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23

Neurotensin as Modulator of Basal Ganglia-Thalamocortical Motor Circuit – Emerging Evidence for Neurotensin NTS_1 Receptor as a Potential Target in Parkinson's Disease

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1. Introduction

This chapter is focused on the putative role of neurotensin in the development of Parkinson's disease, a neurodegenerative disorder mainly characterized by a progressive loss of nigrostriatal dopaminergic neurons (Schimpff et al., 2001). Although a direct causal role of neurotensin in Parkinson's disease has not yet clearly demonstrated, some convincing animal and human studies support the potential role of the peptide in the etiopathogenesis of this motor disorder. Special emphasis is placed on the significance that neurotensin plays on basal ganglia neuroplasticity and neurodegeneration. This is mainly supported by recent findings clearly demonstrating that neurotensin enhances glutamate excitotoxicity in mesencephalic dopamine neurons and that neurotensin receptors are involved in the modulation of NMDA-induced excitotoxicity (Antonelli et al., 2002; 2004). Through these mechanisms neurotensin could contribute to the development and/or the progression of neurodegenerative disorders. The possible use of neurotensin receptor antagonists, in combination with conventional therapy, in the treatment of Parkinson's disease, is also discussed.

2. Basal ganglia

In Parkinson's disease, the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the consequent striatal dopamine deficiency lead to a cascade of functional modifications in the activity of the basal ganglia-thalamocortical motor circuit, responsible for the motor disturbances characteristic of the pathology (Silkis, 2001). The basal ganglia are a collective group of structures, which include the neostriatum (caudate nucleus and putamen), the external and internal parts of the globus pallidus, the subthalamic nucleus, the substantia nigra pars reticulata and the substantia nigra pars compacta.

From a simplistic point of view, motor information coming from glutamatergic neurons located in several areas of the cerebral cortex, reach the striatum, which represents the primary input nucleus of the basal ganglia. These information, processed in the striatum, are transmitted by the so called "direct" and "indirect" pathways, to the main output nuclei of the basal ganglia (substantia nigra pars reticulata and the internal part of the globus pallidus; Fig. 1). The "indirect pathway" encompasses a trisynaptic link including *i)* GABAergic/enkephalinergic neurons, which connect the striatum to the external part of the globus pallidus; *ii)* the external part of the globus pallidus GABAergic neurons projecting to subthalamic nucleus and *iii)* glutamatergic subthalamic nucleus neurons, which project to the basal ganglia output structures (internal part of the globus pallidus/substantia nigra pars reticulata) and send collaterals to external part of the globus pallidus (Gerfen, 1992). On the other hand, the "direct" monosynaptic pathway consists of GABAergic neurons which directly connect the striatum to the main basal ganglia output structures (substantia nigra pars reticulata and the internal part of the globus pallidus). Outputs from these nuclei consist of inhibitory GABAergic neurons projecting to the ventral-anterior and ventrolateral nuclei of the thalamus which, through excitatory glutamatergic fibers, project back to the prefrontal and motor cortices. The differences in neuronal connectivity between the "direct" and "indirect" pathways show dissimilar functional consequences: the stimulation of the "direct pathway" inhibits substantia nigra pars reticulata and the internal part of the globus pallidus activity, thus leading to a disinhibition of thalamocortical neurons and a consequent facilitation of motor initiation. On the contrary, the stimulation of the "indirect pathway" produces motor inhibition. In spite of the model of the "direct" and "indirect" pathways is an oversimplification of the basal ganglia organization, it still represents the cornerstone for modern research on the basal ganglia functions (for review, Smith and Villalba, 2008).

Dopamine released by terminals of neurons located in substantia nigra pars compacta markedly affects the functional activity of the striatum. In the striatum dopamine D_1 and D_2 receptor subtypes are respectively expressed on the "direct" and "indirect" striatonigral pathways and modulate motor information (Gerfen, 2003). Although the degree of this anatomical separation of D_1 and D_2 receptors has been for a time a controversial topic, recent studies, using transgenic mice have confirmed that dopamine receptor subtypes have mainly a different expression on separate populations of GABAergic medium-spiny projection neurons (Wang et al., 2006; Galvan and Wichmann, 2008). Due to the different location of its receptor subtypes, striatal dopamine physiologically activates the "direct pathway" (D_1 receptors) and inhibits the "indirect pathway" (D_2), leading to an increase of thalamocortical motor drive (*see* above). In addition, striatal glutamate release from corticostriatal glutamatergic terminals is tonically inhibited by dopaminergic input coming from the substantia nigra pars compacta and activating dopamine D_2 heteroreceptors (Bamford et al., 2004). In this synaptic arrangement, dopamine depletion within the striatum not only removes tonic dopamine inhibitory control over corticostriatal glutamatergic drive, but also induces an imbalance between the "direct" and the "indirect" pathways (Fig. 1). In particular, this deficit produces an overactivity of the GABAergic projections from the striatum to the external part of the globus pallidus, leading to an excessive inhibition of thalamocortical and brainstem motor systems. From a pathological point of view, the hyperactivity of striatopallidal GABAergic neurons is considered one of the anomaly responsible for generation of motor parkinsonian symptoms. Pharmacological interventions

