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Pathophysiology of L-Dopa Induced Dyskinesia — Changes in D1/D3 Receptors and Their Signaling Pathway

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic mesencephalic neurons. The most used and successful therapy for this condition is L-3, 4 dihydroxyphenylalanine (L-DOPA), a precursor in the synthesis of dopamine. However long-term treatment leads to disabling abnormal involuntary movements known as L-DOPA-induced Dyskinesia (LID), which are uncontrolled and repetitive movement in the axis, arms, legs and oro-facial zone [1-2]. The LID is a serious limitation in the usage of L-DOPA and it can be thought that solving the dyskinesia by new therapeutic targets could extend the time of treatment with L-DOPA in the parkinsonian patients with an acceptable quality of life. To propose new alternatives is necessary to know the pathogenesis and pathophysiology of this phenomenon.

According with the classical basal ganglia model [3], PD is the result of an imbalance in the motor networks that stimulate and/or inhibit the initiation of movements. There are two main pathways that have been studied in the basal ganglia. The direct pathway, which is associated with D1-like dopamine receptors, and the indirect pathway that it has been related with D2-like dopamine receptors. The adequate balance between the direct (stimulatory) and indirect (inhibitory) networks facilitates the execution of movements [4]. In PD the loss of dopaminergic control leads to a hyperactivity of the inhibitory pathway, which produces bradykinesia the main symptom of this disease [5]. The restoration of dopamine with L-DOPA counteract the unbalance of the two pathways, nevertheless several cellular and molecular changes caused by L-DOPA move the system toward the opposite side, producing a

hyperactivity of the direct pathway and originating the dyskinesia phenomenon [5]. Many changes in basal ganglia circuitry have been associated with dyskinesia [6]; one of the most studied is the hyperactivity of direct pathway that produces an increased GABAergic neurotransmission on striato-nigral neurons, which are controlled by dopamine D1 receptors, and it seems to be the most relevant finding. The dopamine D₃ receptors have been involved in dyskinesia since was reported that L-DOPA treatment increases its expression in basal ganglia [7], suggesting the use of ligands of these receptors as a target for dyskinesia, but the neurobiological basis of these changes and the site of action is not well understood since conflicting results in experimental assays have been reported [8-12]. The recent finding of co-existence and interaction between D₁ and D₃ dopamine receptors in the direct pathway [13-16] could contribute to solve this question.

The aim of this review is provide a global view of the pathophysiology of dyskinesia based on the changes reported in animal models and parkinsonian patients that involve the direct pathway and the dopamine D₁ and D₃ receptors, the understanding of this changes could result in a potential novel therapeutic approaches to treat the dyskinesia.

2. Basal ganglia, the control of movement and Parkinson's disease

Basal ganglia are organized in four segregated circuits: motor, oculo-motor, limbic and associative [17]. In PD the motor loop is altered in these structures. The basal ganglia circuit originates in glutamatergic cortical neurons from motor and premotor areas that project to caudate (C) and putamen (P), the striatum in rats (Str). The main phenotype of striatum is the GABAergic medium-size spiny neurons (MSNs), which projects to the direct and indirect pathways. The substance P/Dynorphyn positive MNSs GABAergic neurons project to substantia nigra pars reticulata (SNr) and/or to the internal segment of globus pallidus (GPi), the entopeduncular nucleus (EPn) in rats. SNr and GPi is the output nucleus of the motor loop to the thalamic glutamatergic nucleus, which in turn stimulates the motor cortex; this network is called the direct pathway. While the striatal enkephaline positive MNSs GABAergic neurons project to the external segment of the globus pallidus (GPe), pallidal GABAergic neurons which in turn project their axons to the glutamatergic neurons of the Subthalamic nucleus (Sth) and this neurons project to the output nuclei forming the indirect pathway [17]. (See Fig. 1).

Neurons of the thalamic relay nucleus are subject to a tonic inhibitory control from GABAergic GPi/SNr neurons, the removal of this control leads to the activation of thalamus that in consequence activates the motor cortex facilitating the movement. The activity of GPi/SNr neurons is maintained by a tonic stimulatory action of the Sth controlled reciprocally by the GPe. Stimulation of the MNSs GABAergic striatal neurons by the cortex in the direct pathway produces inhibition of the output nucleus through the release of GABA. The remotion in the inhibition of the thalamus toward to the cortex turns in the initiation of the movement, thus the activation of the direct pathway allows the movement. In contrast the activation of MNSs GABAergic neurons from the indirect pathway inhibits GPe neurons, which

removes the tonic inhibitory action on Sth, the increased activity of the glutamatergic neurons stimulates the output nuclei, producing inhibition of thalamus and in consequence inhibit the motor cortex, which means that the activation of the indirect pathway inhibits the movements.

Simultaneous activation of the direct and indirect pathway will produce an antagonistic action on movement. The adequate balance between direct and indirect pathway is maintained by dopamine. The Substantia nigra pars compacta (SNc) is the source of dopamine in the basal ganglia since SNc neurons project to all the basal ganglia nuclei (Fig.1A) in normal conditions [18].

