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7 Nitric oxide system and basal ganglia physiopathology

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Abstract

Nitric oxide (NO) is a pleiotropic molecule that is needed for physiological functions, especially in the brain NO induces vasodilatation, inhibits apoptosis and plays an important role in memory processes. A population of interneurons has been distinguished in the striatum by nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) staining, an enzyme that is identical with NO synthase (NOS). These interneurons are aspiny cells with dendritic branches and axonal arborisation extending to form a wide field. Single action potentials in these cells produce

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large inhibitory postsynaptic currents in medium-sized spiny neurons. Release of NO from these neurons facilitates the concurrent release of dopamine and glutamate (GLU). Although the influence of NOS-positive interneurons on striatal neuronal activity remains to be thoroughly characterized, evidence has accumulated suggesting that NO signaling may mediate and/or regulate multiple aspects of striatal neurotransmission.

Striatal NO signaling has a major impact on the responsiveness of dopaminergic (DA) neurons to electrical stimulation of the striatum and to some extent, the prefrontal cortex. Moreover, it is likely that NO signaling plays an important role in regulating the activity of striatal output neurons. Thus, striatal NOS interneurons may be critically involved in integrating corticostriatal sensorimotor information within striatal networks and synchronizing the activity of functionally related striatonigral sub-systems.

Our studies showed that systemic injections of the inhibitors of NOS decrease either elevate plus maze exploration or rearing in an open field arena. These results may involve motor effects of these compounds, since inhibitors of NOS induced catalepsy in mice. This effect was also found in rats after systemic, intracebroventricular or intrastriatal administration. Chronic NO synthesis inhibition induces plastic changes in NO producing neurons in areas related to motor control. In the same way, the application of NOS inhibitor twice a day, during four days caused cross-tolerance to the cataleptic effect of haloperidol. This raises the possibility that such treatments could decrease motor side effects associated with antipsychotic medications.

However, NO can be harmful mainly under oxidative stress conditions due to the oxidation and nitrotyrosilation of functional proteins. Considerable existing evidences indicate a role for NO–DA interactions in pathophysiological conditions such as Parkinson's disease (PD) and schizophrenia. However, the findings on the impact of nitrergic mechanisms in schizophrenia and PD are contradictory. In addition, the slow progression of these diseases, complicates experimental approaches to modeling their pathophysiological mechanism. Inducing experimental Parkinson in rats we found an interaction between NO system and neurodegenerative processes in the nigrostriatal pathway. Because NOS is an enzyme widely distributed and involved in a plethora of necessary physiological responses inside and outside the brain, the role of NO in human neurodegenerative disease is not as easily understood.

Introduction

In 1664 anatomist Thomas Willis termed a prominent subcortical region of the telencephalon corpus striatum. Neuronal tracing techniques developed by Nauta and colleagues in the mid-1950s allowed for elucidation of connectivity of the broadly defined corpus striatal region, and the term basal ganglia was

adopted to refer to a collection of nuclei deep within the cerebrum. These nuclei include the caudate, the nucleus accumbens and the putamen – which are collectively called the striatum, and also the globus pallidus, the subthalamic nucleus and the substantia nigra (pars compacta and reticulata). Heimer and colleagues subsequently adopted the term ventral striatum to delineate the most ventral aspects of the striatum (i.e., nucleus accumbens and portions of the olfactory tubercle) from more dorsal regions (i.e., caudate nucleus or dorsal striatum). Thus, the core structures of the mammalian basal ganglia include the dorsal striatum, the ventral striatum, and the globus pallidus. Other nuclei, such as the central complex of the thalamus or the pedunculopontine nucleus and the ventral tegmental area also play a major role in basal ganglia functioning [1-3].

The basal ganglia

The basal ganglia receive inputs from the neocortex and project massively to thalamic nuclei, which in turn project to the frontal cortex (corticocortical loop) [4]. Striatal information is transferred also to the pars reticulata of the substantia nigra which projects to the medial part of the thalamus complex (the parafascicular nucleus), going back to the caudate nucleus (Nauta-Mehler's loop) [5]. The globus pallidus internal segment neurons provide inhibitory inputs to the thalamus, the pedunculopontine nuclei and the superior colliculus. The subthalamic nucleus (corpus Luysi) is a relatively small nucleus located ventrally to the zona incerta and dorsally to the cerebral peduncle, is a relay nucleus controlling pallidal function [6]. The human substantia nigra pars compacta is a melanin-rich structure located dorsal to the pyramidal tracts (crus cerebri) in the midbrain. The pedunculopontine nuclei have prominent projections to the basal ganglia, mainly the pars compacta of the substantia nigra and the subthalamic nucleus.

The brain stem input to the striatum (dorsal and ventral) and, to a lesser degree, the globus pallidus and subthalamic nucleus is primarily from the DAergic cell groups in the ventral tegmental area (A10), substantia nigra (A9), and retrorubral area. The axons of these neurons run along the medial forebrain bundle to reach the dorsal striatum (the nigrostriatal pathway). The substantia nigra pars reticulata neurons send inputs to the pedunculopontine nuclei. The ventral part of the striatum also receives a prominent projection from the amygdala [2,3].

Although they are highly complex, the anatomical connections have been schematized in block diagrams in order to test specific hypotheses. Basically, there are three distinct pathways from striatum to thalamus, of primary importance, named the direct, the indirect and the hyperdirect pathways (Figure 1). The direct pathway is inhibitory and passes monosynaptically from the striatum to the globus pallidus internal segment. The indirect pathway reaches the same destination but synapses first in the external segment of the globus pallidus and then in the

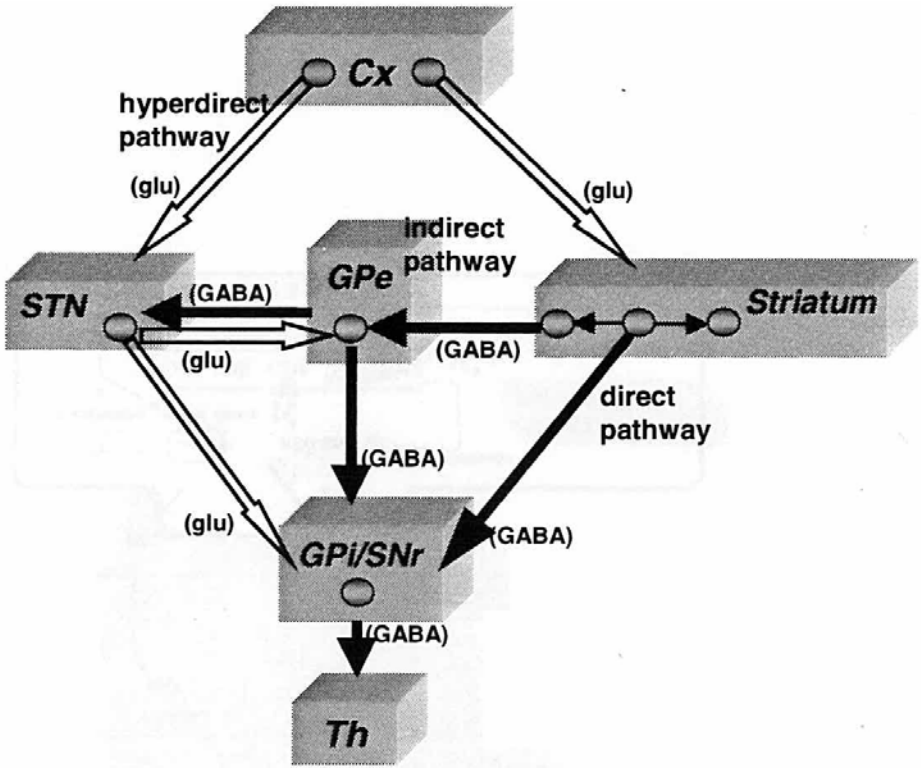

Figure 1. A schematic diagram of the cortico-STN-GPi/SNr hyperdirect, corticostriato-GPi/SNr direct and cortico-striato-GPe-STN-GPi/SNr indirect pathways. Open and filled arrows represent excitatory GLUergic and inhibitory GABAergic projections, respectively. Cx cerebral cortex; GPe external segment of the globus pallidus; GPi internal segment of the globus pallidus; SNr substantia nigra pars reticulata; STN subthalamic nucleus; Str striatum; Th thalamus [modified from 7].

subthalamic nucleus. Recently there has been growing evidence of a direct cortico–subthalamic nucleus–pallidal pathway described as hyperdirect pathway [7,8].

