontal cortex or the lateral habenula [63]. Additional data are needed to determine the precise mechanism of this inhibitory influence as well as to determine the contribution of this inhibition to the benefits and side effects of HFS-STN.

Mechanism of Action of L-DOPA and 5-HT Neurons

Since the mid-1960s [71], L-DOPA has been used as the gold standard medication for treating motor symptoms in Parkinson's disease. L-DOPA is the metabolic precursor of DA, and its therapeutic efficacy has long been attributed to its ability to restore DA content in the striatum of parkinsonian patients through spared DA neurons [23, 24, 72]. However, this picture has become more complicated. Growing evidence has progressively discarded a prominent role for DA neurons in the ability of L-DOPA to increase DA extracellular levels. First, the fewer DA neurons that are spared, the more pronounced is the release of DA induced by L-DOPA [73, 74]. Furthermore, although the feedback inhibitory controls of DA neurons involving D_2 receptors are still functional in DA-depleted rats [75–78], L-DOPA-induced DA release is not sensitive to DA autoregulatory processes (DA-D_2 autoreceptor stimulation and blockade of DA transporter) [73, 78]. Second, the decarboxylation of L-DOPA by aromatic amino

acid *l*-decarboxylase (AADC) into DA occurs in various brain areas, including regions that are sparsely innervated by DA neurons physiologically [79]. AADC is not specific to DA neurons and is found in numerous cell types including endothelial and glial cells, as well as in various neuronal systems [80, 81]. Indeed, 5-HT neurons that express AADC to convert L-DOPA into DA and the vesicular membrane transporter type 2 (VMAT2) that packages DA into exocytosis vesicles [82–85] have been shown to store the newly synthesized DA from cell bodies and terminals ([83, 86–88]; see Fig. 2).

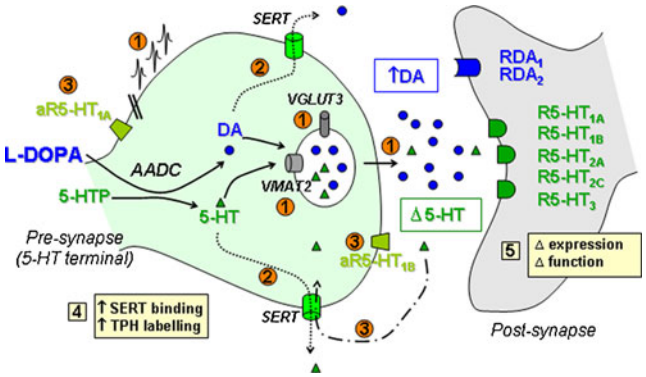

Fig. 2 Consequences of L-DOPA decarboxylation in 5-HT neurons. In the absence of DA neurons in advanced stages of Parkinson's disease, exogenous L-DOPA competes with 5-hydroxytryptophan (*5-HTP*) to be decarboxylated into dopamine (*DA*) by the amino acid decarboxylase (*AADC*) inside serotonergic neurons. *1* The newly synthesized DA together with serotonin (*5-HT*) are stored inside exocytosis vesicles through the VMAT2 (reserpine-sensitive process) and is co-released with 5-HT by exocytosis (tetrodotoxin- and calcium-dependent process) in the synaptic cleft. In a subset of 5-HT terminals, other membrane proteins such as the vesicular glutamate transporter 3 (*VGLUT3*) participate with VMAT2 to a vesicular-filling synergy that enhance the efficiency of monoamine storage capacity and the quantum of monoamines released [64]. *2* A non-exocytotic release of DA and 5-HT also occurs whose relative contribution to total monoamine extracellular levels may depend on the dose of L-DOPA administered. Competition between DA and 5-HT at the level of VMAT2 increases the 5-HT cytosolic pool which can be cleared by inversion of the 5-HT transporter (*SERT*). Huge amounts of newly synthesized DA in the cytosol are also cleared via the SERT, an effect that can be blocked by selective inhibitors of SERT like citalopram [89]. *3* L-DOPA-induced DA release is sensitive to 5-HT autoregulatory mechanisms involving 5-HT_{1A} autoreceptors (aR5-HT_{1A}) at 5-HT cell bodies, 5-HT_{1B} autoreceptors (aR5-HT_{1B}) at 5-HT terminals and blockade of SERT. Overall, the entry of L-DOPA inside 5-HT neurons leads to a massive increase in extracellular DA levels in all brain regions innervated by 5-HT neurons while 5-HT release is altered in a region-specific manner depending on the anatomo-functional heterogeneity of 5-HT fibres [62, 89, 95, 105]. *4* While chronic L-DOPA treatment homogeneously reduces 5-HT biochemical indexes (reduction of tissue and extracellular levels of 5-HT and its metabolite 5-hydroxyindolacetic acid, *5-HIAA*), numerous region-dependent changes occur at the level of 5-HT terminals (increased sprouting and changes of 5-HT varicosities morphology) and 5-HT receptors (changes of expression and sensitivity to 5-HT compounds). The profound alteration of 5-HT transmission together with the dysregulated DA transmission throughout the parkinsonian brain may participate in the emergence of the numerous motor and non-motor side effects of L-DOPA

Three recent arguments have demonstrated that 5-HT neurons are responsible for L-DOPA-induced DA release. First, a selective lesion of 5-HT neurons with the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) abolished the increase in DA extracellular levels induced by a wide dose range of L-DOPA (3–100 mg/kg) ([89, 90]; Fig. 3). The hypothesis that other cellular systems participate significantly in the conversion of L-DOPA and the release of DA was discarded because the magnitude of the decrease in L-DOPA-induced DA release was dependent on the percentage of 5-HT denervation [89]. Second, 5-HT auto-regulatory mechanisms triggered through the stimulation of 5-$HT_{1A/1B}$ autoreceptors [91, 92] and blockade of 5-HT transporter [89, 93] strongly decrease L-DOPA-induced DA release (see Fig. 2). Third, L-DOPA induces an ectopic release of DA in a pattern that follows the widespread innervation of the entire forebrain by 5-HT raphe neurons [7, 94]. Using four microdialysis probes implanted ipsilaterally (Fig. 3a), we found that L-DOPA-induced DA release is not restricted to the striatum but also occurs in the PFC, HIPP and substantia nigra pars reticulata (SNr) [62, 89, 95]. This effect is sensitive to 5-HT lesion and 5-HT pharmacological manipulation ([89, 92]; Fig. 3b). All these brain regions display various levels of 5-HT terminal density and express DA receptors [96] on which the newly synthesized DA can exert its numerous effects and promote DA transmission. It is noteworthy that the magnitude of the increase in extracellular DA concentration induced by a therapeutic dose range of L-DOPA (3–12 mg/kg) is far higher in extrastriatal brain regions than in the striatum compared to the physiological situation (Fig. 3b). In other words, while the striatum constitutes the prime locus for DA transmission in physiological conditions, its contribution to the effects of L-DOPA may be counterbalanced by the increase in DA transmission in other brain regions in parkinsonian conditions. A deeper analysis of the neurochemical and behavioural results questions the functional role of striatal DA release in the effect of L-DOPA. Briefly, 5,7-DHT lesion dramatically reduces 6 mg/kg L-DOPA-induced dyskinesia without altering the motor score [97]. A correct motor score in rats could therefore be achieved with L-DOPA in a situation in which striatal DA extracellular levels are barely detectable (40 times lower than in intact rats), as shown in Fig. 3b (last image). Alternatively, these data suggest that the decrease in 5-HT function could also facilitate the therapeutic effects of L-DOPA. Taken together these data indicate that 5-HT neurons, by mediating the effects of L-DOPA, create a new system state in DA transmission throughout the parkinsonian brain [98].