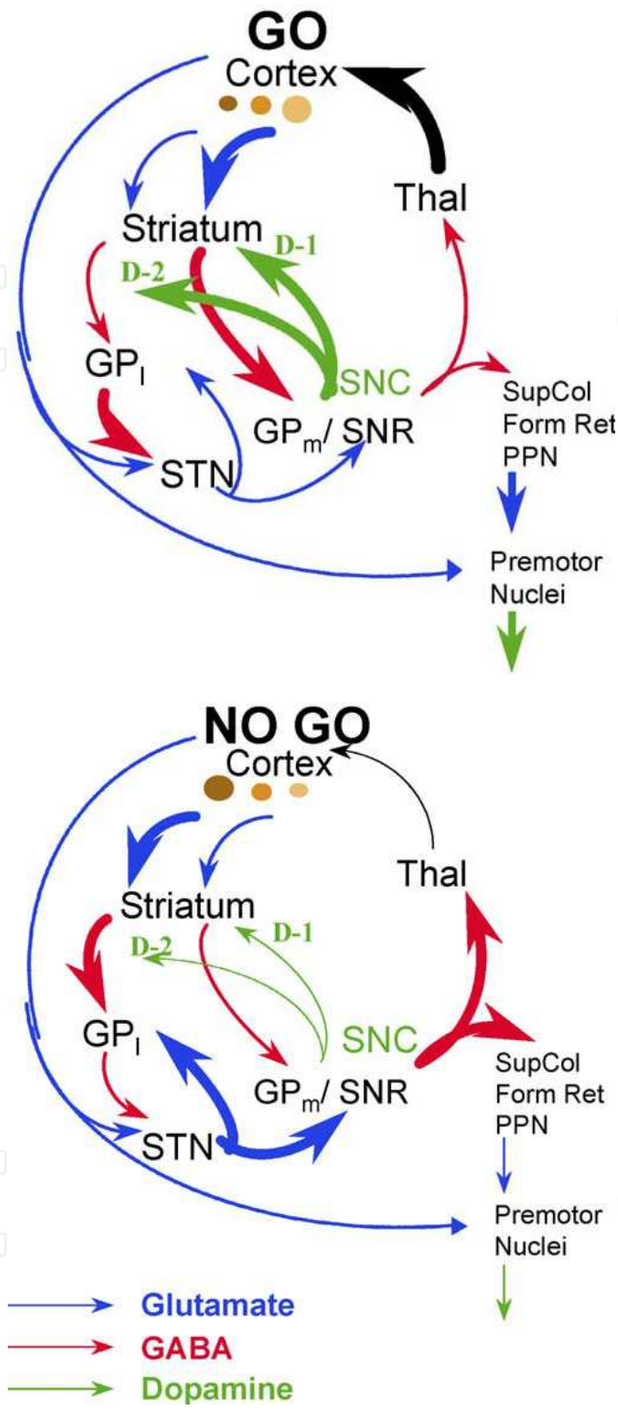


Fig. 1. The changes in the activity of basal ganglia circuits in normal state ('GO') vs Parkinson's Disease ('NO GO') are indicated. Heavy arrows, high activity; thin arrows, low activity. Abbreviations used: GP_l, globus pallidus, lateral; GP_m, globus pallidus, medial; SNC, Substantia nigra, zona compacta; SNR,Substantia nigra, zona reticulata; SupCol, Superior colliculus; Form Ret, formatio retucularis; PPN, Pedunculo pontine nucleus (from Tanganelli et al., 2004).

that can compensate for loss of dopamine and suppress the expression of motor symptoms in the pre-motor stages of Parkinson's disease are represented by the reduction of: *i)* the excitatory corticostriatal inputs that excite striatal output neurons of the "indirect pathway" or *ii)* the overactivity of striato-pallidal GABAergic neurons. The use of selective D_2 receptor agonist, A_{2A} adenosine receptor antagonism, blockade of GABA receptors in the external part of the globus pallidus or reduction of the excitatory NMDA receptor-mediated corticostriatal inputs, impinging upon striatal output neurons of the "indirect pathway", can be helpful for slowing progression of Parkinson's disease symptoms.

3. Neurotensin and its receptors

Neuropeptides represent undoubtedly one of the most common signaling molecules in the central nervous system. Accumulating evidence have implicated a vast number of neuropeptides and their receptors in the control of a wide range of physiological functions and pathological events, including neurodegenerative disorders.
Like all neuropeptides, neurotensin, an endogenous 13 amino acid peptide (Figure 2), is synthesized as part of a larger inactive precursor (Proneurotensin/neuromedin N).

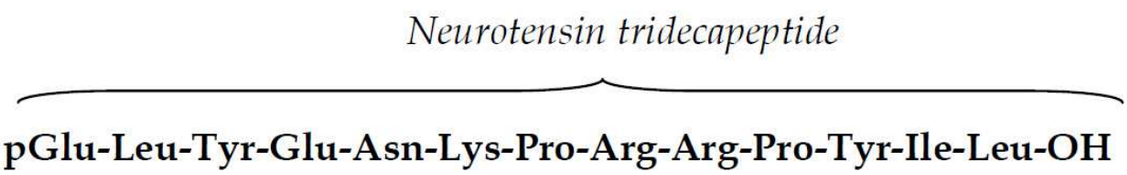


Fig. 2. Sequence of neurotensin (modified from Ferraro et al., 2009).

The precursor molecule, a highly conserved polypeptide of 169-170 amino acid, contains one copy each of neurotensin and neuromedin N near the C-terminus and undergoes a differential tissue-specific cleavage at its four dibasic sites by proprotein convertases. Pro-neurotensin/neuromedin N may therefore be processed to generate different sets of peptides. Four biologically active products of Pro-neurotensin/neuromedin N processing have been described: neurotensin, neuromedin N, large neurotensin and large neuromedin N (Kitabgi, 2010). In the brain, Pro-neurotensin/neuromedin N processing mainly depends on proprotein convertase 2 activity and leads to high amounts of neurotensin and neuromedin N and small quantities of large neurotensin and large neuromedin N (Kitabgi, 2010). Using radioimmunoassay techniques, it has been demonstrated that the regional distribution of neurotensin and neuromedin N in brain tissues is, generally, the same. However, marked differences in the ratio of neurotensin over neuromedin N have been observed in different brain areas, being neurotensin generally more abundant in dopaminergic region such as substantia nigra pars compacta and ventral tegmental area.
Once processed as an active peptide in neurons, neurotensin is stored in dense core vesicles. The physiological inactivation of neurotensin is operated by endopeptidases belonging to the family of metallopeptidases, which act on primary cleavage sites in the peptide sequence: Arg8-Arg9, Pro10-Tyr11 and Tyr11-Ile12 bonds. Another mechanism that produces an inactivation of neurotensin transmission is the process of neurotensin internalization.
Neurotensin is widely expressed in nerve cells, fibers and terminals (Uhl, 1982; Emson et al., 1985) and exhibits diverse biological actions in the regulation of central nervous system