Interaction between these pathways has not yet been fully elucidated. Activation of the direct pathway has an excitatory effect on the thalamocortical projection, which results in a production of movement or different behaviors. Activation of the indirect pathway leads to an activation of the subthalamic nucleus and then to an increased inhibition of the thalamocortical projection. The hyperdirect pathway conveys powerful excitatory effects from the motor-related cortical areas to the pallidum, bypassing the striatum, with shorter conduction time than effects conveyed through the direct and indirect pathway. The competing pathways act like the brake and accelerator in a car. The brake–accelerator model suggests that release (disinhibition) of the thalamus by the direct pathway is opposed by the indirect pathway. The signals through the hyperdirect pathway may inhibit motor programs widely, and then the signals through the direct pathway may adjust the selected motor program according to the situation [4,6-8].

This anatomy means the basal ganglia are in a prime position to influence the executive functions of the forebrain. Through their extensive cortical

connections, the basal ganglia can influence both motor and cognitive functions [2-3,9]. There has been increasing evidence for the involvement of the basal ganglia in behavioral syndromes [10,11].

Striatal neurons consist mainly (96%) of medium-sized densely spiny neurons (cell body 20-25 μm in diameter) from which radiate branched spherical dendritic arborization densely laden with spines [12,13]. Their axon gives rise to a dense local collateral arborization, which contacts other spiny neurons. The dendritic arbors extend in a domain approximately 150-250μm in diameter such that neighboring neurons share common inputs. The medium spiny neurons use GABA as its neurotransmitter and also contain neuropeptides, some substance P and dynorphyn, whereas others contain enkephalin. The dendrites express receptors for numerous other neurotransmitters.

Spiny neurons are silent in the rest condition and discharge when they receive an input from an active cortical region. Pyramidal cortical neurons located primarily in layer 5 (also some in layers 2, 3 and 6), provide inputs to striatum. These inputs utilize the amino acid GLU as a neurotransmitter. Cortical and thalamic excitatory inputs make asymmetric synaptic contact mainly with the heads of the spines. Input from the substantia nigra pars compacta, the thalamus, or other intrinsic striatal neurons contact the dendritic shafts. DA fibers from the midbrain cell groups make symmetric synaptic contact primarily with the necks of dendritic spines and on the interspine dendritic shafts. The latter input is, therefore, in crucial position to modulate or inhibit cortical input [1-3].

The activity of individual and ensembles of medium-sized spiny neurons is also dependent upon local axon collaterals of other medium-seized neurons or from striatal interneurons whose axons do not exit the striatum. Interneurons comprise about 10% of the neostriatal GABAergic neuron population. GABAergic interneurons establish contacts with the dendritic shaft of neighboring spiny neurons, thus providing, in addition to the local collateral arborization of spiny neurons, the structural basis for a local surrounding inhibition. Among the neurons that have been clearly identified in this class are (i) the large aspiny or spidery neurons that utilize acetylcholine as a transmitter (2%, containing choline acetyltransferase) and, (ii) several types of aspiny neurons, which include those that contain either somatostatin and neuropeptide Y or somatostatin and NOS/NADPH-d.

The striosome and matrix compartments of the striatum are vividly demarcated by their differential expression of neurotransmitter-related compounds ranging from second messengers to neurotransmitters, neuropeptides, and their receptors [14]. The different connections of striosomes and matrix suggest that they participate differentially in limbic-based (striosome) and sensorimotor/associative (matrix) forebrain circuits. Further on, sriatal medium

spiny neurons are segregated into separate populations that form the basis of the striosomes or patches and matrix (80% of the striatum) compartments, whose connections are related to the laminar and regional organization of the cortex. Cortical afferents form synapses on the cell body and proximal dendrites of somatostatin-neuropeptide Y–NOS-containing interneurons. Striatal interneurons, including cholinergic and NOS neurons, are largely confined to the borders of the striosomes and the matrix, but their dendrites and axonal fields ignore compartmental boundaries. Given this preferential localization, cholinergic and NOS neurons are believed to mediate interactions between striatal projection neurons of both compartments.

A brief history of and introduction to physiological and pathological role of nitric oxide in the striatum

NITRIC OXIDE (NO) is a poisonous, unstable gas that has been known for years to be a constituent of car fumes, probably involved in depletion of the ozone layer. Drugs that release NO, such as nitroprusside and nitroglycerines, have been used successfully in cases of angina pectoris and other blood-supply problems. Alfred Nobel, who invented nitroglycerine, was prescribed the drug himself to support his ailing heart.

NO is a neurotransmitter that is synthesized from L-arginine by three isoforms of NOS: constitutive neuronal (nNOS, NOS-1), endothelial (eNOS, NOS-3), and inducible (iNOS, NOS-2). In the brain, the 160kDa nNOS is the predominant splice variant, and contains an N-terminal PSD/Discs-large/ZO-1 homologous (PDZ)-binding domain, which anchors this complex to the postsynaptic density in the vicinity of the N-methyl-D-aspartate type-glutamate receptor (NMDAR). The PDZ domain of nNOS binds to a similar PDZ domain from the postsynaptic density protein, PSD-95, which in turn binds to the cytosolic tail of the NMDAR [15]. These molecular interactions explain how Ca^{2+} influx through NMDA receptors is efficiently coupled to NO synthesis and activity. Following its synthesis at postsynaptic site NO may diffuse back to the presynaptic terminal and increase guanosine 3', 5'-monophosphate (cGMP) levels through activation of soluble guanylate cyclase (GC). The same cerebral neurons stain for NOS and NADPH-d, and purified brain NOS has NADPH-d activity (see Figure 2). Systemic application of L-arginine analogues such as NG-nitro-L-arginine (LNOARG) has been shown to produce an in vivo and in vitro time-dependent irreversible inhibition of brain NOS [14] (Figure 2).

Inhibition of NOS in rodents may modify many brain physiological and/or pathological conditions as such synaptic plasticity [16,17], neurotransmitter release [18], regulation of gene expression, reduction on basal motor activity [19,20] (Figure 5) and either degenerative (Parkinson, Huntington) or neuropsychiatric (schizophrenia) diseases [21-24].

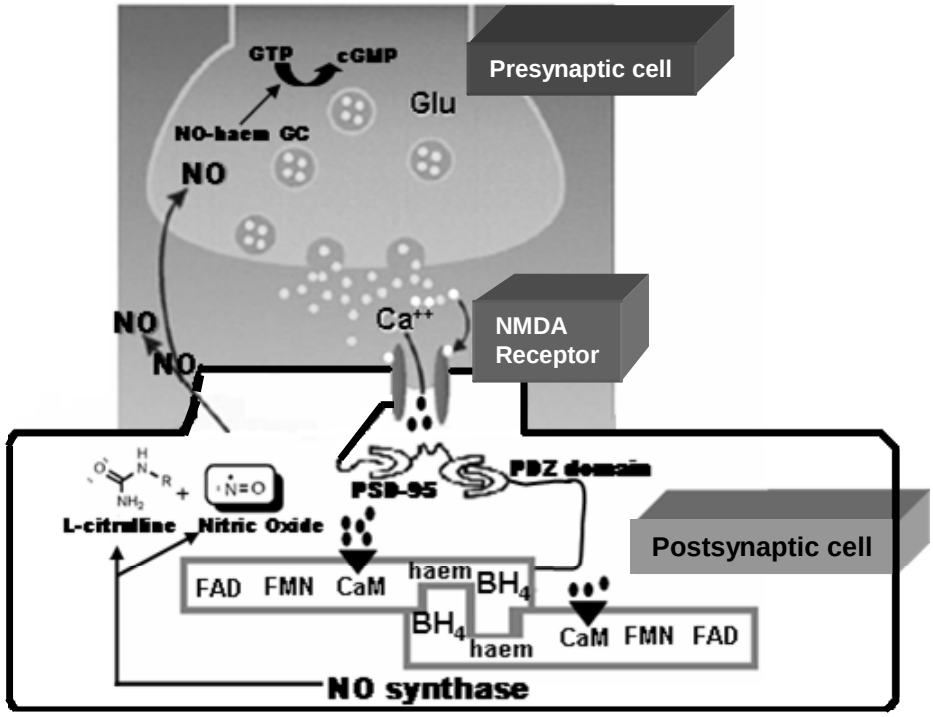

Figure 2. Biosynthetic pathway of NO in neurons catalyzed by the nNOS dependent on calcium and calmodulim. NMDA receptors are coupled to nNOS through a PSD95 multimer. NMDA receptor-modulated calcium influx results in an increased catalytic activity of nNOS mediate by PDZ domains/PSD95 interaction. Oxidation of one of the guanidino nitrogens of L-arginine, and its intermediate leads to the formation of L-citrulline and NO. All NOS isoforms are homodimeric enzymes that depend on the substrate L-arginine as well as on the cofactors/coenzymes nicotinamide adenine dinucleotide phosphate (NADPH), tetrahydrobiopterin (BH_4), flavin adenine dinucleotide (FAD), flavine mononucleotide (FMN), oxygen (O_2) and protoporphyrin IX. The presence of heme, BH_4 and L-arginine promotes dimer formation and stabilization. NOS dimerisation is crucial for catalysis because each reductase domain transfers NADPH-derived electrons to the heme located in the adjacent subunit, whereas, electron transfer between reductase and oxygenase domains on the same subunit does not occur.