Modifications of 5-HT Transmission by Acute and Repeated L-DOPA Treatment

Along with the crucial involvement of 5-HT neurons in the action of L-DOPA, it is necessary to consider that the offside

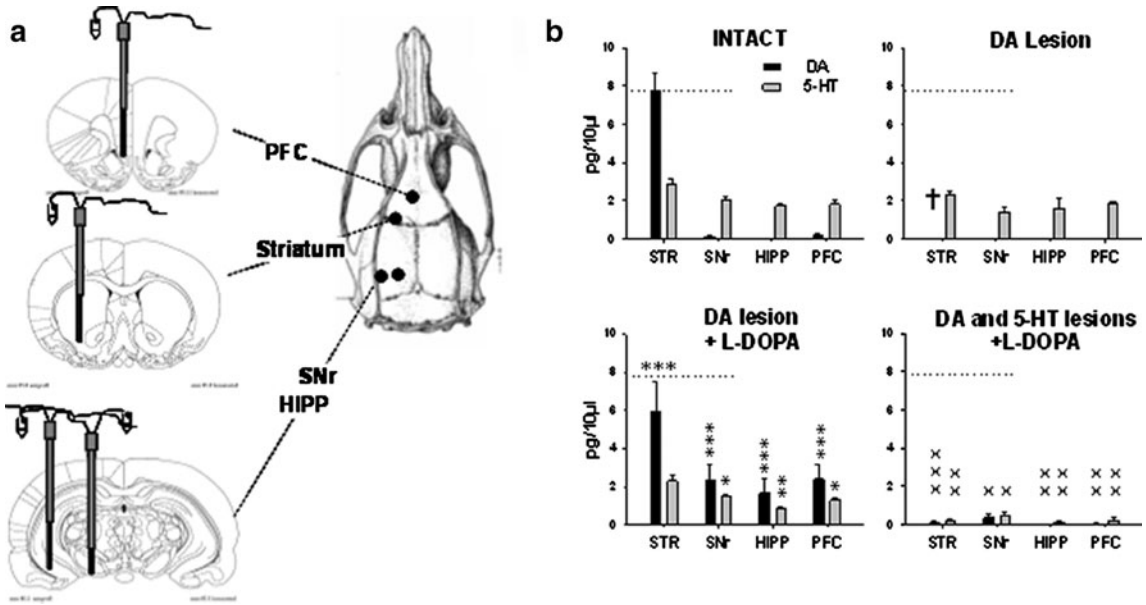

Fig. 3 Widespread effect of L-DOPA on DA and 5-HT releases in the brain via 5-HT neurons. **a** Drawings representing the simultaneous implantation of four microdialysis probes (2 or 4 mm of membrane length) in the ipsilateral prefrontal cortex (*PFC*), the striatum (*STR*), the hippocampus (*HIPP*) and the substantia nigra (*SNr*). **b** Extracellular levels of DA and 5-HT (in pg/10 µl±standard error of the mean) measured in these regions in intact rats (*upper left panel*), in 6-hydroxydopamine (*6-OHDA*) rats (*upper right panel*), in 6-OHDA receiving 6 mg/kg L-DOPA (+15 mg/kg benserazide) (*lower left panel*), in 6-OHDA and 5-HT-lesioned rats using the 5-HT neurotoxin 5,7-dihydroxytryptamine and receiving 6 mg/kg L-DOPA (+15 mg/kg benserazide) (*lower right panel*). The extracellular levels of striatal DA obtained in intact rats (*dotted line*) are reported in *all panels*. *Upper panels* correspond to baseline levels measured before drug treatment if any. *Lower panels* correspond to the mean of the quantity of DA and 5-HT extracellular levels averaged for 3 h monitoring after L-DOPA treatment. Statistics correspond to the followings: $*p<0.05$ and $***p<0.001$ with respect to extracellular levels obtained in saline treated 6-OHDA rats; $^{x}p<0.05$, $^{xx}p<0.01$, $^{xxx}p<0.001$ with respect to DA or 5-HT extracellular levels obtained in rats receiving L-DOPA and bearing the lesion of DA neurons; $^{+}p<0.001$ with respect to values obtained in intact rats. Adapted from Navailles et al. [62, 95] and unpublished observations

effects due to L-DOPA may not solely be attributed to an imbalanced DA transmission but also to profound changes of 5-HT transmission throughout the parkinsonian brain. These changes of 5-HT transmission are poorly known, but they could condition the benefit and side effects of L-DOPA.

The presence of massive amounts of newly synthesized DA inside 5-HT neurons could account for the drastic alteration of 5-HT neuronal function [62, 99–102]. Accumulating evidence since the 1970s shows that L-DOPA-derived DA displaces 5-HT from exocytosis vesicles thus increasing the cytosolic pool of 5-HT ([83]; see Fig. 2). This substitution process could result in a decrease in 5-HT exocytotic release but also in a non-exocytotic efflux of 5-HT from 5-HT transporters (SERT) ([1, 103, 104]; for review, see [105]). A non-exocytotic efflux of 5-HT induced by L-DOPA is possible as the SERT reversal likely contributes to the impulse-independent release of DA induced by L-DOPA from 5-HT neurons [89, 92, 105]. This pharmacological issue is important to take into an account in elaborating therapeutic strategies because it implies that a full control of the excitability of 5-HT neurons using 5-HT_{1A} and/or 5-HT_{1B} agonists will have a partial influence on the secretion of DA and 5-HT induced by L-DOPA. Moreover, the reversal of the SERT could become a technical limit when going deeper into the mechanism of action of L-DOPA using intracerebral microdialysis. Indeed, extracellular levels of monoamines measured by intracerebral microdialysis correspond to the equilibrium between neuronal uptake and microdialysis probe uptake. The blockade or the reversion of uptake sites introduces a bias towards the probe uptake, indirectly magnifying impulse-dependent release of the monoamine [106]. The relative contribution of exocytotic and non-exocytotic mechanisms of 5-HT release is therefore unknown and may depend on the dose of L-DOPA used (high doses favouring the non-exocytotic process) and the regional heterogeneity of 5-HT terminals [105] characterized by the variable expression of numerous regulatory proteins (SERT, VGLUT3 etc…; [64]). Thus, we have found that 6 mg/kg L-DOPA decreases 5-HT extracellular levels in the SNr, the HIPP, the PFC but not the striatum (Fig. 3b, levels of 5-HT in "6-OHDA" compared to "6-OHDA+L-DOPA"). At 12 mg/kg, a biphasic effect was observed in the HIPP and no effect in the striatum [62, 95].

This region-dependent effect is also observed after chronic L-DOPA treatment [95]. The inhibitory effect of L-DOPA on 5-HT release was potentiated in the SNr and HIPP of L-

DOPA-treated rats but not in the PFC. In the striatum of L-DOPA-treated rats, 5-HT release remained unaltered by L-DOPA [92, 95]. Importantly, this region-dependent reactivity of 5-HT terminals to L-DOPA has a direct impact on the ability of L-DOPA to increase DA release [95]. While L-DOPA-induced DA release is preserved in the striatum, it is greatly decreased in the SNr where 5-HT terminals display the highest sensitivity to L-DOPA. These data have to be considered together with the fact that a chronic L-DOPA treatment at 12 mg/kg decreases basal extracellular levels of 5-HT and its metabolite 5-HIAA and also tissue concentrations of 5-HT and 5-HIAA [95, 97, 100], suggesting a negative impact of L-DOPA on 5-HT neuron integrity [95]. However, these neurochemical changes in 5-HT levels vary depending on whether animals develop dyskinesia or not. A positive correlation between L-DOPA-induced dyskinesia and tissue levels of DA has been reported in the striatum [102] while the severity of L-DOPA-induced dyskinesia is negatively correlated with striatal tissue levels of 5-HT [107]. Lindgren and colleagues [92] reported higher basal extracellular and tissue 5-HT levels in the striatum, but not the SNr, of awake dyskinetic animals compared to non-dyskinetic animals. These authors suggested that the denser 5-HT innervation in the striatum of dyskinetic animals could account for the higher 5-HT levels and the stronger response on DA release induced by L-DOPA although Lundblad et al. [108] could not establish a correlation between the level of 5-HT nerve density in lesioned striata and the magnitude of DA release. The relationship between 5-HT levels and L-DOPA-induced dyskinesia may also depend on the dose of L-DOPA used. Chronic treatment with L-DOPA at 12 mg/kg, which elicits dyskinesia in all animals, homogeneously decreased 5-HT and 5-HIAA extracellular and tissue levels in multiple brain regions [95]. At 6 mg/kg, chronic L-DOPA treatment also decreased tissue levels of 5-HT, but not 5-HIAA, in the striatum of both dyskinetic and non-dyskinetic animals [92]. These results suggest that L-DOPA may have detrimental effects on 5-HT neurons even at moderate doses.

These data fit with numerous clinical studies reporting a decrease in 5-HT markers [8–14, 17–20]. This putative loss of 5-HT neurons in Parkinson's disease could be attributed to the progressive neurodegenerative process of the disease [109, 110] and/or to pharmacological treatments [8, 11]. Long-term L-DOPA use has been shown to produce a larger decrease in 5-HT markers in some [101] but not all studies [14]. When considering its toxic properties [111–114], L-DOPA may constitute a contributing factor to neuronal damage of 5-HT neurons along with the progression of the disease. Quinones formed from L-DOPA and newly synthesized DA inactivate tryptophan hydroxylase (TPH) [115], the initial enzyme in the biosynthesis of 5-HT, by converting TPH to a redox-cycling quinoprotein that may participate in 5-HT neuronal toxicity [6, 116, 117]. These mechanisms could be involved in the overall decrease in 5-HT function observed in the parkinsonian brain. A reduction of 5-HT metabolism (reduced 5-HIAA/TPH ratio) has been reported in parkinsonian patients and DA-depleted rats receiving L-DOPA treatment [118]. In line, chronic L-DOPA treatment reduced tissue 5-HT and 5-HIAA concentrations in multiple brain regions [95, 97, 98, 119] and TPH expression in the DRN of animals with a bilateral and partial DA depletion [6].

