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## The serotonin system: a potential target for anti-dyskinetic treatments and biomarker discovery.

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## Title page

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## Abstract

L-DOPA-induced dyskinesia is a major problem in the treatment of Parkinson's disease. Today there are few anti-dyskinetic treatments available for the patients, and all of them have major limitations.

Recent findings have revealed an important role of the serotonin system in L-DOPA-induced dyskinesia. In the parkinsonian brain, serotonin axon terminals can compensate for the dopamine loss by converting L-DOPA into dopamine and releasing it as a false neurotransmitter. However, the terminals represent an aberrant source of dopamine release, increasing the risk for dyskinesia. In line with this, a relatively high density of serotonin axon fibres in striatum has been reported in dyskinetic animals and patients. Furthermore, serotonin can influence dyskinesia by modulating glutamate or GABA signalling in the basal ganglia via receptors located on non-serotonergic neurons. Through either mechanism, modulation of certain serotonin receptors has shown to reduce the severity of dyskinetic movements.

The serotonin system represents an interesting target for developing anti-dyskinetic treatments. Future therapies may take advantage of the synergistic effect produced by the modulation of different serotonin receptors or pursue a region-specific modulation of certain receptors. Moreover, morphological or biochemical features of the serotonin system could be used to develop biomarkers for patient stratification in clinical trials of anti-dyskinetic compounds.

## Introduction

L-DOPA-induced dyskinesia (LID) is defined as abnormal involuntary movements that arise as a side effect of L-DOPA treatment, the most effective and common drug used to treat Parkinson's disease (PD). The development of LID can be attributed to a pathological neuroplasticity of the brain, attempting to adapt to a progressive dopamine denervation, (from the disease itself), and a consecutive dopamine efflux from pulsatile L-DOPA administrations. The brain's plastic capacity has shown to be variable and depends on several factors, such as the patient's age and genetics [1]. On top of these factors, lies an important neuromodulator in the serotonin (5-HT) system. Serotonergic neurons in the raphe pontis of the brain stem project axonal fibres to multiple brain areas including the basal ganglia. The system is particularly vulnerable to neurodegeneration and 5-HT levels become greatly reduced with age as well as in neurodegenerative diseases, e.g. PD [2]. The variable extent of 5-HT loss in the parkinsonian brain could be an important determinant for dyskinesia [3].

## Serotonin's multiple mechanisms of actions in the basal ganglia

The underlying mechanisms, by which 5-HT influences dyskinesia, have shown to be complex and are under extensive investigation. The system has several different types of receptors distributed in many brain areas, especially the hippocampus, basal ganglia and striatum. Among the most studied are the autoreceptors 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub>. The 5-HT<sub>1A</sub> receptor is mainly located somatodendritically on raphe-striatal neurons where it regulates neuronal activity and transmitter release. The 5-HT<sub>1B</sub> receptor, on the other hand, is expressed presynaptically, controlling the terminal release. The receptors can also be found on non-serotonergic neurons, such as medium-sized spiny neurons (5-HT<sub>1B</sub>) and corticostriatal neurons (5-HT<sub>1A</sub>), where receptor stimulation reduces pallidal GABA- or striatal glutamate release, respectively. The corticostriatal neurons also

express the 5-HT<sub>2A</sub> receptor, which regulates striatal glutamate release (See Figure 1) [4].

Recent discoveries from rat and primate models of PD suggest multiple mechanisms of action by which the 5-HT system influences LID. One general view is the dopamine-releasing role of striatal 5-HT fibre terminals. These terminals are especially good candidates for converting L-DOPA into dopamine in the dopamine denervated brain, as they express both the DOPA converting enzyme and the vesicular transporter needed for processing dopamine [5, 6]. By releasing dopamine into the extracellular space, the 5-HT terminals facilitate the therapeutic action of L-DOPA, but the release has detrimental consequences. The raphe-terminals lack auto-regulatory feedback mechanisms for dopamine release and cause an aberrant release with excessively enhanced dopamine levels in the extracellular space. Such fluctuations between high and low dopamine levels will lead to supersensitive responses of striatal neurons and trigger dyskinesia [7, 8].

Clinical studies have supported a presynaptic role of the 5-HT system in LID by showing excessive swings in striatal dopamine levels in dyskinetic PD patients [9]. Similar findings have been reported in dyskinetic rats [8]. Blunting the efflux of dopamine, by a 5-HT-specific lesion, dramatically reduces the severity of LID [6]. In contrast, enhancing the striatal 5-HT fibre outgrowth in the dopamine-denervated striatum, by a 5-HT neuronal transplant, exacerbates LID [10].

