PRE-SYNAPTIC MECHANISMS IN L-DOPA-INDUCED DYSKINESIAS: ROLE OF DOPAMINE/SEROTONIN INTERACTION

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Dyskinesia is a severe side effect of chronic L-DOP administration in Parkinson’s disease (PD) patients, which limits the therapeutic benefits of the drug in advanced stage of disease. It has been reported that within 5 years from initiation of the treatment about 50% of the patients develop these motor complications (Obeso et al., 2000). This percentage raises to about 90% after the first decade (Ahlskog and Muenter, 2001). Therefore, dyskinesias affect the quality of life of almost all advanced PD patients.

The reason behind the appearance of dyskinesias, after an initial period of optimal therapeutic response to L-DOPA (honeymoon period), is still subject of debate. Indeed, it is unclear whether long-term exposure to the drug plays an important role, or whether the delayed appearance of the side effect is only the result of the progression of dopamine (DA) neurodegeneration.

We have recently proposed that ad an early stage of disease L-DOPA acts by being taken up into the spared dopaminergic neurons and terminals, where it is converted to DA, stored into synaptic vesicles and released in a physiological-regulated manner (Carta et al., 2007). In this situation, a fine regulation of the level of neurotransmitter in the synaptic cleft is assured by the presence of the D2 autoreceptor and DA transporter. Transmitter re-uptake through the DA transporter provides an effective mechanism for eliminating excess DA from the synaptic cleft, and the D2 autoreceptor is capable of finetuning release from DA terminals in response to changes in extracellular DA levels. The auto-regolatory feedback mechanism of DA release from the spared DA terminals represents, therefore, an important element in providing the therapeutic efficacy of L-DOPA medication at early stages of the disease.

To investigate the mechanisms underlying the appearance of dyskinesias, we took advantage the rat model of L-DOPA-induced dyskinesias, where abnormal involuntary movements are produced in hemiparkinsonian rats upon chronic treatment with low L-DOP doses (6 to 12 mg/kg per day), resembling peak-dose dyskinesias seen in PD patients (Cenci et al., 1998). Both pre- and post-synaptic mechanisms have been described to play a role in the side effect of L-DOPA using this model.
Recently, the functional role of the spared pre-synaptic dopaminergic innervation in preventing the appearance of L-DOPA-induced dyskinesias has found further experimental support by the work of Ulusoy et al (Ulusoy et al., 2010). In this study, the authors have employed short-hairpin RNA technology to knock-down tyrosine hydroxylase levels in the dopaminergic neurons, to produce significant reduction of striatal DA levels (by about 70%) in absence of any cell loss. When these animals were exposed to chronic apomorphine treatment they develop significant dyskinesias, suggesting that post-synaptic, modifications at the level of striatal neurons are dependent on depletion of DA itself, rather than loss of neurons. However, the same rats did not show any abnormal response to L-DOPA, even when DA receptor sensitazation was fully established by chronic apomorphine treatment.

This may suggest that in early phase of disease the spare DA neurons can inhibit development of L-DOPA-induced dyskinesias by providing a site of conversion and regulated release, therefore preventing excessive synaptic DA levels. In agreement with this scenario, partial DA-lesioned rats are more resistant to L-DOPA-induced dyskinesias than complete lesioned-ones, and higher doses of L-DOPA have to be given to establish significant involuntary movements.

With the progression of DA neuron degeneration, fewer and fewer DA terminals can contribute to the conversion of peripheral administered L-DOP. In this scenario, other neuronal and non-neuronal cell types are suggested to play a role in DA production. Among these cells, serotonergic neurons represent an interesting element because they express the aminoacid aromatic decarboxylase (AADC) and the vesicular monoamine transporter 2 (VMAT2), which are responsible for conversion of L-DOPA to DA and storage of DA into synaptic vesicles, respectively. A number of experimential paradigms have indeed demonstrated the ability of the serotonergic neurons to store and release DA both in vivo and in vitro (Ng et al., 1970; Arai et al., 1995). In line with these reports, Tanaka and co-workers have shown that lesion of the serotonin system by the specific toxin 5,7-dihydroxytryptamine (5,7-DHT) reduced L-DOPA-derived extracellular DA by about 80% in complete DA lesioned rats (Tanaka et al., 1999).

The susceptibility to dyskinesias increases overtime in PD patients, raising the possibility that exogenous DA is released from non-dopaminergic cells in a non-physiological, dysregulated manner. In fact, serotonin neurons do not possess an auto-regulatory mechanism for the release of DA. In support of this hypothesis, we have recently shown that toxin-induced lesion of the serotonin system by 5,7-DHT, or pharmacological silencing of these neurons by selective 5-HT1A and 5-HT1B agonists, produced a near complete abolishment of dyskinesias induced by repetitive daily injection of L-DOPA (at 6 mg/kg dose) (Carta et al., 2007). Similar results were also obtained in the MPTP-treated monkey model of PD, the gold standard model for studying this pathology (Munoz et al., 2008). Interestingly, we found a potent synergistic effect between the 5-HT1A agonist (±)-8-OHDPAT and the 5-HT1B agonist CP-
94253 in blocking L-DOPA-induced dyskinesia in both parkinsonian rats and monkeys. Thus, sub-threshold doses of the two compounds, which individually produced either none or only a mild effect, completely suppressed dyskinesia when administered in combination. This synergistic action might have interesting clinical applications and deserves further investigation. Indeed, we have now identified a mixed 5-HT$^{1A/1B}$ agonist with a safe pharmacological profile and potent antidyskinetic efficacy in the animal models, which will be soon investigated in a first double-blind prove-of-concept clinical study employing 24 advanced patients with dyskinesias. Results from this trial are expected for the spring 2011.

In support of the involvement of the serotonin system in the etiology of dyskinesia in PD patients, Rylander et al (in press) have recently found higher serotonin innervation (measured as increased SERT binding) in the putamen of dyskinetic patients compared to non-dyskinetic subjects.

To summarize, pre-synaptic alterations at striatal level may play a major role in the appearance of dyskinesias. These include, progression of DA neurodegeneration paralleled by an over-time increase in the contribution of L-DOPA-derived DA production from the serotonin neurons. These parallel alterations would eventually determine a switch from a situation where L-DOPA-derived DA release is physiologically regulated (in DA neurons), to a situation in which dysregulated release of DA from the serotonin terminals would generate abnormal synaptic levels of this neurotransmitter following peripheral L-DIPA administration. These non-physiological levels of DA would then contribute to the pulsatile stimulation of striatal DA receptors, which appears to be the key factor for the appearance of dyskinesias.

References