Changes in 5-HT Reactivity Induced by L-DOPA

As well as the issue of whether L-DOPA has a toxic effect on 5-HT neurons [6], numerous studies have shown evidence for alteration of 5-HT transmission after chronic L-DOPA treatment, as revealed by changes in 5-HT receptor expression, sensitivity and changes in 5-HT terminal morphology and plasticity (see Fig. 2).

Most (if not all) 5-HT receptors are sensitive to chronic alteration of DA transmission, though in a region-dependent manner [48, 49, 120–125]. Beyond changes induced by the loss of DA neurons in parkinsonian patients and experimental models of Parkinson's disease, chronic L-DOPA treatment has been shown to further alter the expression and function of some 5-HT receptors in a region-specific manner. While the loss of nigrostriatal DA neurons decreases the responses to 5-HT_{1A} receptor stimulation of both raphe neurons [48] and pyramidal neurons of the medial PFC [49] in 6-OHDA rats, it increases 5-HT_{1A} receptor binding in the neocortex of parkinsonian patients [126] and in the putamen [127], caudate nucleus and middle layers of premotor–motor cortices of MPTP-treated monkeys [128]. Chronic treatment with L-DOPA further increases 5-HT_{1A} receptor binding in the caudate nucleus of MPTP-lesioned monkeys [128]. No alteration in 5-HT_{1B} binding has been observed in the striatum and substantia nigra of parkinsonian patients [129] or 6-OHDA rats [130], although an increase in 5-HT_{1B} receptor expression in these brain regions has been reported after chronic L-DOPA treatment in 6-OHDA-lesioned rats [131]. Contradictory effects have been observed for 5-HT_{2A} receptors depending on the experimental Parkinson's disease model used. While 5-HT_{2A} receptors in interneurons [132] and pyramidal neurons [50] of the medial PFC are downregulated by unilateral 6-OHDA lesion in rats, an increase in 5-HT_{2A} receptor expression is observed in the striatum, which is reversed by L-DOPA treatment [133]. Li et al. [134] have reported a decrease in 5-HT_{2A} receptor binding in the insular, prefrontal, cingulate and primary somatosensory cortices, as well as in the caudate nucleus of 6-OHDA-lesioned rats. The loss of DA neurons induced by MPTP in monkeys has no effect on 5-HT_{2A} expression while chronic L-DOPA treatment specifically increases 5-HT_{2A} receptor binding in the dorsomedial caudate nucleus of MPTP-treated monkeys [135].

Concerning 5-HT_{2C} receptors, their expression is decreased in the striatum but not in the STN of 6-OHDA rats without any change after L-DOPA treatment [133]. Interestingly, the increased expression of 5-HT_{2C} receptors in the SNr of parkinsonian patients [136] appears to participate in the overactivity of this brain region by dampening the antiparkinsonian action of DA drugs in 6-OHDA rats primed with L-DOPA [123, 124]. Changes of 5-HT_3 receptor have also been reported after unilateral 6-OHDA lesion in rats showing a dysfunction and/or downregulation of 5-HT_3 receptors expressed on interneurons and pyramidal neurons of medial PFC [125, 137], but the effects of L-DOPA on these receptors have not yet been investigated.

All these receptors have been identified as putative therapeutic targets to improve L-DOPA therapy by reducing motor and non-motor side effects induced by L-DOPA [105, 122, 138–144]. Clinical studies have reported the ability of 5-HT_{2A} antagonists to reduce hallucinations and psychosis induced by L-DOPA [145–148] in line with an increased 5-HT_{2A} receptor binding in the ventral visual pathway, bilateral dorsolateral PFC, medial orbitofrontal cortex and insula of parkinsonian patients developing visual hallucinations [128, 145]. 5-HT_{2A} antagonists have also been shown to alleviate L-DOPA-induced dyskinesias in parkinsonian patients [149] and MPTP-treated monkeys [150] and to improve motor impairments in MPTP-treated mice [151]. 5-HT_{2C} antagonists have been proposed to reduce depression and improve motor function in depressed parkinsonian patients [138, 152]. The use of 5-HT_3 antagonists could help reducing excess cortical transmission induced by L-DOPA in psychotic episodes without altering the motor score of patients [143, 144].

Other changes in 5-HT indexes have been associated with L-DOPA treatment and more specifically with motor side effects such as L-DOPA-induced dyskinesias (LIDs) [98]. In particular, studies in rats and marmosets [153, 154] have shown that chronic L-DOPA treatment alters the morphology of 5-HT neurons (increased SERT binding densities and sprouting of 5-HT varicosities with high synaptic incidence), an effect that underlies a maladaptive synaptic plasticity of 5-HT terminals that may predispose to dyskinesia [102, 153–158]. By using SERT binding and TPH immunolabeling, studies have consistently described a sprouting of 5-HT axon terminals in the DA-lesioned striatum and motor–premotor cortices of dyskinetic rats [153] and in caudate nucleus and putamen of MPTP-treated monkeys that develop LIDs [153, 154]. In parkinsonian patients, SERT binding levels are also significantly increased in both the putamen and globus pallidus of dyskinetic patients [153]. The 5-HT hyperinnervation and/or the marked hypertrophy of 5-HT axon varicosities could participate in the fluctuations of synaptic DA levels induced by L-DOPA treatment. The fluctuation of synaptic DA has been proposed to be responsible for the emergence of peak-dose dyskinesia in parkinsonian patients [28, 29, 92, 97, 108, 153].

In conclusion, the present data demonstrate that 5-HT neurons are the prime target of L-DOPA in the parkinsonian brain. This pathophysiological scenario results in an ectopic release of DA induced by L-DOPA together with an overall decrease in 5-HT transmission that occurs in a time- and

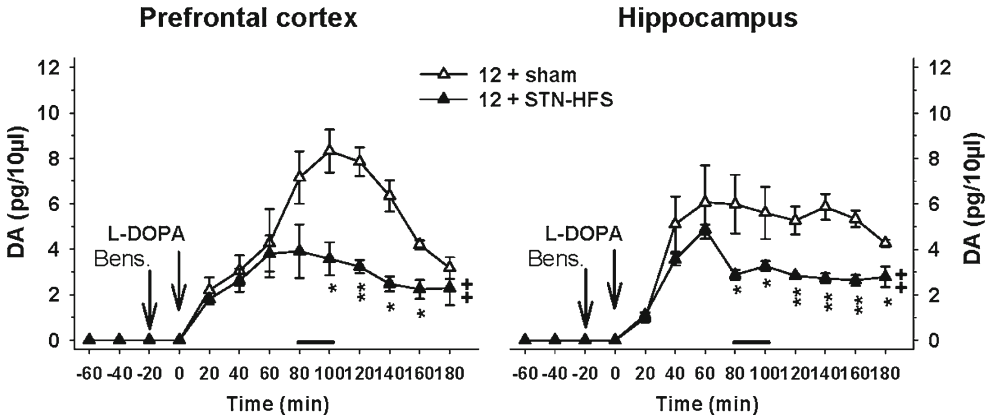

Fig. 4 High-frequency stimulation of the subthalamic nucleus (*STN-HFS*) reduces L-DOPA-induced DA release in the prefrontal cortex and hippocampus of 6-OHDA-lesioned rats. The intraperitoneal administration of L-DOPA at 12 mg/kg (preceded by the intraperitoneal administration of the inhibitor of peripheral decarboxylase benserazide (*Bens.*) at 15 mg/kg; see *vertical bars*) increases DA extracellular levels in the prefrontal cortex (*left panel*) and the hippocampus (*right panel*) of 6-OHDA-lesioned rats. STN-HFS (130 Hz, 30 µA) applied for 20 min and starting 80 min after the injection of L-DOPA significantly reduces L-DOPA-induced DA release in both brain regions ($^{++}p<0.01$ for 12+STN-HFS group versus 12+sham group, Student's *t* test). This effect of STN-HFS could be related to its inhibitory action on 5-HT neuronal activity in line with the ability of 5-$HT_{1A/1B}$ agonists to reduce L-DOPA-induced DA release through a reduction of 5-HT firing rate [91, 92]. $*p<0.05$, $**p<0.01$ for each time point of the 12+STN-HFS group versus the corresponding time point of the 12+sham group, Student's *t* test. Figure taken from Navailles et al. [62]

region-dependent manner with L-DOPA medication, with changes of 5-HT receptor expression and 5-HT terminal morphology. These modifications have been associated with the emergence of numerous side effects, which has validated the use of 5-HT drugs (5-HT antagonists, SSRI…) in an attempt to reduce LIDs and/or cognitive, depressive and psychiatric complications in parkinsonian patients.