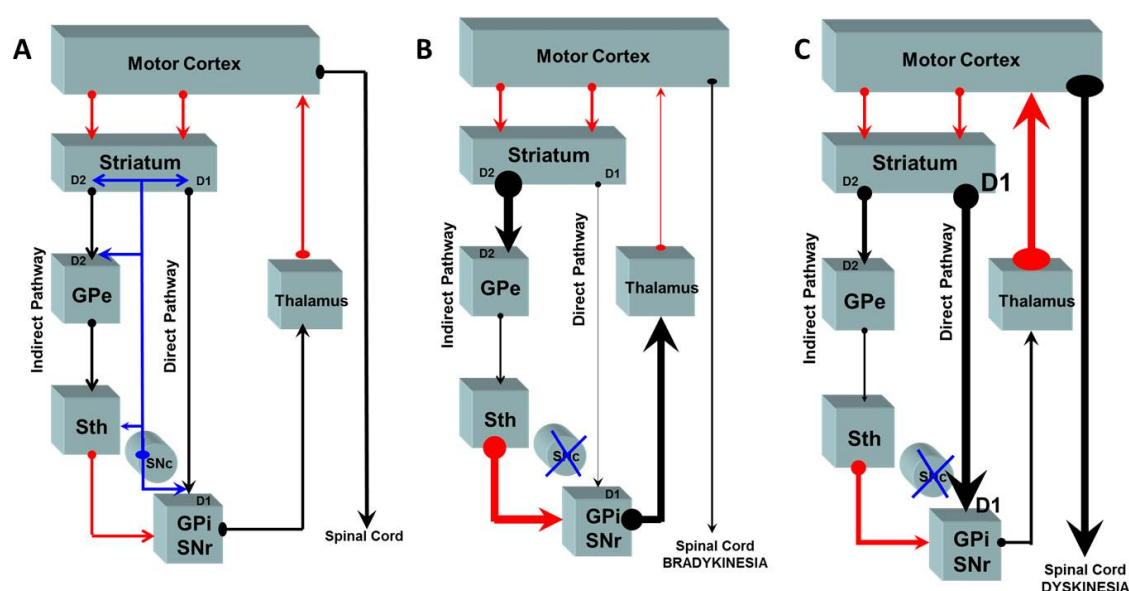


Figure 1. The basal ganglia motor circuits in normal (A), parkinsonism (B) and L-DOPA-induced dyskinesia (C). GPe, external globus pallidus; Sth, subthalamic nucleus; GPi, internal globus pallidus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta, D1, dopamine D1 receptor and D2, dopamine D2 receptor.

Two families of receptors mediate the action of dopamine through the basal ganglia, D1-like (D_1 and D_5 subtypes) and D2-like (D_{2short} , D_{2long} , D_3 and D_4 subtypes). D1-like receptors are expressed predominantly in substance P/Dynorphin positive MNSs GABAergic neurons and their activation increases the firing rate at soma and also the GABA release in the terminals [19-22]. It has been reported that some population of striato-nigral neurons also expresses D_3 receptors [14, 23]. While the dopamine D2-like receptors are associated to striatal enkephalin positive MNSs GABAergic neurons and their activation decreases the firing at soma and the GABA release at the terminals [20, 24-26]. Some population of striato-pallidal neurons also expresses D_5 receptors [23]. Dopamine via D1-like receptors potentiates the stimulation of the direct pathway, while via D2-like receptors decreases indirect pathway activity, synergizing the activity of both pathways and facilitating movement [17]. Other association of dopamine receptors subtypes with neuronal elements of these circuits occurs [27-32], however the role of their function in the integral circuitry is not well understood.

The progressive loss of dopaminergic neurons of the SNc causes the neurodegenerative disorder called Parkinson's disease. The loss of dopamine has serious consequences in the balance of direct and indirect pathways, in fact a hyperactivity of the indirect pathway with a decrease in the activity of the direct pathway coexists and that explains the hypomotility or bradykinesia observed in patients and in animal models of PD (Fig. 1B) [17].

3. Pathophysiology of L-DOPA-induced dyskinesia (LID)

Dopamine replacement therapy with L-DOPA restores the lack of the neurotransmitter in the basal ganglia [33]. It has been shown that L-DOPA (a precursor in dopamine synthesis, Fig. 2) is transformed to dopamine in the central nervous system by decarboxylation via central aromatic acid decarboxylase (DCAA) [34]; also it has been proposed that remaining dopaminergic neurons (Fig. 2) and/or serotonergic neurons are host candidates for transformation of L-DOPA [35], mediating an ectopic and false transmitter release [36] in fact any cell that express DCAA can eventually transform L-DOPA into dopamine. The dopamine synthesized from L-DOPA activates D1-like and D2-like family of receptors. However it has been also suggested the existence of DOPAergic receptors [37], since direct effects of L-DOPA on dopamine receptors have been reported [19, 38 -39] but also effects are mediated by either L-DOPA or their metabolites [39, 40-41] that could participate in their therapeutic or side effects including dyskinesia [42-43]. Probably the effectiveness of L-DOPA over dopamine receptor agonist is due to a variety of actions in the central nervous system [44].