functions of mammals, including man. The peptide is also highly expressed in the periphery, where it mainly acts as a modulator of the gastrointestinal and cardiovascular systems (Wang and Evers, 1999). Neurotensin was originally isolated and sequenced from bovine hypothalamus (Carraway and Leeman, 1973). Subsequent anatomical and functional studies have provided evidence that, in the brain, neurotensin behaves as neurotransmitter and/or neuromodulator (Nemeroff and Cain, 1985; Mendez et al., 1997). Neurotensin is released by neurons through sodium and calcium-dependent mechanisms. Once released, neurotensin produces its biological effects by interacting with three different receptor subtypes (NTS_1, NTS_2 and NTS_3/sortilin). The large distribution in the central nervous system of this family of membrane receptors explains the wide range of physiologic and pathologic effects mediated by the neuropeptide (Barroso et al., 2000). NTS_1 and NTS_2 receptors belong to the family of G-protein-coupled receptors with seven transmembrane domains, which share 60% homology. The NTS_1 receptor displays a high affinity for neurotensin, while NTS_2 receptor has a substantially lower affinity for the peptide and a high affinity to levocabastine, a histamine H_1 receptor antagonist (Chalon et al., 1996; Vincent et al., 1999). NTS_3/sortilin receptor is a single transmembrane protein located in intracellular vesicles of neurons and glia and appears involved in cell sorting and in tropism in cancer cells (Nouel et al., 1999; Mazella et al., 1998). NTS_1 receptor is coupled to a variety of signaling cascades, including production of inositol phosphates through activation of phospholipase C, formation of cAMP and cGMP, and induction of mitogen-activated protein kinase phosphorylation. Autoradiographic ligand binding, in situ hybridization, and immunohistochemical studies have yielded abundant information on the distribution of NTS_1 receptors in mammalian brain. NTS_1 receptors are markedly expressed in brain regions rich in dopamine cell bodies, such as the substantia nigra pars reticulata and pars compacta, the ventral tegmental area, and in projection areas of both nigrostriatal and mesocorticolimbic dopaminergic pathways, such as striatum, nucleus accumbens and frontal cortex (Palacios and Kuhar, 1981; Goulet et al., 1999; Boudin et al., 1998; Binder et al., 2001). In the striatum and nucleus accumbens, NTS_1 receptors are co-localized at post-synaptic level with dopamine D_2 receptors and, although in low density, at the pre-synaptic levels too (Pickel et al., 2001; Delle Donne et al., 2004). This receptor co-distribution together with the demonstration that neurotensin is localized within the nigrostriatal and mesolimbic dopamine neurons explain the role that the neuropeptide plays in the modulation of dopamine neurotransmission (Jennes et al., 1982). It is worth noting that in the striatum, NTS_1 receptors are significantly located on cortical glutamatergic terminals as well as on the striatopallidal GABA neurons (Boudin et al., 1996; Alexander and Leeman, 1998; Tanji et al., 1999). Finally, in the globus pallidus, neurotensin receptors (NTS_1 and NTS_2) exist in different neurons and are located both pre-synaptically and post-synaptically (Fassio et al., 2000; Sarret et al., 2003) thus regulating (mainly NTS_1 receptors), both pallidal glutamatergic and GABAergic transmission (Chen et al., 2004; 2006). Such distribution of NTS_1 receptors justifies the modulation that neurotensin exerts on the mesolimbic, mesocortical and nigrostriatal dopamine neurons, as well as on glutamatergic and GABAergic neurones (Deutch and Zahm, 1992; Fuxe et al., 1992 a,b; Rostene et al., 1992; Binder et al., 2001; Dobner et al., 2003; Petrie et al., 2005). Most of the central and peripheral functions controlled by NTS_1 receptors have been elucidated by the use of the non-peptide neurotensin antagonist SR48692, which preferentially binds NTS_1 receptors (Gully et al., 1993; Rostene et al., 1997).

4. Neurotensin levels, neurotensin binding sites and Parkinson's disease

The high concentrations of neurotensin in brain regions associated with dopaminergic cell bodies and projections, such as the striatum, substantia nigra, ventral tegmental area and globus pallidus (for a review, see Binder et al., 2001) indicate that neurotensin and dopamine are closely linked. In particular, the influence of neurotensin on nigrostriatal and mesocorticolimbic dopaminergic systems suggests that neurotensin may play a relevant role in dopamine-associated pathologies, such as some neurodegenerative disorders and neuropsychiatric diseases (Rostene et al., 1992; Lambert et al., 1995; St-Gelais et al., 2006).

In the following part of this section, data obtained from human and animal studies providing the existence of relationships between neurotensin and neurodegenerative disorders, will be shortly summarized.

Numerous studies have tried to determine whether, in humans, changes in the neurotensinergic system could be associated to Parkinson's disease. In an early study, high levels of neurotensin-like immunoreactivity were detected in lumbar cerebrospinal fluid from Parkinson's disease patients, whilst no significant changes in neurotensin content were observed (Emson et al., 1985). Successively, Fernandez et al. (1995, 1996) found that in post-mortem samples from basal ganglia of Parkinson's disease patients there were changes in the levels of different neuropeptides. In particular, substantia nigra neurotensin levels were two-fold higher in Parkinson's disease patients than in healthy subjects. It is worth noting that in incidental Lewy body disease, which is considered as a pre-symptomatic phase of Parkinson's disease, neurotensin levels tended to increase as in parkinsonian patients, even if this increase was not statistically significant (Fearnley and Lees, 1991). Similarly, in 6-hydroxydopamine-lesioned rats or in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys, two well-characterized animal models of Parkinson's disease, an increase in striatal and globus pallidus neurotensin levels was found, and such an enhancement was not modified by L-dopa treatment**.** In view of the above results, the authors suggested that changes in neurotensin levels and other neuropeptides may be considered as an early component of an integral part of the pathology rather than a secondary biochemical alteration resulting from loss of the nigrostriatal pathway or a drug-induced event. However, in contrast to the above results, in a previous study, Taylor et al. (1992) showed that substantia nigra neurotensin levels were unchanged following 6-hydroxydopamine lesion, but increased by a prolonged treatment with L-dopa. The authors concluded that changes in neurotensin levels appear to be only a secondary event, due to dopamine neuron loss in combination with protracted drug therapy. Despite these contrasting results, the hypothesis that an enhancement of neurotensin levels, associated to an activation of NTS_1 receptor located on the nigral dopamine neurons, contributes to the degeneration of these dopamine cells in Parkinson's disease, is supported by other animals studies. In particular, these findings indicate that a neurotensin-induced increase in both striatal and cortical endogenous glutamate release, is significantly coupled to an enhancement of neuronal excitotoxicity, which can contribute to nigral dopamine cell loss. In addition, it has been demonstrated that the neuropeptide increases the energy demands due to an increased firing rate in the dopamine cells. These enhancements are, at least in part, caused by a reduction of the D_2 autoreceptor signaling via an antagonistic NTS_1/D_2 receptor interaction (Fuxe et al., 1992a). These neurochemical and morphological results will be carefully described in the subsequent sections (5 and 6).

Besides the changes in neurotensin levels, biochemical and histological investigations in post-mortem brain tissues of parkinsonian patients have shown a significant reduction of neurotensin-binding sites in several specific brain areas of the basal ganglia as respect to healthy subjects (Chinaglia et al. 1990; Fernandez et al., 1994). In particular, Chinaglia et al. (1990), using a receptor autoradiography technique, compared the distribution of neurotensin receptors in post-mortem brain tissues from parkinsonian patients, with that found in patients affected by progressive supranuclear palsy and-in age-matched controls. Significant decreases in neurotensin receptor density were found in the substantia nigra, caudate nucleus, putamen and globus pallidus of both groups of patients in comparison to healthy subjects. In addition, a significant decrement of neurotensin receptor density was found in the ventral tegmental area, nucleus accumbens and dorsal part of caudate in patients with Parkinson's disease as regards to patients with progressive supranuclear palsy, indicating differential involvement of neurotensin receptor alterations in these two neurological disorders. Interestingly, in this cohort of Parkinson's disease patients, the reduction of striatal neurotensin binding sites was lower than the decrease of dopamine content in this nucleus, suggesting only a partial localization of neurotensin receptors on nigrostriatal dopaminergic projections. Using in situ hybridization, it has been possible to more specifically illustrate that NTS_1 receptor mRNA levels were decreased in the substantia nigra of patients with parkinsonism (Yamada and Richelson, 1995). These human results were confirmed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys, where a decrease in the number of neurotensin-binding sites in the striatum and substantia nigra was found (Goulet et al., 1999; Tanji et al., 1999). The reduction of NTS_1 receptors in the substantia nigra of parkinsonian patients might be related to the loss of the nigrostriatal dopaminergic neurons. In contrast, the interpretation of the decrease in neurotensin-binding sites observed in the striatum of Parkinson's disease patients is certainly more difficult since, at present, the results concerning the pre-synaptic or the post-synaptic localization of striatal neurotensin receptors are still contradictory (Quirion et al., 1985; Cadet, 1991). However, it may be suggested that the decrease in striatal neurotensin-binding sites may reflect the loss of neurotensin receptors not only on dopaminergic nigrostriatal terminals but also on striatal GABAergic medium spiny neurons.