HFS-STN and L-DOPA

In most parkinsonian patients, a resistance to dopatherapy and/or DA agonists and an aggravation of side effects induced by antiparkinsonian drugs develop over time, prompting the alternative use of the surgical approach of HFS-STN [159–162]. HFS-STN and L-DOPA are often concomitantly used in parkinsonian patients, which reduces L-DOPA-induced motor fluctuations [163–166]. The mechanisms underlying the improvement of motor symptoms remain unclear [167–169] despite the fact that this surgical strategy allows the discontinuation or large reduction in daily doses of L-DOPA or DA agonists [164, 170–172]. Of particular importance is the ability of HFS-STN to decrease LIDs in parkinsonian patients [159, 165, 166], although this has not been consistently reproduced in animal models, showing an exacerbation [173], a reduction [174] or no alteration [175] of LIDs.

According to the hypothesis that large fluctuations in synaptic DA levels are responsible for the emergence of peak-dose dyskinesias [29], clinical data have shown that the efficacy of HFS-STN to alleviate LIDs may rely on its ability to stabilize striatal synaptic DA concentrations in parkinsonian patients [176]. Preclinical studies have also reported either a prolongation of the increase in striatal DA release induced by a high dose of L-DOPA (50 mg/kg) in partially 6-OHDA-lesioned rats [177] or a dampening of the peak increase in DA release induced by a therapeutic dose of L-DOPA (12 mg/kg) in the PFC and HIPP of fully 6-OHDA-lesioned rats ([62]; see Fig. 4). It has been proposed that the effects of HFS-STN and L-DOPA may rely on their ability to reduce central 5-HT transmission [62]. Both antiparkinsonian approaches reduce 5-HT release in the PFC, HIPP and striatum through distinct mechanisms (cf. paragraphs II and III; [62]), an effect that may participate in the emergence of cognitive and depressive complications [9, 56, 178]. The combination of both approaches did not further inhibit 5-HT release in limbic structures [62] suggesting that it may not exacerbate the occurrence of these unwanted non-motor side effects associated with a decreased 5-HT function while limiting cognitive side effects such as pathological gambling or psychosis associated with excessive DA transmission [179–181].

Conclusions

HFS-STN and L-DOPA therapies impact the 5-HT system. Both strategies tend to lower 5-HT release in various brains regions via different mechanisms. The decrease in 5-HT function occurs in a context of altered expression of various 5-HT receptors in the brain of parkinsonian patients and animal models of the disease. The 5-HT system being involved in virtually all functions attributed to the brain, and it is likely that it plays a pivotal role in the success of these two antiparkinsonian therapies. It cannot be excluded that the decrease in 5-HT function participates in the clinical superiority of these antiparkinsonian treatments compared to other medications. Nonetheless, the clinical and preclinical data suggest rather that the decrease in 5-HT function may lead to mood and cognitive disorders.

Acknowledgments This work was supported by grants from "Centre National de la Recherche Scientifique", Bordeaux 2 University and the Fondation de France. The authors thank Dr Martin Guthrie for linguistic assistance.

Conflict of Interest The authors report no biomedical financial interest or potential conflict of interest.

References

1. Melamed E, Zoldan J, Friedberg G, Ziv I, Weizmann A (1996) Involvement of serotonin in clinical features of Parkinson's disease and complications of L-DOPA therapy. Adv Neurol 69:545–550
2. McDonald WM, Richard IH, DeLong MR (2003) Prevalence, etiology, and treatment of depression in Parkinson's disease. Biol Psychiatry 54:363–375
3. Tandberg E, Larsen JP, Aarsland D, Cummings JL (1996) The occurrence of depression in Parkinson's disease. A community-based study. Arch Neurol 53:175–179
4. Schuurman AG, van den Akker M, Ensinck KT, Metsemakers JF, Knottnerus JA, Leentjens AF, Buntinx F (2002) Increased risk of Parkinson's disease after depression: a retrospective cohort study. Neurology 58:1501–1504
5. Shiba M, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, Schaid DJ, Rocca WA (2000) Anxiety disorders and depressive disorders preceding Parkinson's disease: a case–control study. Mov Disord 15:669–677
6. Eskow Jaunajars KL, Angoa-Perez M, Kuhn DM, Bishop C (2011) Potential mechanisms underlying anxiety and depression in Parkinson's disease: consequences of L-DOPA treatment. Neurosci Biobehav Rev 35:556–564
7. Steinbusch HW (1984) Serotonin-immunoreactive neurons and their projections in the CNS. In: Björklund A, Hökfelt T, Kuhar MJ (eds) Handbook of chemical neuroanatomy—classical transmitters and transmitters receptors in the CNS Part II. Elsevier, Amsterdam, pp 68–125
8. Kish SJ (2003) Biochemistry of Parkinson's disease: is a brain serotonergic deficiency a characteristic of idiopathic Parkinson's disease? Adv Neurol 91:39–49
9. Scholtissen B, Verhey FR, Steinbusch HW, Leentjens AF (2006) Serotonergic mechanisms in Parkinson's disease: opposing

results from preclinical and clinical data. J Neural Transm 113:59–73
10. Birkmayer W, Birkmayer JD (1987) Dopamine action and disorders of neurotransmitter balance. Gerontology 33:168–171
11. Kish SJ, Tong J, Hornykiewicz O, Rajput A, Chang LJ, Guttman M, Furukawa Y (2008) Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease. Brain 131:120–131
12. Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y (1983) Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res 275:321–328
13. Kerenyi L, Ricaurte GA, Schretlen DJ, McCann U, Varga J, Mathews WB, Ravert HT, Dannals RF, Hilton J, Wong DF, Szabo Z (2003) Positron emission tomography of striatal serotonin transporters in Parkinson disease. Arch Neurol 60:1123–1129
14. Politis M, Wu K, Loane C, Kiferle L, Molloy S, Brooks DJ, Piccini P (2010) Staging of serotonergic dysfunction in Parkinson's disease: an in vivo 11C-DASB PET study. Neurobiol Dis 40:216–221
15. Caretti V, Stoffers D, Winogrodzka A et al (2008) (2008) Loss of thalamic serotonin transporters in early drug-naïve Parkinson's disease patients is associated with tremor: an [(123)I]beta-CIT SPECT study. J Neural Transm 115:721–729
16. Roselli F, Pisciotta NM, Pennelli M, Aniello MS, Gigante A, De Caro MF, Ferrannini E, Tartaglione B, Niccoli-Asabella A, Defazio G, Livrea P, Rubini G (2010) Midbrain SERT in degenerative parkinsonisms: a 123I-FP-CIT SPECT study. Mov Disord 25:1853–1859
17. Doder M, Rabiner EA, Turjanski N, Lees AJ, Brooks DJ (2003) Tremor in Parkinson's disease and serotonergic dysfunction: an 11C-WAY 100635 PET study. Neurology 60:601–605
18. Halliday GM, Blumbergs PC, Cotton RG, Blessing WW, Geffen LB (1990) Loss of brainstem serotonin- and substance P-containing neurons in Parkinson's disease. Brain Res 510:104–107
19. Jellinger KA (1991) Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. Mol Chem Neuropathol 14:153–197
20. Kovacs GG, Klöppel S, Fischer I, Dorner S, Lindeck-Pozza E, Birner P, Bötefür IC, Pilz P, Volk B, Budka H (2003) Nucleus-specific alteration of raphe neurons in human neurodegenerative disorders. Neuroreport 14:73–76
21. Ungerstedt U, Arbuthnott GW (1970) Quantitative recording of rotational behaviour in rats after 6-hydroxy-dopamine lesion of the nigrostriatal dopamine system. Brain Res 24:485–493
22. Henry B, Crossman AR, Brotchie JM (1998) Characterization of enhanced behavioural responses to L-DOPA following repeated administration in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. Exp Neurol 151:334–342
23. Ungerstedt U (1971) Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behaviour. Acta Physiol Scand Suppl 367:49–68
24. Zetterstrom T, Herrera-Marschitz M, Ungerstedt U (1986) Simultaneous measurement of dopamine release and rotational behaviour in the 6-hydroxydopamine denervated rats using intracerebral dialysis. Brain Res 376:1–7
25. Herrera-Marschitz M, Arbuthnott G, Ungerstedt U (2010) The rotational model and microdialysis: significance for dopamine signalling, clinical studies and beyond. Prog Neurobiol 90:176–189
26. Pearce RK, Jackson M, Smith L, Jenner P, Marsden CD (1995) Chronic L-DOPA administration induces dyskinesias in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated common marmoset (Callithrix Jacchus). Mov Disord 10:731–740
27. Cenci MA, Ohlin KE (2009) Rodent models of treatment-induced motor complications in Parkinson's disease. Parkinsonism Relat Disord 15:S13–S17
28. Olanow CW, Obeso JA (2000) Preventing levodopa-induced dyskinesias. Ann Neurol 47(Suppl 1):S167–S176
29. de la Fuente-Fernandez R, Sossi V, Huang Z, Furtado S, Lu JQ, Calne DB, Ruth TJ, Stoessl AJ (2004) Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. Brain 127:2747–2754
30. Cenci MA, Lundblad M (2006) Post- versus presynaptic plasticity in L-DOPA-induced dyskinesia. J Neurochem 99:381–392
31. Cenci MA (2007) L-DOPA-induced dyskinesia: cellular mechanisms and approaches to treatment. Parkinsonism Relat Disord 13:S263–S267
32. Perez-Otano I, Herrero MT, Oset C, De Ceballos ML, Luguin MR, Obseo JA, Del Rio J (1991) Extensive loss of dopamine and serotonin induced by chronic administration of MPTP in the marmoset. Brain Res 567:127–132
33. Pifl C, Schingnitz G, Hornykiewicz O (1991) Effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on the regional distribution of brain monoamines in the rhesus monkey. Neuroscience 44:591–605
34. Russ H, Mihatsch W, Gerlach M, Riederer P, Przuntek H (1991) Neurochemical and behavioural features induced by chronic low dose treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset: implications for Parkinson's disease? Neurosci Lett 123:115–118
35. Boulet S, Mounayar S, Poupard A et al (2008) Behavioral recovery in MPTP-treated monkeys: neurochemical mechanisms studied by intrastriatal microdialysis. J Neurosci 28:9575–9584
36. Hara K, Tohyama I, Kimura H, Fukuda H, Nakamura S, Kameyama M (1987) Reversible serotoninergic neurotoxicity of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mouse striatum studied by neurochemical and immunohistochemical approaches. Brain Res 410:371–374
37. Nayyar T, Bubser M, Ferguson MC, Neely MD, Shawn Goodwin J, Montine TJ, Deutch AY, Ansah TA (2009) Cortical serotonin and norepinephrine denervation in parkinsonism: preferential loss of beaded serotonin innervation. Eur J Neurosci 30:207–216
38. Rousselet E, Joubert C, Callebert J, Parain K, Tremblay L, Orieux G, Launay JM, Cohen-Salmon C, Hirsch EC (2003) Behavioral changes are not directly related to striatal monoamine levels, number of nigral neurons, or dose of parkinsonian toxin MPTP in mice. Neurobiol Dis 14:218–228
39. Vuckovic MG, Wood RI, Holschneider DP, Abernathy A, Togasaki DM, Smith A, Petzinger GM, Jakowec MW (2008) Memory, mood, dopamine, and serotonin in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. Neurobiol Dis 32:319–327
40. Rozas G, Liste I, Guerra MJ, Labandeira-Garcia JL (1998) Sprouting of the serotonergic afferents into striatum after selective lesion of the dopaminergic system by MPTP in adult mice. Neurosci Lett 245:151–154
41. Breese GR, Baumeister AA, McCown TJ, Emerick SG, Frye GD, Crotty K, Muller RA (1984) Behavioral differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. J Pharmacol Exp Ther 231:343–354
42. Erinoff L, Snodgrass SR (1986) Effects of adult or neonatal treatment with 6-hydroxydopamine or 5,7-dihydroxytryptamine on locomotor activity, monoamine levels, and response to caffeine. Pharmacol Biochem Behav 24:1039–1045
43. Iwamoto ET, Loh HH, Way EL (1976) Circling behavior in rats with 6-hydroxydopamine or electrolytic nigral lesions. Eur J Pharmacol 37:339–356
44. Zhou FC, Bledsoe S, Murphy J (1991) Serotonergic sprouting is induced by dopamine-lesion in substantia nigra of adult rat brain. Brain Res 556:108–116