NOS/NADPH-d activity was associated with functional properties of extrapyramidal areas. Vincent and Kimura [25], using NADPH-d histochemical technique, demonstrated that NOS is present in not only DA terminal regions such as the striatum medium spiny neurons and nucleus accumbens, but also in the site of origin of DA cells, in the substantia nigra pars compacta and ventral tegmental area (Figure 3).

NOS-positive interneurones representing 1–2% of striatal neurons are aspiny cells of 12–25 μM in diameter with fusiform or polygonal somata. The axonal arborisation extends to form a wider field (1000 μm). Within the striatal complex, neuronal NOS activity is primarily responsible for the generation of

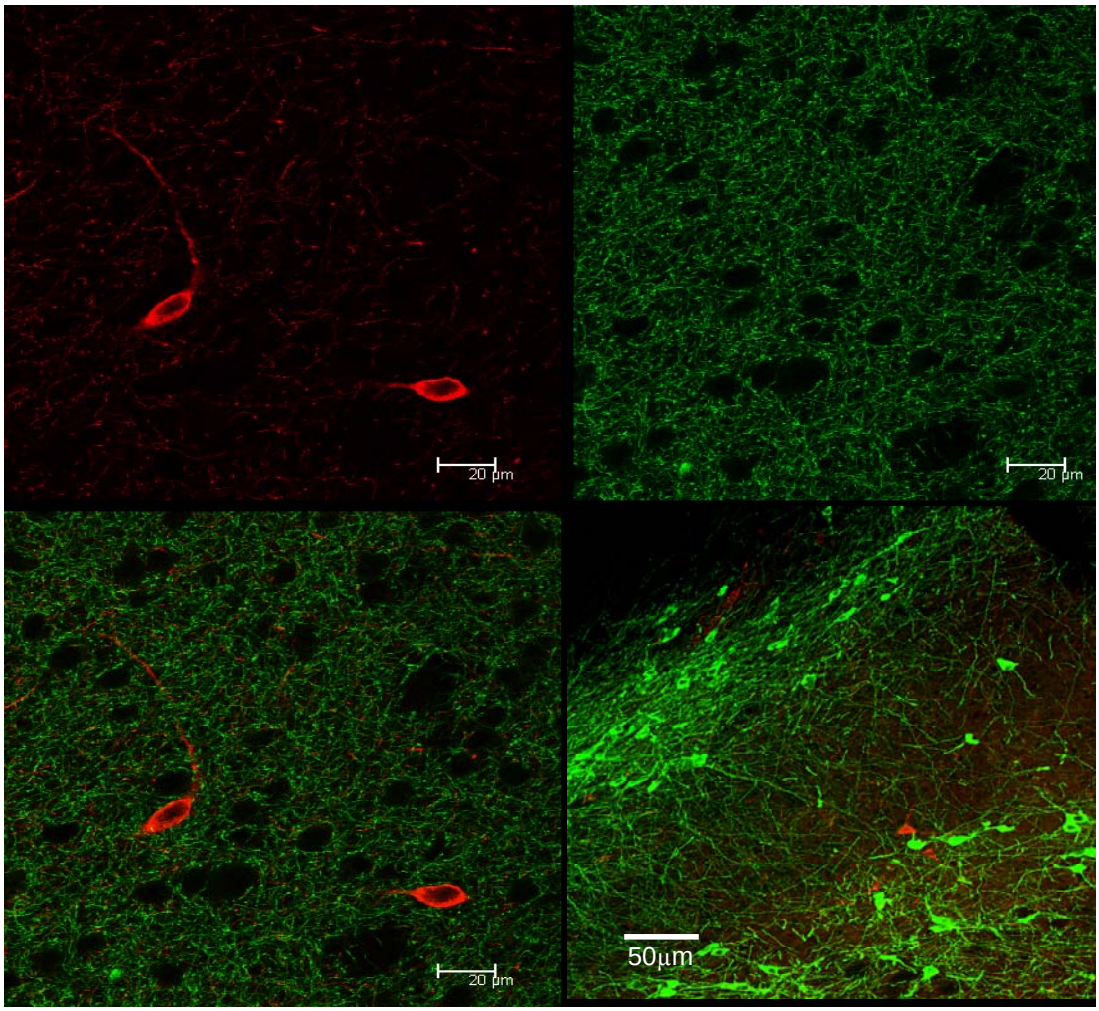

Figure 3. Double labeling of nNOS and TH in the Striatum and Substantia nigra in the rat brain. Confocal micrography (A-C, Leyka SP5) of double-staining labeling using TH and nNOS immunohystochemistry in the striatum (A-C) and substantia nigra (D) of the rat brain. NOS (A), is labeled in red and TH (B), is labeled in green; C and D are representative micrographys of the simultaneous visualization of DA and NO innervation in brain regions. D: Double-stained sections were analyzed using fluorescence microscopy (Nikon, Japan). The close proximity of nNOS (red) and TH (green) neurons and fibers immunopositive reaction in the striatum and substantia nigra (D) gives hysthochemical support for interaction between DAergic and NOS neurotransmission.

NO and is localized exclusively to a subclass of aspiny interneurons that colocalize somatostatin, neuropeptide Y, and GABA [26,27].

Nitric oxide and dopamine in the striatum

NO generation is critically involved in mediating electrotonic coupling between medium spiny neurons [28]. NMDA receptor stimulation both in vivo and in vitro modulates the striatal release of DA [29,30]. NOS interneurons are profoundly influenced by the level of DAergic activity [31-35]. Striatal

interneurons have been shown to receive synaptic input from tyrosine hydroxilase immunopositive processes [34] and corticostriatal boutons [35]. In neurochemical studies aimed at examining the impact of exogenous NO on striatal DA neurotransmission, the most consistent effect is a facilitatory influence. Endogenous NO enhances DA efflux in the striatum through the elevation of GLUergic tone [36]. NO-generating agents increase striatal DA efflux or inhibit its reuptake both in vitro [37] and in vivo [31]. Given the proximity of glutamatergic and DAergic (Figure 3) inputs on the NOS interneuron dendrites [34,38], it is likely that these afferents interact via presynaptic and/or postsynaptic mechanisms to regulate striatal NOS activity [39]. In particular, the release of NO might modulate the activity of other striatal cells over a wide area.

A role for striatal NO in modulating inhibitory GABAergic striatonigral systems first was reported by Greengard and colleagues [40] in a study demonstrating that sodium nitroprusside activates guanylyl cyclase in striatonigral terminals leading to the enhancement of cGMP-dependent protein kinases phosphorylation of DA and cyclic AMP-regulated phosphoprotein (DARPP-32) [40]. Ultrastructural studies of striatal NOS-containing interneurons have reported that NOS-containing terminals synapse on dual-input dendritic spines of striatal medium spiny neurons known to contain high levels of Guanilate Cyclase, cGMP-dependent protein kinase and other components of the cGMP signaling system [41, 43, 38]. The NO/cGMP pathway recently has been shown to be critically involved in the induction of long-term depression of excitatory postsynaptic potentials in striatal spiny neurons produced after high-frequency stimulation of corticostriatal pathways [43]. In addition, NOS-positive cells might control local blood flow in the striatum by releasing NO acting directly on guanylate cyclase in the vascular smooth-muscle and causing vasodilatation [44].

NO: Integration of striatal convergent motor information?

NO generated as a consequence of activation of corticostriatal pathways may be involved in regulating the activity of striatal local circuit and projection neurons and/or their respective afferents inputs. NO might also act as a transmitter to affect striatal activity, either through direct interactions with ligand-gated channels or by influencing, through the stimulation of second messenger systems, surrounding striatal projecting neurons. Although the influence of NO on striatal neuronal activity remains to be thoroughly characterized, evidence has accumulated suggesting that NO may participate in the integration of convergent motor information within striatal networks.

Modulation of nNOS activity by multiple signaling cascades permits the regulated production of NO in response to neuronal stimulation because NO cannot be stored in synaptic vesicles like other neurotransmitters. Non-specific subtotal NOS-inhibition reduced exploratory activity decreased the open arm

exploration of an elevated plus maze [45-47] accompanied by a decrease in the number of enclosed arm entries, a measure related to general exploratory activity in this test. In the open field test LNOARG and 7Nitroindazole (7NIO) [48], a selective neuronal NOS inhibitor, decreased exploratory behavior [45,49-51] (Figure 4). Rats and mice treated with various NOS inhibitors show problems with fine motor control [51-55]. Thus, behavioral studies have demonstrated that pharmacological blockade of NO signaling decreases basal locomotor activity [20] and behaviors induced by substance P, D_1 and D_2 agonists [56-59], NMDA receptor antagonists [60].