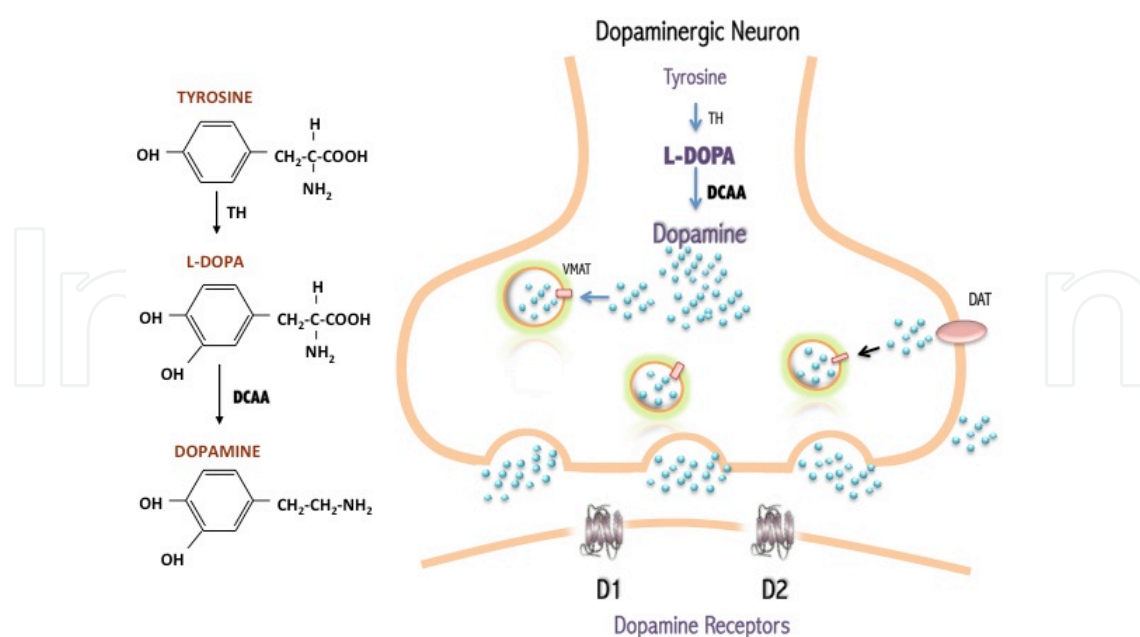


Figure 2. Synthesis of dopamine from L-DOPA in the dopaminergic nerve terminals. DCAA, aromatic acid decarboxylase; DAT, dopamine transporter, TH, Tyrosine Hydroxylase; D1, D1-like dopamine receptor; D2, D2-like dopamine receptor.

During L-DOPA treatment the activation of dopamine receptors restores the movement in PD patients and the locomotor activity in experimental animal models. L-DOPA treatment produces a priming effect where the brain is sensitized to L-DOPA after chronic administration and finally produces dyskinesia as main side effect [45] with a prevalence of 30-45% in patients [46]. However early age of Parkinsonism onset and severity of disease have been classified as risk factors in the development of LID [47] and more recently the nigral-associated pathology has been related with early onset of LID [48]. It has been shown that pharmacokinetic properties of L-DOPA are also related with the onset of dyskinesia with phenomenological differences in the altered movements. When the higher plasma levels of L-DOPA are reached the maximum antiparkinsonic effect can be achieved. In contrast dyskinesia occurs at intermedium L-DOPA plasma levels either when bioavailability is increasing or decreasing due to metabolism of L-DOPA, interesting when the lower L-DOPA plasma levels are reached generalized dystonic postures occurs [49].

The dyskinesia also has been observed in experimental models of PD under chronic L-DOPA treatment [50], the effect is dose and species dependent, since different population with high and low dyskinesia score have been reported [51-52].

The mechanism of the genesis of dyskinesia is essentially unknown. Initial studies suggested that L-DOPA or metabolites could be responsible of the side effects, however the inhibition of L-DOPA decarboxylation, does not correlate with LID scores [53]. Plenty evidence has been published recently showing that several compensatory effects occur after dopamine denervation and LID.

The changes in nuclear function of striato-nigral and striato-pallidal neurons have been related with denervation, most of them are associated with proteins involved in the dopamine receptors signaling and in the regulation of glutamatergic transmission by dopamine [54], it can be thought that L-DOPA therapy should restore these parameters. However that is not the case since the major alterations related to LID occur on these cellular systems [52, 55-60].

It has been reported alteration in gene expression during L-DOPA therapy particularly on transcription factors. Early gene expression which are markers of neural activity has been studied and increased expression of the transcription factor Δ FosB has been associated with L-DOPA induced dyskinesia in rats and related with sensitization process [61-64], while accumulated Δ JunD has been shown drop the severity of LID in monkeys without reduction of antiparkinsonian effects [63]. Also zif-268 has been related with a persistent stimulation of D1 receptors by L-DOPA and has been proposed like a potential marker for the onset of the dyskinetic phenomena [65]. On the other hand histone activation mediated by D1 receptors it has also been related with dyskinesia [66-67] suggesting that changes in gene transcription factors are altered, then is plausible suggest that many alterations in signaling molecules activated by dopaminergic receptors could contribute to the leading of motor disabilities. The resulting changes of the altered activity culminates with expression of proteins related with the activity of D1-associated neurons like the increased expression of prodynorphin, glutamic acid decarboxylase, adenylyl cyclase, PKA, DARPP-32 and CDk5 [52, 54-60].

Nevertheless LID can be also pathophysiologically explained by a change in the balance of the direct/indirect pathway. In this condition an increase in the activity of the direct pathway that facilitates movements can explain the phenomena (Fig. 1C) [5]; since the direct pathway stimulates movement, dyskinesia can be considered a pathologic condition with over-activation of this pathway generated by pulsatile activity of striato-nigral neurons. In fact experimental data supports this idea; a higher release of GABA in SNr/EP has been shown in experimental models of LID [52,68], which in turns facilitates the inhibition of the output neurons and removes the inhibition of premotor nuclei leading activation of the movement.

