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Involvement of canonical and non-canonical D1 dopamine receptor signalling pathways in L-dopa-induced dyskinesia

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SUMMARY

Chronic L-3,4-dihydroxyphenylalanine (L-dopa) treatment of Parkinson Disease (PD) often leads to debilitating involuntary movements, termed L-dopa-induced dyskinesia (LID). The past few years have seen an unprecedented increase in understanding the neural mechanisms underlying LID manifestation in PD associating them mostly with D1 dopamine (DA) receptor sensitisation and deregulated homologous desensitisation as well as hyperactivity of both canonical and non-canonical DA signalling pathways. We here review these recent findings and demonstrate that decreasing DA receptor-mediated signalling (i) by increasing D1 receptor internalization and (ii) by inhibiting the Ras-Extracellular signal-Regulated Kinase 1/2 non-canonical DA signalling cascade, might reduced LID severity. Strategy (i) uses the lentivirus-mediated over-expression of the G protein-coupled receptor kinase 6 that control the desensitisation of DA receptors. Strategy (ii) proposes to use statins that, besides being specific inhibitors of the rate-limiting enzyme in cholesterol biosynthesis, can also inhibit Ras isoprenylation and activity and subsequently the phosphorylation of ERK1/2. Experiments were performed in both the rodent and primate models of LID. Those results strongly suggest that different strategies might represent a treatment option for managing LID in PD.

Abbreviations

AC:	adenylyl cyclase
AIMs:	abnormal involuntary movements
AMPA:	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
cAMP:	cyclic adenosine 3′,5′-monophosphate
DA:	dopamine
DARPP-32:	dopamine and cyclic adenosine 3′,5′-monophosphate-regulated phosphoprotein, 32 kDa
D1R:	D1 dopamine receptor
D2R:	D2 dopamine receptor
D3R:	D3 dopamine receptor
ERK:	extracellular signal-regulated kinase
GPCR:	G protein-coupled receptors
LID:	L-dopa-induced dyskinesia
MPTP:	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSN:	medium spiny neurons
6-OHDA:	6-hydroxydopamine
L-dopa:	L-3,4-dihydroxyphenylalanine
PD:	Parkinson's disease
RGSL:	regulatory GPCR signalling protein
SNc:	substantia nigra pars compacta

The discovery that the death of dopaminergic neurons is responsible for the debilitating motor syndrome observed in Parkinson's disease (PD) has led to the development of various pharmacological therapies to compensate for this loss. Levodopa therapy that the dopamine (DA) precursor L-3,4-dihydroxyphenylala-nine (L-DOPA) to enhance synaptic transmission remains the standard treatment 40 years after its introduction. Even if L-DOPA reduces tremor, bradykinesia and rigidity, the major features of PD, long-term L-DOPA treatment leads to the development of fluctuations in motor response and involuntary movements, known as L-DOPA-induced dyskinesia (LID) [1,2]. While the mechanisms involved in LID occurrence are still unclear, denervation-induced supersensitivity of DA receptors (D1-like and D2-like), which are members of the G protein-coupled receptor (GPCR) superfamily, has been widely suggested as the most plausible mechanism of LID [3,4]. The design of novel agents for the prevention of LID requires the elucidation of the adaptive changes produced in the parkinsonian brain by repeated administration of L-dopa.

The main targets of the L-DOPA-derived DA are the GABAergic medium spiny neurons (MSNs) of the dorsal striatum and represent approximately 95% of all neurons. These neurons give rise to two pathways that connect the striatum to the output nuclei of the basal ganglia, namely the globus pallidus pars internalis and the substantia nigra pars reticulata [5]. MSNs of the "direct pathway" project directly from the putamen to globus pallidus pars internalis and the substantia nigra pars reticulata. Neurons of the "indirect pathway" connect the putamen with the globus