The effect of NOS inhibition on movement coordination function can be measured by the footprint pattern test (Figure 5). It analyzes complex movements during locomotion by taking into account limb position or gait patterns [63-65]. In this test standing support seems to be related to the integrity of the propriospinal system, controlled by both descending and segmental afferent input [61]. Drugs that produce ataxia in humans, such as ethanol or diazepam, decrease locomotor and rearing activity in rats [66] and induce deficits in coordinated hind limb movements [67]. Rats tested while walking under LNOARG treatment do not show any modification in their locomotion pattern [51] (Figure 6). In contrast, haloperidol treatment results in a significant doses dependent increase in the animal's base of support (DBL in Figure 7) and a significant decrease in the animal's right and left (RSL/LSL in Figure 7) Therefore, the reduced exploratory activity induced by LNOARG do not involve changes in motor coordination.

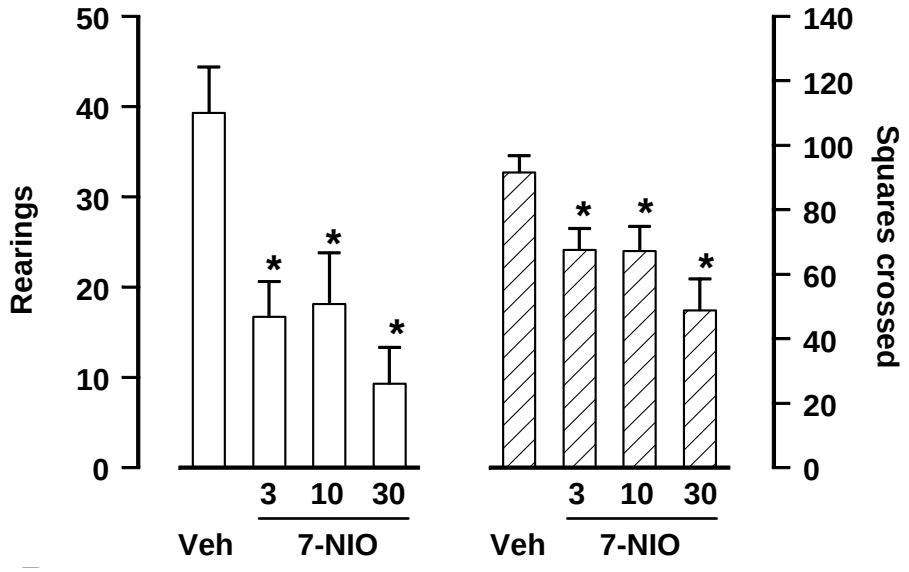

Figure 4. Effects of a single 7NIO or vehicle (Veh) treatment on exploratory behavior of mice tested in an open field. Animals received a single 7NIO (3-30 mg/kg) or vehicle (Veh) injection and the number of squares crossed (right side, hatched bars) and rearings (left side, open bars) were recorded.

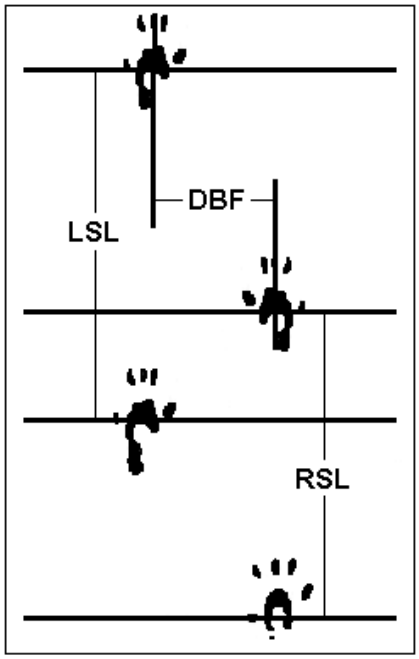

Figure 5. Reconstruction of the hind paw prints illustrating the measurements used. Base of support (DBF), right (RSL) and left (LSL) stride length were measured from the prints. Figure is based on Kunkel-Bagden [61] with modifications. The animal's fore-and hindpaws were inked and footprints were made on paper covering a confined walkway wooden platform (15cm wide by 45 cm long) with a dark shelter. The paper was saturated with bromophenol blue, wich changes from orange to dark blue when contacted with moisturized hindfeet of the rat [62]. The forepaw prints were used to standardize the direction of locomotion. Three steps were used to determine the locomotion pattern. The base support was determined by measuring the core to core distance between the central pads of the hindfeet. Stride length was measured between the central pads of two consecutive prints on each side does not relate to any gross impairment of locomotion pattern.

In contrast, neuronal NOS (nNOS) knockout mice have no grossly evident defects in locomotor activity [68]. However, the studies were all conducted during the day (between 14:00 and 16:00, lights on at 07:00). Krigsfield et al [69] reported striking, discrete abnormalities in balance and motor coordination in nNOS knockout mice reflected selectively at night. Furthermore, eNOS knockout knockout mice were hypoactive during the first exposure to the open field test [70] and show improved motor-coordination [71]. Those observations suggest that eNOS-derived NO might be involved in the control of general activity [70,72] or the motivation to explore novel environments. A possible hypothesis is eNOS and nNOS might be functional antagonists in regulating motor coordination and balance.

There are several important distinctions of acute experiments using NOS inhibitors (lasting hours) from experiments involving genetically altered mice.

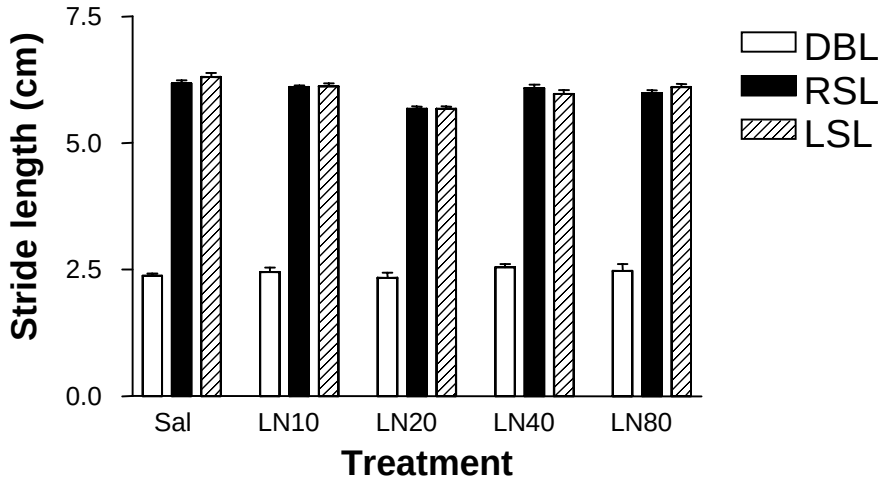

Figure 6. Footprint analysis of rats 2 hs after receiving LNOARG or saline. None of the LNOARG doses significantly modified the spontaneous walking of the mice. The mean (+SEM) distances for controls and animals which received LNOARG (10-80mg/kg) are presented.

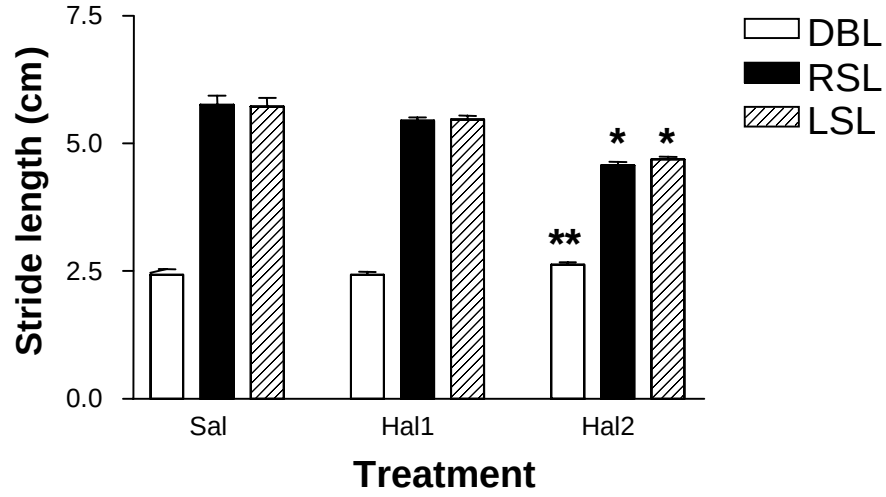

Figure 7. Rats base of support and stride length measured from the footprints after haloperidol treatment. The distance between the central pads of the hind paws increased after haloperidol 2 mg/kg treatment when compared with haloperidol 1mg/kg (DBL, t18=-2,53, p=0,021). The stride length decreased in group haloperidol 2mg/kg as compared with group saline (RLS, $F_{2,27}$=8,06, p<0,001; LSL $F_{2,27}$=8,4, p<0.001). The mean (+SEM) distances for controls and animals which received Haloperidol are presented. Asterisk indicates significant difference from sal. Double asterisk indicate difference from Hal 1mg/kg.