Taken together, the above mentioned studies from Parkinson's disease patients suggest a significant relationship between the alteration of neurotensinergic system and Parkinson's disease. On the basis of these findings, Schimpff et al. (2001) evaluated whether plasma neurotensin concentrations in parkinsonian patients could be considered as a marker in diagnosis and severity of this motor disorder. The results emerging from this study showed that the plasma neurotensin concentrations were significantly higher in Parkinson's disease patients than in healthy controls. Accordingly, neurotensin concentration in the plasma of untreated patients was higher than that observed in treated patients. It is worth noting that these findings were compatible with the enhancement of neurotensin levels detected in post-mortem brain tissues from parkinsonian patients and data obtained from animal studies. Thus, the authors concluded that in addition to the diagnostic criteria for Parkinson's disease "*measurement of extracted plasma neurotensin concentrations in patients with Parkinson may prove useful as an index in diagnosis*".

In summary, it can be concluded that the increase in striatal and nigral neurotensin tissue concentrations, as well as in cerebrospinal fluid and plasma levels may be due either to a loss of dopamine neurons and/or to a dysregulation of neurotensin transmission on striatal output, favoring the striatopallidal GABAergic pathway. Further work is needed to better understand the role of neurotensin in the pathophysiology of Parkinson's disease.

5. Striatal neurotensin and Parkinson's disease: neurochemical animal studies

5.1 Neurotensin modulation of pre- and post-synaptic D_2 receptors. Relevance for the control of striatopallidal GABAergic projections

As stated above, the motor deficits that characterize Parkinson's disease are associated to an imbalance on the functional activity of the "direct"–"indirect" circuits in favor of the "indirect pathway", *i.e.* reduced activity in the "direct pathway" and/or increased activity in the "indirect pathway" (Obeso et al., 2000; 2008). Several lines of evidence indicate that neurotensin is co-localized and co-distributed with dopamine neurons of the basal ganglia, including the somatodendritic complex and axon terminals of various neuronal elements in the substantia nigra and striatum. This close anatomical relationship, reinforces functional findings demonstrating the existence of reciprocal modulations between neurotensinergic and dopaminergic systems in these brain areas (Hökfelt et al., 1984; Nemeroff and Cain, 1985; Blaha et al., 1990; Castel et al., 1994; Tanganelli et al., 1994; Rostène et al., 1997; Werkman et al., 2000). Intensive animal studies have well documented that neurotensin, in addition to its direct excitatory effects on dopamine neurons, significantly modulates D_2 auto- and hetero-receptors functions through the activation of its high-affinity NTS_1 receptor (Kalivas and Duffy, 1990; Werkman et al., 2000; Binder et al., 2001). The regulation of dopaminergic transmission, especially at the level of nigrostriatal and mesocorticolimbic dopamine pathways, by neurotensin (Kitabgy et al., 1989; Deutch and Zahm, 1992) is mainly due to an antagonistic action of the activated NTS_1 receptor on D_2 receptor recognition and signaling. In the striatum, neurotensin has been shown to reduce the affinity of D_2 agonist binding sites and their transduction signals through a receptor-receptor interaction at both pre- and post-synaptic levels (Agnati et al., 1983; von Euler and Fuxe 1987; Shibata et al., 1987; Da-Silva et al., 1989; Fuxe et al., 1992 a,b). In particular, neurotensin by increasing the Kd value of D_2 receptor agonist binding, significantly decreases the affinity of D_2 receptors for endogenous dopamine and dopamine receptor agonists. The neurotensin-induced reduction of D_2 receptor agonist affinity has been demonstrated both in sections and in membrane preparations. The presence at the cellular level of NTS_1 and D_2 receptors in the same axon terminals and dendrites (Delle Donne et al., 2004), together with the demonstrated antagonistic intramembrane NTS_1/D_2 receptor–receptor interactions using biochemical radioligand binding analysis in striatal membranes (Agnati et al., 1983; von Euler and Fuxe 1987; Tanganelli et al., 1989; Fuxe et al., 1992b; Li et al., 1995; Diaz-Cabiale et al., 2002; Antonelli et al., 2007), give indirect evidence for the existence of NTS_1/D_2 receptor heteromerization. By using intrastriatal monoprobe microdialysis and measuring dopamine release from striatal terminals, in vivo evidence has been obtained that the neurotensin/D_2 antagonistic receptor–receptor interaction exists at the pre-junctional level in striatal dopamine transmission. This study demonstrate that, as expected, intrastriatal perfusion with the preferential dopamine D_2 receptor agonist pergolide decreased local dopamine outflow, an effect which reflects a stimulation of terminal D_2 auto-receptors causing the inhibition of striatal dopamine outflow. Interestingly, when neurotensin was co-perfused at a low nanomolar threshold concentration, together with pergolide, the inhibitory effect of the preferential dopamine D_2 receptor agonist on dopamine release is fully abolished as measured in the striatum of awake unrestrained rats. This provides a functional in vivo correlate to the binding results indicating the existence of antagonistic neurotensin/D_2 receptor–receptor interactions previously shown in neostriatal membranes and sections. A

possible direct interaction between D_2 and NTS_1 receptors with the formation of heteromers has also been considered by Jomphe et al. (2006) as one of the possible, but not the exclusive, mechanisms underlying the functional control of striatal dopamine D_2-mediated transmission by neurotensin.

