CANADIAN ASSOCIATION OF NEUROSCIENCES REVIEW: The Role of Dopamine Receptor Function in Neurodegenerative Diseases

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ABSTRACT: Dopamine (DA) receptors, which are heavily expressed in the caudate/putamen of the brain, represent the molecular target of several drugs used in the treatment of various neurological disorders, such as Parkinson's disease. Although most of the drugs are very effective in alleviating the symptoms associated with these conditions, their long-term utilization could lead to the development of severe side-effects. In addition to uncovering novel mediators of physiological DA receptor functions, recent research advances are suggesting a role of these receptors in toxic effects on neurons. For instance, accumulating evidence indicates that DA receptors, particularly D1 receptors, are central in the neuronal toxicity induced by elevated synaptic levels of DA. In this review, we will discuss recent findings on DA receptors as regulators of long term neuronal dysfunction and neurodegenerative processes.

RÉSUMÉ: Les récepteurs dopaminergiques, exprimés notamment dans les noyaux caudé et putamen du cerveau, sont la cible pharmacologique de plusieurs médicaments employés dans le traitement de maladies neurologiques telle que la maladie de Parkinson. Bien que ces médicaments soient efficaces pour renverser les symptômes cliniques de la maladie, ils sont associés au développement d'effets secondaires incommodants majeurs lorsque utilisés à long terme. L'avancement de la recherche sur la fonction des récepteurs dopaminergiques a mis en lumière plusieurs nouvelles voies de signalisation, dont certaines sont reconnues pour initier la neurodégénérescence. Ainsi, des études récentes ont démontré l'implication des récepteurs dopaminergiques D1 dans la toxicité induite par des niveaux synaptiques élevés de dopamine. Cet article a pour but d'exposer le rôle potentiel d'un dérèglement de la signalisation des récepteurs dopaminergiques dans l'apparition de dysfonctions neuronales, voire même la neurodégénérescence.

Dopamine (DA) is the predominant catecholamine neurotransmitter in the mammalian brain, where it controls various functions: endocrine regulation, food intake, cognition, emotion, addiction and locomotion.[1] This catecholamine also plays multiple roles in the periphery as a modulator of the cardiovascular system, catecholamine release, hormone secretion, vascular tone, renal function, and gastrointestinal motility. These physiological effects are all mediated through DA receptors (D1-D5) which are members of the large family of G protein-coupled receptors.[1,2] DA receptors can be subdivided into D1 and D2 classes: the D1-like receptor subfamily which includes D1 and D5 receptors, and the D2-like subfamily, which includes D2, D3 and D4 receptors. D1 and D2 receptors constitute major DA receptor subtypes that are expressed differentially in various regions of the human brain. The intensity and duration of these effects are primarily regulated by the rapid reuptake of DA by the plasma membrane DA transporter (DAT) back into presynaptic DA neurons.[3-8] DAT is a member of the $NaCl_2$-coupled neurotransmitter transporter family, which constitutes plasma membrane transporters for serotonin and noradrenaline. Inhibition of DA reuptake increases the extracellular and synaptic concentrations and lifespan of DA, which, in turn, leads to prolonged DA receptor stimulation. In addition, DAT is found exclusively in DA neurons and appears to be the defining molecule of DA neurons. Once inside the presynaptic nerve terminal, DA is transported into small synaptic vesicles by the vesicular monoamine transporter VMAT2, also responsible for packaging serotonin, noradrenaline, adrenaline and histamine in their respective neurons.[9,10]

Dysfunction of DA neurotransmission is associated with several pathological conditions, such as hyperprolactinemia,

Parkinson's disease, schizophrenia, Tourette's syndrome, attention deficit/hyperactivity disorder, and Huntington's disease.[11-18] Drugs acting at DA receptors are commonly used to alleviate symptoms associated with these conditions. Dopamine receptor antagonists have been developed to block hallucinations and delusions that occur in schizophrenia patients, whereas the DA synthesis precursor levodopa and DA receptor agonists are effective in the hypokinesia of Parkinson's disease. However, therapies of disorders resulting from DA transmission imbalance are associated with severe side-effects. Chronic blockade of DA receptors can induce extrapyramidal effects similar to those resulting from DA depletion and, conversely, chronic administration of levodopa and DA agonists can cause fluctuations in motor control (end of dose deterioration, on-off phenomenon) and dyskinesia, a neurological syndrome characterized by repetitive, involuntary, purposeless movements.[19-22] These side-effects can become more disabling than most other symptoms of such conditions. Consequently, one of the challenges in recent years has been to understand the etiology of these clinical problems and to discover drugs without adverse effects. This effort has led to the development of a number of new therapeutic agents which have contributed to increasing our knowledge of DA receptor function, although they have not resolved the causes of the clinical maladies.[1,18]

This short review discusses recently documented evidence of novel mediators of the molecular and cellular consequences of DA receptor activation. We will focus on the potential that the D1 receptor signaling cascade might have in neurodegenerative disorders. While recent advances in understanding of D1 receptor functions have highlighted the importance of several intracellular pathways, it is only now that these signaling cascades have been associated with motor symptoms and long-term striatal neuronal degeneration and dysfunction.