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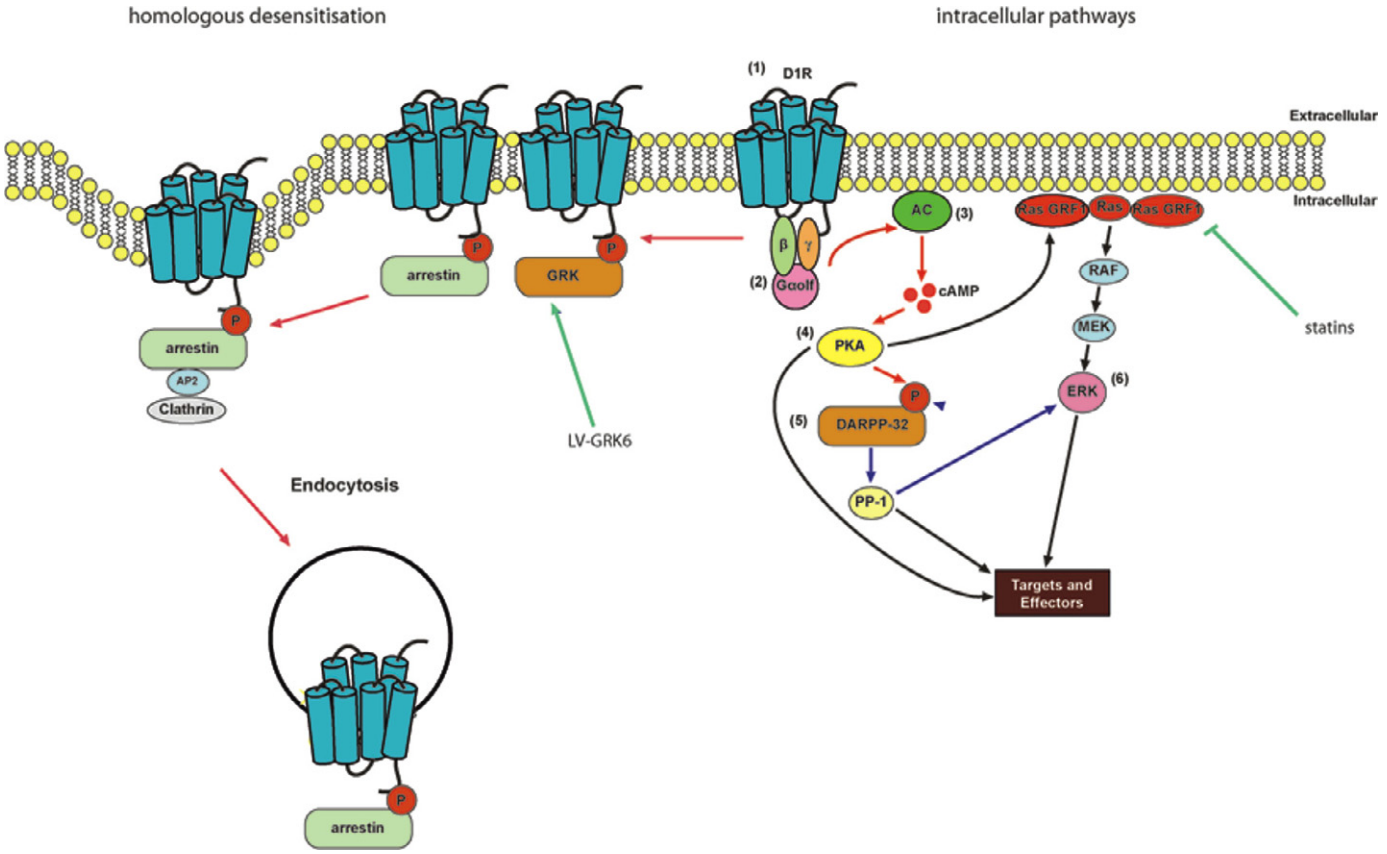