Biochemical and functional evidence suggests the existence of an antagonistic NTS_1/D_2 receptor-receptor interaction in rat neostriatum also at the post-synaptic level (Fuxe et al., 1992a; Ferraro et al., 1997). Post-synaptic D_2 receptors in the neostriatum exist predominantly on medium sized GABAergic neurons of the "indirect pathway", which project to the globus pallidus and exert an inhibitory influence on striopallidal GABA transmission (Reid et al., 1990; Ferre' et al., 1993). Converging evidence suggests that the behavioural catalepsy associated with blockade of striatal D_2 receptors is mediated by increased striopallidal GABA transmission, which leads to a decrease in thalamocortical motor drive (Drew et al., 1990; Osborne et al., 1994). Neurochemical findings, obtained employing in vivo dual-probe microdialysis technique, whereby one probe was implanted into the striatum and the other into the ipsilateral globus pallidus, demonstrated that intrastriatal perfusion with D_2 agonists inhibits striopallidal GABA release (Reid et al., 1990; Ferre' et al., 1993). On the contrary, D_2 receptor antagonists enhance striopallidal GABA release (Drew et al., 1990). Interestingly, intrastriatal co-perfusion of neurotensin, at a concentration by itself ineffective on pallidal extracellular GABA levels, in combination with pergolide, fully antagonizes the inhibitory effects of the preferential D_2 agonist on pallidal GABA release. The presence in the perfusate medium of the selective neurotensin receptor antagonist SR48692 removes the antagonistic effect of neurotensin, thus restoring the pergolide-induced inhibition of pallidal GABA levels. It is worth noting that higher concentrations of neurotensin, via a direct activation of NTS_1 receptor subtypes, significantly increase pallidal GABA outflow. SR48692 fully counteracts the facilitatory effects of neurotensin, indicating the involvement of NTS_1 receptors located on striopallidal GABAergic neurons in this effect. In view of the evidence showing that behavioural catalepsy in rodents and akinesia in humans are mediated by an increased striopallidal GABA transmission (Scheel-Kruger, 1986; Drew et al., 1990; Osborne et al., 1994), these findings suggest that the cataleptic profile of neurotensin (Shibata et al., 1987; Da-Silva et al., 1989) may be explained by its ability to influence neurotransmission in the "indirect pathway". In particular, the cataleptic action of neurotensin may be in part related to an enhancement of endogenous neurotensin signalling and in part to a reduction of post-synaptic D_2 receptors affinity. The existence of this intramembrane antagonistic neurotensin/D_2 receptor interaction is also supported by the finding that haloperidol-induced catalepsy is associated with an increase in pallidal GABA release (Drew et al., 1990; Osborne et al., 1994). Briefly, neurotensin-induced increase of pallidal GABA release and the consequent activation of striopallidal GABA transmission, may represent the neurochemical substrate to explain the behavioural data indicating that the activation of striatal NTS_1 receptors reduces motor activity (Poncelet et al., 1994).

5.2 Neurotensin modulation of striatal pre- and post-synaptic D_2 receptors. Functional consequences on the activity of the "indirect pathway"

As previously reported, in the "indirect pathway" the striatopallidal GABAergic projection corresponds to the first neuron of the trisynaptic connection that projects to the substantia nigra pars reticulata. The GABAergic projection from the globus pallidus to the subthalamic nucleus represents the second neuron whereas the subthalamic nucleus glutamatergic cells

projecting terminals to the substantia nigra pars reticulata and collaterals to the internal part of the globus pallidus, the third one. Thus, changes in the activation of striatopallidal GABA neurons lead to modifications of the activity of subthalamic nucleus glutamate neurons and consequent variations in substantia nigra pars reticulata and pallidal glutamate release. In view of the above data and to analyze the functional relevance of striatal NTS_1 receptor activation on the activity of the "indirect pathway", a dual-probe microdialysis analysis was planed. One probe was implanted into the striatum and the other one in the ipsilateral globus pallidus of the awake rat; the effects of neurotensin on striatal and pallidal glutamate levels were then measured. In this part of the present section the results coming from these microdialysis studies, will be summarized.

5.2.1 Effects of striatal NTS_1 receptor activation on pallidal glutamate levels

Extracellular pallidal glutamate levels are mainly derived from the collaterals of the subthalamic nucleus-substantia nigra pars reticulata neurons (*see* above). Intrastriatal infusion with a high concentration of neurotensin increases striatal and pallidal glutamate as well as pallidal GABA levels (*see* also the above section). All these effects are counteracted by the local perfusion with the NTS_1 receptor antagonist SR48692. Thus, the intrastriatal neurotensin-induced increase of pallidal glutamate levels may be related to a direct activation of somatodendritic NTS_1 receptors located on the striatopallidal GABA neurons or to the antagonistic NTS_1/D_2 receptor-receptor interaction. The demonstration that the striatal neurotensin-induced increase in pallidal glutamate levels is counteracted by the intrapallidal perfusion of the $GABA_A$ receptor antagonist (-)-bicuculline, suggests that this effect is mediated via the activation of striatopallidal neurons. In fact, it seems likely that the stimulation of striatal NTS_1 receptors, by increasing striatopallidal GABA release, reduces the activity of GABAergic neurons projecting from the globus pallidus to the subthalamic nucleus, thus increasing pallidal glutamatergic transmission. In other words, this sequence of GABA-mediated inhibitory modulations induces a disinhibition of the excitatory glutamatergic subthalamic nucleus-substantia nigra pars reticulata efferents which send axon collaterals to the globus pallidus (Alexander and Crutcher, 1990). The intrapallidal (-)-bicuculline perfusion was employed since previous studies demonstrated the role of $GABA_A$ receptor activation in regulating the pallidal output system toward the subthalamic nucleus (Kita, 1992; Amalric et al., 1994). Accordingly, an electrophysiological study (Soltis et al., 1994) demonstrated that the infusion of bicuculline into subthalamic nucleus increased the firing rate of pallidal neurons.

5.2.2 Effects of NTS1 receptor activation on striatal glutamate levels

Extracellular striatal glutamate levels are derived in part, from the terminals of cortical and thalamic afferents (Sirinathsinghji and Heavens, 1989; Parent and Hazrati, 1995). As previously stated, intrastriatal perfusion with neurotensin at a high concentration increases striatal glutamate levels and this effect is fully counteracted by SR48692. Immunohistochemical studies have shown that in the striatum and nucleus accumbens, NTS_1 receptors and dopamine D_2 receptors are expressed on axon terminals, including the glutamatergic ones (Delle Donne et al., 2004). In this context, it seems possible that at least two mechanisms might underlay the neurotensin-mediated enhancement of striatal glutamate release. The first one may be related to a direct activation of local NTS_1 receptors expressed on striatal glutamate terminals. The second mechanism implies that the formation

of a NTS_1/D_2 heteromeric receptor complex mainly located on the plasma membrane of striatal glutamate terminals, antagonizes the inhibitory D_2 receptor mediated signaling (*see* above) on the glutamate terminals, leading to an increase of glutamate release. The presence of a functional antagonistic pre-synaptic NTS_1/D_2 interaction on glutamatergic striatal terminals has been demonstrated since a threshold concentration of neurotensin counteracts the D_2 agonist quinpirole-induced inhibition of K^+-evoked striatal glutamate levels.

5.3 Neurochemical studies: concluding remarks

The analysis of all the above microdialysis results suggests that the over-activity of striatopallidal GABA pathway is under the control of NTS_1 receptors located both on medium size spiny striatal GABAergic neurons and on striatal glutamatergic terminals. The mechanisms involved in this control are mainly associated to a direct activation of NTS_1 receptor homomer or to an antagonistic NTS_1/D_2 receptor-receptor interaction (Figure 3). Based on these molecular mechanisms, it might be suggested that the activation of NTS_1 receptors suppresses the inhibitory control mediated by nigrostriatal dopaminergic neurons on striatopallidal GABAergic neurons and enhances the excitatory cortico-striatal glutamatergic signaling. The final consequence of these combined opposite modulations is the hyperactivity of the striatopallidal GABAergic neurons of the "indirect pathway" which is considered one of the anomaly responsible for generation of motor parkinsonian symptoms (*see* section 2). Thus, neurotensin receptor antagonists, by counteracting the neurotensin-induced hyperactivity of striatopallidal GABAergic neurons, could be useful to reduce motor symptoms in Parkinson's disease patients.