DOPAMINE RECEPTORS

Localization of D1-like receptor expression in the brain

D1 receptors are the most widespread of all receptors, with the highest overall density in the brain. In the human central nervous system, the relative abundance of DA receptors is D1> D2> D3> D5> D4.[23] D1 receptor proteins are mainly expressed in the caudate-putamen (striatum) and nucleus accumbens where they are primarily located on gamma-amino butyric acid (GABA) medium-sized spiny neurons that project to the internal segment of the globus pallidus and the substantia nigra pars reticulata (direct pathway) and co-localize with substance P and dynorphin.[24-29] In the substantia nigra pars reticulata, binding of D1-specific ligands has been demonstrated, but no mRNA has been detected. Generally, D1 receptors are mainly post-synaptic but are present on the presynaptic terminals of glutamatergic projections from the cortex and thalamus. Moderate D1 receptor protein levels are found in the globus pallidus, substantia nigra and cerebellum. Low levels are seen in most areas of the cortex and other brain regions.[1,23,30,31]

Low levels of D5 receptors are localized on medium-sized, spiny GABAergic neurons and large cholinergic neurons of the dorsal striatum, while higher levels are observed in the ventral striatum (nucleus accumbens, olfactory tubercle, islands of Calleja) and septal area.[32] Outside the striatum, D5 receptors are present in the substantia nigra pars compacta, hypothalamus,

cerebral cortex, globus pallidus and hippocampus of the human brain.[32-34] Moreover, it has been reported that D5 receptors display higher affinity for DA than the D1 subtype.[35,36] The high affinity of D5 receptors for DA and their presence in DAergic pathways suggest that they may participate in some activities of DA neurotransmission.

Localization of D2-like receptor expression in the brain

The distribution of D2 receptors in the brain is very similar to that of D1 receptors. D2 receptors are also mainly expressed in the caudate/putamen, nucleus accumbens and olfactory tubercle, but additionally in the substantia nigra pars compacta and in the ventral tegmental area, where they presumably function as autoreceptors.[30,31,37] Functionally, various lines of evidence indicate that striatal D2 receptors are expressed mainly by both striatal cholinergic interneurons as well as striatal GABAergic medium spiny neurons projecting to the external segment of the globus pallidus (indirect pathway) and co-localize with enkephalin.[27-29] Low levels of D2 receptor proteins are detectable in the lateral segment of the globus pallidus and hippocampus, with very low amounts in the internal segment of the globus pallidus, cortical regions and cerebellum.[24-26,38,39] D2 receptors are at the presynaptic level on DA neuron terminals in the striatum, and some evidence suggest their presence on the terminals of corticostriatal neurons originating from the prefrontal cortex.[40]

Although the D1 and D2 receptors may be preferentially localized to distinct striato-fugal neuron types, a significant percentage of striatal projection neurons contains both D1 and D2.[41-45] The percent of neurons showing such colocalization has varied in these studies, ranging from 10% to 25% of striatal neurons,[41] to about 30–40% of striatal neurons,[42] to nearly all striatal neurons.[45] Single-cell RT-PCR studies further indicate that striatal projection neurons express both D1 and D2, with 20–50% of SP+ neurons containing mRNA for D1 and D2, and 10% of ENK+ neurons expressing D1 and D2.[44]

The D3 receptors are localized in the forebrain limbic areas. The largest receptor densities are in granule cells of the islands of Calleja and in GABAergic medium spiny neurons of the rostral and ventromedial shell of the nucleus accumbens.[46-48] In extrastriatal regions, moderate to low levels of D3 receptor protein are present in both segments of the globus pallidus, thalamus, hypothalamus, amygdala, substantia nigra and ventral tegmental area. It is noteworthy that D1 and D3 receptors mRNAs colocalize in single neurons of the nucleus accumbens and several studies have demonstrated their interactions at both cellular and behavioral levels.[49-52]

The D4 receptor level is low in the basal ganglia and higher in the frontal cortex, medulla, amygdala, hypothalamus, hippocampus and mesencephalon.[53-55] The highest densities of binding sites are found in the lateral septal nucleus and dorsomedial thalamus.

