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Review

Role of nitric oxide in the regulation of motor function. An overview of behavioral, biochemical and histological studies in animal models

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Abstract:
A compelling body of evidence suggests that nitric oxide (NO), a unique gaseous neurotransmitter and neuromodulator plays a key role in the regulation of motor function. Recently, the interest of researchers concentrates on the NO – soluble guanylyl cyclase (sGC) – cyclic GMP (cGMP) signaling pathway in the striatum as a new target for the treatment of Parkinson's disease (PD). The aim of the study is to review the available literature referring to the role of NO in the integration of basal ganglia functions. First, attention has been focused on behavioral effects of NO donors and neuronal nitric oxide synthase (nNOS) inhibitors in the modulation of motor behavior. Then, disturbances in the nitrergic neurotransmission in PD and its 6-OHDA animal model have been presented. Moreover, the most current data demonstrating the contribution of both dopamine and glutamate to the regulation of NO biosynthesis in the striatum have been analyzed. Finally, the role of NO in the tonic and phasic dopamine release as well as in the regulation of striatal output pathways also has been discussed.

Key words:
cGMP, nitric oxide, locomotor activity, 6-OHDA, Parkinson's disease, soluble guanylyl cyclase

Abbreviations: AMPA – α-amino-3-hydroxyl-5-methyl-4--isoxazole propionate, BH_4 – tetrahydrobiopterin, cAMP – cyclic adenosine monophosphate, cGMP – cyclic guanosine monophosphate, CNQX – 6-cyano-7-nitroquinoxaline-2,3-dione, DA – dopamine, eNOS – endothelial nitric oxide synthase, GPe – external segment of the globus pallidus, GPi – internal segment of globus pallidus, 5-HT – serotonin, iNOS – inducible nitric oxide synthase, IRF-1 – interferon regulatory factor-1, L-Arg – L-arginine, L-NAME – N^G-nitro-L-arginine methyl ester, L-NMMA – N^G-monomethyl-L-arginine, L-NNA – N^G-nitro-L-arginine, MSNs – medium-sized spiny neurons, mtNOS – mitochondrial nitric oxide synthase, NADPH – the reduced nicotinamide adenine dinucleotide phosphate, NADPH-d – nicotinamide adenine dinucleotide phosphate-diaphorase, NF-κβ – nuclear factor κβ, 7-NI – 7-nitroindazole, NMDA – N-methyl-D-aspartic acid, nNOS – neuronal nitric oxide synthase, NO – nitric oxide, 6-OHDA – 6-hydroxydopamine, PCP – phencyclidine, PD – Parkinson's disease, PDEs – cyclic nucleotide phosphodiesterases, PKG – cGMP-dependent protein kinase, sGC – soluble guanylyl cyclase, SNP – sodium nitroprusside, SNr – substantia nigra pars reticulata

Introduction

Although modern molecular biology revealed enormous profuseness of different proteins and genes regulating body functions, investigations of the last 20 years have attributed a fundamental role in neuronal communications, modulation of blood vessel relaxation and immune response to a very simple mole-

cule that is nitric oxide (NO). In the central nervous system, NO plays an important role in many different processes, such as neurodevelopment [51], release and uptake of neurotransmitters [88], synaptic plasticity [32, 54, 71, 80, 120, 163] regulation of gene expression [78] and what is a subject of this review, in the control of motor function.

Nigrostriatal dopamine plays a crucial role in the regulation of motor behavior [61] but also other neurotransmitter systems (noradrenergic, serotonergic, glutamatergic, cholinergic, GABAergic) contribute to the modulation of this process. NO as an easily cell membrane-penetrating molecule is involved in communication between these systems and acts as an ideal mediator of nonsynaptic interactions [89, 142, 151, 152]. *In vitro* studies on striatal slices and *in vivo* microdialysis experiments have revealed that NO evokes the release of dopamine (DA) and other neurotransmitters [66, 74, 84, 98, 99, 138, 144, 145, 155–157, 164] in the striatum as well as affects the function of DA, serotonin (5-HT) and noradrenaline transporters [88, 90, 118]. Moreover, it has been demonstrated that NO can act as a neuroprotective agent [22, 24, 28, 84, 87, 124], although at a high concentration it can be a mediator of excitotoxic neuronal damage [33, 121].