6. Neurotensin and Parkinson's disease: biochemical and morphological analyses in neuronal cell cultures

The substantial elevation in extracellular glutamate accompanied by an excessive activation of excitatory amino acid receptors generates neuronal cell death (Sonsalla et al., 1998). Glutamate has been one of the major focus of research into the excitotoxic basis of neurodegenerative diseases (Choi, 1988; Meldrum and Garthwaite, 1990). In vivo and in vitro studies have shown that neurotensin significantly increases endogenous glutamate outflow in discrete rat brain regions, such as the striatum, globus pallidus, frontal cortex, substantia nigra and parabrachial nucleus-ventrobasal thalamus (Sanz et al., 1993; Saleh, 1997; Ferraro et al., 1998, 2000, 2001). These findings suggest that neurotensin may play a relevant role in reinforcing the effects exerted by glutamate on a variety of central nervous system functions. In particular, the observations that neurotensin amplifies glutamate levels and antagonizes the dopamine D_2 receptor-mediated inhibition of dopamine transmission in the basal ganglia (Fuxe et al., 1992 a,b), indicate that neurotensin may contribute to enhance the firing rate and energy demands in the nerve cells. In this context, as illustrated in section 4, a putative role of neurotensin in the development of Parkinson's disease, has been suggested (Fernandez et al., 1995, 1996; Tanji et al., 1999; Schimpff et al., 2001).

In this paragraph, the effects of neurotensin in modulating the glutamate-induced neurodegenerative effects in cultured rat mesencephalic dopaminergic (Antonelli et al., 2002) and cortical (Antonelli et al., 2004) neurons will be shortly summarized.

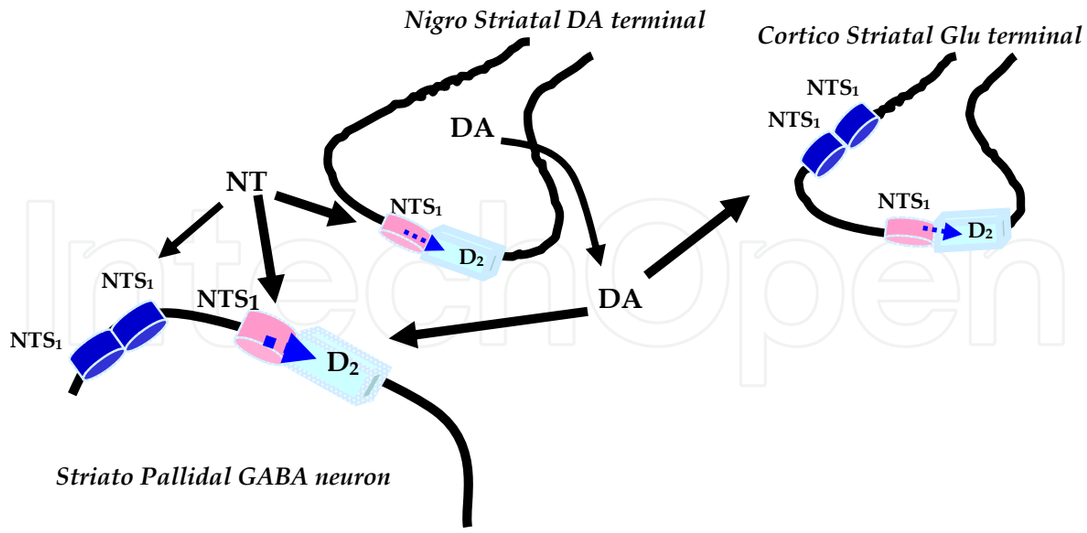


Fig. 3. Schematic representation of the pre-and postjunctional neurotensin (NT) receptor (NTS_1) and dopamine (DA) D_2 receptor interactions in the striatum taking place in NTS_1/D_2 heteromers in balance with excitatory NT receptor homomers (Modified from Ferraro et al., 2008).

6.1 Effects of neurotensin on glutamate-induced excitotoxicity in primary cultures of mesencephalic neurons

Biochemical and morphological approaches (Antonelli et al., 2002), provided evidence that the neurotoxic effects of glutamate on primary cultures of mesencephalic neurons are exacerbated by neurotensin.

Mesencephalic cell cultures, which contain dopaminergic neurons, express glutamate receptors (Meltzer et al., 1997; Yung, 1998; Mateu et al., 2000) as well as functional neurotensin receptors (Nalivaiko et al., 1998; Nouel et al., 1999). Thus, this in vitro preparation represents a suitable model for testing the influence of neurotensin on glutamate-induced neurotoxicity. Measurement of [^{3}H]dopamine uptake in mesencephalic cell cultures has been proved a reliable parameter with which to evaluate the metabolic and structural integrity of the dopaminergic neurons in culture (Mount et al., 1989; Antonelli et al., 2002). In particular, in mesencephalic cell cultures intoxicated with glutamate, a reduction of [^{3}H]dopamine uptake, is observed. The exposure of cells to neurotensin exacerbates the glutamate-induced neurotoxicity, causing a further reduction of [^{3}H]dopamine uptake. Similar results were also obtained by evaluating the vulnerability of the mesencephalic cells to glutamate using tyrosine hydroxylase immunoreactivity. The tyrosine hydroxylase-immunoreactive cell count allows to quantify dopamine cell survival or loss of phenotype (Bowenkamp et al., 1996). As shown in Figure 4, the enhancing action of neurotensin on glutamate-induced toxicity in dopaminergic neurons has also been demonstrated by the increased disappearance of tyrosine hydroxylase-immunoreactive neurons pretreated with glutamate and neurotensin in combination. The selective neurotensin receptor antagonist SR48692 counteractes the above-mentioned effects of neurotensin, indicating that NTS_1 receptor was mainly involved in the neurotensin-induced