Dopamine receptor signaling

The signal transduction pathways coupled to DA receptors have been characterized in various cellular systems.[1,2,56] In most of these systems, stimulation of the D1-like receptor subfamily activates adenylyl cyclase (AC) by G_s/G_{olf} coupling protein, whereas the D2-like receptor subfamily inhibit AC by G_i/G_o
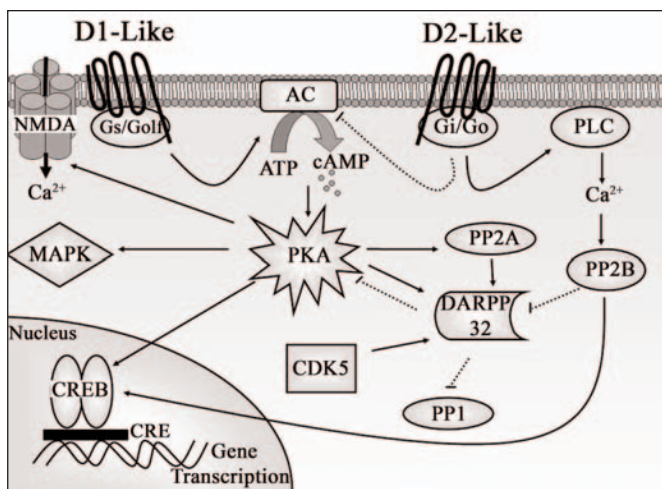
Figure 1: DA receptor signaling pathway. Stimulation of the D1-like receptors subfamily activates adenylate cyclase (AC) through Gs/Golf protein coupling whereas D2-like receptors inhibit AC through Gi/Go protein coupling. AC catalyzes the conversion of ATP to cyclic AMP (cAMP), which activate cAMP-dependent protein kinase A (PKA). PKA, through phosphorylation of cAMP response element-binding protein (CREB), allow the transcriptional activation of target genes. PKA also induces phosphorylation of ion channels like NMDA, leading to increased levels of intracellular calcium. Moreover, PKA is recognized to induce activation of protein phosphotase 2A (PP2A), mitogen activated protein kinase (MAPK) and phosphorylation of cAMP-regulated phosphoprotein of 32 kDa (DARPP-32). DARPP-32 can also be phosphorylated by cyclin dependant kinase 5 (CDK5), resulting to PKA inhibition. Stimulation of D2-like receptors subfamily activates phospholipase C (PLC) which will, in turn, activates the calcium-dependent protein calcineurin (PP2B) by mobilization of cytoplasmic calcium. PP2B induces the phosphorylation of CREB and inhibits the phosphorylation of DARPP-32.

coupling protein [Figure 1]. It is, therefore, thought that the classical functions of D1-and D2-like receptors increase or decrease, respectively, the intracellular levels of cAMP, which, in turn, influences the activity of cAMP-dependent protein kinase A RIIβ (PKA).

PKA has several targets such as cAMP response element-binding protein (CREB), ion channels (NMDA, AMPA, GABA) and cAMP-regulated phosphoprotein of 32kDa (DARPP-32). D1 receptor activation of CREB involves PKA-dependent phosphorylation of CREB at ser133.[57] This transcription factor is also phosphorylated by the Ca^{2+}-dependent protein calcineurin (PP2B). As both DA receptors can influence intracellular Ca^{2+} levels via N-methyl-D-aspartate (NMDA) receptors or phospholipase C (PLC), the calcineurin-phosphorylation of CREB is an additional important signaling pathway.[2,58,59] In this pathway, D1 receptor mediates CREB phosphorylation via phosphorylation of the NMDA receptor at Ser897-NR1,[60] whereas D2 receptor activates a cytosolic Gβγ-stimulated form of PLC, PLCβ1, causing inositol triphosphate-induced mobilization of cytoplasmic Ca^{2+}.[61] Another fundamental target of PKA activation is the phosphorylation of DARPP-32 at thr34,

which leads to inhibition of protein phosphatase 1 (PP1). A second function of this regulatory protein occurs following phosphorylation of DARPP-32 at thr75 by cyclin-dependent kinase 5 (cdk5) and results in PKA inhibition.[62] Note that stimulation of D2 receptor could decrease the phosphorylation of DARPP-32 through both the activation of the PLC/ Ca^{2+}/ calcineurin pathway and by reducing levels of cAMP.[58,63] Recently, a number of studies suggest that PKA could activate mitogen-activated protein kinases (MAPK) such as extracellular signal-regulated kinase, (ERK), p38 MAPK and c-Jun N-terminal kinase (JNK).[64-68]