The aim of the study is to review the available literature referring to the role of NO in the integration of dopaminergic and glutamatergic neurotransmission in the striatum that is the main structure of basal ganglia. First, attention has been focused on behavioral effects of NO donors and neuronal nitric oxide synthase (nNOS) inhibitors in the modulation of motor behavior. Then, disturbances in the nitrergic neurotransmission in Parkinson's disease (PD) and its 6-OHDA animal model have been presented. Moreover, the most current data demonstrating contribution of both dopamine and glutamate to the regulation of NO biosynthesis in the striatum have been analyzed. Finally, the interaction between dopaminergic and glutaminergic systems under physiological conditions and after degeneration of the nigrostriatal dopaminergic neurons as in PD will be discussed in support of the 6-OHDA animal model of the disease.

NO synthesis in brain

NO is a soluble, short-lived, membrane-diffusible gaseous neurotransmitter synthesized enzymatically by the nitric oxide synthase (NOS) through two successive reactions which require oxygen, the reduced nicotinamide adenine dinucleotide phosphate (NADPH), and the substrate L-arginine (L-Arg) for generation of equimolar concentrations of NO and citrulline [65, 105, 114]. In contrast to conventional neurotransmitters, NO cannot be stored in synaptic vesicles, hence, factors regulating the synthesis are critical for its function. In the mammalian organisms, NO is synthesized by four enzymes belonging to the NOS family [65]. Three of them are constitutive NOS isoforms [65], i.e., neuronal nitric oxide synthase (referred to as nNOS or NOS-I) originally found in neurons, endothelial nitric oxide synthase (referred to as eNOS or NOS-III) being mainly expressed in vascular endothelium and mitochondrial nitric oxide synthase (mtNOS) present in the inner mitochondrial membrane [45]. The fourth member of the NOS family, i.e., the inducible nitric oxide synthase (known as iNOS or NOS-II) is expressed in astrocytes and microglia cells in response to immunological or inflammatory stimulation [11, 56, 65]. Enzymatic activities of nNOS, eNOS and mtNOS are Ca^{2+}-calmodulin--dependent while iNOS is independent of Ca^{2+} due to a tight constitutive interaction with calmodulin [23]. Enzymatic activity of iNOS is regulated transcriptionally by inflammatory stimuli, such as interferon regulatory factor-1 (IRF-1) [79] and nuclear factor κβ (NF-κβ) [161].

Of the three constitutive NOS isoforms, nNOS is the predominant source of NO in neurons although this enzyme has been also found in rat astrocytes [4]. nNOS and eNOS generate small, short-lasting (few minutes) increases in NO contents while iNOS produces high amount of NO lasting hours or days [73]. Similarly like nNOS and eNOS, also mtNOS generates small quantities of NO. The function of NO in the mitochondria could be related to the regulation of O_2 consumption by inhibiting the cytochrome c oxidase [14, 25, 112]. The modulation of O_2 consumption by mitochondrial NO is transient and reversible.

All the NOSs share between 50–60% sequence homology [96]. The human nNOS consists of 1434 amino acids with a predicted molecular weight of 160.8 kDa [9]. Monomer of nNOS is an inactive enzyme while dimer is its active form and the dimerization requires tetrahydrobiopterin (BH_4), heme and L-Arg binding [125]. nNOS monomer exhibits a bidomain structure containing an oxygenase N-terminal domain and a reductase C-terminal domain which can

be separated by a calmodulin binding motif [162]. The oxygenase domain which binds the substrate L-Arg contains a BH_4 binding site and cytochrome P-450-type heme active site. This domain possesses also a binding site for zinc which facilitates nNOS dimerization. The reductase domain which binds the substrate NADPH contains a binding site for flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) [111, 130]. Electrons donated by NADPH can be transferred from the reductase domain to the oxygenase domain via FAD and FMN. The latter process of electron flow can be facilitated by Ca^{2+}/calmodulin binding [127].