The role of the indirect pathway and dopamine D2-like receptors is less understood and explored. An over-activity of the GPe is associated with LID [55], and dopamine D2 receptors [69- 71]; however pallidotomy does not modify significantly LID in hemiparkinsonian monkeys [72]. Some D2-like agonist has beneficial effect on L-DOPA induced dyskinesia [73], but the genetic inactivation of dopamine D₂ receptor expression in striatum does not modify the development of LID [66]. On the other hand D₂ dopamine receptor agonist treatment in PD models produce lower LID compared with D₁ receptor agonist treatment suggesting a predominantly role of dopamine D₁ receptors [65,74]. Interesting recent reports have shown that L-DOPA restores spine density in D2-expressing striatal neurons of LID mice [75], suggesting an undefined role of striato-pallidal in the dyskinetic phenomenon. On the other hand adenosine A_{2A} receptors are selectively expressed in the indirect pathway and an increased expression of these receptors was found in patients with LID [76], the A_{2A}/D₂ receptor heterodimer interaction has been suggested is modified during LID in the indirect pathway [77]. All this data suggested a role of the indirect pathway in LID development; however further studies are needed to clarify the role of D₂ receptor and the indirect pathway in the dyskinesia phenomenon.

Other non-dopaminergic alterations have been involved in LID, which contributes to this phenomenon. The idea of a role of the glutamatergic system in LID comes from the use of amantadine in Parkinson's disease and as an adjuvant in the management of LID [78], in fact amantadine increases extracellular dopamine from L-DOPA in parkinsonian rats [79]. Dopaminergic denervation decreases the expression and phosphorylation of NR1 subunit of the NMDA receptor without change in NR2 subunit. L-DOPA restores the expression of the subunit but also increases the phosphorylation level of the NR2A subunit with a consecutive high activity of the NMDA channel [80-81]. It has been shown also that D1-like receptors increase the phosphorylation of the channel subunits through the PKA signaling pathway [82-83]. Furthermore D1 receptor promotes the expression of NMDA in membrane [80] and can interact at the level of protein [84], in consequence if a generalized hypersensitivity of D1-like receptor activity occurs, the NMDA receptor activity will also be potentiated [80, 85]. Dopamine modulates long-term potentiation (LTP) of the glutamatergic system, in consequence in dyskinesia, L-DOPA could contribute to the prolongation of this effects [78, 86]. It has been shown in dyskinetic rats an increased levels of PSD-95 and SAP97 proteins of the postsynaptic density, those proteins are involved in the interaction of NMDA and AMPA receptors in the membrane, but their participation in the phenomenon has not been com-

pletely determined [87-89]. The consequence in all these alterations of the glutamatergic system is a higher excitatory transmission to the direct pathway. An interesting review on the role of D1/NMDA interaction and LID is found in Fiorentini et al., 2008 [90]. Changes in synaptic plasticity induced by L-DOPA also occur in the output nuclei [91].

The role of the serotonergic system on LID comes from the hypothesis of conversion of L-DOPA to dopamine in serotonergic neurons and nerve terminals within the basal ganglia [92, 93]. It has been suggested a false-transmitter release of dopamine from this neurons [36, 94], in consequence a higher dopaminergic activity would be the responsible of LID. According with this hypothesis the role of serotonin system in LID is related with effects on dopamine formed in the terminals. Some studies indicates that increasing serotonin levels suppress LID, the effect seem to be mediated by 5-HT_{1A} receptors [95], since these receptors are also located at cortico-striatal glutamatergic terminals is plausible that blockade of D₁ receptor activity explains the therapeutically effect [96]. Moreover blockade of serotonin transporter also attenuates LID suggesting that a reduce turnover [95] and activation of serotonin receptors is involved in its beneficial effect.

Dopamine denervation and L-DOPA treatment increases mRNA codifying opioid precursors pro-enkephaline A and B, which correlates with the development of dyskinesia [55, 97]. This effect has been observed in striato-nigral neurons [98] and has been postulated participate in LID due to an enhanced coupling of opioid receptors to G protein [99]. However the blockade of these receptors in dyskinetic rats does not prevent symptoms and in fact there is an increase in the dyskinesia score [100, 101]. It seems that the over-expression is just consequence of denervation, recent studies have been shown that modification of δ -opioid receptor modify dyskinesia in hemiparkinsonian rats [102], but the role of opioids in LID remains unclear and needs further study. Finally the role of noradrenergic system in LID is poorly studied but it has been suggested that an increased norepinephrine transmission in Str could be related with dyskinesia since the blockade of norepinephrine receptors reverts LID [103].

Since the direct pathway of the basal ganglia and D₁ receptors activity is associated with dyskinesia, the research has been focusing on changes in these neurons, their activity, neurochemical tracers and their receptors particularly dopamine D₁ and D₃ receptors, in order to propose alternatives to the therapeutic management of the Parkinson patients.

4. The dopamine D1-like receptors signaling in the direct pathway

D1-like family of dopamine receptors includes D₁ and D₅ subtypes. D₁ has 466 amino acids and D₅ has 477 with a homology of 80% located mainly in the transmembrane domains [104]. D₁ and D₅ receptors have a differential distribution in the central nervous system; moreover there is a controversy of their signaling pathway. Initially was proposed that both receptors stimulate adenylyl cyclase; however some dopamine effects on PLC activity seem to be mediated by the D₅ type [105].

Dopamine D1 receptors are members of the G protein coupled receptors family (GPCRs) stimulates adenylyl cyclase trough $G\alpha_{olf}$ or $G\alpha_s$ proteins [106]. In the D1-like receptors asso-

ciated to the striato-nigral neurons, the subunit $G\alpha_{olf}$ interacts with the catalytic domain of adenylyl cyclase V [107], increasing the activity and therefore cAMP formation [108]. It has been reported $G\alpha_{olf}$ is expressed in the direct pathway and the level of expression can change after dopamine denervation [52].