Fig. 1. D1 receptor (D1R) signalling cascades involved in L-DOPA-induced dyskinesia. Right side: Agonist binding to D1R stimulates adenylyl cyclase (AC), increases the production of cyclic adenosine 3′,5′-monophosphate (cAMP) and activates protein kinase A (PKA). PKA phosphorylates various targets, among which the dopamine and cAMP-regulated phosphoprotein, 32 kDa (DARPP-32), an inhibitor of protein phosphatase 1 (PP-1). The Ras-extracellular signal-regulated kinase (ERK) cascade, a member of the mitogen-activated protein kinase (MAPK) family, parallels this canonical signalling cascade. Both cascades activate various targets and effectors.
Left side: Homologous desensitisation process of D1R. After ligand binding, D1R is rapidly phosphorylated by GRKs, followed by binding of the phosphorylated receptors to arrestins. The arrestin–GPCR interaction promotes the recruitment of an endocytic complex, leading to receptor internalisation via the dynamin-dependent, clathrin-coated vesicle-mediated endocytic pathway. Arrestins also serve as adaptors and scaffolds that interact with numerous signalling molecules and organize some G protein-independent signalling pathways.

pallidus pars internalis/substantia nigra pars reticulata via the globus pallidus pars externalis and subthalamic nucleus. The MSNs of the direct and indirect pathways differ also with their different expression of neuropeptides and receptors. Thus, the striatonigral neurons of the direct pathway express preferentially D1 dopamine receptor (D1R) and produce the neuropeptides dynorphin and substance P, whereas the MSNs of indirect pathway are enriched in D2 dopamine receptor (D2R) and express enkephalin [6]. Even if, these two pathways are distinct anatomically, in non-human primates, a significant proportion (25–30%) of the MSNs co-express the D1R and D2R [7]. *In fine*, the direct and indirect pathways have opposing effects on movements: activation of the direct striatonigral pathway disinhibits thalamocortical neurons and facilitates motor activity, whereas activation of the indirect striatopallidal pathway enhances inhibition on thalamocortical neurons and reduces motor activity [5].

Expression levels of both D1R [6,8] and D2R [6,8] have not clearly correlated with LID, whereas a linear relationship between D1R sensitivity and LID severity has been established [8]. Activation of D1R is coupled to olfactory type G-protein α-subunit (G_{olf})-mediated stimulation of adenylyl cyclase (AC) (Fig. 1) and induces accumulation of cyclic adenosine 3′,5′-monophosphate (cAMP). The increase in cAMP activates the protein kinase A (PKA), which in turn phosphorylates its targets, such as DA and cAMP-regulated phosphoprotein, 32 kDa (DARPP-32), the DA signal amplifier (Fig. 1). This phosphorylation at Thr34 converts DARPP-32 into an inhibitor of protein phosphatase-1 (PP-1). Elevated levels of G_{olf} protein have been found in parkinsonian patients [9] and in the striata of DA-depleted rats [9]. Chronic L-DOPA or D1R agonist (but not D2R/D3R agonists) treatments normalize its levels in rats model [9]. Study performed using the gold standard 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkey model has shown that the coupling of the D1R to G_{olf} is significantly increased in dyskinetic monkeys compared to L-DOPA-treated non-dyskinetic monkeys [8]. In rat models, unilateral lesion of substantia nigra led to an increase in cAMP levels in the ipsilateral striatum [10,11]. At the peak of LID as well as 24 hours after the last administration of drug, L-dopa treatment reverses the elevated levels of cAMP in striatum [10,11]. In this canonical D1 signalling pathway, the phosphorylation of DARPP-32 at Thr34 appears as a critical player. Indeed, a dramatic increase in pDARPP-32 at Thr34 was observed in 6-OHDA rats with overt abnormal involuntary movements (AIMs) [12,13] or behavioural sensitisation [14] after L-dopa treatment. A strong increase in DARPP-32 levels was also observed in dyskinetic MPTP-monkeys compared to non-dyskinetic monkeys [8]. It seems not only to reflect LID or AIMs severity but also it would play a permissive role on LID by exacerbating the sensitised response of D1R to L-DOPA. Indeed, the genetic inactivation of DARPP-32 protects 6-OHDA-lesioned mice from severe AIMs [15]. All together these data highlight a relationship between pDARPP-32 level and LID severity, but what are the consequences of the sensitised canonical signalling pathway? One immediate effect is the upregulation of the phosphorylation of downstream effectors proteins potentially involved in the