NO formed in the two-step reaction stimulates its target receptor, i.e., soluble guanylyl cyclase (sGC) to produce the second messenger cGMP that then affects other effectors localized pre- and post-synaptically in the brain [8, 52, 53]. NOS has been found in the brain in discrete neuronal populations, in particular in the areas, such as the cerebellum, hippocampus, striatum, cortex, hypothalamus, midbrain, olfactory bulb and medulla of the rat [12, 13, 31, 53]. nNOS-expressing interneurons and their processes are readily labeled using nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) histochemical staining techniques [12, 68, 82, 86, 149, 150]. NADPH-d activity arises from the catalytic domain of the nNOS enzyme [31, 62, 68] which converts the substrate nitroblue tetrazolium to a formazan salt in a manner that accurately reflects nNOS enzymatic activity [107, 134]. However, in the aldehyde-fixed rat brain, NADPH-d is suggested to be related not only to nNOS but also to other isoforms of this enzyme as well as to several non-related types of NADPH-oxidoreductases [128]. Hence, especially for the identification and subcellular localization of the different nitric oxide synthase isoforms, and to distinguish them from other types of NADPH-oxidoreductases, independent techniques other than NADPH-d histochemical staining, such as immunocytochemistry and *in situ* hybridization, should be applied [128].

The effects of NO donors and nNOS inhibitors on motor function

A growing body of evidence from animals studies indicates that NO is a key modulator of neuronal activity in the dorsal striatum and a critical factor for the regulation of motor function and synaptic plasticity [37, 158]. Behavioral studies carried out on rodents demonstrated that non-selective and selective nNOS inhibitors reduced spontaneous locomotor activity [43, 137, 143] and hyperlocomotion induced by cocaine [122, 123], morphine [19], substance P [100] as well as by amphetamine or metamphetamine [1, 113, 122]. Also locomotor activity stimulated by selective dopamine D_1 and D_2 receptor agonists [122, 141] and the N-methyl-D-aspartic acid (NMDA) receptor antagonist MK-801 [39] was decreased by these inhibitors. Although MK-801-stimulated locomotor activity was reduced by nNOS inhibitors, contradictory results were obtained with another NMDA receptor antagonist phencyclidine (PCP). In particular, it has been shown that stimulatory effect of the latter NMDA receptor antagonist on locomotor activity was blocked by both the NO donor sodium nitroprusside (SNP) [15] or by diverse nNOS inhibitors [76, 77, 91]. Moreover, another series of studies demonstrated that nNOS inhibitors potentiated PCP-induced hyperlocomotion [16, 109, 110]. Hence, the exact role of NO in modulating locomotor activity in conditions of NMDA receptor blockade is unclear and these discrepancies still need to be elucidated.

Apart from reduction of the spontaneous and stimulated locomotor activities, nNOS inhibitors induced in rodents and pigeons a distinct catalepsy [20, 34, 75, 92, 103]. Catalepsy induced by a non-selective nNOS inhibitor N^G-nitro-L-arginine (L-NNA) was attenuated by the NO precursor L-Arg [34, 103] and the NO donor molsidomine [92]. Krząścik and Kostowski [92] have demonstrated that catalepsy induced by haloperidol administration (0.4 mg/kg) was dose-dependently reduced by molsidomine (10–100 mg/kg) and by L-Arg at a dose of 100 mg/kg. Low non-cataleptic doses of the nNOS inhibitor L-NNA (0.1 mg/kg) and haloperidol (0.1 mg/kg) administered jointly induced a long-lasting catalepsy. Additive effects of dopamine D_2 receptor antagonists (haloperidol, triapride) and nNOS inhibitors on catalepsy was also described by others [20, 103]. Cataleptic activity of nNOS inhibitors was also intensified by serotonin 5-HT_{1A} (WAY 100135), 5-HT_{2A} (ketanserin) and 5-HT_{2C} (ritanserin) receptor antagonists [37].

In contrast to the above-mentioned dopamine and serotonin receptor antagonists, antimuscarinic compounds, like atropine and biperiden blocked catalepsy induced by nNOS inhibitors [37]. After subchronic (4-days) administration of the non-selective nNOS in-

hibitor L-NNA cataleptogenic activity of this compound was attenuated due to the development of tolerance [36, 38, 103]. In the majority of the reported studies, nNOS inhibitors were administered systemically. In order to check whether the striatum is involved in catalepsy induced by nNOS inhibitors these compounds were administered directly into this structure [35, 37]. The latter studies confirmed that both non-selective (L-NNA; N^G-nitro-L-arginine methyl ester, L-NAME; N^G-monomethyl-L-arginine, L-NMMA) and selective (7-nitroindazole , 7-NI) nNOS inhibitors injected into the striatum induced a distinct catalepsy in rodents. Catalepsy induced in rats by intrastriatal administration of the non-selective nNOS inhibitor L-NAME was antagonized by L-Arg injected locally into this structure [35]. All the above-reported studies distinctly indicate that NO can modulate motor behavior of animals by affecting dopaminergic, serotoninergic or cholinergic transmission in the striatum [37].