In addition findings in acute experiments may be quite different from those of chronic NO depletion states. A caveat with the use of knockout models is the possibility of undefined effects and adaptations secondary to the targeted gene [73]. Mice lacking NOS throughout embryonic development may present structural changes and changes in other mediators and processes that may induce compensatory increases in other mediators or functions. For example,

on the basis of the blocking effects of LNAME, NO was thought to be an essential retrograde messenger in postsynaptic neurons that feed back to postsynaptic neurons for long- term potentiation. Surprisingly, long term potentiation was not affected in nNOS and eNOS knockout animals. On the other hand, long-term potentiation was abolished in nNOS and eNOS double-knockout animals [74]. In addition, the striatum of nNOS knockout mice displays only about a 50% loss in nNOS positive neuronal cells [75,69]; by contrast, cerebellar and amygdala staining is abolished. Conceivably, residual nNOS, which is prominent in areas such as the cerebral cortex and striatum, protects nNOS knockout mice from more extensive abnormalities.

Basal ganglia: Neurologic and neuropsychiatric disorders

In the early 1900, Kinnier-Wilson coined the term extrapyramidal system to describe the basal ganglia system that interacts with brain-stem structures independently from the pyramidal tract to influence motor behavior [76]. He conceived of the term the extrapyramidal system refers to the basal ganglia with their anatomical connections, and extrapyramidal disorders are hypokinetic and hyperkinetic states that ensue from lesions in these anatomical sites. Wilson's emphasis on the role of the basal ganglia in motor behavior was driven by his early discoveries revealing motor disorders in humans following damage to this brain region [76].

Many common neurological and psychiatric disorders, such as PD, attention deficit-hyperactivity disorder, Huntington’s disease, and Tourette syndrome are primarily due to basal ganglia dysfunction, and many other diseases such as schizophrenia and drug addiction have a large basal ganglia component. There is growing evidence to support a role for NO in the etiology of neurologic conditions including chronic neurodegenerative diseases. The medium spiny neurons are among the first neurons to degenerate during the development of Huntington's chorea [77]. The poverty of movement in PD results from over-activity of the indirect pathway, whereas excess movement in disorders such as Huntington’s disease represents over-activity of the direct pathway. In addition, the basal ganglia have been implicated in a range of neuropsychiatric disorders, and basal ganglia function is disrupted in addictive states. A large series of studies has implicated the ventral striatum (including the nucleus accumbens), the ventral pallidum and the corresponding medial parts of the DA-containing cell groups of the midbrain (the ventral tegmental area) in the pathogenesis of schizophrenia. The fact that the prefrontal cortex is implicated in this disorder, and that the basal ganglia pathways linked to the caudate nucleus direct their outputs to prefrontal areas, raises the possibility that basal ganglia malfunction occurs in schizophrenia.

Neurological disorders in humans can be modeled in animals using standardized procedures that recreate specific pathogenic events and their behavioral outcomes. Animals in which the nigrostriatal pathway has been experimentally destroyed are considered useful model for study PD [78]. These lesioned animals have clarified the anatomy, neurochemistry and electrophysiology of DA neurons and their relationships with other associated brain nuclei.

Experimental Parkinson

PD was described by James Parkinson as a single disease entity in the year 1817. It is a devastating neurological condition that affects at least four million people. Typical clinical features are extreme underactivity, poverty of movement (hypokinesia), infrequency of swallowing, abnormal postural reflexes, absence of arm swing in walking and reduced velocity of a movement (bradykinesia) up to inability to walk forwards (freezing). Firm and tense muscles (rigidity) and a low-frequency resting tremor are also seen in many patients, often beginning in one limb and spreading to the whole side of the body. A striking feature of this disorder is the preferential loss of DA-producing neurons in the midbrain [79,80]. Several etiological triggers have been linked to PD, including genetic mutations and environmental toxins, but the pathway that leads to cell death is unknown.

NO was linked to PD by several lines of evidences: for instance, increased nNOS expression as well as tyrosine nitration in Lewy bodies in the substantia nigra were found in postmortem studies [81]. Levecque et al. [82] data tend to implicate both nNOS and iNOS genes in the development of PD. Post-mortem brains examination suggest that NO system in the basal ganglia is altered in PD [83]. NOS cell numbers and mRNA are significantly reduced in postmortem parkinsonian brains [81,84]. Biochemical data from human brain autopsy studies and from animal models point out to an ongoing oxidative stress process in the substantia nigra, mediated by oxygen reactive species (ROS) [85] which could induce degeneration of nigrostriatal DA neurons [86,87]. Several studies suggest that ONOO− plays an important role in the pathogenesis of the disease [88]. TH can be inhibited by nitrotyrosination [89]. Further, MAO B, whose activity increases with aging [90], is located in the external mitochondrial membrane and generates H_2O_2 during the catecholamine metabolism [91], possibly acting as a source of $O_2{\cdot}^-$, and subsequent $ONOO^-$ production. Then DA neurons would be highly exposed to $ONOO^-$ damage [92]. Moreover, the production of NO by circulating neutrophils was enhanced by 50% in line with a several-fold overexpression of nNOS [93].

In modeling experimental Parkinson a major advance was the introduction of the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA) [94,95]. 6-OHDA destroys DAergic neurons through free radical-mediated mechanisms.

Microinjection of 6-OHDA into the medial forebrain bundle can cause a total destruction of substantia nigra compacta and area tegmental ventral neurons [96] (Figure 8). It results in a well-described syndrome that includes i. near total depletion of DA in the ipsilateral striatum; ii. denervation supersensitivity of post-synaptic DA receptors in the ipsilateral striatum; and iii. a characteristic functional asymmetry, with quantifiable turning behavior contralateral to lesion side, in response to the direct DA agonist apomorphine [97,98]. Pavon et al. [99] report that chronic L-DOPA, the major treatment of PD, induces dyskinesia in hemiparkinsonian mice and induces FosB staining in every diaphorase-NOS-containing interneuron in the lesioned striatum.

Similarly, 1-methyl-4-pheyl-1,2,3,6- tetrahydropyridine (MPTP) and MPP+ induced impairment of the mitochondrial respiratory chain enhances superoxide formation that then can initiate apoptotic cell death through a decrease in mitochondrial membrane potential. MPTP, which contaminated batches of illicit drugs in the 1970s, produces Parkinsonian-like symptoms in humans [100] MPTP causes pathology by targeting the destruction of nigrostriatal DA neurons, the same cells that are selectively lost in idiopathic PD. This is accompanied by an up-regulation of iNOS gene expression in glial cells [101]. The majority of the studies conducted toward identifying the fundamental mechanism of MPP+ induced cytotoxicity in substantia nigra focused on cGMP independent mechanisms of NO action. These include oxidation of thiols as well as nitrosation and nitration of proteins. A recent study shows that MPP+ inhibits complex I of the mitochondrial electron transport chain, leads to the formation of superoxide anion and peroxinitrite thereby causing DNA damage, poly(ADP-ribose) polymerase (PARP I) activation and neuronal cell death [102]. A form of PD is caused by the production and accumulation of mutated cellular protein, parkin [103], and this accumulation results in increased nNOS activity with subsequent NO-mediated damage [102]. In this form of Parkinson's as well as in other forms of PD, nitrated proteins can be found by immunohistochemistry and immunoblotting [103].

Indirect evidence implicates NO in the mechanisms underlying nigral cell degeneration because NOS inhibitors protect against MPTP toxicity in mice and monkeys (although some of these data are disputed – 104, 105]. A significant resistance to MPTP induced cytotoxicity was exhibited by mice lacking either iNOS or nNOS [104,105]. 7NI also inhibited MPTP-induced PD-like neuropathological changes in baboons and degeneration of the TH positive positive neurons in substantia nigra [106,107]. In addition, degeneration of the nigrostriatal pathway by malonate was prevented by LNAME and 7NI.