45. Commins DL, Shaughnessy RA, Axt KJ, Vosmer G, Seiden LS (1989) Variability among brain regions in the specificity of 6-hydroxydopamine (6-OHDA)-induced lesions. J Neural Transm 77:197–210
46. Kaya AH, Vlamings R, Tan S, Lim LW, Magill PJ, Steinbusch HW, Visser-vanderwalle V, Sharp T, Temel Y (2008) Increased electrical and metabolic activity in the dorsal raphe nucleus of parkinsonian rats. Brain Res 1221:93–97
47. Temel Y, Boothman LJ, Blokland A, Magill PJ, Steinbusch HW, Visser-Vandewalle V, Sharp T (2007) Inhibition of 5-HT neuron activity and induction of depressive-like behavior by high-frequency stimulation of the subthalamic nucleus. Proc Natl Acad Sci U S A 104:17087–17092
48. Wang S, Zhang GJ, Liu J, Wu ZH, Wang T, Gui ZH, Chen L, Wang Y (2009) Unilateral lesion of the nigrostriatal pathway induces an increase of neuronal firing of the midbrain raphe nuclei 5-HT neurons and a decrease of their response to 5-HT (1A) receptor stimulation in the rat. Neuroscience 159:850–861
49. Wang S, Zhang GJ, Liu J, Wu ZH, Ali U, Wang Y, Chen L, Gui ZH (2009) The firing of pyramidal neurons in medial prefrontal cortex and their response to 5-hydroxytryptamine-1A receptor stimulation in a rat model of Parkinson's disease. Neuroscience 162:1091–1100
50. Wang S, Zhang QJ, Liu J, Ali U, Wu ZH, Chen L, Gui ZH, Wang Y, Hui YP (2009) In vivo effects of activation and blockade of 5-HT(2A/2C) receptors in the firing activity of pyramidal neurons of medial prefrontal cortex in a rodent model of Parkinson's disease. Exp Neurol 219:239–248
51. Takeuchi Y, Sawada T, Blunt S, Jenner P, Marsden CD (1991) Serotonergic sprouting in the neostriatum after intrastriatal transplantation of fetal ventral mesencephalon. Brain Res 551:171–177
52. Guiard BP, El Mansari M, Merali Z, Blier P (2008) Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions. Int J Neuropsychopharmacol 11:625–639
53. Bejjani BP, Damier P, Arnulf I et al (1999) Transient acute depression induced by high-frequency deep-brain stimulation. N Engl J Med 340:1476–1480
54. Deuschl G, Fogel W, Hahne M et al (2002) Deep-brain stimulation for Parkinson's disease. J Neurol 249(suppl 3):36–39
55. Houeto JL, Damier P, Bejjani PB et al (2000) Subthalamic stimulation in Parkinson disease. Arch Neurol 57:461–465
56. Tan SK, Hartung H, Visser-Vandewalle V, Steinbusch HW, Temel Y, Sharp T (2011) A combined in vivo neurochemical and electrophysiological analysis of the effect of high-frequency stimulation of the subthalamic nucleus on 5-HT transmission. Exp Neurol. doi:10.1016/j.expneurol.2011.08.027
57. Thobois S, Mertens P, Guenot M et al (2002) Subthalamic nucleus stimulation in Parkinson's disease. J Neurol 249:529–534
58. Kulisevsky J, Berthier ML, Gironell A et al (2002) Mania following deep brain stimulation for Parkinson's disease. Neurology 59:1421–1424
59. Doshi PK, Chaya N, Bhatt MH (2002) Depression leading to attempted suicide after subthalamic nucleus stimulation for Parkinson's disease. Mov Disord 17:1084–1100
60. Houeto JL, Mesnage V, Mallet L et al (2002) Behavioral disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 72:701–707
61. Saint-Cyr JA, Trépanier LL, Kumar R et al (2000) Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 123:2091–2108
62. Navailles S, Benazzouz A, Bioulac B, Gross C, De Deurwaerdère P (2010) High-frequency stimulation of the subthalamic nucleus and L-3,4-dihydroxyphenylalanine inhibit in vivo serotonin release in the prefrontal cortex and hippocampus in a rat model of Parkinson's disease. J Neurosci 30:2356–2364
63. Tan SK, Janssen ML, Jahanshahi A, Chouliaras L, Visser-Vandewalle V, Lim LW, Steinbusch HW, Sharp T, Temel Y (2011) High frequency stimulation of the subthalamic nucleus increases c-fos immunoreactivity in the dorsal raphe nucleus and afferent brain regions. J Psychiatr Res 45:1307–1315
64. Amilhon B, Lepicard E, Renoir T, Mongeau R, Popa D, Poirel O, Miot S, Gras C, Gardier AM, Gallego J, Hamon M, Lanfumey L, Gasnier B, Giros B, El Mestikawy S (2010) VGLUT3 (vesicular glutamate transporter type 3) contribution to the regulation of serotonergic transmission and anxiety. J Neurosci 30:2198–2210
65. Hale MW, Lowry CA (2011) Functional topography of midbrain and pontine serotonergic systems: implications for synaptic regulation of serotonergic circuits. Psychopharmacology (Berl) 213:243–264
66. Kiyasova V, Fernandez SP, Laine J, Stankovski L, Muzerelle A, Doly S, Gaspar P (2011) A genetically defined morphologically and functionally unique subset of 5-HT neurons in the mouse raphe nuclei. J Neurosci 31:2756–2768
67. McQuade R, Sharp T (1997) Functional mapping of dorsal and median raphe 5-hydroxytryptamine pathways in forebrain of the rat using microdialysis. J Neurochem 69:791–796
68. Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K (2009) Optical deconstruction of parkinsonian neural circuitry. Science 324:354–359
69. Sesia T, Bulthuis V, Tan S, Lim LW, Vlamings R, Blokland A, Steinbusch HW, Sharp T, Visser-Vandewalle V, Temel Y (2010) Deep brain stimulation of the nucleus accumbens shell increases impulsive behavior and tissue levels of dopamine and serotonin. Exp Neurol 225:302–309
70. Hartung H, Tan SK, Steinbusch HM, Temel Y, Sharp T (2011) High-frequency stimulation of the subthalamic nucleus inhibits the firing of juxtacellular labelled 5-HT-containing neurones. Neuroscience 186:135–145
71. Cotzias GC (1968) L-Dopa for Parkinsonism. N Engl J Med 278:630
72. Hornykiewicz O (1966) Dopamine (3-hydroxytyramine) and brain function. Pharmacol Rev 18:925–964
73. Miller DW, Abercrombie ED (1999) Role of high-affinity dopamine uptake and impulse activity in the appearance of extracellular dopamine in striatum after administration of exogenous L-DOPA: studies in intact and 6-hydroxydopamine-treated rats. J Neurochem 72:1516–1522
74. Sarre S, De Klippel N, Herregodts P, Ebinger G, Michotte Y (1994) Biotransformation of locally L-dopa in the corpus striatum of the hemi-parkinsonian rats studies with microdialysis. Naunyn Schmiedebergs Arch Pharmacol 350:15–21
75. Bunney BS, Aghajanian GK, Roth RH (1973) Comparison of effects of L-dopa, amphetamine and apomorphine on firing rate of rat dopaminergic neurons. Nat New Biol 245:123–125
76. Mercuri NB, Calabresi P, Bernardi G (1990) Responses of rat substantia nigra compacta neurones to L-DOPA. Br J Pharmacol 100:257–260
77. Harden DG, Grace AA (1995) Activation of dopamine cell firing by repeated L-DOPA administration to dopamine-depleted rats: its potential role in mediating the therapeutic response to L-DOPA treatment. J Neurosci 15:6157–6166
78. Maeda T, Kannari K, Suda T, Matsunaga M (1999) Loss of regulation by presynaptic dopamine D2 receptors of exogenous L-DOPA-derived dopamine release in the dopaminergic denervated striatum. Brain Res 817:185–191
79. Lloyd K, Hornykiewicz O (1970) Parkinson's disease: activity of L-dopa decarboxylase in discrete brain regions. Science 170:1212–1213
80. Kannari K, Tanaka H, Maeda T, Tomiyama M, Suda T, Matsunaga M (2000) Reserpine pretreatment prevents increases in extracellular striatal dopamine following L-DOPA administration in rats with nigrostriatal denervation. J Neurochem 74:263–269