The cAMP formed by D1 receptor activation stimulates PKA, and recent studies suggested the activation of the GEF (nucleotide interchange factor) EPAC and the consequent activation of Rap1 a low weight G protein that activates MAPK [109]. The activation of PKA phosphorylates several substrates that include: Na^+ , voltage depending K^+ and GIRKs channels, producing inhibition; whereas Ca^{2+} L, N, P, Q, NMDA, AMPA and $GABA_A$ channels are stimulated by the phosphorylation. PKA also phosphorylates DARPP-32 at threonine 34, DARPP-32 phosphorylated inhibits protein phosphatase 1 (PP1). Phosphorylation of NMDA channels by D1 receptor signaling through DARPP-32, synergize their stimulatory action, whereas by the same pathway attenuates $GABA_A$ inhibitory currents. PP1 has several substrates such as Ca^{2+} L, N, P and AMPA channels (for references see Udieh, 2010 [105]).

D1 receptors also induce activation of anti-apoptotic signals. PKA phosphorylates Akt (also known like PKB), which phosphorylates CREB that translocate to the nucleus inducing gene expression related with cellular survival. D1 receptors interact with other receptors, ionic channels and cytoskeleton proteins. Protein-protein interaction between NMDA at the level of NR1 subunit produces signaling via PI3K, interaction with NR2 subunit decreases NMDA current [105]. D1 receptors form heterodimers with adenosine A1 receptors producing decrease in GABA release [110], while D_5 receptor interacts with $GABA_A$ channels decreasing Cl^- current [111]. Neurofilament M, COP gamma and DIRP78 are cytoskeleton proteins related with expression, sensitization, and transport of D1 receptors [105].

D1 receptor interactions with other dopamine receptors have been described. Dimmers between D_1 - D_2 receptors induce an increased intracellular Ca^{2+} probably mediated by the $G_{\alpha q}$ → PLC pathway [112]. It has also been reported the interaction of dopamine D_1/D_3 receptors, here we will discuss latter the role of this dimmer in PD and LID.

The adenylyl-cyclase → PKA stimulated by D1-like receptors induces GABA release in the Str and SNr [19, 22, 113] and increases the firing rate MNSs [21], mechanism that has been related with the facilitation of movement in the direct pathway. Dopamine D1 receptor effects on firing rate and GABA release are mediated by DARPP-32 and PP1 [21, 83, 113, 114]. The effects on firing rate and release have been associated to modulation of L-type and P/Q calcium channels [21, 113-116].

5. Mechanisms of D1 dopamine receptors sensitization in PD and LID: Changes in signal transduction pathways

As we discuss before the loss of dopamine innervation induces molecular and signal transduction changes in the neurons of the basal ganglia attributed to a compensatory response. Most of the experimental studies have been assessed using toxins to induce experimental

models of PD like 6-hydroxydopamine (6-OHDA) for rats or 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) for mice or non-human primates, because their ability to induce the degeneration of dopaminergic neurons [117-118]. The changes after dopamine denervation have been studied in particular on striato-nigral (direct pathway) and pallido-nigral (indirect pathway) neurons and plenty evidence shows that cellular and functional changes occurs, this phenomenon is called supersensitivity to dopamine denervation [119, 120]. The supersensitivity has been shown in expression levels of mRNA for enkephalins, substance P and dynorphins [121] but also up-regulation of more than 30 genes including zif 268, c-fos, c-jun and MAPK-1, most of them related with neuronal activity [54, 122]. Interesting several of those genes and changed proteins convey to D1 dopamine receptors and their signal transduction pathways [54].

Perhaps one of the most studied effects of denervation is the altered expression of dopamine receptors in the basal ganglia [20]. D2-like dopamine receptors increase in number, sensibility and consistently with that the mRNA in the striato-pallidal neurons [20], which explain the hypomotility. In contrast despite some contradictory results [56, 123], there is evidence that not only the mRNA of D1-like dopamine receptors decreases in the striatal neurons [20] but also the expression [124-125], with no changes in the affinity studied by radioligand binding techniques in SNr [125]. Proteasome altered activity observed in L-DOPA treatment produces an altered D1-like receptor abnormal trafficking that might be responsible for this changes [126]. Contrary to the decrease of D1-like dopamine receptors an increased response to their activation is observed in the striatum [120, 122, 127], and also a substantial increase in GABA release in the striato-nigral terminals [68, 125]. However despite the supersensitivity phenomenon the lack of endogenous dopamine in PD to activate the receptors explains the poor activation of basal ganglia pathways and therefore the hypomotility.

The activation of dopamine receptors would be the target in order to restore the balance in the circuit of the basal ganglia. The gold-standard therapy in PD is L-DOPA, because is converted to DA, or even can activate dopamine receptors directly increasing firing rate in striatal neurons and inducing GABA release in SNr. In addition the activation of D1 receptors leads an increase of GABA release in striato-nigral terminals promoting the activation of the direct pathway related with the movement, which is the main purpose of the pharmacological approach to treat PD.