In contrast, Hunot et al. [108] found a significant increase in NADPH-d-positive cell density in DA cell groups characterized by neuronal loss in PD. We showed that the number of NADPH-d and NOS positive neurons increase

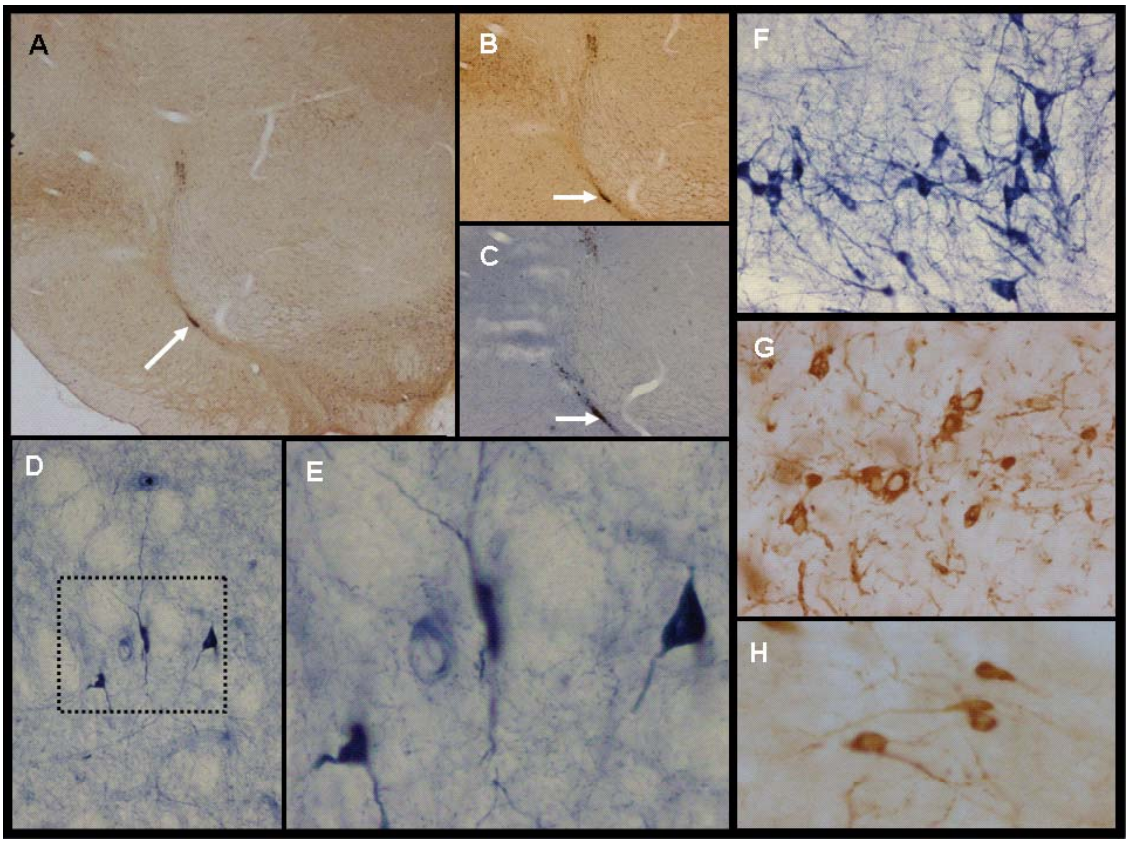

Figure 8. Rat brain positive neurons labeled for NADPH-d (blue) and NOS (brown) located in the Substantia nigra (A, B and C), striatum (D and E) and pedunculopontine tegmental nuclei F, G and H). Triple photomicrography (A-C), from the same microscopic field with distinct amplification, showing the substantia nigra pars compacta. The white arrow indicates the site of microinjection of the neurotoxin 6OHDA. There is no positive neurons for NOS and NADPH-d. D-H: Double photomicrography showing striatal cells from adult rat brain, stained histochemically for NADPH-d (D and E) and NOS (H), respectively. E is a higher magnification of A. The labeled neurons are striatal cells, with fewer dendritic spines, with fusiform or polygonal somata, considered interneurons [109]. Pedunculopontine tegmental nuclei (F, G) labeled neurons for NADPH-d (blue) and NOS (brown), respectively.

in ipsilateral striatum and decrease in the substantia nigra after either 6-OHDA or electrolytic lesions of the MFB [110]. Only in animals that received 6-OHDA the number of cells decreased in contralateral nucleus accumbens. This evidence may raise questions regarding which brain NO containing structure is mainly affected on PD. Moreover, recent studies demonstrate that the activity of striatal NOS is depressed in 6-OHDA-lesioned animals [111,112] and patients with PD [81,84], indicating that agents designed to target nitrergic signaling may be useful for the treatment of movement disorders. Results from our laboratory suggest that sub-chronic administration of LNOARG partially protect DA neurons in 6-OHDA animals [Gomez, personal comunication].

Barthwal et al [113] described that LNAME pretreatment blocked the amphetamine-induced rotations and inhibited the iNOS activity at the 3rd day after the 6-OHDA injection and also significantly restored the striatal DA, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid levels in 6-OHDA treated rats. In addition, NO donors protected animals against Fe-induced DAergic neurodegeneration. Our findings are in agreement with previous studies of our group [114], showing an increase in striatal NADPH-d neurons after lesion of substantia nigra compacta caused by manganese chloride. In this study, a protective role of NO was suggested since systemic LNOARG treatment increased apomorphine-induced rotations. In contrast, low concentrations of manganese, unlike other transition metals, caused induction of iNOS activity in astrocytes and glial cells. Glial derived neural factor which exerts a protective effect in PD [115], inhibits nNOS activity [116].

Recently, the group of West demonstrated that striatal nNOS is stimulated in vivo by phasic activation of midbrain DA cells via a DA D1/5 receptor-dependent mechanism. These findings are consistent with previous reports that D1/5 receptor activation increases indirect measures of NOS activity [33,117] and firing activity of electrophysiologically identified NOS interneurons [118]. D_1 receptors are weakly expressed on a small number of NOS-positive interneurons in the striatum [119]. While D_1 receptors are highly expressed in projection neurons, D_5 receptors are mostly present in cholinergic interneurons and all the other types of chemically defined striatal GABAergic interneurons expressing parvalbumin, somatostatin or calretinin [120]. Thus, striatal NOS interneurons may be potently activated by DA cell burst firing in specific behavioural contexts. This implicates DA-induced release of NO in the control of motivational behavior and thus suggests novel potential therapeutic targets for the treatment of neurological and psychiatric disorders.

To summarize, there are several direct demonstrations of changes in neuronal NO systems following DA denervation. The data suggests that neuronal NO systems are regulated in response to altered input. Either NOS mRNA or protein appears to be differentially regulated in different basal ganglia structures in response to DA depletion. Such altered activity of NO-containing neurons may play a role in the compensatory upregulation of nigrostriatal DA neurotransmission in PD, but might also exert an excitotoxic effect on striatal neurons and nigrostriatal terminals. Therefore, it seems probable that these changes in NOS reflect a physiological response to DA denervation rather than resulting from direct involvement in the pathological process of PD.

Experimental schizopreny

The close connection between frontal cortex and the basal ganglia has provided support for a fundamental role of basal ganglia in schizophrenia. Interestingly, Graybiel [121] has proposed a concept that basal ganglia acts as “cognitive pattern

generators", in that is a set of common neural circuits that regulate both motor and mental action. Based on this concept, Graybiel and colleagues [122] have proposed that similar circuitry to that used to coordination of motion sequences may be used to coordinate thinking, planning, and other cognitive acts.

Schizophrenia is a severe mental disorder, which is characterized by thought disturbance, abnormal perception, impaired cognition, and bizarre behavior. Although progress has been made during the past decade in identifying potential biological state and trait markers of the disease, the ideal indicator of schizophrenia has still not been detected. Moreover, given the complexity and heterogeneity of the disease, one may have doubts concerning its existence at all. One of the many candidates found to be linked to schizophrenia is NO. Historically, the first hints of a possible link between NO metabolism and schizophrenia can be found in two Russian papers, which dealt with the diagnostic value of Black's reaction (detecting methylene blue, an inhibitor of NOS and soluble guanylate cyclase) in psychiatric patients [123,124]. However, systematic research on this topic began in the early 1990s. At that time histochemists had introduced NADPH-d histochemistry as a tool to label certain neuronal populations [125], and the immense importance of NO and its synthesizing enzyme NOS had emerged. Even at that time, the search for the roles of NO in schizophrenia was not restricted to the brain [126], but also included body fluids [127].

NO has been functionally linked to both DAergic and glutamatergic neurotransmission in the brain, both of which are strongly implicated in the pathophysiology of schizophrenia [39]. Figure 9 shows the proximity of nNOS and TH immunopositive reaction in neurons and fibers in the frontal cortex and amygdale giving hysthochemical support for interaction between DAergic and NOS neurotransmission. Neuroanatomic studies have reported abnormal distributions of NOS-containing interneurons in the frontal and temporal lobes of schizophrenia patients, suggesting altered neuronal migration during development [21]. It has also been observed an increase in a correlate of NOS activity in the striatum of rats modeling the developmental cortical abnormalities of schizophrenia [128]. Remarkably, both decreases and increases in NOS activity, NOS protein and mRNA content were found in schizophrenia.