Extracellular DA-induced striatal neuronal deterioration

Considerable evidence indicates that DA may, under certain circumstances, play a role in the mediation of central nervous system tissue damage. DA toxicity to nigrostriatal DAergic neurons has been studied extensively in animal models.[69-72] However, an increasing number of observations suggests that striatal DA could also contribute to the deterioration of other neuronal populations. For instance, DA appears to be involved in the striatal neuropathology associated with several conditions, including ischemia,[73,74] direct exposure of the area to high levels of excitatory amino acids,[75-77] mitochondrial dysfunction,[78,79] and systemic methamphetamine treatment.[80,81] Evidence for the involvement of DA in this neuropathology originates from the observation that, in each case, toxicity is attenuated by pharmacologically or surgically reducing striatal DA availability prior to the insult. For example, it was documented that depletion of striatal DA in rodents, using the neurotoxin 6-hydroxydopamine, is neuroprotective against tissue damage induced by the administration of mitochondrial toxins, such as malonate and 3-nitroproprionic acid.[78,79]

Because striatal neurons do not produce DA or express DAT, the mechanism of DA-mediated neurotoxicity in these neurons occurs probably through DA present extracellularly at the synapses. Normally, DA released into the synapses is cleared rapidly and recycled by the DAT of presynaptic neurons.[3,5,7,82,83] DAT is a molecular gateway for toxins, and many potentially toxic substances which resemble DA could be substrates for DAT and could accumulate in DAergic neurons via DAT.[8,84-86] However, in the case of treatments with mitochondrial toxin MPTP as well as amphetamine and its analogue methamphetamine, DAT uptake activity is reduced, and large amounts of DA accumulate at the extracellular level at the synapses, which is associated with striatal neuronal death.[87-91] Consistent with this idea, DA uptake is decreased in striatal synaptosomes whereas striatal DA levels are increased in rodents exposed to mitochondrial toxins.[92,93] Similarly, in amphetamine and methamphetamine treatments, elevated synaptic levels of DA accumulate not only because of reduced DAT uptake activity but also by presynaptic depletion of DA from storage vesicles, with enhanced DA release into the synapses.[80]

Molecular mechanism of DA-induced neurodegeneration

Two general hypotheses are formulated for the striatal neuronal toxicity of DA: (1) DA, via its oxidation, can produce quinones and reactive oxygen species (ROS) that are known to lead to oxidative stress, and (2) DA, through excessive activation

of its receptors, can alter the intracellular signaling of neurons, initiating long-term neuronal dysfunction and degeneration.

Dopamine autoxydation and oxidative stress

It is well documented that high concentrations of DA and/or its metabolites are directly toxic to neuronal cells, as shown by striatal injection of DA in the rat brain or by the addition of DA to cultures of striatal neurons.[69,94-103] DA toxicity can be explained by the inherent instability of its catechol moiety that produces damaging ROS, such as hydrogen peroxide, superoxide radical, and hydroxyl radical.[104] These may occur through DA metabolism that is evoked by the enzyme monoamine oxidase and produce hydrogen peroxide.[105] However, growing evidence indicates that oxidation of the DA molecule generates a reactive quinone moiety that is capable of covalently modifying and damaging cellular macromolecules.[91,106] This quinone formation is spontaneous, can be accelerated by metal ions (manganese or iron), and arises from selected enzyme-catalyzed reactions. Macromolecular damage, combined with increased oxidant stress, may trigger cellular responses that eventually lead to neuronal death.[107] Other *in vitro* studies have documented that DA toxicity is associated with elevated levels of p53 and transcription factors NFkappaB, [108-110] DNA damage,[111-113] heightened nitric oxide production[100-102] and caspase-3 activation.[114-116] In conclusion, reactive quinones have long been known to represent environmental toxins and, within the context of DA metabolism, may also play a role in pathological processes evoking neurodegeneration.

Dopamine receptor activation

Several studies on DA toxicity suggest that DA can induce neuronal death in both receptor-independent and receptor-dependent ways. However, DA receptor overactivation is the most compelling hypothesis to explain the trans-synaptic nature of DA toxicity *in vivo*, when post-synaptic DA target neurons are affected. While recent advances in understanding DA receptor functions have highlighted the importance of several intracellular pathways, it was only recently shown that DA receptor signaling has been connected with long-term striatal neuronal dysfunction and degeneration [Figure 2, Table]. One of the first *in vivo* proofs of DA receptor-induced striatal cell death came from the demonstration that acute methamphetamine administration in rats, which causes the massive release of vesicular DA into the synapses, increased the frequency of striatal lesion formation generated by threshold concentrations of 3-nitroproprionic acid.[79] In this study, blocking D1 receptors prevented the effect of elevated striatal DA levels on 3-nitroproprionic acid toxicity, whereas blocking D2 receptors had no effect. The role of D2 receptor signaling in the toxicity induced by DA has been reviewed recently;[117] the present paper therefore focuses on the latest relevant research studies regarding D1 receptor signaling in neurodegenerative disease [Table].