NO in Parkinson's disease and its animal model

Progressive loss of DA neurons in the substantia nigra pars compacta (SNc) which leads to a severe depletion of DA in the caudate-putamen (in the rat corresponding to the corpus striatum) is the most characteristic pathological feature of PD that gives rise to the motor deficit. Apart from this well-documented pathological alteration in the nigrostriatal dopaminergic system, it has been demonstrated that the number of NO synthesizing neurons [10] and the expression of nNOS mRNA were markedly decreased in the putamen of parkinsonian brain [47]. In contrast to the putamen, in the medial medullary lamina of the globus pallidus and in the subthalamic nucleus (STN), nNOS mRNA expression was significantly increased [47]. However, in the cerebrospinal fluid of PD patients, the level of nitrate, which is considered to be a measure of NO biosynthesis in the brain, was found to be significantly reduced when compared to controls [95]. The latter effect may be related to the biosynthesis of NO by nNOS that is strictly dependent on the cofactor (6R)-tetrahydrobiopterin (BH_4), the concentration of which is greatly reduced in the caudate nucleus of parkinsonian patients [95].

Consistently with these clinical data Sancesario et al. [134] have reported that the level of nNOS protein was decreased by 42% and the number of nNOS-immunopositive intrastriatal fibres but not nNOS-immunopositive cell bodies was markedly reduced in the DA-deafferented rat striatum. Moreover, using an enzymatic method based on conversion of ^{3}H-L-arginine to ^{3}H-citruline for assessment of nNOS activity, it has been demonstrated that lesion of the nigrostriatal dopaminergic innervation resulted in a 50% decrease in the activity of this enzyme in the ipsilateral striatum [40]. These few clinical and experimental studies suggest that the loss of striatal DA due to degeneration of the nigrostriatal dopaminergic neurons can be expected to induce changes in the NO-mediated neurotransmission in the basal ganglia. These aspects will be discussed in the next chapters of this review.

The role of NO in signal transduction

Nitrergic transmission in the brain requires a fast and controlled supply of NO to the target cells. Due to unique properties of NO a precise control of transmission mediated by this specific neurotransmitter is mainly regulated by the level of NO biosynthesis. L-Arg, a precursor of NO, enters the brain parenchyma from the blood through the endothelial cells or from the cerebrospinal fluid through the ependymal cells [57]. Astrocytic processes are in a direct contact with the endothelium and ependymum, hence, astrocytes are the main source of L-Arg in the brain [3, 119]. However, NO synthesizing enzyme is localized predominantly in neurons and, therefore, is defined as nNOS [30, 55]. Thus, to complete neural pool of L-Arg, it is absolutely necessary to transport this amino acid from glial cells to neurons. The experiments performed on brain slices as well as in cultured astrocytes and neurons have demonstrated that nNOS activity is dependent on accessibility of L-Arg which is delivered from glial cells [63, 64]. The latter studies showed that agonists of ionotropic glutaminergic receptors (glutamate, NMDA) administered to brain slices and to astrocyte culture induced the release of the labeled L-Arg. In contrast to astrocyte culture, such effect was not observed in the cultured neurons. A subsequent series of studies revealed that ionotropic

non-NMDA receptors, especially α-amino-3-hydroxyl-5-methyl-4-isoxazole propionate (AMPA) receptors, contributed to the release of L-Arg by glial cells. Blockade of these receptors by the specific antagonist, compound 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), led to a very distinct decrease in basal level of the released L-Arg [64, 139]. Apart from glutamate also peroxynitrite anion ($ONOO^-$) stimulates the release of L-Arg from cultured rat astrocytes [147] by direct activation of L-Arg transport system y(+) which is localized in membranes of these cells [146]. So availability of L-Arg is a limiting factor for NO biosynthesis, hence, peroxynitrite anion formed in neurons diffuses to astrocytes transmitting the signal to release L-Arg. The described process may be considered as a form of neuroprotection since in conditions of L-Arg deficit, the activated nNOS produces, instead of NO, toxic superoxide radical that may react even with a minimal amount of NO forming peroxynitrite anion [30, 72]. L-Arg delivered by astrocytes to neurons normalizes production of NO and in this way prevents generation of superoxide radical.