NO is increased in plasma of schizophrenic patients [22] and abnormalities in populations of cells containing NADPH-d [129], has been detected in these patients [21]. There is a low density of NADPH-d neurons in the frontal and temporal cortical grey and an increased density of these cells inthe deep (frontal) or subcortical (medial temporal) white matter [21] schizophrenic patients. This altered distribution has been related to the diminished levels of the stable metabolites of NO, nitrite and nitrate, in the cerebrospinal fluid of schizophrenic patients [23]. In contrast, an overproduction of NO found in schizophrenic

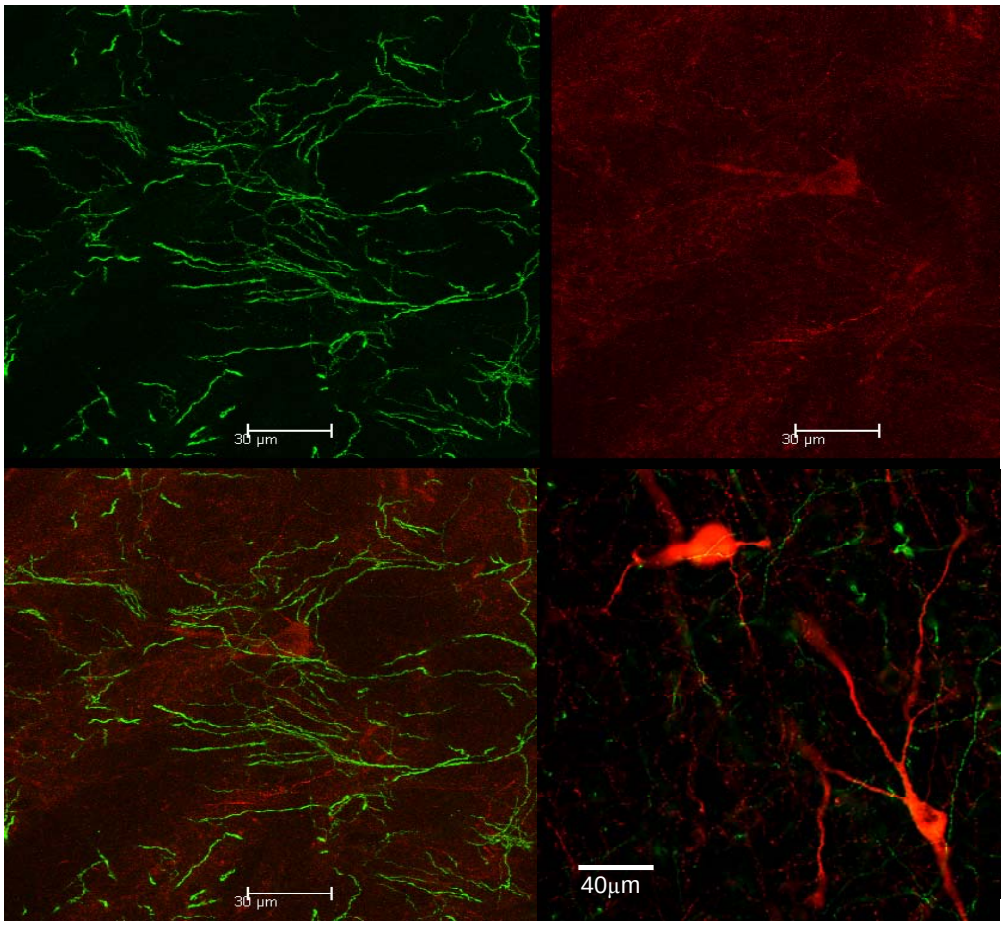

Figure 9. Double labeling of nNOS and TH in the Amygdala and Cerebral cortex of the rat brain. Confocal micrography of double-staining labeling using TH and NOS immunohystochemistry in the amygdala (A-C) and cerebral cortex (D) of the rat brain. D: Double-stained section was analyzed using fluorescence microscopy (Nikon, Japan) C and D are representative micrographys of the simultaneous visualization of DA and NO innervation in brain regions. The close proximity of nNOS(red) and TH (green) neurons and fibers immunopositive reaction in the frontal cortex and amygdala gives hysthochemical support for interaction between DAergic and NOS neurotransmission.

brains, related to an excess of NADPH-d-positive neurons in the mesopontine tegmental region, is proposed to provide critical excitatory input to the midbrain DA systems [130].

Catalepsy test is widely used to evaluate motor effects of drugs, particularly those related to the extrapyramidal system [131-133]. It is defined as a failure to correct an externally imposed posture. Administration of DA antagonists, such as haloperidol, induces catalepsy in rodents [134,135] and Parkinson symptoms in humans [132,136]. NOS inhibitors themselves have antipsychotic actions [60]. Systemic injections of LNOARG and 7NI induced catalepsy in mice and had an additive effect with haloperidol [51,52,137,138]. These effects were obtained with doses commonly used in the literature

[49,56,139,] and were similar to those that significantly inhibit nNOS (> 10 mg kg-1) [140]. The cataleptic effects were detected both in the hanging-bar and in the wire-ring tests [51]. Figure 10 illustrate the correlation between results obtained in he wire-ring and hanging-bar tests after treatment with saline or LNOARG. There are some studies dealing with the modification of brain NO synthesis by classical neuroleptics (mostly haloperidol). The observation by Iwahashi et al. [141] that haloperidol inhibits the activity of nNOS has been confirmed by others [142,143], but there are also reports showing quite the opposite [144]. Chlorpromazine was also shown to inhibit the activity of constitutive NOS [145]. Atypical neuroleptics do not influence brain levels of nNOS [146]. Curiously, they are capable of partly reversing haloperidol-evoked suppression of NOS activity, which is accompanied by a "normalization" of behavior in rats [142,147].

Chronic treatment with LNOARG increased the number of NADPH-d-positive cells in the dorsal part of the caudate and accumbens nuclei, as compared to haloperidol-treated animals and in the pedunculopontine tegmental nucleus, as compared to saline-treated rats. In contrast, it decreases NADPH-d neuron number in the substantia nigra, pars compacta, an effect also found after chronic haloperidol treatment [47].

Similar to the effects obtained after systemic administration, catalepsy was also induced after intracerebroventricular [148], or intra-striatal injection of NOS inhibitors such as NG-monomethyl-L-arginine (LNMMA), 7NI, LNOARG,

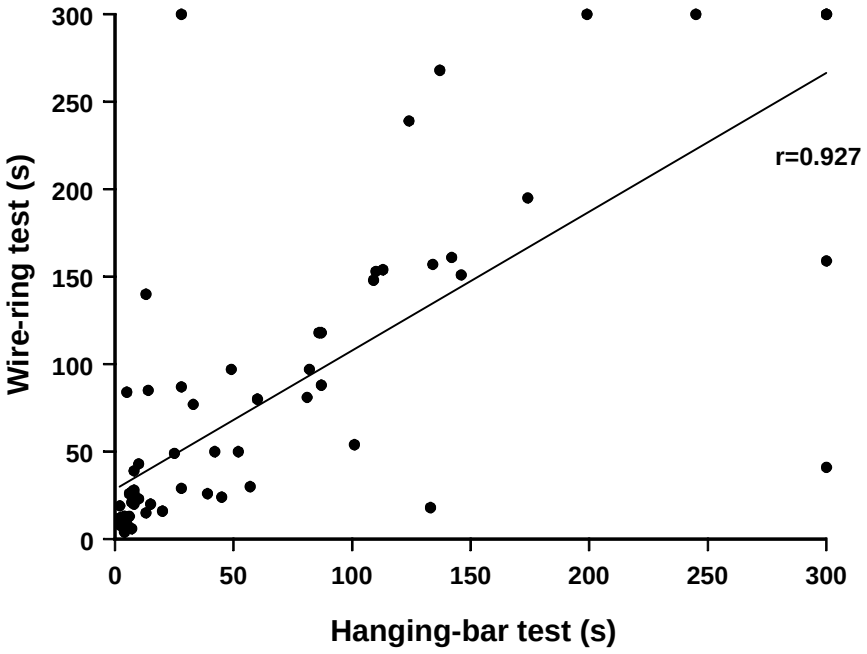

Figure 10. Hanging-bar and Ring-test catalepsy test procedure: Acute treatment with LNOARG significantly induced catalepsy in both the hanging-bar and wire-ring test. Results from both tests were highly correlated ($r=0.927$, $p<0.001$).

LNAME in rats. The effect of i.c.v. injected LNOARG was completely prevented by pretreatment with L-arginine but not by D-arginine. Both i.c.v. and intra-striatal injection of LNOARG or LNAME produced bell-shaped dose-response curves. These results confirm that interference with striatal formation of NO induces significant motor effects in rats. Spina et al. [149] failed to find any cataleptic effect of another NOS inhibitor LNAME (50mg/kg i.p.), in the wire ring test. This test was proposed by Pertwee [150] to measure immobility in addition to catalepsy effects produced by cannabinoids agonists. These contrasting results probably are related to methodological issues such as the interval between injection and the test and/or the dose of LNAME.

