We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Noradrenergic Mechanisms in Parkinson's Disease and L-DOPA-Induced Dyskinesia: Hypothesis and Evidences from Behavioural and Biochemical Studies

Amal Alachkar
University of Aleppo
Syria

1. Introduction

The key pathological characteristic of Parkinson's disease PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta SNc that project to the striatum (Barolin and Horykiewicz 1967). The depletion of dopamine leads to abnormalities of the transmission in striatal projections to the lateral or medial segments of the globus pallidus, or to the substantia nigra reticulata SNr (Brotchie et al, 1993; Albin et al., 1989). It is well known, however, that in PD, besides dopaminergic degeneration, a considerable loss of noradrenergic neurons, as well as, a decrease of noradrenaline levels in several brain regions occurs (Hornykiewicz & Kish 1987).

Interestingly, the neural loss in PD in Locus coeruleus is greater than that of dopamine in the substantia nigra (Zarow et al., 2003).

The influence of noradrenergic neurotransmission on dopamine-mediated behaviour has been the focus of several studies over the last four decades, and has confirmed the importance of the relationship between dopaminergic and noradrenergic pathways in the control of locomotor activity. The progressive neurodegeneration of the main noradrenergic nucleus – the locus coeruleus LC – might influence not only the progression of Parkinson's disease but also the response to dopaminergic replacement. Furthermore, additional evidences support the notion that noradrenaline deficit might be relevant for the pathogenesis of long-term complications of L-DOPA treatment such as the wearing-off phenomenon and dyskinesias (Bezard et al., 2001; Obeso et al., 2000; Marsden and Parkes, 1976).

However, in spite of the bulk of data on the influence of the alterations of noradrenergic transmission on locomotor behaviour, much of these data is conflicting and not conclusive. Therefore, definitive conclusions, as to the specific role of the noradrenergic system in the generation of symptoms of Parkinson's disease and L-DOPA-induced dyskinesia LID, cannot yet be drawn.

Based on a number of behavioural studies, demonstrating the alleviation of dyskinesia by α_2 adrenergic receptor antagonists, in addition to other biochemical studies, this chapter aims to test the hypothesis that the noradrenergic system plays a role in the neural mechanisms underlying Parkinson's disease and L-DOPA-induced dyskinesia.

The model presented here suggests that the degeneration of noradrenergic neurons contributes to the pathophysiology and symptomatology of PD, and that the remaining intact noradrenergic neurons exert a compensatory mechanism in PD. Furthermore, we suggest a role for L-DOPA metabolites in the mechanism of LID; this role might be mediated through the activation of α_2 adrenoceptors.

Our data and other studies presented in this chapter demonstrate a potential role for noradrenergic system in Parkinson's disease and LID.

2. Parkinson's disease and L-DOPA-induced dyskinesia

Parkinson's disease is a progressive hypokinetic neurodegenerative disorder, characterised by bradykinesia, rigidity, tremor, akinesia, and abnormal posture. Non-motor symptoms such as cognitive decline, depression, sleep disturbances and autonomic and sensorimotor dysfunction also occur (Marsden, 1990; Remy et al., 2005; Schapira, 2008). The key pathological characteristic of Parkinson's disease is the degeneration of dopaminergic neurons in the substantia nigra that project to the striatum (Barolin and Horykiewicz 1967).

Dopamine neurons degenerate with advancing age more than other neuronal systems in the brain (Fearnley & Lees, 1991). Neurons in the SNc and VTA are lost at a rate of 1% per year in parkinsonian patients compared to 0.5% per year in non-parkinsonian subjects (Scherman et al, 1989). Parkinsonian symptoms become apparent when striatal dopamine levels fall by about 70% (Altar and Marien, 1989). Post-mortem studies show substantial depletion of dopamine in the putamen. In caudal parts of the putamen, dopamine content is less than 1% of control levels, whereas the dopamine content of the caudate nucleus is relatively well preserved i.e. 40% of control levels (Hornykiewicz, 1973; Kish et al, 1988). The degeneration of cells in the SNc is accompanied by the presence of eosinophilic intraneuronal, cytoplasmic inclusions called Lewy bodies, which are characterised by a central core and peripheral halo (McGeer et al, 1988; Quinn et al, 1989). Lewy bodies show immunoreactivity for tubulin and ubiquitin (Jellinger, 1990).

The loss of dopaminergic neurons in the substantia nigra pars compacta, which results in a reduction in the level of dopamine in the striatum, leads to alterations in the activity of striatal output nuclei. This results in changes in the other nuclei basal ganglia, which can be summarized as following: (a) Degeneration of the nigrostriatal pathway, (b) the underactivity of the GABA/dynorphin striato-medial pallidal/SNr nigral pathway, (c) the overactivity of the GABA/enkephalin striato-lateral-pallidal pathway, (d) the overactivity of the subthalamic nucleus, (e) the overactivity of the GABA medial pallidal/SNr (output regions of the basal ganglia) -thalamic projection (Brotchie et al, 1993). The overactivity of basal ganglia output results in increased inhibition of excitatory glutamatergic projections from the thalamus to the cortex. Cortical motor outputs are, thus, underactive leading to the movement paucity in Parkinson's disease (Albin et al., 1989).