Contribution of NO to the regulation of the striatum function

In the striatum, NO biosynthesis takes place in a subpopulation of striatal GABAergic medium-sized aspiny interneurons, which colocalize with neuropeptide Y and somatostatin [48, 86, 93, 94, 129, 148, 149]. These neurons are mainly concentrated in the matrix while striosomes are practically devoid of them [83, 136, 148]. Studies using stereological techniques estimate that NOS/somatostatin-containing interneurons constitute less than 5% (~21,000 cells/hemisphere) of the total neuronal population of the striatum [156]. However, the axons of individual NOS cells give rise to a dense net of collaterals that extend much further than other striatal interneurons enabling the NO produced by these cells to exert a considerable functional impact on both blood flow and neurotransmission across large striatal subregions [46, 116, 142]. Striatal nNOS expressing interneurons are robustly innervated by dopaminergic input from the SN and by glutamatergic projections from the cortex [50, 67, 85, 104, 131, 153]. Moreover, these nNOS positive interneurons make synaptic contacts with the medium-sized spiny neurons (MSNs) that constitute 95% of all striatal neurons and provide the only output from the striatum [18, 106, 135]. Striatal MSNs, similarly like nNOS-positive interneurons, are innervated by dopaminergic input from the SN and by glutamatergic routes from the cortex and thalamus [26]. Hence, nitrergic, dopaminergic and glutamatergic transmission converge in the striatum at the nNOS-positive interneurons [49, 50, 67, 104] and medium spiny projection neurons [17, 106, 135]. Therefore, striatal nNOS expressing interneurons play a critical role in the integration of dopaminergic and glutamatergic interactions as well as in the modulation of corticostriatal synaptic plasticity [17, 18, 81, 83, 155, 158–160].

Role of glutamate and DA in the regulation of NO synthesis in the striatum

It is widely accepted that nNOS enzyme expressed constitutively in neuronal cells is activated following transient elevations in intracellular Ca^{2+} levels mediated *via* stimulation of NMDA receptors by glutamate [52]. Hence, it has been thought that robust corticostriatal glutamatergic transmission activates striatal nNOS and NO signaling largely *via* the stimulation of NMDA receptors [29, 44, 74, 101, 102]. However, striatal nNOS interneurons express not only NMDA, AMPA and metabotropic glutamate receptors [60, 81, 108] but also dopamine $D_{1/5}$ receptors [21, 97, 126]. Moreover, a considerable evidence indicates that besides NMDA receptors, also DA D_1 and D_2 receptor activation regulates the striatal nNOS activity [70, 115, 132, 133]. Recently, it has been demonstrated that electrical and chemical stimulation of the SN as well as systemic administration of the DA D_1 agonist SKF81297 robustly increase striatal NO efflux measured by the combined techniques of *in vivo* amperometry and reverse microdialysis [132]. Both these effects were attenuated by systemic administration of the nNOS inhibitor 7-NI and DA D_1/D_5 receptor antagonist SCH23390 [132]. The latter effects provide a strong evidence that phasic DA transmission activates striatal nNOS *via* D_1/D_5 receptor-dependent mechanism. Moreover, the facilitatory effect of the SN stimulation on striatal NO efflux was attenuated by systemic administration of the DA D_2 receptor agonist

quinpirole [133]. Quinpirole pretreatment also decreased the facilitatory effect of SKF81297 on striatal NO efflux and nNOS activity measured indirectly as NADPH-d histochemistry [70, 133]. The observation that DA D_2 receptor activation potently suppresses transient efflux of NO elicited by SKF81297 administration indicates that the DA D_2 receptor-mediated effect does not function to simply decrease terminal DA release (and DA D_1 receptor activation) *via* stimulation of autoreceptors, but rather acts at a site postsynaptic to DA terminals in a manner which opposes the facilitatory influence of DA D_1 receptor activation. Conversely, administration of DA D_2 receptor antagonist etaclopride increases NO efflux measured by means of microsensor and striatal NOS activity assessed as NADPH-d histochemistry [107, 133].