D1 RECEPTOR SIGNALING AND STRIATAL DETERIORATION

Abnormal elevation in Ca^{2+} levels

A newly emerging notion of the DA receptor signaling is the modulation of synaptic plasticity by the D1 receptors. This modulation of synaptic plasticity is poorly understood but has
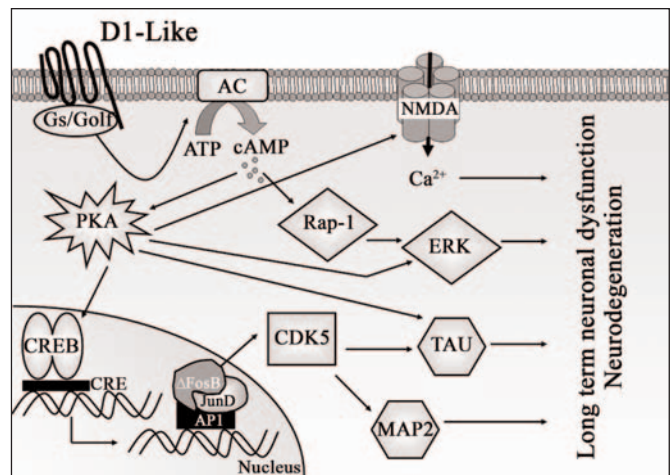

Figure 2: *Possible role of D1 receptor signaling in striatal deterioration. A long-term dysregulation in D1 receptors signaling cascades, subsequent to a treatment with drugs acting at DA receptors or consequently to pathological conditions such as Huntington's disease, could alter striatal neuronal functions and lead to motor movement dysfunctions. Several molecular determinants of the D1 receptors signaling cascades have been associated recently with striatal neuronal deterioration. This figure depicts three potential pathways. (1) The relationship between D1 receptor activation and NMDA receptor function, which are colocalized in several striatal neurons, is well-documented. Activation of PKA phosphorylates the NMDA receptors, and this may lead to a slow excitotoxicity phenomenon, through abnormal Ca2+entry. (2) Stimulation of D1 receptor can turn on the ERK signal via a PKA-dependent pathway or via activation of the small GTPase Rap1 through cAMP accumulation. ERK pathway has been associated with maladaptive changes and neurodegeneration in striatal neurons. (3) Chronic stimulation of D1-like receptors induces the transcription of a truncated form of FosB known as DFosB, a protein that persists in the striatum long after the end of treatment and for which CDK5 is a downstream target gene. CDK5 could alter striatal functions via the regulation of important structural proteins of the neuronal cell body such as the microtubule associated proteins MAP2 and Tau.*

been suggested to be partly dependent of NMDA receptors. In fact, several neurons of the striatum co-express both NMDA and DA receptors. Several studies had shed in light a relation between D1 receptors activation and the NMDA receptors function.[118-124] More recently, other studies have reported a direct interaction between D1 and NMDA receptors.[125-127] In these studies, oligomerization between NMDA and D1 receptors prevent D1 receptor internalization and desensitization after D1 receptor agonist stimulation.[126] Consequently, activation of either receptor type can modify the function of the other. This might explain why treatment of striatal tissue with a D1 receptor agonist produces rapid alteration in the distribution of the NMDA receptor subunits NR1, NR2A, and NR2B, with accumulation of these proteins in synaptosomal membranes and enhanced tyrosine phosphorylation of NR2A and NR2B.[122] It is believe that the protein tyrosine kinase Fyn participates in the regulation of these components by D1 activation.[128] Other mechanisms include DARPP-32, since its genetic inactivation

Table: Research studies documenting a role for D1 receptor activation in mediating striatal neuronal dysfunction and neurodegeneration

Effect on striatal neurons	Models	Intracellular pathway
Neuroadaptative changes	Chronic levodopa treatment or D1 receptor agonists in 6-OHDA lesioned rats.	-Dopamine receptors mediated phosphorylation of NMDA receptors.[134-136] -Activation of the ERK pathway.[67] -Activation of the activity regulated cytoskeletal -associated proteins.[172]
	Chronic levodopa treatment or D1 receptor agonists in MPTP lesioned monkeys.	-Increased levels of ΔFosB.[173] -Increased levels of cdk5 through D1 receptors supersensitivity.[165]
	Parkinson's disease patients treated with levodopa.	-Increased levels of ΔFosB.[185]
Cytotoxicity	Methamphetamine administration in 3-NP rat model.	-NI[79]
	Direct D1 receptor agonist treatment of dissociated striatal neurons.	-Increased levels of neuronal and inducible NOS, and in a PKA-dependent manner.[102]
	Direct D1 receptor agonist treatment of SK-N-MC cells.	-Activation of the ERK pathway in a PKA-dependent manner.[100,101]