Although the predominant pathology of PD is the loss of dopaminergic cells in the substantia nigra, however, there is also degeneration of other neurotransmission systems, such as cholinergic, noradrenergic, serotonergic and peptidergic brainstem nuclei (Jellinger, 1991).

Some of these alterations in neurotransmitters occur before the appearance of parkinsonian symptoms (Bezard et al, 2001). Noradrenaline (NA) is particularly implicated in certain symptoms of Parkinson's disease. Biochemical analysis revealed that 40-80% of the brain's content of NA is depleted in PD (Agid, et al., 1987; Gerlach et al, 1994).

Current strategies for the treatment of PD still depend largely on the replacement of lost dopamine. Levodopa, a precursor of dopamine, has proved very successful as an antiparkinsonian agent (Cotzias et al 1967). L-DOPA can cross the blood-brain barrier and is converted to dopamine by aromatic amino acid decarboxylase, presumably in the striatum at the synaptic sites of surviving nigrostriatal cells (Melamed et al 1984). However, due to the massive degeneration of nigrostriatal terminals, it is unlikely that the majority of dopamine synthesis occurs in nigrostriatal terminals (Snyder & Zigmond, 1990). Within the striatum, 5-HT terminals, striatal interneurons and glial cells also contain aromatic amino acid decarboxylase, and these sites may play a role in the conversion of L-DOPA to dopamine in the degenerated striatum (Opacka-Juffry, 1995; Mura et al, 1995).

Initially, L-DOPA is successful in reversing parkinsonian symptoms, akinesia, rigidity and tremor. However, as treatment progresses, the effectiveness of L-DOPA treatment decreases and dyskinesia, fluctuations in mobility and freezing episodes, occur (Marsden & Parkes, 1976; Mouradian et al, 1991). With the progress of treatment, the dose of L-DOPA required to induce dyskinesia gradually decreases and the dose of L-DOPA required to alleviate parkinsonian symptoms is increased, thereby, resulting in the development of a narrow therapeutic window (Mouradian et al, 1988).

The mechanism, underlying L-DOPA-induced dyskinesia, is still far from being fully understood. The fact, that dyskinesia results from prolonged replacement of dopamine, suggests that it arises through the overactivity of dopaminergic mechanisms. Similarities in the choreic dyskinesia seen among various brain disorders, i.e. L-DOPA-induced dyskinesia, tardive dyskinesia and hemiballism, has led to the suggestion of a common mechanism for all dyskinesia (Crossman (review) 1990).

According to the most acceptable model, L-DOPA-induced dyskinesia is associated with an imbalance of basal ganglia circuitry in favour of the direct pathway. Data obtained from animal models of PD have implicated a relative underactivity of the indirect pathway, and overactivity of the direct pathway. The net effect of the overactive GABAergic projection in the direct and indirect pathways and the underactive glutamatergic projection of the STN, will lead to the cumulative inhibitory effects on the output nuclei of the basal ganglia. This, in turn, leads to the decrease of the inhibition of thalamocortical neurons and overactivation of cortical motor areas.

- PD.: Decreased activity in the dopaminergic nigrostriatal pathway, Overactivity of the GABA striato-lateral-pallidal pathway, Overactivity of the subthalamic nucleus, Overactivity of the regions of the basal ganglia that project to non-basal ganglia motor regions, i.e., the medial pallidal segment and the SNr (Blandini et al, 2000).

Fig. 1. Diagram illustrating the changes in the organisation of the basal ganglia in Parkinson's disease and L-DOPA-induced Dyskinesia.

- LID: Increased activity in the dopaminergic nigrostriatal pathway, Underactivity of the GABA striato-lateral-pallidal pathway, Underactivity of the subthalamic nucleus, Underactivity of the regions of the basal ganglia that project to non-basal ganglia motor regions, i.e., the medial pallidal segment and the SNr.

3. Noradrenergic system

The main noradrenergic system is the locus coeruleus LC (A6-cell group), in which about 45% of brain noradrenergic cells are present.

The total estimated number of noradrenergic neurons in the LC of the normal young adult human brain ranges from 45,000 to 60,000 (Baker et al, 1989; , German et al., 1988). The vast majority (90%) of LC efferent projections remain ipsilateral (Ader et al., 1980; Mason & Fibiger, 1979; Room et al., 1981). There are two types of LC axonal terminals: regular synaptic terminals, and varicosities that are believed to cause an extra-synaptic release of noradrenaline, which then may diffuse over a distance (Aoki, 1992; Beaudet & Descarries, 1978; Koda et al., 1978; Parnavelas & Papadopoulos, 1989).

The main projections of the LC are to the neocortex, where LC neurons project to all layers of the neocortex, although the density of fibres varies according to the cortical regions and the species (Morrison et al, 1979; Morrison et al, 1982). The LC also sends efferents to the hippocampus, amygdala, septum, thalamus and hypothalamus. Morphologically different types of neurons in the locus coeruleus project to different regions of the CNS (Loughlin, et al, 1986), and the axons of LC neurons are extensively ramified, as one axon may branch up to 100,000 times (Moore & Bloom, 1979). Noradrenaline may co-exist with other

neurotransmitters and modulators, and the type of modulators co-existing with NA depends, in part, on species. For instance, noradrenergic neurons have been reported to have immunoreactive staining for enkephalin in cats, vasopressin in rats, and neuropeptide Y (NPY) in rats and humans (Caffe et al, 1985).