81. Lee WY, Chang JW, Nemeth NL, Kang UJ (1999) Vesicular monoamine transporter-2 and aromatic L-amino acid decarboxylase enhance dopamine delivery after L-3,4-dihydroxyphenylalanine administration in parkinsonian rats. J Neurosci 19:3266–3274
82. Arai R, Karasawa N, Nagatsu I (1995) L-DOPA is converted to dopamine in serotonergic fibers of the striatum of the rat: a double-labeling immunofluorescence study. Neurosci Lett 195:195–198
83. Ng LK, Chase TN, Colburn RW, Kopin IJ (1970) L-Dopa-induced release of cerebral monoamines. Science 170:76–77
84. Tison F, Mons N, Geffard M, Henry P (1991) The metabolism of exogenous L-dopa in the brain: an immunohistochemical study of its conversion to dopamine in non-catecholaminergic cells of the rat brain. J Neural Transm Park Dis Dement Sect 3:27–39
85. Yamada H, Aimi Y, Nagatsu I, Taki K, Kudo M, Arai R (2007) Immunohistochemical detection of L-DOPA-derived dopamine within serotonergic fibers in the striatum and the substantia nigra pars reticulate in parkinsonian model rats. Neurosci Res 59:1–7
86. Arai R, Karazawa N, Nagatsu I (1996) Aromatic L-amino acid decarboxylase is present in serotonergic fibers of the striatum of the rat. A double-labeling immunofluorescence study. Brain Res 706:177–179
87. Ng LK, Chase TN, Colburn RW, Kopin IJ (1972) L-Dopa in Parkinsonism. A possible mechanism of action. Neurology 22:688–696
88. Ng LK, Colburn RW, Kopin IJ (1972) Effects of L-dopa on accumulation and efflux of monoamines in particles of brain homogenates. J Pharmacol Exp Ther 183:316–325
89. Navailles S, Bioulac B, Gross C, De Deurwaerdère P (2010) Serotonergic neurons mediate ectopic release of dopamine induced by L-DOPA in a rat model of Parkinson's disease. Neurobiol Dis 38:136–143
90. Tanaka H, Kannari K, Maeda T, Tomiyama M, Suda T, Matsunaga M (1999) Role of serotonergic neurons in L-DOPA-derived extracellular dopamine in the striatum of 6-OHDA-lesioned rats. Neuroreport 10:631–634
91. Kannari K, Yamato H, Shen H, Tomiyama M, Suda T, Matsunaga M (2001) Activation of 5-HT(1A) but not 5-HT(1B) receptors attenuates an increase in extracellular dopamine derived from exogenously administered L-DOPA in the striatum with nigrostriatal denervation. J Neurochem 76:1346–1353
92. Lindgren HS, Andersson DR, Lagerkvist S, Nissbrandt H, Cenci MA (2010) L-DOPA-induced dopamine efflux in the striatum and the substantia nigra in a rat model of Parkinson's disease: temporal and quantitative relationship to the expression of dyskinesia. J Neurochem 112:1465–1476
93. Yamato H, Kannari K, Shen H, Suda T, Matsunaga M (2001) Fluoxetine reduces L-DOPA-derived extracellular DA in the 6-OHDA-lesioned rat striatum. Neuroreport 12:1123–1126
94. Azmitia EC, Segal M (1978) An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. J Comp Neurol 179:641–667
95. Navailles S, Bioulac B, Gross C, De Deurwaerdère P (2011) Chronic L-DOPA therapy alters central serotonergic function and L-DOPA-induced dopamine release in a region-dependent manner in a rat model of Parkinson's disease. Neurobiol Dis 41:585–590
96. Seeman P (1980) Brain dopamine receptors. Pharmacol Rev 32:229–313
97. Carta M, Carlsson T, Kirik D, Björklund A (2007) Dopamine released from 5-HT terminal sis the cause of L-DOPA-induced dyskinesia in parkinsonian rats. Brain 130:1819–1833
98. Navailles S, De Deurwaerdère P (2012) Imbalanced dopaminergic transmission mediated by serotonergic neurons in L-DOPA-induced dyskinesia. Parkinson's Disease. doi:10.1155/2012/323686
99. Bartholini G, Da Prada M, Pletscher A (1968) Decrease of cerebral 5-hydroxytryptamine by 3,4-dihydroxyphenylalanine after inhibition of extracerebral decarboxylase. J Pharm Pharmacol 20:228–229
100. Everett GM, Borcherding JW (1970) L-DOPA: effect on concentrations of dopamine, norepinephrine, and serotonin in brains of mice. Science 168:849–850
101. Tohgi H, Abe T, Takahashi S, Takahashi J, Hamato H (1993) Alterations in the concentration of serotonergic and dopaminergic substances in the cerebrospinal fluid of patients with Parkinson's disease, and their changes after L-dopa administration. Neurosci Lett 159:135–138
102. Gil S, Park C, Lee J, Koh H (2010) The roles of striatal serotonin and L: -amino-acid decarboxylase on L: -DOPA-induced dyskinesia in a hemiparkinsonian rat model. Cell Mol Neurobiol 30:817–825
103. Héry F, Simonnet G, Bourgoin S, Soubrié P, Artaud F, Hamon M, Glowinski J (1979) Effect of nerve activity on the in vivo release of [3H]serotonin continuously formed from L-[3H]tryptophan in the caudate nucleus of the cat. Brain Res 169:317–334
104. Thorré K, Sarre S, Smolders I, Ebinger G, Michotte Y (1998) Dopaminergic regulation of serotonin release in the substantia nigra of the freely moving rat using microdialysis. Brain Res 796:107–116
105. Navailles S, Carta M, Guthrie M, De Deurwaerdère P (2012) L-DOPA and serotonergic neurons: functional implication and therapeutic perspectives in Parkinson's disease. CNS Agents Med Chem (in press)
106. Navailles S, De Deurwaerdère P (2011) Presynaptic control of serotonin on striatal dopamine function. Psychopharmacology (Berl) 213:213–242
107. Gil SJ, Park CH, Lee JE, Minn YK, Koh HC (2011) Positive association between striatal serotonin level and abnormal involuntary movements in chronic L-DOPA-treated hemiparkinsonian rats. Brain Res Bull 84:151–156
108. Lundblad M, af Bjerkén S, Cenci MA, Pomerleau F, Gerhardt GA, Strömberg I (2009) Chronic intermittent L-DOPA treatment induces changes in dopamine release. J Neurochem 108:998–1008
109. Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Snadmann-Kell D, Rub U (2002) Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J Neurol 249(Suppl 3): III/1-5
110. Pavese N, Simpson BS, Metta V, Ramlackhansingh A, Chaudhuri KR, Brooks DJ (2011) [(18)F]FDOPA uptake in the raphe nuclei complex reflects serotonin transporter availability. A combined [(18)F]FDOPA and [(11)C]DASB PET study in Parkinson's disease. Neuroimage. doi:10.1016/j.neuroimage.2011.09.034.
111. Alexander T, Sortwell CE, Sladek CD, Roth RH, Steece-Collier K (1997) Comparison of neurotoxicity following repeated administration of l-dopa, d-dopa and dopamine to embryonic mesencephalic dopamine neurons in cultures derived from Fisher 344 and Sprague-Dawley donors. Cell Transplant 6:309–315
112. Basma AN, Morris EJ, Nicklas WJ, Geller HM (1995) L-Dopa cytotoxicity to PC12 cells in culture is via its autoxidation. J Neurochem 64:825–832
113. Cheng N, Maeda T, Kume T, Kaneko S, Kochiyama H, Akaike A, Goshima Y, Misu Y (1996) Differential neurotoxicity induced by L-DOPA and dopamine in cultured striatal neurons. Brain Res 743:278–283
114. Pardo B, Mean MA, de Yebenes JG (1995) L-Dopa inhibits complex IV of the electron transport chain in catecholamine-rich human neuroblastoma NB69 cells. J Neurochem 64:576–582
115. Hashiguti H, Nakahara D, Maruyama W, Naoi M, Ikeda T (1993) Simultaneous determination of in vivo hydroxylation of tyrosine