Apoptosis	Direct D1 receptor activation in NMDA-mediated excitotoxicity
	    In striatal slices.
	    In dissociated striatal neurons.
		-NI[132]
		-PI-3 kinase dependent pathway.[125]

	Hypoxia mouse model.	-NI[210]
	DAT knockout mice.	-Increased levels of ΔFosB, cdk5 and tau hyperphosphorylation.[150]
	D1 receptor agonist treatment of SK-N-MC cells.	-Hyperphosphorylation of tau in a PKA-dependent manner.[171]

Abbreviations: NI, Not investigate; 6-OHDA, 6-hydroxydopamine; NMDA, N-methyl-D-aspartate; ERK, extracellular signal-regulated kinase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 3-NP, 3-nitroproprionic acid; NOS, nitric oxide synthase; PKA, protein kinase A; PI-3, Inositol 1,4,5-trisphosphate 3; DAT, dopamine transporter.

blocks the D1-induced serine phosphorylation of NR1,[129] reduces D1-dependent enhancement of NMDA currents in dissociated striatal neurons,[121] and prevents D1-dependent induction of long-term potentiation and depression in striatal slices.[130]

Increased DA transmission activates NMDA receptors, and this may lead to a slow excitotoxicity phenomenon, through abnormal Ca^{2+} entry [Figure 2].[121,125,131,132] Excessive cytosolic Ca^{2+} is known to subsequently initiate cell-death pathways.[133] Activation of DA receptors in the absence of NMDA may not have any outcome, but DA and D1 receptor agonists are able to increase excitotoxicity when NMDA is applied directly to striatal slices.[132] This D1 receptor modulation of NMDA-mediated excitotoxicity is documented to imply a phosphatidyl-inositol 3 kinase dependent pathway.[125] Along with these data, activation of D1 receptors by specific agonists elicits robust, repetitive Ca^{2+} transients (oscillations) in dissociated striatal neurons in culture.[59] Whether abnormal cytosolic Ca^{2+} and slow excitotoxicity could occur after long-term D1 receptor stimulation would require further investigation. However, a growing body of evidence has demonstrated altered phosphorylation of NMDA receptor subunits in the striatum of rat models of Parkinson's disease treated chronically with levodopa, and these changes have been suggested to represent a molecular basis for persistence of dyskinesia.[134-137]

Activation of the ERK signaling pathway

Mitogen-activated protein kinases (MAPK) have been implicated in a wide variety of cellular processes in which their persistent stimulation is well-known to mediate apoptosis in many cell types. In mammals, three major groups of MAPK have been identified: ERK,[138] p38 MAPK[139] and c-Jun N-terminal kinase (JNK).[140] Recently, Chen et al[101,103] documented the presence of two distinct signaling pathways by which DA neurotoxicity is manifests in dissociated striatal neurons. In these studies, selective stimulation of D1 receptors with the agonist SKF-38393 caused ERK activation in a manner sensitive to the receptor-selective antagonist SCH-23390, whereas DA-induced oxidative stress evoked activation of the stress-signaling kinases JNK and p38 MAPK in a time- and dose-dependent manner. The latter results are in agreement with a previous investigation showing that DA autoxydation stimulates the JNK pathways.[99] Stimulation of D1 receptors can turn on the ERK signal via a PKA-dependent pathway that leads to CREB and Elk-1 phosphorylation or activation of the small GTPase Rap1 through cAMP accumulation.[64,68] Along with these *in vitro* studies, the D1 receptor agonist SKF-38393 and levodopa administration in unilateral 6-hydroxydopamine-lesioned rodents have been documented to enhance striatal ERK phosphorylation in direct pathway neurons bearing D1 receptors.[67,141] Furthermore, immediate-early gene transcription in the DA-depleted striatum

is ERK-dependent, a finding that suggests ERK pathway involvement in adaptive changes occurring in these animals. Although these observations seem to be less perceptible in monkey models of Parkinson's disease,[142] they underscore the importance of elucidating the role of the ERK pathway in the etiology of striatal deterioration induced by DA receptor stimulation.