It can be thought that replacement of DA with L-DOPA should restore the number, sensitivity and response of the activation of dopamine receptors observed in experimental conditions. Nevertheless that is not the case, chronic L-DOPA treatment only produces a partial recovery of D1-like dopamine receptors [125], whereas increases even more the biological response to their activation, producing a very high level of GABA release in the striato-nigral terminals than occurred only with dopamine denervation in hemiparkinsonian rats [125, 128-129]. An analysis of D1 receptor expression in striatum in L-DOPA treated rats indicates that D1-like receptors activity does not go back to healthy conditions in LID [126]. During L-DOPA treatment the expression of early genes like c-fos, c-jun and zif 268 is increased more than observed in dopaminergic denervation [55]. Furthermore the effect was mimetized [122] and synergized by D1 dopamine receptor agonists [130]. This suggested that the DA

converted by L-DOPA treatment, activates D1 dopamine receptors producing high gene expression and translation, causing an overstimulation of the direct pathway [119]. The high activity of D1 dopamine receptors is also supported by the high expression of substance P and dynorphin both markers of direct pathway neurons [55].

The abnormal activation of the direct pathway with increased GABA release in SNr (related with the activation of the movement) could be occurring during LID as we mention before. The changes in GABA transmission is supported by studies in which has been shown altered metabolic activity measured by 2-deoxyglucose during LID in striato-nigral terminals [131] but also the increased expression of the enzymes responsible of synthesize GABA [132]. The mechanism underlying the increased GABA release in the striato-nigral neurons during LID has been studied by several groups of investigation [125, 128, 132-133] and some hypothesis has been proposed.

First was postulated that the increased GAD_{65} and GAD_{67} expression observed in denervation and L-DOPA treatment, induces an enhanced synthesis of GABA, which is available for the release [132, 134]. However the fact that GABA contents in SNr is not altered by denervation [135] indicates that the synthesis of GABA is not a simple cause-effect relationship.

Then, studies of D1 dopamine receptors signaling in the striato-nigral terminals turned to be the most studied and strong hypothesis. Since the level of expression of D1 dopamine receptors was contradictory and the down-regulation does not explain the hyperactivity of direct pathway, their signal transduction pathways had been dissected. Cai and coworkers (2002) [123] showed an increased coupling between D1 dopamine receptors and $G\alpha_{olf}$ proteins in hemiparkinsonian rats, but the level of protein expression of $G\alpha_{olf}$ remained unchanged. In contrast studies in postmortem patients with PD showed increased expression of $G\alpha_{olf}$ proteins [136] and the effect was also observed in hemiparkinsonian rats, interesting the effect was reverted by chronic but not acute L-DOPA treatment [134], which was also demonstrated in either mild or severe dyskinetic rats after chronic L-DOPA treatment [52]. Recent studies have shown a persistent increase in $G\alpha_{olf}$ expression in dyskinetic mice [59] however the reason for this discrepancy is unknown and requires more study.

In next steps downstream the activation of D1 receptors induces the activity of adenylyl cyclase isoform V by coupling of $G\alpha_{olf}$ protein, which in turn induces the production of a second messenger cAMP in striato-nigral neurons and PKA activation, supersensitivity of D1 receptors could be in these proteins. Since cAMP modulates firing rate and GABA release in striatum and SNr [113-114] and stimulates the protein kinase activated by cAMP (PKA) which in turn can produce several effects that are related with GABA release, a higher expression/or activity of adenylyl cyclase, PKA and DARPP-32 signaling was related with LID [54]. Consequent with the activation of D1 receptors Ras-mTOR-ERK induced altered mRNA translation was found in the nucleus striatum [57-58, 67, 120, 137]. However other studies have been suggested that ERK hypersensitivity is not related with cAMP/PKA signaling and this is a condition is needed for the development of LID, whereas hypersensitivity of cAMP/PKA has a permissive role [59]. Recent studies suggested that Shp-2 phosphatase is the link between D1 receptor activation and ERK, and that is persistent activated in LID [60]. Probably ERK supersensitivity is related with control of the expression of

proteins related with cAMP/PKA pathway supersensitivity. The activation of cAMP/PKA is the mechanism that conduces to the increased GABA release in the striato-nigral terminals of the direct pathway of basal ganglia since GABA release is highly sensitive to cAMP (Fig. 3) [114, 125] and the increased activity through the direct pathway is a necessary condition to produce the involuntary movements.

Rangel-Barajas and coworkers (2011) [52] have shown that a persistent increase in activity and expression of adenylyl cyclase V/VI occurs in LID animals without changes in activity of PKA of striato-nigral terminals. This change on the adenylyl cyclase V/VI is correlated with an increased GABA release in SNr in severe dyskinetic rats and did not happened in mild dyskinesia. It was also suggested an increased phosphorylation of DARPP-32 in Thr34 found in denervation and LID, this change cannot be associated exclusively with higher GABA release since not all GABA released in striatum by D1 receptor stimulation is related with DARPP-32, inferred from DARPP-32 know-out mice studies [138] and it's likely that the increased activity of adenylyl cyclase V could mediate the phosphorylation and therefore activation of DARPP-32 via PKA [139]. Thus a higher expression/activity of adenylyl cyclase seems to have a central role in the LID. Probably several beneficial effects that helps in experimental therapies to control LID can be related with antagonistic actions on adenylyl cyclase for example, 5HT_{1A} receptor activation, which modulates negatively AC by Gα_i proteins reducing LID [96, 140], CB1 receptor also coupled to Gα_i proteins decreased LID and PKA activation [141] and finally mGlu4 receptors modify also LID [142]. According with a recent study showed by single exon sequencing, that the only gene codifying for adenylyl cyclase V was mutated in a familiar form of dyskinesia [143]. Further *in vivo* studies are needed to targeting adenylyl cyclase V in LID, to asses if the therapeutic is plausible, since adenylyl cyclase V has a wide distribution and also plays an important role in cardiac function [144], anxiety modulated by D1 dopamine receptors [145] and depression [146]. This data suggested that the indirect modulation of the activity of adenylyl cyclase could be effective in LID.