and tryptophan in rat striatum by microdialysis-HPLC: relationship between dopamine and serotonin biosynthesis. J Neural Transm Gen Sect 93:213–223
116. Kuhn DM, Arthur R Jr (1998) Dopamine inactivates tryptophan hydroxylase and forms a redox-cycling quinoprotein: possible endogenous toxin to serotonin neurons. J Neurosci 18:7111–7117
117. Kuhn DM, Arthur RE Jr (1999) L-DOPA-quinone inactivates tryptophan hydroxylase and converts the enzyme to a redox-cycling quinoprotein. Brain Res Mol Brain Res 73:78–84
118. Maruyama W, Naoi M, Takahashi A, Watanabe H, Konagaya Y, Mokuno K, Hasegawa S, Nakahara D (1992) The mechanism of perturbation in monoamine metabolism by L-dopa therapy: in vivo and in vitro studies. J Neural Transm Gen Sect 90:183–197
119. Eskow Jaunajars KL, Dupre KB, Ostock CY, Button T, Deak T, Bishop C (2010) Behavioral and neurochemical effects of chronic L-DOPA treatment on nonmotor sequelae in the hemiparkinsonian rat. Behav Pharmacol 21:627–637
120. Cao J, Liu J, Zhang QJ, Wang T, Wang S, Han LN, Li Q (2007) The selective 5-HT1A receptor antagonist WAY-100635 inhibits neuronal activity of the ventromedial prefrontal cortex in a rodent model of Parkinson's disease. Neurosci Bull 23:315–322
121. De Deurwaerdère P, Chesselet MF (2000) Nigrostriatal lesions alter oral dyskinesia and c-Fos expression induced by the serotonin agonist 1-(m-chlorophenyl)piperazine in adult rats. J Neurosci 20:5170–5178
122. De Deurwaerdère P, Mignon L, Chesselet MF (2010) Physiological and pathophysiological aspects of 5-HT_{2C} receptors in basal ganglia. In: Di Giovanni G, Neve K (eds) The pathophysiology of central 5-HT_{2C} receptors, vol The receptors series. Springer, New York
123. Fox SH, Moser B, Brotchie JM (1998) Behavioral effects of 5-HT2C receptor antagonism in the substantia nigra zona reticulata of the 6-hydroxydopamine-lseioned rat model of Parkinson's disease. Exp Neurol 151:35–49
124. Fox SH, Brotchie JM (2000) 5-HT2C receptor binding is increased in the substantia nigra pars reticulata in Parkinson's disease. Mov Disord 15:1046–1049
125. Gui ZH, Zhang QJ, Liu J, Ali U, Wang Y, Wang T, Chen L, Hou C, Fan LL (2010) In vivo modulation of the firing activity of putative slow- and fast-spiking interneurons in the medial prefrontal cortex by 5-HT3 receptors in 6-hydroxydopamine-minduced parkinsonian rats. Neuroscience 169:1315–1325
126. Chen CP, Alder JT, Bray L, Kingsbury AE, Francis PT, Foster OJ (1998) Post-synaptic 5-HT1A and 5-HT2A receptors are increased in Parkinson's disease neocortex. Ann NY Acad Sci 861:288–289
127. Frechilla D, Cobreros A, Salside L, Moratalla R, Insausti R, Luquin M, Del Rio J (2001) Serotonin 5-HT(1A) receptor expression is selectively enhanced in the striosomal compartment of chronic parkinsonian monkeys. Synapse 39:288–296
128. Huot P, Johnston TH, Koprich JB, Winkelmolen L, Fox SH, Brotchie JM (2010) Regulation of cortical and striatal 5-HT (1A) receptors in the MPTP-lesioned macaque Neurobiol Aging, in press.
129. Castro ME, Pascual J, Romon T, Berciano J, Figols J, Pazos A (1998) 5-HT1B receptor binding in degenerative movement disorders. Brain Res 290:323–328
130. Quirion R, Richard J (1987) Differential effects of selective lesion of cholinergic and dopaminergic neurons on serotonin-type 1 receptors in rat brain. Synapse 1:124–130
131. Zhang X, Andren PE, Greengard P, Svenningsson P (2008) Evidence for a role of the 5-HT1B receptor and its adaptor protein, p11, in L-DOPA treatment of an animal model of Parkinsonism. Proc Natl Acad Sci U S A 105:2163–2168
132. Zhang QJ, Wang S, Liu J, Ali U, Gui ZH, Wu ZH, Hui YP, Wang Y, Chen L (2010) Unilateral lesion of the nigrostriatal pathway decreases the response of interneurons in medial prefrontal cortex to 5-HT 2A/2C receptor stimulation in the rat. Brain Res 1312:127–137
133. Zhang X, Andren PE, Svenningsson P (2007) Changes on 5-HT2 receptor mRNAs in striatum and subthalamic nucleus in Parkinson's disease model. Physiol Behav 92:29–33
134. Li Y, Huang XF, Deng C, Meyer B, Wu A, Yu Y, Ying W, Yang GY, Yenari MA, Wang Q (2010) Alterations in 5-HT2A receptor binding in various brain regions among 6-hydroxydopamine-induced parkinsonian rats. Synapse 64:224–230
135. Riahi G, Morissette M, Parent M, Di Paolo T (2011) Brain 5-HT (2A) receptors in MPTP monkeys and levodopa-induced dyskinesias. Eur J Neurosci 33:1823–1831
136. Fox SH, Brotchie JM (2000) 5-HT(2C) receptor antagonists enhance the behavioural response to dopamine D(1) receptor agonists in 6-hydroxydopamine-lesioned rat. Eur J Pharmacol 398:59–64
137. Zhang QJ, Li LB, Niu XL, Liu J, Gui ZH, Feng JJ, Ali U, Hui YP, Wu ZH (2011) The pyramidal neurons in the medial prefrontal cortex show decreased response to 5-hydroxytryptamine-3 receptor stimulation in a rodent model of Parkinson's disease. Brain Res 1384:69–79
138. Di Giovanni G, Di Matteo V, Pierucci M, Benigno A, Esposito E (2006) Serotonin involvement in the basal ganglia pathophysiology: could the 5-HT2C receptor be a new target for therapeutic strategies? Curr Med Chem 13:3069–3081
139. Di Matteo V, Pierucci M, Esposito E, Cresimanno G, Benigno A, Di Giovanni G (2008) Serotonin modulation of the basal ganglia circuitry: therapeutic implication for Parkinson's disease and other motor disorders. Prog Brain Res 172:423–463
140. Durif F, Vidailhet M, Assal F, Roche C, Bonnet AM, Agid Y (1997) Low-dose clozapine improves dyskinesias in Parkinson's disease. Neurology 48:658–662
141. Ikeguchi K, Kuroda A (1995) Mianserin treatment of patients with psychosis induced by antiparkinsonian drugs. Eur Arch Psychiatry Clin Neurosci 244:320–324
142. Nicholson SL, Brotchie JM (2002) 5-hydroxytryptamine (5-HT, serotonin) and Parkinson's disease—opportunities for novel therapeutics to reduce the problems of levodopa therapy. Eur J Neurol S3:1–6
143. Zoldan J, Friedberg G, Livneh M, Melamed E (1995) Psychosis in advanced Parkinson's disease: treatment with ondansetron, a 5-HT3 receptor antagonist. Neurology 45:1305–1308
144. Zoldan J, Friedberg G, Weizman A, Melamed E (1996) Ondansetron, a 5-HT3 antagonist for visual hallucinations and paranoid delusional disorder associated with chronic L-DOPA therapy in advanced Parkinson's disease. Adv Neurol 69:541–544
145. Ballanger B, Strafella AP, van Eimeren T, Zurowski M, Rusjan PM, Houle S, Fox SH (2010) Serotonin 2A receptors and visual hallucinations in Parkinson disease. Arch Neurol 67:416–421
146. Meltzer HY, Mills R, Revell S, Williams H, Johnson A, Bahr D, Friedman JH (2010) Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. Neuropsychopharmacology 35:881–892
147. Rabey JM (2009) Hallucinations and psychosis in Parkinson's disease. Parkinsonism Relat Disord 15:S105–S110
148. Weiner DM, Vanover KE, Brann MR, Meltzer HY, Davis RE (2003) Psychosis of Parkinson's disease: serotonin 2A inverse agonists as potential therapeutics. Curr Opin Investig Drugs 4:815–819
149. Meco G, Stirpe P, Edito F, Purcaro C, Valente M, Bernardi S, Vanacore N (2009) Aripiprazole in L-dopa-induced dyskinesias: a one-year open-label pilot study. J Neural Transm 116:881–884
150. Vanover KE, Betz AJ, Weber SM, Bibbiani F, Kielaite A, Weiner DM, Davis RE, Chase TN, Salamone JD (2008) A 5-HT2A receptor inverse agonist, ACP-103, reduces tremor in a rat model