The above-described studies indicate that DA modulates nNOS activity in the striatum *via* both facilitatory (D_1 receptor stimulation) and inhibitory (D_2 receptor stimulation) signaling. Since striatal nNOS interneurons express DA D_1/D_5 receptors, nNOS activation is likely to result from a direct influence of DA D_1 agonists on these neurons. In opposition, an effect mediated by D_2 receptors seems to be indirect because co-localization of these receptors with markers of striatal NOS interneurons has not been reported. However, striatal nNOS interneurons receive synaptic input from glutamatergic, GABAergic, dopaminergic and cholinergic neurons [49, 50, 67, 106, 131, 153] and all these populations express DA D_2 receptors [7, 154]. It has been demonstrated that DA D_2 receptors detected on excitatory glutamatergic and cholinergic terminals in the striatum attenuate excitatory synaptic transmission in medium spiny neurons [7, 154]. Hence, it is possible that the inhibitory effect of DA D_2 agonists on NO efflux reported in the abovementioned studies occurs *via* a DA D_2 heteroreceptor-mediated suppression of excitatory glutamatergic and/or cholinergic inputs involved in functional control of the striatal NOS-containing interneurons.

Considering NMDA-mediated regulation of striatal NOS activity, recently Park and West [115] have demonstrated that striatal D_1/D_5 receptor stimulation is necessary for the activation of nNOS by glutamatergic corticostriatal afferents. On the other hand, Hoque et al. [70] have shown that activation of NMDA receptors is necessary for modulation of striatal NOS activity by both facilitatory (D_1 receptor activation) and inhibitory (D_2 receptor activation) dopaminergic signaling mechanisms. Both these studies revealed that reciprocal DA-glutamate interactions play a critical role in stimulating striatal nNOS activity. Since in PD, the function of dopaminergic system is dramatically decreased, it seems clear that also NO production can be disturbed.

The role of NO-soluble guanylyl cyclase-cyclic GMP (NO-sGC-cGMP) signaling in the regulation of output pathways of the striatum

The GABAergic MSNs that provide the only output from the striatum are the major target of dopaminergic innervations. These neurons form two main efferent pathways that differ in the expression of DA receptors. MSNs that project to the substantia nigra pars reticulata (SNr) and internal segment of globus pallidus (GPi) (named the direct pathway) express DA D_1 receptors whereas those projecting to the external segment of the globus pallidus (GPe) (named the indirect pathway) express DA D_2 receptors. Signal transmission through the "direct pathway" provides a powerful inhibitory control of SNr and GPi. By contrast, signalling through the parallel "indirect pathway" leads to increased activity of excitatory glutamatergic neurons in the subthalamic nucleus (STN), which induces a strong excitation of the SNr and GP. A thinly regulated balance of output nuclei activity by the direct and the indirect pathways is thought to be essential for normal function of the basal ganglia. Accordingly, a reduced dopaminergic innervations to the striatum, due to the loss of DA neurons in the SN during PD leads to the alterations of MSNs activity and to the onset of severe motor symptoms.

MSNs of the direct pathway primarily express DA D_1 receptors that are positively coupled to adenylyl cyclase while that of indirect pathway expressing DA D_2 receptors are negatively coupled to adenylyl cyclase. The striatal MSNs have been shown to receive synaptic inputs from NO producing interneurons [49, 67, 135]. These synaptic inputs, terminate on the shafts of dendritic spines of MSNs known to express the highest levels of sGC in the brain [5, 41]. Apart from sGC, MSNs also express high levels of cGMP, cGMP-dependent protein kinase (PKG) and cyclic nucleotide phosphodiesterases (PDEs) [6, 27, 41, 58]. The major physiological action of NO consists in the

activation of sGC to increase intracellular cGMP level. NO acts *via* cGMP to regulate ion channels, protein kinases (PKG) and PDEs. The NO/cGMP signal transduction pathway is involved in integrating corticostriatal transmission and regulating synaptic plasticity in striatal networks. Some recent studies have demonstrated an important role for striatal NO-sGC pathway in the generation of spontaneous and drug-induced motor behavior [37].