In addition to a presynaptic mechanism, the 5-HT system also influences LID through its action on receptors located on non-serotonergic neurons, i.e. through a post-synaptic mechanism. Cortical expression of 5-HT<sub>2A</sub> receptors has shown to be enhanced in dyskinetic monkeys [4], probably contributing to the corticostriatal overactivity and the excessive striatal glutamate release that has been associated to LID. Likewise, there is an increased expression of 5-HT<sub>1B</sub> proteins on striatonigral neurons in dyskinetic mice [13]. Recently, 5-HT has been closely linked to glutamate signalling in the striatum by inducing long-term depression, an effect that was coupled to the 5-HT<sub>1B</sub> receptor [11]. These mechanisms might be of particular interest since specific alterations in synaptic plasticity have been associated to LID [12].

### **Growth of raphe-striatal fibres in dyskinesia: implications for a potential biomarker?**

Given the negative role of raphe-striatal projections in LID and the plastic character of this system, it seems possible that the variable extent of 5-HT loss in parkinsonian patients may affect the individual susceptibility to LID. Recent evidence has positively correlated the density of 5-HT axonal fibres in the striatum with the severity of LID in both rat and primate models as well as in post-mortem tissue from PD patients. L-DOPA treatment was able to induce a growth-promoting effect on the raphe-striatal terminals along with a dose-dependent upregulation of brain-derived neurotrophic factor (BDNF) [3], promoting regenerative sprouting of 5-HT neurons. The sprouting effect was further coupled to an increased activity-dependent dopamine release in rat striatal slices [3].

These findings demonstrate a previously unappreciated maladaptive plasticity of the 5-HT system in the dyskinetic brain and are in agreement with several clinical studies. Indeed, late-onset PD patients are less susceptible for developing LID while entailing degenerative changes of the 5-HT system. In contrast, young PD patients are much more susceptible for developing dyskinesia, and have a larger plasticity potential in the brain along with a higher 5-HT fibre innervation and BDNF expression [1]. Furthermore, morphological or biochemical features of the 5-HT system could be used

to devise biomarkers for patient stratification in clinical trials for anti-dyskinetic compounds. The extent of the 5-HT innervation in the striatum might also be used as a susceptibility marker for LID. If the degree of striatal 5-HT innervation could be measured at the time of diagnosis, e.g. by labelling SERT using PET imaging, the risk for developing LID could be predicted and support the choice of treatment. In such way it would be possible to initially treat patients with a greater risk for LID, i.e. those with high 5-HT innervation or young patients, with a less dyskinesigenic treatment (e.g. dopamine agonist or MAO inhibitors).

### **Hope for new anti-dyskinetic drugs by 5-HT receptor modulation**

The importance of the 5-HT system in LID has received great attention in the search for new anti-dyskinetic drugs. Stimulating the 5-HT autoreceptors has shown to reduce the activity of the raphe-striatal neurons, blunt the extracellular dopamine release in the striatum and attenuate the expression of LID in animal models of PD [7, 8]. Stimulation of 5-HT<sub>1A</sub> and/or 5-HT<sub>1B</sub> receptors is also able to reduce D1-agonist-induced dyskinesia through a postsynaptic mechanism, (although, this requires higher doses than those for attenuating LID) [14-16]. In line with this, recent data points to a role of 5-HT<sub>1A</sub> receptors expressed in primary motor cortex in the modulation of LID [17]. An effective alleviation of LID can also be achieved by antagonising 5-HT<sub>2A</sub> receptors, most probably attenuating corticostriatal glutamate or nigrostriatal dopamine release [4].

Serotonin modulators are now under investigation in clinical trials. Most of the tested drugs provide a reduction in LID but at the expense of an attenuated anti-parkinsonian efficacy of L-DOPA. In the rat PD model, a high concentration of 5-HT<sub>1A</sub> receptor agonist, (stimulating both pre- and post-synaptic receptors), results in something called "serotonin syndrome" with flat body posture associated with motor depression. In patients, a worsening in parkinsonism has been speculated to depend on non-specific binding by the drugs to extrastriatal targets or to other receptor types e.g. the D2 receptor. However, the selectivity seems not to be the solely problem since the lack of anti-parkinsonian effect persists also with highly specific substances. Instead, stimulation of anatomically distinct subpopulations of receptors has been postulated as a better way of treating dyskinesia without compromising the anti-parkinsonian efficacy [4]. To exclusively target e.g. 5-HT<sub>2A</sub> receptors on corticostriatal neurons would reduce LID by attenuating striatal glutamate release, whereas stimulating the same receptors on residual nigrostriatal terminals would impair the anti-parkinsonian effect by reducing dopamine release [4] (See Figure 1). Taken together, less advanced patients that still possess some residual striatal dopamine terminals, might provide better targets for anti-dyskinetic treatment with 5-HT agonists since their dopamine release would not be attenuated as much by the 5-HT agonists [6].