and levodopa-induced dyskinesias in a monkey model. Pharmacol Biochem Behav 90:540–544
151. Ferguson MC, Nayyar T, Deutch AY, Ansah TA (2010) 5-HT2A receptor antagonists improve motor impairments in the MPTP mouse model of Parkinson's disease. Neuropharmacology 59:31–36
152. Werneck AL, Rosso AL, Vincent MB (2009) The use of an antagonist 5-HT2a/c for depression and motor function in Parkinson's disease. Arq Neuropsiquiatr 67:407–412
153. Rylander D, Parent M, O'Sullivan SS, Dovero S, Lees AJ, Bezard E, Descarries L, Cenci MA (2010) Maladaptive plasticity of serotonin axon terminals in levodopa-induced dyskinesia. Ann Neurol 68:619–628
154. Zeng BY, Iravani MM, Jackson MJ, Rose S, Parent A, Jenner P (2010) Morphological changes in serotoninergic neurites in the striatum and globus pallidus in levodopa primed MPTP treated common marmosets with dyskinesia. Neurobiol Dis 40:599–607
155. Berthet A, Porras G, Doudnikoff E, Stark H, Cador M, Bezard E, Bloch B (2009) Pharmacological analysis demonstrates dramatic alteration of D1 dopamine receptor neuronal distribution in the rat analog of L-DOPA-induced dyskinesia. J Neurosci 29:4829–4835
156. Picconi B, Pisani A, Barone I, Bonsi P, Centonze D, Bernardi G, Calabresi P (2005) Pathological synaptic plasticity in the striatum: implications for Parkinson's disease. Neurotoxicology 26:779–783
157. Picconi B, Ghiglieri V, Calabresi P (2010) L-3,4-Dihydroxyphenylalanine-indued sprouting of serotonin axon terminals: a useful biomarker for dyskinesias? Ann Neurol 68:578–580
158. Prescott IA, Dostrovsky JO, Moro E, Hodaie M, Lozano AM, Hutchison WD (2009) Levodopa enhances synaptic plasticity in the substantia nigra pars reticulata of Parkinson's disease patients. Brain 132:309–318
159. Krack P, Hamel W, Mehdorn HM, Deuschl G (1999) Surgical treatment of Parkinson's disease. Curr Opin Neurol 12:417–425
160. Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, Benabid AL (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 339:1105–1111
161. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Macias R, Alvarez L, Guridi J, Vitek J, DeLong MR (2000) Pathophysiologic basis of surgery for Parkinson's disease. Neurology 55 (Suppl 6):S7–S12
162. Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, Arnulf I, Pidoux B, Dormont D, Cornu P, Agid Y (2002) Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 125:575–583
163. Benabid AL, Chabardes S, Seigneuret E, Pollak P, Fraix V, Krack P, Lebas JF, Grand S, Piallat B (2005) Functional neurosurgery: past, present, and future. Clin Neurosurg 52:265–270
164. Fraix V, Pollak P, Van Blercom N, Xie J, Krack P, Koudsie A, Benabid AL (2000) Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia in Parkinson's disease. Neurology 26:1921–1923
165. Krack P, Limousin P, Benabid AL, Pollak P (1997) Chronic stimulation of subthalamic nucleus improves levodopa-induced dyskinesia in Parkinson's disease. Lancet 350:1676
166. Krack P, Batir A, Van Blercom N et al (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 349:1925–1934
167. Benabid AL, Benazzouz A, Pollak P (2002) Mechanisms of deep brain stimulation. Mov Disord 17(Suppl 3):S73–S74
168. Dostrovsky JO, Lozano AM (2002) Mechanisms of deep brain stimulation. Mov Disord 17(Suppl 3):S63–S68
169. McIntyre CC, Savasta M, GoffL Kerkerian-Le, Vitek JL (2004) Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol 115:1239–1248
170. Lopiano L, Rizzone M, Bergamasco B, Tavella A, Torre E, Perozzo P, Valentini MC, Lanotte M (2001) Deep brain stimulation of the subthalamic nucleus: clinical effectiveness and safety. Neurology 27:552–554
171. Molinuevo JL, Valldeoriola F, Tolosa E, Rumia J, Valls-Sole J, Roldan H, Ferrer E (2000) Levodopa withdrawal after bilateral subthalamic nucleus stimulation in advanced Parkinson disease. Arch Neurol 57:983–988
172. Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A (1999) Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 53:85–90
173. Oueslati A, Sgambato-Faure V, Melon C, Kachidian P, Gubellini P, Amri M, Kerkerian-Le Goff L, Salin P (2007) High-frequency stimulation of the subthalamic nucleus potentiates L-DOPA-induced neurochemical changes in the striatum in a rat model of Parkinson's disease. J Neurosci 27:2377–2386
174. Simonin C, Tir M, Devos D, Jreisler A, Dujardin K, Salleron J, Delval A, Blond S, Defebvre L, Destee A, Krystkowiak P (2009) Reduced levodopa-induced complications after 5 years of subthalamic stimulation in Parkinson's disease: a second honeymoon. J Neurol 256:1736–1741
175. Gubellini P, Eusebio A, Oueslati A, Melon C, Kerkerian-Le Goff L, Salin P (2006) Chronic high-frequency stimulation of the subthalamic nucleus and L-DOPA treatment in experimental parkinsonism: effects on motor behaviour and striatal glutamate transmission. Eur J Neurosci 24:1802–1814
176. Nimura T, Yamaguchi K, Ando T, Shibuya S, Oikawa T, Nakagawa A, Shirane R, Itoh M, Tominaga T (2005) Attenuation of fluctuating striatal synaptic dopamine levels in patients with Parkinson disease in response to subthalamic nucleus stimulation: a positron emission tomography study. J Neurosurg 103:968–973
177. Lacombe E, Carcenac C, Boulet S, Feurstein C, Bertrand A, Poupard A, Savasta M (2007) High-frequency stimulation of the subthalamic nucleus prolongs the increase in striatal dopamine induced by acute l-3,4-dihydroxyphenylalanine in dopaminergic denervated rats. Eur J Neurosci 26:1670–1680
178. Zesiewicz TA, Hauser RA (2002) Depression in Parkinson's disease. Curr Psychiatry Rep 4:69–73
179. Nieoullon A (2002) Dopamine and the regulation of cognition and attention. Prog Neurobiol 67:53–83
180. Siri C, Cilia R, De Gaspari D, Canesi M, Meucci N, Zecchinelli AL, Pezzoli G, Antonini A (2010) Cognitive status of patients with Parkinson's disease and pathological gambling. J Neurol 257:247–252
181. Voon V, Fernagut PO, Wickens J, Baunez C, Rodriguez M, Pavon N, Juncos JL, Obeso JA, Bezard E (2009) Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. Lancet Neurol 8:1140–1149