In the striatum under physiological conditions, DA released from the nigrostriatal dopaminergic terminals interacts with DA D_1 receptors and in this way stimulates synthesis of adenosine 3',5'-cyclic monophosphate (cAMP). As revealed by more recent studies, the stimulation of these receptors, through an increase in the striatal nNOS activity, also leads to upregulation of NO-guanylate cyclase pathway [133] and cGMP production [2, 42, 140]. Hence, a deficit of DA in the striatum, as it is in PD, should imply a reduced stimulation of D_1 receptor and decreases in the cAMP and cGMP synthesis. Unexpectedly, a lesion of nigrostriatal dopaminergic pathway with 6-hydroxydopamine (6-OHDA) induces an increase in cAMP level several weeks thereafter, as evidenced by an increased basal adenylate cyclase activity in the DA-denervated rat striatum when compared to the contralateral side [69]. Unlike cAMP, cGMP level decreases in response to striatal DA loss [134]. Such a decrease in cGMP level is associated with decreased nNOS expression and activity, probably leading to a downregulation of NO-sGC pathway [134]. The intracellular levels of cAMP and cGMP are controlled not only by the rate of their synthesis *via* adenylate and guanylate cyclase, respectively, but also by the rate of their degradation *via* PDEs. It has been demonstrated in 6-OHDA lesioned rats that DA loss in the striatum is associated with an increased expression and activity of phosphodiesterase 1B (PDE1B) [134], a calcium/calmodulin dependent phosphodiesterase, which is abundant in the striatum and which preferentially hydrolyzes cGMP. In turn, activity and protein level of phosphodiesterase 10A (PDE10A), which is also abundant in the striatum and hydrolyzes cAMP with higher specificity than cGMP, was decreased under conditions of striatal DA deficit [59].

Administration of L-dopa, the commonly used drug for the treatment of PD, affects levels of both cyclic nucleotides in the striatum [58, 69]. After chronic treatment with this drug, high cAMP levels observed in the ipsilateral denervated striatum are reduced and return to the control levels of the contralateral non-lesioned side [58, 69]. Recently, Giorgi et al. [58] have demonstrated that chronic L-dopa treatment regulates levels of cAMP and cGMP in a different way in dyskinetic and non-dyskinetc 6-OHDA-lesioned rats. In non-dyskinetic rats the cAMP level increased in the cortex and striatum but decreased in the globus pallidus of both ipsi- and contralateral sides, whereas the cGMP content decreased below the baseline levels in all these structures only on the contralateral side. In dyskinetic animals, chronic L-dopa treatment led to a severe decrease in cAMP and cGMP levels in the cortex, striatum and globus pallidus on both sides of the brain. Pretreatment with the PDE inhibitor zaprinast reduced the severity of L-dopa-induced dyskinesias and partially prevented the decrease in the levels of cyclic nucleotides [58]. Moreover, using electrophysiological methods it has been demonstrated that L-dopa-induced dyskinesia was associated with the loss of long-term depression (LTD) expression at glutamatergic striatal synapses onto medium spiny projection neurons. Zaprinast was able to rescue the induction of this form of synaptic plasticity *via* a mechanism requiring modulation of intracellular levels of cGMP [117]. The latter finding suggests that drugs selectively targeting phosphodiesterases can ameliorate L-dopa induced dyskinesia, possibly by restoring physiological synaptic plasticity in the striatum [117].

Summary

The above short review of the most current studies referring to the role of NO in the regulation of the neuronal circuits within the striatum indicates that disturbances in the nitrergic transmission are an important pathological factor in PD. It is clear that further characterization of NO-sGC-cGMP signaling pathway is critical for understanding of both normal striatal function and pathophysiological changes observed during the course of the disease. Moreover, the above-presented studies suggest that modulation of the NO-sGC-cGMP signaling pathway during L-dopa therapy may have beneficial effects in preventing L-dopa induced dyskinesia. Hence, further studies in this field may not only extend our knowledge on the role of NO

and cGMP in the regulation of the striatum function but also may contribute to the development of a new form of PD therapy.

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