Another solution for avoiding the motor depressant effect would be to use the synergistic effect between 5-HT<sub>1A/1B</sub> receptor agonists, using sub-threshold doses. This regimen can prevent the appearance of LID as well as the induction of a LID-associated transcription factor in striatal neurons [7, 16]. A proof-of-concept clinical trial is now investigating the efficacy of 5-HT<sub>1A/1B</sub> receptor agonists in advanced PD patients.

### **A therapeutic or a dyskinetic effect in transplantation?**

Intra-striatal transplantations of ventral mesencephalic tissue are still under development as a potential future treatment for PD. Serotonin neurons are often included in the grafts to a variable extent, and are suspected to worsen LID by providing an additional source of unregulated dopamine release. Serotonin neurons could also

influence the occurrence of graft-induced dyskinesia, (i.e. dyskinesia without L-DOPA administration).

Studies using special dissection protocol, yielding grafts rich in either dopamine or 5-HT neurons, have shown that transplants enriched in dopamine neurons induce good functional recovery, while those enriched in 5-HT neurons cause a dramatic worsening of LID and no improvement of physiological motor tasks [10]. In a mixed graft however, the behavioural outcome is not affected by the amount of 5-HT neurons as long as the graft also contains only a small amount of dopamine neurons. Thus, the relative densities, and not the absolute number of 5-HT neurons in the graft, seem to determine whether 5-HT grafted neurons have detrimental effects or not [18]. Taken into the clinical situation, these findings suggest less severe PD patients, who still possess some residual dopamine fibres in striatum, as the optimal patients for neural transplantation.

The role of 5-HT neurons in graft-induced dyskinesia is more vague than their role in LID. Also for these complications, the dopamine content seems to have the greatest impact even if the contribution of 5-HT system cannot be ruled out. Graft-induced dyskinesia is worsened by SERT inhibition and attenuated by 5-HT<sub>1A</sub> receptor stimulation [19], but a possible contribution of the 5-HT system seems to depend on the endogenous system as the removal of the grafted 5-HT neurons has no effect [19]. On the other hand, a recent study of two transplanted PD patients showed a pronounced role of grafted 5-HT neurons in graft-induced dyskinesia. In these patients, graft-induced dyskinesia was associated with an abnormally large striatal 5-HT innervation and was effectively attenuated by the administration of a 5-HT<sub>1A</sub> agonist [20].

Taken together, the role of the 5-HT system in the occurrence of graft-induced dyskinesia remains an intriguing question that needs further evaluation in order to develop this potential future therapy for PD.

## Conclusion

Vast evidences are today clearly demonstrating the importance of the 5-HT system in the pathophysiology of LID, acting either as a dopamine-releasing compartment or on receptors located on non-serotonergic neurons. By influencing striatal dopamine and glutamate signalling, the 5-HT system does provide major influence on the aberrant striatal signalling that underlies LID. A growth-promoting effect on the raphe-striatal fibres in L-DOPA-treated dyskinetic subjects, along with its dopamine-releasing properties, further puts the brain at greater risk for developing dyskinesia. In line with this, a graft-induced 5-HT hyperinnervation from intrastriatal grafts would expect to worsen the dyskinesia. Yet, the respective role of endogenous versus exogenous 5-HT contribution to this requires further evaluation.

The 5-HT system can be seen as a particular interesting target for anti-dyskinetic treatment and new evidence of plastic responses in this system could further provide tools for how to individually treat dyskinetic complications in PD.

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### Figure legend

*Figure 1: A simplified view illustrating the location of potential anti-dyskinetic targets (i.e. the 5-HT receptors) and potential biomarker (i.e. SERT). An anti-dyskinetic effect can be achieved by i) modulating serotonin autoreceptors on raphe-terminals inhibiting dopamine release, ii) on corticostriatal neurons inhibiting glutamate release or iii) on striatonigral medium-sized spiny neurons inhibiting GABA release. Abbreviations: Glu = glutamate, DA = dopamine, 5-HT = serotonin, SERT = serotonin uptake transporter, MSN = medium-sized spiny neurons.*