In summary LID could represent an exaggerated supersitivity of D1 receptor response to the denervation induced by L-DOPA treatment leading to a pulsatile and high GABA release on striato-nigral terminals through the sensitization of adenylyl cyclase activity.

6. Role of D₃ dopamine receptors in Parkinson's disease

The D₃ dopamine receptors are expressed mostly in limbic system, islands of Calleja, olfactory bulb, and the pituitary intermediate lobe, with a low but significant expression in basal ganglia structures [147]. The amino acid sequence homology for the helical transmembrane spanning (TMS) segments of the D₂ and D₃ dopamine receptor subtypes was found to be 75-80%. Since the TMS regions are involved in the construction of the orthosteric-binding site, the pharmacologic profiles of D₂ and D₃ receptors are very similar [148-150]. Probably that is the reason why in PD the role of D₃ dopamine receptors were poorly studied. The pharmacological approach to treat PD besides L-DOPA was because D₂-like dopamine ago-

nist showed effectiveness to treat bradykinesia [151]. In the past two decades with advanced pharmacological and molecular tools, the role of D₃ dopamine receptors became a potential field of study in PD and LID animal models.

With very good agreement is known that during denervation, the D2-like dopamine receptors are up-regulated in pallido-nigral neurons of the basal ganglia [20], then it was unclear whether or not the D₃ dopamine receptors subtype was participating in the supersensitivity by dopamine denervation, however their low expression in striatum made focus the attention in D2 dopamine receptors [152]. It was pointed out that in the basal ganglia, the segregation of the expression of D1-like and D2-like dopamine receptors in the direct and indirect pathways respectively was not precisely accurate, but a relative low abundance of D₃ receptors were expressed also in the direct pathway [23]. Probably disease conditions enhance their expression, according with that; recently it has been shown that D₃ dopamine receptors are up-regulated in caudo-putamen and SNc in Lewy Body disease and Parkinson disease Dementia [153].

Bordet and coworkers (1997)[7] showed that mRNA codifying to D₃ dopamine receptors remains unchanged during dopamine denervation, but the L-DOPA treatment induces a remarkable increase in dynorphin positive striatal neurons, which project to the SNr where D₃ dopamine receptors normally has moderate expression. Interesting the binding for D₃ dopamine receptors was decreased in hemiparkinsonian rats [148,154] but up-regulated when animals were treated with L-DOPA [7]. Since then, the ectopic over-expression of D₃ dopamine receptors has been related with L-DOPA induced behavioral sensitization in hemiparkinsonian rats [119], and several studies support the idea that D₃ dopamine receptors can attenuate the LID by normalizing their function [8, 11, 120]. However the location of D₃ receptor sensitized by L-Dopa treatment is not clear. On the other hand D₃ dopamine receptors interact with proteins and/or form heterodimers with other receptors that can change signal pathways and responses, e.g. D₂/D₃, D₁/D₃ heterodimers [14-16]. Recently it has been shown that the up-regulation of D₂ dopamine receptors in denervated striatum is probably mediated by D₃ receptors through Ca²⁺ channels [155]. All these finding together shown that several changes in D₃ receptor expression and function can be related with Parkinson Disease and L-DOPA treatment.

7. D₁/D₃ dopamine receptors interaction in LID like a novel therapeutic target

D₃ receptors are members of the D2-like receptors are coupled to Gα_i proteins [106]. It has been shown classical Gα_i responses mediated by these receptors: inhibition of adenylyl cyclase, blockade of Ca²⁺ channels, open of K⁺ channels etc [106]. However interaction with D1 receptors produces an antagonistic and synergistic response [14, 156]; that depends of the nuclei studied. In the antagonist interactions, D₃ receptors prevent D1 receptor stimulatory effects by the inhibition of adenylyl cyclase stimulated by D1 receptor, an interaction explained by cross-talk inhibition the AC activity. In the synergistic interaction D₃ receptors

potentiates D₁ effects, and this interaction seems to be more complex and explained in terms of heterodimerization, where D₃ receptor induces an increased sensitivity of D₁ receptor for dopamine, potentiating cAMP formation and stabilizing them in the membrane (Fig. 3) [15-16]. This synergistic interaction occurs at the striato-nigral pathway and it's regulated by CAMKII α during neural activity [13-14].

D₃ receptors have been associated with different elements of the basal ganglia. The mRNA codifying for D₃ receptors have been shown in dopaminergic neurons [147], subthalamo-nigral neurons [30] and striato-nigral neurons [23]. In dopaminergic neurons D₃ receptors controls the firing rate and dopamine release [157] and has neurotrophic effects [158]; probably the decreased expression in D₃ receptors observed in dopaminergic denervation [148, 154] occurs by the degeneration of the dopaminergic neurons. Several studies have pointed out the importance of these receptors in nigral neurogenesis [158], neuro-protection and repair in PD [160] and other cognitive conditions related to PD [153].