Cyclin-dependent kinase 5 dysregulation

Cyclin-dependent kinase 5, a serine/threonine kinase, is a unique cyclin dependent kinase that is activated by noncyclin activators of the brain, p35 and p39. Cyclin-dependent kinase 5 lacks a role in cell-cycle control, but is implicated in neuronal function and survival. For example, up-regulation of cdk5 activity is linked to neuronal death in several neurodegenerative disorders.[143-146] A close relationship between D1 receptor stimulation and activation of cdk5 is well-documented. Chronic D1-like agonist administration, but not D2, relates to the transcription of a truncated form of FosB known as ΔFosB, a protein that persists in the striatum long after the end of treatment and for which cdk5 is a downstream target gene.[147-149] Our recent observations reveal that persistently-elevated striatal DA levels in mice lacking the DAT (DAT knockout mice) lead to an up-regulation of striatal ΔFosB and increased levels of activated cdk5.[150] These findings are in agreement with other studies demonstrating that chronic exposure to the indirect DA agonist cocaine heightens the expression of cdk5 and its coactivator p35 through accumulation of the stable transcription factor ΔFosB.[148,151] Numerous studies have documented that cdk5 may alter the function of several downstream effectors influencing intracellular signaling, as it phosphorylates the NR2A subunit of the NMDA receptor,[152] PSD95,[153] protein phosphatase inhibitor-1,[154] as well as DARPP-32.[62] The Cdk5 activity also affects the cytoskeletal dynamics that underlie morphological changes as roscovitine, an inhibitor of cdk5, attenuates the cocaine-evoked increase in the spine density of medium spiny neurons bearing DA receptors in rats.[155,156] Consequently, apart from their impact on the rate of neurotransmission, cocaine-evoked alterations in the expression of p35 and cdk5 may also influence brain morphology. These observations underscore the functional significance of cdk5 activation after induction of ΔFosB subsequent to DA receptor stimulation.

The microtubule associated protein (MAP) tau is a well-documented substrate for cdk5.[157] Activation of cdk5 leads to hyperphosphorylation of tau, and this could play a causative role in neurodegeneration and the development of neurofibrillary pathology.[143,158] Interestingly, in a subpopulation of DAT knockout mice, increased levels of activated cdk5 in striatal neurons were associated with robust phosphorylation of tau.[150] Remarkably, the appearance of soluble hyperphosphorylated tau was linked with motor dysfunction and significant neuropathological changes, such as selective degeneration of striatal GABAergic neurons. At the same time as the motor behavioral deficits seen in DAT knockout mice were observed by others,[159] we have demonstrated that decreased numbers of striatal neurons correlate with a reduction in striatum volume.[160] These findings raise the interesting possibility that activation of DA receptors might have an effect on striatal function via the regulation of important structural proteins of the neuronal cell body, through ΔFosB/cdk5 pathways [Figure 2]. In line with this hypothesis, activation of D1 receptors elevated the phosphorylation of another known substrate of cdk5, MAP2.[161] Note that chronic treatment with the antipsychotic haloperidol, which induces a robust increase of ΔFosB expression,[162,163] also augments the levels of MAP2 phosphorylation.[164] Recently, Aubert et al [165] reported that increased D1 receptor sensitivity was associated with higher levels of cdk5 in the striatum of levodopa-treated parkinsonian monkeys. Whereas D1 receptor expression itself is not related to dyskinesia, D1 sensitivity per D1 receptor, measured by D1 agonist-induced [^{35}S]GTPγS binding, is linearly related to dyskinesia. Further evidence also revealed the importance of D1 receptors in mediating the long-lasting action of chronic levodopa treatment.[166,167] Whether higher cdk5 levels lead to the dysregulation of cytoskeletal proteins in these dyskinetic monkeys would require further investigations. However, these observations are in accordance with the idea that dysfunction in D1 receptor signaling might play a role in the development of dyskinesia via the regulation of important structural proteins.

It is noteworthy that further delineation of the precise role of cdk5 activity in DA receptor-induced neuroadaptive changes is clearly required. For instance, increasing evidence suggests that PKA can phosphorylate tau directly at multiple sites.[168-170] We recently found that stimulation of D1 receptors, a strong PKA activator, could enhance the phosphorylation of tau at PKA sites in SK-N-MC neuroblastoma cells endogenously expressing these receptors.[171] In this study, the soluble accumulation of phosphorylated tau was reversed by selective D1 receptor antagonists and was associated with caspase-3 activation. Interestingly, another investigation has shown that activity-regulated cytoskeletal-associated protein is strongly upregulated in the striatum of rat models of Parkinson's disease chronically treated with levodopa, and this correlates with the emergence of locomotor alterations.[172] These findings support the existence of a relationship between cytoskeletal modifications and the long-lasting action of chronically-administered levodopa, in which D1 receptors likely play a pivotal role.