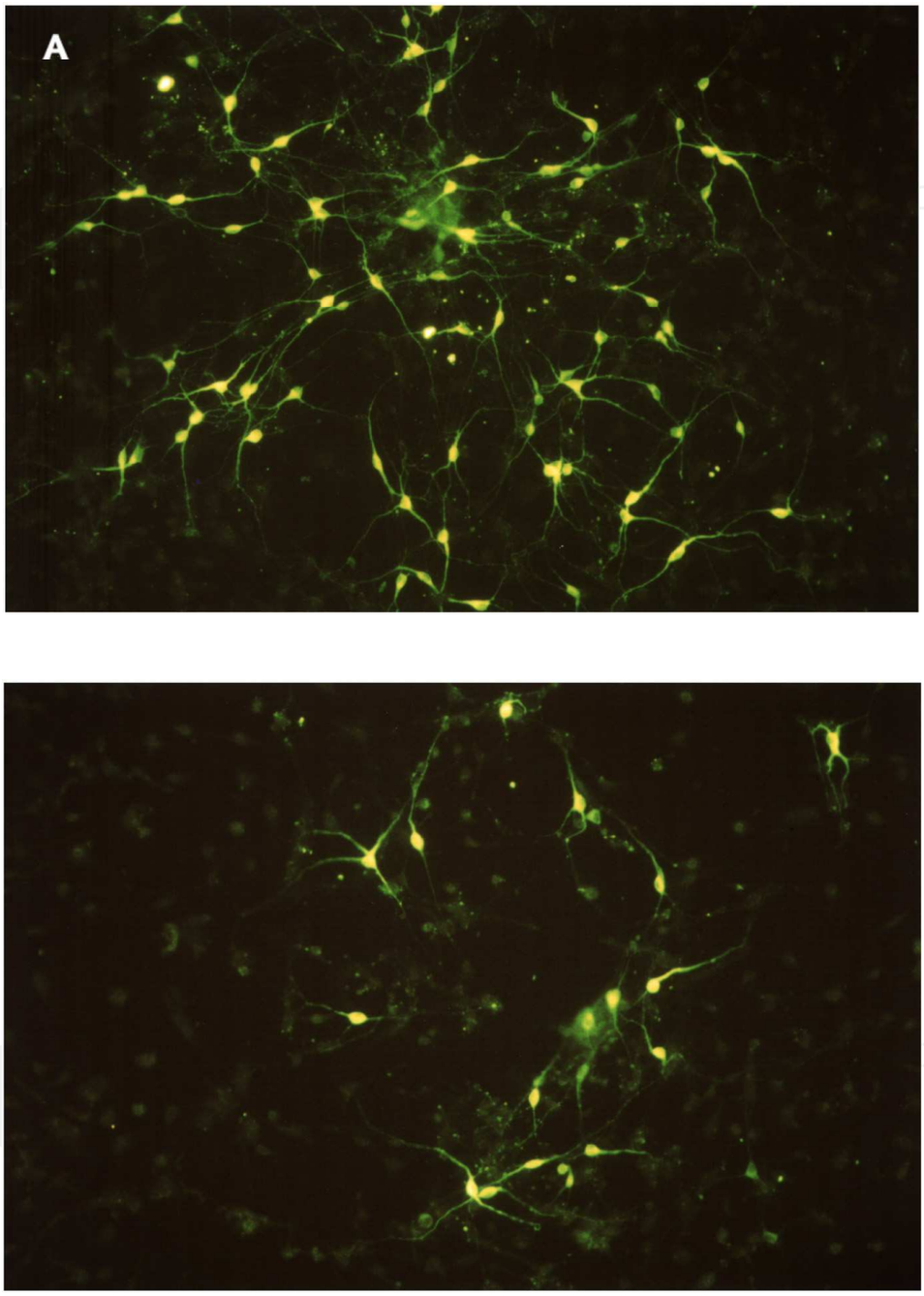


Fig. 4. Representative photomicrographs of tyrosine hydroxylase-immunoreactive mesencephalic cells in culture. **A** (control) shows a typical culture of tyrosine hydroxylase-immunoreactive neurons, with long processes and network. **B** shows a field of tyrosine hydroxylase-immunoreactive neurons exposed to 100 μM glutamate for 10 min, in which there is an evident neuronal loss (from Antonelli et al., 2002).

enhancement of glutamate injury. Since NTS_1 receptors are coupled to phospholipase C (Cathala and Paupardin-Tritsch, 1997; Trudeau, 2000), the effect of the combination of neurotensin with glutamate on [^{3}H]dopamine uptake was also evaluated in the presence of the specific protein kinase C inhibitor calphostin C (Kobayashi et al., 1989). The neurotensin-induced enhancement of glutamate neurotoxicity is completely prevented by calphostin C. Thus, it seems possible that the nigral NTS_1 receptors located on dopamine cells (Nalivaiko et al., 1998) enhance glutamate receptor subtype signaling through a protein kinase C activation. This finding suggests that neurotensin-mediated rise of glutamate excitotoxicity could be mediated by phosphorylation(s) of receptor-associated protein(s) involved in receptor signaling and/or trafficking.

6.2 Effects of neurotensin in modulating the neuronal activity of NMDA receptor in primary cortical cell cultures of rat

Evidence has been accumulated that the excessive activation of glutamate receptors, particularly NMDA receptors, may contribute to the neuronal cell death associated with chronic neurodegenerative disorders including Parkinson's disease and Alzheimer's disease. In this paragraph, the evidence for a functional role of NTS_1 receptors in modulating the neuronal activity of NMDA receptor in cortical glutamatergic nerve cells, will be discussed.

Accordingly to the above in vivo and in vitro experiments, neurotensin increases basal endogenous glutamate release from rat cortical cell cultures. The involvement of NTS_1 receptors in this increase is further supported by the antagonistic effect of SR48692. The exposure of cortical cell cultures to NMDA induces a concentration-dependent increase in endogenous extracellular glutamate levels, an increase that is enhanced in the presence of a sub-threshold concentration of neurotensin. These results indicate that NTS_1 receptor activation enhances the NMDA-receptor signaling and suggest the existence of facilitatory NTS_1/NMDA interactions at the membrane level. The lack of a neurotensin-mediated enhancement of glutamate outflow in the presence of NMDA receptor blockade further supports the hypothesis that neurotensin is a modulator of NMDA receptor function. Morphological analysis strengths the above hypothesis since neurotensin, in threshold concentration, enhances the glutamate-induced increase in the number of the apoptotic cells and such an effect is counteracted by SR48692 (Antonelli et al., 2004). A direct facilitatory NTS_1/NMDA interaction may therefore produce plastic changes in glutamate transmission and, if excessive, produce increases in glutamate-induced excitotoxicity. Under physiological conditions such a postulated NTS_1/NMDA heteromeric complex may modulate metaplasticity which is another main mode of homeostatic plasticity (*see* Perez-Otano and Ehlers, 2005), which serves to establish that receptor plasticity may exist in a proper working range, avoiding *e.g.* a dramatic NMDA receptor internalization and downregulation.