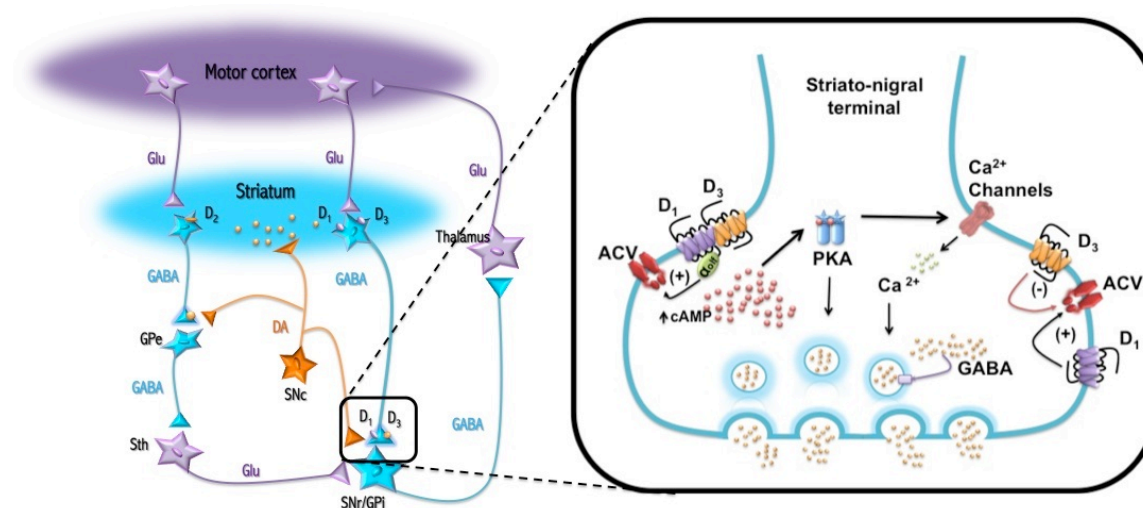


Figure 3. Synergistic and antagonistic interaction between D₁ and D₃ dopamine receptors in the striato-nigral neurons. Glu, glutamate; DA, dopamine; GPe, external globus pallidus; Sth, subthalamic nucleus, SNr, substantia nigra pars reticulata, GPI, internal globus pallidus; ACV, adenylyl cyclase V; PKA, protein kinase activated by cAMP.

In subthalamo-nigral neurons D₃ receptors are probably controlling the firing rate and glutamate release that have been attributed to members of the D₂-like receptor family [31-32]. Since during denervation subthalamic neurons shown high activity rates and contribute to hypomotility, the D₂-like agonist used in the control of Parkinson disease like pramipexole or ropirinole are able to decrease neuronal firing or glutamate release leading a clinical improve of symptoms. Interesting these D₃-preferring agonists decrease the dyskinesia.

As we mention D₃ receptors interact with D₁ receptors at striato-nigral neurons. The synergistic interaction has been shown in striatum [15-16] and substantia nigra on nerve terminals [14]. In the interaction D₃ receptors increases D₁ receptor affinity for dopamine, increasing cAMP formation and GABA release in striato-nigral terminals, this effect is very important since the higher release of GABA seems to mediate LID. Co-precipitation in native tissue

and studies using transferred energy like FRET and BRET in heterologous expression system indicate that the heterodimerization is the cause for the observed effects [13-16].

The D_1/D_3 dopamine receptors interaction is important in dopaminergic denervation and L-DOPA treatment? The expression of D_3 receptors in the striato-nigral and subthalamo-nigral neurons leads the speculation that D_3 receptors are involved in the motor control by potentiation of GABA release stimulated by D_1 receptors and inhibition of glutamate release leading to a decreased activity of the output neurons and increased activation of motor cortex. These effects are expected occur by the administration of L-DOPA and explain their powerful therapeutic effect; however the role of D_3 receptors in subthalamo nigral and D_1/D_3 interaction at striato-nigral neurons during denervation and L-DOPA treatment is unknown. However behavioral experiments suggested that D_3 dopamine receptor agonists potentiate the D_1 receptor-induced rotation in hemiparkinsonian rats only after L-DOPA treatment [161] suggesting that the D_1/D_3 interaction persist.

Chronic L-DOPA therapy sensitizes D_3 receptor expression, which has been related with LID development and the therapeutic management was experimentally evaluated. Two current opinions are in literature, one proposed that the normalizing D_3 function decreases LID with partial agonists [8, 12], another one propose that antagonist also are able to do that [10-11] while other suggested that antagonist does not modify LID [9].

The mechanisms through D_3 dopamine receptors selective compounds can help to LID is still unclear, but recent studies have suggested that it could be due to a modulation of D_1 dopamine receptors or direct actions on D_3 receptors. Albarran and coworkers [162] reported that activation of D_3 receptors in hemiparkinsonian dyskinetic rats prevents the D_1 dopamine receptor stimulation of GABA release at striato-nigral terminals and the effect is mediated by an antagonist interaction between the receptors explained by a cross-talk as previously described [156]. This change in the D_1/D_3 relationship observed in dyskinesia with respect normal conditions could explain why D_3 receptor agonist prevents dyskinesia in L-DOPA treatment models, antagonizing adenylyl cyclase stimulated by D_1 receptors and in consequence GABA release. This observation also suggested that the maintenance of the dyskinesia is due to the sensitization of the D_1 receptor signaling pathway in the direct pathway that has been related with the LIDs [52]. If the heterodimeric interaction between D_1 and D_3 receptor is modified by L-DOPA remains unclear and more studies are needed to clarify it. The effect of antagonist in LID need to be also clarified since current basal ganglia models does not predict the effect observed, also the wide expression of D_3 receptors in other brain areas can contribute to the observed effect. However all the studies suggest that the use of D_3 receptors ligands on LID is promising.

8. Conclusion

The D_1 dopamine receptors supersensitivity in striato-nigral neurons are closely related with LID with a central role of adenylyl cyclase, co-expression of D_3 receptors with D_1 receptors and the modifications of their interaction during experimental Parkinson and LID

suggested a promissory therapeutical alternative in the management of motor disabilities related with L-DOPA administration.

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