CONCLUDING REMARKS

Motor complications arise after long-term levodopa treatment, and may last five to ten years. This end-of-dose phenomenon initially presents itself as so-called predictable fluctuations of movement and appears with increased, more severe onset of motor symptoms in a time-dependent manner from the last levodopa intake.[173-175] In the course of Parkinson's disease, these motor fluctuations become more and more intense and unpredictable, often in combination with the onset of psychosis-like symptoms and/or dyskinesias.[19,20,22] There are several hypotheses on the origin of such long-term motor complications of chronic levodopa administration. For instance, evidence indicates that this side-effect of chronic levodopa dose-dependently and individually contributes to the progression of neurodegeneration, according to the results from *in vitro* and animal models.[176-178] However, loss of presynaptic DAergic autoreceptor function with the resulting abnormally-high synaptic DA concentrations and altered postsynaptic DA receptor activation represent one of the most widely-accepted theories.[18,179,180] In accordance with this hypothesis, levodopa is

well-documented to induce ΔFosB transcription in the striatum of Parkinson rat[173,181,182] and monkey models,[172,173,183,184] which has been associated with increased levels of cdk5, a ΔFosB gene target.[165] Notably, the protein ΔFosB is upregulated in the caudate nucleus and putamen obtained at autopsy from Parkinson's disease patients treated with levodopa.[185] Considering that no obvious striatal degeneration is reported after levodopa treatment, whether the alterations in DA receptor signaling discussed in this review might be relevant to Parkinson's disease would clearly require further investigation. On the other hand, there is some morphological evidence for the atrophy of striatal dendrites and subtle neuronal death that supports the view of striatal contribution; although it is not severe enough to be easily recognized by conventional neuropathological examination as contributing to the progressive loss of benefit that most patients experience during chronic levodopa treatment.[186,187] These questions are important since levodopa is still the gold standard for the treatment of Parkinson's disease, and DA receptor agonists are initially prescribed in the early stages of Parkinsonism.[18]

Striatal degeneration represents the neuropathological hallmark of a number of neurological disorders such as levodopa-unresponsive Parkinsonism associated with multiple system atrophy and Huntington's disease.[188-190] In Huntington's disease, DAergic transmission is interrupted by progressive loss of striatal neurons bearing postsynaptic D1 and D2 receptors. An expansion in the CAG repeat of the IT15 (huntingtin) gene underlies the development of Huntington's disease. However, the basis for the specific vulnerability of dopamine-receptive striatal neurons remains unclear. It is believed that excessive accumulation and prolonged retention of DA at nigrostriatal synapses could play a role in these neuropathies.[14,189] Clinical data support this hypothesis as DA-depleting agents, such as tetrabenazine, reduce chorea in Huntington's disease patients, whereas levodopa administration enhances dyskinetic symptoms.[191-197] Depletion of striatal DA, using the neurotoxin 6-hydroxydopamine, is neuroprotective against administration of 3-nitropropionic acid-induced experimental model of Huntington's disease in rat.[78,79] In opposition, in DAT-/- mice, the enhanced DA transmission is associated with a higher susceptibility to striatal neurodegeneration after 3-nitropropionic acid administration.[198] Recent in vitro studies have documented that striatal primary culture containing a portion of the human huntingtin gene with expanded CAG repeats are more susceptible to DA-related ROS and degeneration induced by excessive stimulation of DA receptors.[199-201] In these studies, DA receptors activation enhanced the aggregation of huntingtin into toxic inclusions. We recently confirmed these observations using a double mutant mouse strain with both enhanced DA transmission and endogenous expression of a mutant huntingtin gene.[202] This strain was generated by crossing the DAT knock out mouse, which exhibits elevated extracellular DA levels in the striatum and locomotor hyperactivity, with a knock in mouse model of Huntington's disease containing 92 CAG repeats. Our data demonstrated that persistently-enhanced DA transmission exacerbated the locomotor abnormalities and accelerated the formation of mutant huntingtin aggregates in striatal projection neurons. These findings are in line with previous works showing that before apparition of any cognitive and motor symptoms in

Huntington disease mice, brain regions with early formation of aggregates all receive dense DAergic inputs.[203-205] This is an interesting issue as cdk5, a protein linked to chronic DA receptor activation and known to be upregulated in DAT knockout mice,[150] directly phosphorylated mutant huntingtin protein and thus affected aggregation.[206] Up to now, there is no clear correlation between decreasing efficacy of DA transmission, by using DA antagonists or depleters, and the rate of illness progression in Huntington disease.[207-210] However, these treatments are initiated only after overt manifestation of clinical symptoms, when the causal mechanisms are already in place. Overall these studies suggest a molecular basis for a clinical strategy of inhibiting DA system activity in this disease.

In conclusion, the fine line between the mechanisms producing constructive versus destructive changes in brain striatal neuronal signaling is largely unknown. Although some of the D1 receptors signaling changes presented in this review are based on rather artificial paradigm, they suggest the interesting possibility that dysfunction in striatal elements of the D1 receptor signaling pathway may be maladaptive and contribute to the emergence of dyskinesia. Central DAergic systems have anatomical as well as organizational properties that render them unique in comparison to other neurotransmission systems. In particular, because of the link between DA dysregulation and numerous neurological disorders, identification of novel molecular pathways for the regulation of DA receptor function may lead to fascinating new avenues for understanding the etiology of such disorders and perhaps for the development of novel therapeutic interventions.

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