Both the cataleptic effect and the decrease in exploratory activity induced by acute doses of LNOARG suffered tolerance after 4 days of treatment and haloperidol [19,47,138]. The mechanism involved in this rapid tolerance development is unknown. Although chronic treatment with haloperidol is also able to induce tolerance for its catalepsy-inducing effect, it usually needs 25 days of chronic treatment [132,151]. Accordingly, no tolerance was detected in our study after 4 days of haloperidol administration. Several studies have shown that antagonism of NMDA-mediated transmission attenuates catalepsy induced by DA receptor antagonists such as haloperidol [33,152]. Since animals that became tolerant to LNOARG are also tolerant to haloperidol effects, and NO has complex effects on NMDA mediated-neurotransmission, it is also possible that an influence of NO on DA neurotransmission is mediated by effects on NMDA neurotransmission.

We have showed that catalepsy induced by LNOARG is modulated by drugs that modified serotonergic neurotransmission [153]. The cataleptogenic effect of LNOARG was enhanced by pre-treatment with (+)-N-tert-butyl-3-(4-[2-methoxyphenyl] piperazin-1-yl)-2-phenyl-propanamide ((+)-WAY-100135), a 5-HT1A-selective receptor antagonist, or by ketanserin, a 5-HT2A receptor and α1-adrenoceptor antagonist. Prazosin, an α1-adrenoceptor antagonist, and endo - N - (8 - methyl - 8 - azabicyclo [3.2.1] oct - 3yl) - 2, 3- dihydro - 3, 3- dimethyl – indole – 1 - carboxamide HCl (BRL-46470A), a 5-HT3 receptor antagonist, did not interfere with LNOARG-induced catalepsy. Ritanserin, a 5-HT2a and 5-HT2C receptor antagonist, tended to enhance the effect of LNOARG.

It has been reported that schizophrenic patients have a reduced level and a higher dietary requirement of vitamin C [154]. Also, since vitamin C /ascorbic acid is a potent reducing agent and can reduce haloperidol to OH-haloperidol whose pharmacological activity is not well established, its role in augmentation of haloperidol treatment of schizophrenic patients has been tested. In one study, it was found to work synergistically to reduce some psychiatric symptoms [155]. However, in an another study, shorter treatment (2 weeks) at a lower dose did not alter the plasma levels of haloperidol or OH-haloperidol as well as the psychotic symptoms (Psychiatric Symptom

Assessment Scale), [156]. Vitamin E is a lipid soluble antioxidant and effective for the prevention of oxidative injury to plasma membranes. It may be important to use vitamin E in combination with vitamin C, a water soluble antioxidant [157]. There is some evidence of the efficacy of vitamin E in extrapyramidal disorders such as Parkinson's disease and tardive dyskinesia [158,159-162]. In clinical trials, vitamin E therapy is proposed to retard the progression of degenerative process in patients with Parkinson's disease [163,164]. Vitamins C and E can enhance the cataleptic effect induced by inhibition of NO formation or by haloperidol [165]. Treatment with vitamin C did not affect tolerance to LNOARG cataleptic effect induced by sub-chronic treatment. Vitamin E induced catalepsy by itself and, at 100 mg/kg, potentiated the catalepsy induced by LNOARG or Haloperidol.

Novel agents as Ginkgo [166] and methylene blue [60] have shown positive effects on general schizophrenia negative symptoms. The *Ginkgo biloba* extract EGb 761 (Tebonin®, Byk Química) is a standardized mixture of active compounds, including flavonoid and terpenoid substances, obtained from green leaves of the *Ginkgo biloba* tree. Clinical trials support the potential therapeutic usefulness of EGb 761 in the treatment of cerebral insufficiency [167,168], cognitive impairments [169], peripheral and central circulatory disease [170] and an apparent neuroprotective role after various neuronal insults [171]. Chronic administration of *Ginkgo biloba* extracts is proposed to improve aspects of cognitive performance. Repeated treatment with *Gingko biloba* extract EGb 761 (80 mg/kg) produced a significant increase in the cataleptic effect induced by both haloperidol and LNOARG. It also decreased the number of rearings and crossings in the open field test [172].

Numerous efforts have been made to develop animal paradigms of schizophrenia in order to mimic characteristic neurobiological and behavioral features of the human disease [173]. A frequently used model is the application of phencyclidine to rats [174], and many others. Many researchers have used this paradigm to study the impact of NO in experimentally evoked schizophrenia-like behavior. It has been shown that the administration of the NOS inhibitor LNAME to phencyclidine-treated rats disrupts phencyclidine-induced behavior [175-177]. Methylene blue, an inhibitor of NOS and soluble guanylate cyclase [178] has the same effect on the behavior of rats. Phencyclidine does not alter the behavior in nNOS mutant mice and in mice after the application of nNOS antisense [179]. Black et al. [180] have shown that the administration of the NOS inhibitor during brain development increases the sensitivity of adult animals to phencyclidine.

Using the postnatal lesion of the ventral hippocampus [181], Bernstein et al., [182] found an increase in the number of cortical nNOS/NADPH-d-containing neurons in lesioned rats [182]. Recently, the repeated application of subchronic doses of the phencyclidine derivative ketamine has come into use. Ketamine-treated rats are characterized by a reduced cellular expression of

NOS/NADPH diaphorase in hippocampal neurons [183]. Interestingly, there was an increase in hippocampal neurogenesis in these animals [184], which might be connected to the reduced NO production, since NO inhibits neurogenesis in adult animals [185].

Schizophrenia patients display deficits in sensorimotor gating, a process that depends on the hippocampal and DAergic inputs to the striatum [186]. Other behavioral abnormalities in schizophrenia, such as an exaggerated response to novelty or stress, have also been postulated to indicate malfunction of temporal corticostriatal circuits and mesolimbic DAergic transmission. Some of the behaviors displayed by schizophrenia patients are mediated by dysfunction in prefrontal and temporal cortical inputs to the ventral striatum, as well as connections among the amygdala, ventral pallidum, and limbic thalamus [187]. Prepulse inhibition (PPI) is a test that reflects the functioning of the sensorimotor gating and has been commonly used as an animal and human model of the attentional impairments seen in psychiatric disorders such as schizophrenia [168]. PPI is measured as a normal reduction of the acoustic startle response (ASR) to an intense stimulus (pulse) when this stimulus is immediately (30–500 ms) preceded by a weaker stimulus (prepulse) [188]. Whereas the ASR is controlled by brain structures at the level of the brainstem, the mechanism of its inhibition by the prepulse requires forebrain structures, such as the nucleus accumbens, hippocampus, amygdala and prefrontal cortex [184,189,190]. This process seems to be a filter of sensory input that protects the brain against an overflow of information. Our recent findings show that LNOARG reduces the ASRs and reverses the PPI disruption of rats treated systemically with amphetamine, an indirect DA agonist. We suggest that NO interacts with DA on the modulation of sensorimotor gating, probably by a presynaptic mechanism, since this NOS inhibitor did not affect the PPI of rats treated with the direct DA receptor agonists, apomorphine, bromocriptine and SKF38393 [24]. This interaction between NO and DA systems in the modulation of PPI may also underlie the attention deficit of schizophrenics.

Concluding remarks

The NO signalling plays an important role in the integration of information transmitted to basal ganglia output centers via corticostriatal and striatal efferent pathways. The interneurons subtypes producing NO in the striatum are activated by the cortex during the induction phase of striatal plasticity.

The remarkable expansion of knowledge about the anatomy and physiology of the basal ganglia in recent years has encouraged the development of information-processing models. The motivation for constructing such models derives from a pressing need to interpret the growing

mountain of complex biological data associated with the unique neuronal architecture of this brain region. Some of the architectural features that are likely to be important are i) the existence of loops of connectivity between the cerebral cortex and basal ganglia; ii) the specialization of spiny neurons, the principal cells of the striatum, for pattern recognition computations; iii) the division of the striatum into matrix and patch (striossome) compartments with specialized neurochemistry and connectivity; and iv) the activity of midbrain DA neurons, which is an indispensable requisite for reinforcement learning and, consequently, for corticostriatal synapses plasticity. Despite the high relevance of NO in basal ganglia functions, so far, none of the computational models have attempted to simulate these effects. Considering the complexity of the functional dynamics of information processing within the basal ganglia and its interactions with the rest of the brain, quantitative models of all aspects of basal ganglia biology will be needed to proced further understanding of brain region.

In summary, we can conclude from the above studies and it is evident when surveying the literature that in some situations, such as normal cellular metabolism, NO is necessary and helpful for the cell (herein defined as physiological). NO-producing cells may mediate some of the actions of the excitatory corticostriatal afferent pathway involved in regulating the activity of striatal efferent and afferent systems. Yet in other situations, such as in disease, NO can be toxic (pathological). Considerable evidence exists indicating a role for NO–DA interactions in pathophysiological conditions such as Parkinson's disease and schizophrenia. A question to ask is why NO is helpful to the cell in one set of circumstances and yet a toxic agent in another set of circumstances. Understanding the nature of physiological NO and pathological NO is critical and will yield possible therapies for central nervous system disease.

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