At the present, several mechanisms possibly underlying the demonstrated synergistic NTS_1/NMDA receptor interactions can be hypothesized: *i)* both receptors are known to produce an increase in intracellular Ca^{++} levels and their co-activation may therefore lead to a rapid and robust rise of intracellular Ca^{++} levels; *ii)* synergistic NTS_1/NMDA effect may involve a protein kinase C mediated phosphorylation of the NMDA receptors. It is worth noting that the inhibition of the protein kinase C by calphostin C suppresses the NTS_1-mediated enhancement of NMDA-induced increases of extracellular glutamate levels. (Antonelli et al., 2004). This finding assumes a particular relevance in view of the

demonstration that protein kinase C is likely to be an important regulator of neuronal NMDA receptors in vivo. The activation of protein kinase C increases NMDA channel opening rate and a rapid delivery of functional NMDA receptors to the cell surface. Thus, regulation of neuronal NMDA receptors by protein kinases plays a critical role in synaptic transmission and synaptic plasticity of NMDA receptors. Since phospholipase C–protein kinase C–inositol triphosphate pathway is the major signal transduction of NTS_1 receptors, it may be suggested that the existence of a neurotensin-mediated potentiation of NMDA receptors involves the activation of protein kinase C. Similarly to the above hypothesis, it has been demonstrated that mGluR1 activation potentiates NMDA receptors by an activation of protein kinase C (Skeberdis et al., 2001; Matsuyama et al., 2002); *iii)* it also seems possible that NTS_1 receptor by forming a receptor heteromer with the NMDA receptor (NTS_1/NMDA heteromer) may contribute to enhance NMDA receptor signalling and its surface expression; *iv)* a recent paper reported that neurotensin receptor agonists robustly increased extracellular concentrations of glycine in the rat prefrontal cortex (Li et al., 2010). It is well known that normal NMDA receptor function depends on not only the binding of glutamate to the receptor but also the binding of glycine to an allosteric site on this receptor. Thus, it could be suggested that neurotensin modulates NMDA receptor functions by modulating allosteric glycine activity.

Taken together, the results obtained in mesencephalic and cortical cell cultures suggest that neurotensin receptor antagonists, by counteracting the neurotensin-induced amplification of glutamate excitotoxicity could display neuroprotective properties.

7. Neurotensin receptor blockade in an animal model of Parkinson's disease

The postulated neuroprotective properties of neurotensin receptor antagonists are also supported by experiments (Ferraro et al., 2008) carried out in a rat model of Parkinson's disease [unilateral nigral 6-hydroxydopamine induced lesion of the nigrostriatal DA pathway, hemiparkinson model]. In this study, behavioural and biochemical experiments have been performed in control animals and in 6-hydroxydopamine unilaterally lesioned rats chronically treated with saline or with the NTS_1 receptor antagonist SR48692 from one-week before until one-week after the lesion. A conventional behavioural assessment using apomorphine-induced rotation was performed to quantify the unilateral nigrostriatal lesion-induced motor asymmetry after ipsilateral 6-hydroxydopamine injection. As expected, in 6-hydroxydopamine-lesioned rats, but not in control rats, the apomorphine injection produced a controlateral turning behaviour that significantly and progressively increased from week 1 to the 3rd week following the lesion. However, interestingly, in the SR48692-treated group, but not in the vehicle-treated group, the apomorphine-induced rotational behaviour is significantly reduced at each time of evaluation (day 7, 14 and 21 post lesion). Moreover, whereas the treatment stopped 2 weeks before, the effect of the compound remains significant. This finding suggests that systemic administration of NTS_1 antagonist decreased the functional consequence of a partial dopaminergic lesion induced by intranigral application of the neurotoxin 6-hydroxydopamine in the rat.

In view of the above behavioural findings, neurochemical experiments have been carried out in control animals and in rats chronically treated with SR48692 or its vehicle from one-week before until one week after the 6-hydroxydopamine injection. In particular, the responsivity to a challenge with NMDA has been assessed. The results obtained from this study demonstrate that in 6-hydroxydopamine-lesioned control and vehicle-treated rats,

intrastriatal perfusion with NMDA induced a slight increase in glutamate extracellular levels that was significantly lower than that observed in sham-operated animals. Interestingly, in 6-hydroxydopamine-lesioned rats chronically treated with SR48692, the effect of intrastriatal perfusion of NMDA induced an increase in glutamate extracellular levels that was significantly higher with respect to that obtained in the group of 6-hydroxydopamine lesioned rats but still lower to that observed in control rats.
These neurochemical results are in line with previous microdialysis data indicating that dopamine denervation is associated with a reduction of the enhancement of striatal glutamate transmission induced by a high micromolar NMDA concentration. Since it has been demonstrated that endogenous dopamine in the striatum facilitates strong excitatory inputs, the reduction of NMDA-stimulated glutamate levels in lesioned-animals could imply a loss of facilitatory dopamine receptor mediated signals. In this view, the observation that in rats chronically treated with SR48692 the excitatory response to a NMDA stimulus on the striatal glutamatergic transmission is partially restored may support a protective action of the NTS1 antagonist against 6-hydroxydopamine-induced dopamine neuron degeneration.

8. Conclusion

Parkinson's disease is associated to a progressive loss of nigrostriatal dopaminergic neurons. The decrease of dopamine levels in the striatum of parkinsonian patients is responsible for the main motor disturbances characteristic of the disease such as akinesia, muscular rigidity and tremor. The strict interactions between the tridecapeptide neurotensin and the dopaminergic systems lead to hypothesize that the peptide could be involved in some aspects of Parkinson's disease. In this context, the present chapter discusses the putative role of neurotensin in the development and symptoms of Parkinson's disease.
Human studies provide evidence that in the basal ganglia of Parkinson's disease patients there is an increase in neurotensin levels. These changes might be an integral part of the pathology rather than a consequence of the dopamine neuron degeneration. In addition, neurotensin receptor binding sites, especially in the nigrostriatal dopamine system, are reduced in brains of Parkinson's disease patients and in the basal ganglia of hemiparkinsonian rats. This is probably a result of the ongoing degeneration of nigral dopamine cells in which the peptide actively participates.
Based on neurochemical and morphological animals studies, the hypothesis is now introduced that the activation of NTS_1 receptors by enhancing glutamate release and by amplifying the NMDA-mediated glutamate signalling contributes to the degeneration of dopaminergic neurons in Parkinson's disease. In addition, the reduction of the D_2 autoreceptor signaling due to the antagonistic NTS_1/D_2 receptor-receptor interaction, by enhancing the firing rate of dopamine neurons and energy demand may further contribute to this degeneration.
The neurochemical studies have also clearly demonstrated that increased striatal neurotensin levels, by leading to an over-activity to the "indirect pathway" in the basal ganglia, could also play a role in motor Parkinson's disease symptoms.
In closing, in view of the presented results, it could be suggested that NTS_1 antagonists, in combination with conventional drug treatments, may provide a possible novel therapeutic approach for the treatment of neurodegenerative pathologies, especially Parkinson's disease. This hypothesis is supported by studies demonstrating the putative neuroprotective

effects of the neurotensin receptor antagonist SR48692 (systemically administered) in an in vivo animal model of Parkinson's disease. However, Mesnage et al. (2004) in an exploratory study reported that SR48692 could not improve parkinsonian motor disability. However, in this paper the authors reported that the lack of efficacy of NTS_1 receptor antagonists could be attributed to the low dose used, as demonstrated by the absence of adverse events observed in any of the patients tested. In fact, it was concluded that further studies with higher doses of neurotensin receptor antagonists are needed.

Taken together, the reported findings prompt to continue these preclinical studies in order to better understand the role of neurotensin in Parkinson's disease development and symptoms.

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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

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