The firing activity of noradrenergic neurons in the LC is regulated by somatodendritic autoreceptors of the α_2 -adrenergic subtype. These receptors are believed to decrease the firing rate of NA neurons primarily through an increase in potassium conductance.

The firing rate of LC cells is influenced by behavioural activity and sensory input and seems to relate closely to arousal and sleep-waking cycles (Aston-Jones et al, 1991). The LC cells are completely inactive during rapid-eye-movement (REM) sleep (Aston-Jones & Bloom, 1981). The changes in cell firing in sleep-waking cycles suggest a contribution of LC to the mechanisms controlling sleep-waking states (Foote et al, 1980; Mallick, 2002).

Numbers of LC cells and the concentration of brain noradrenaline decline with age in normal brain respectively by 25% and 50% between the fourth and ninth decades of life (Mann, 1983; Mann et al, 1983).

4. Noradrenaline functions

Electrophysiological and behavioural studies have revealed an important role for noradrenaline in attention, arousal and waking (Grant and Redmond 1984; Kumar, 2003). There is an increase in the activity of the LC in rats and primates during high awareness, whereas the activity is decreased during grooming, feeding and sleeping (Grant and Redmond 1984). Furthermore, the α_2 adrenoceptor agonist clonidine increases the total duration of sleep and significantly reduces the duration of REM sleep. In contrast, yohimbine, an α_2 adrenoceptor antagonist, reverses the effects of clonidine (Autret et al, 1977).

Noradrenaline has also been implicated in controlling feeding behaviour (Goldman et al, 1985). Injection of noradrenaline or the α_2 receptor agonist clonidine into the area of the paraventricular nucleus (PVN), caused a potent feeding response in satiated animals, an effect probably mediated via α_2 adrenoceptors located postsynaptically (Weiss & Leibowitz, 1985; Goldman et al, 1985). Further studies have suggested that feeding behaviour is stimulated by low levels of clonidine, and decreased by further production of noradrenaline (Bungo et al, 1999).

The noradrenaline system has also been implicated in anxiety-related behaviours since α_2 agonists are of clinical benefit in treating some types of anxiety (Hoehen-Saric et al, 1981; Crespi, 2009), while α_2 antagonists elicit intense anxiety (Charney et al, 1983; Graeff, 1994). However, it is not clear whether these effects are mediated through pre-or postsynaptic adrenoceptors. A study by Tanak et al., has suggested that the increased release of noradrenaline in the locus coeruleus is, in part, involved in the frustration of anxiety and/or fear in animals exposed to stress (Tanaka et al, 2000). On the other hand, genetic studies on α_{2a} adrenoceptor knock-out mice suggest that α_{2a} may play a protective role in some types of depression and anxiety (Schramm et al, 2001).

Noradrenaline is also involved in cognitive processes such as memory, learning and selective attention (Franowicz, & Arnsten, 1998; Franowicz et al, 2002; Gibbs & Summers, 2002; Marrs et al, 2005; Timofeeva & Levin, 2008). In Alzheimer Type Dementia (ATD), both

the concentration of noradrenaline and the noradrenaline transporters sites are significantly decreased in a number of brain regions including the Locus coeruleus, cingulate gyrus, putamen, hypothalamus, medial thalamic nucleus, and raphe area (Arai et al, 1984; Tejani et al, 1993).

Evidence has accumulated suggesting that noradrenaline is also involved in controlling body temperature (Lin et al, 1981, Sallinen et al, 1997), endocrine secretion (Endroczi et al, 1978; Valet et al, 1989; Ruffolo et al, 1991), and sexual behaviour (Morales et al, 1987; Guiliano & Rampin, 1997).

5. Noradrenaline in the basal ganglia

The synthesis of noradrenaline (Glowinski & Iverson, 1966) and its release (Coyle & Henry, 1973) was initially demonstrated in the striatum. Later studies revealed that the striatum receives little noradrenergic projection from the locus coeruleus and has low levels of dopamine β -hydroxylase (Swanson & Hartman, 1975). Nevertheless, the striatum shows high levels of α_2 adrenoceptor gene expression (mRNA) (Scheinin et al, 1994) and high radioligand binding to α_{2C} adrenoceptors (Uhlen et al, 1997). Noradrenergic terminals and uptake sites have also been demonstrated in the SNc (Fuxe, 1965), subthalamic nucleus (Carpenter et al, 1981b; Parent & Hazrati, 1995; Belujon et al, 2007) and the SNr (Gehlert et al, 1993).

The precise role of noradrenaline in the basal ganglia is not yet clear. However, the noradrenergic inputs to the basal ganglia appear to have a modulatory effect on other neurotransmitters in different structures of the basal ganglia.

Noradrenaline derived from the LC may induce an inhibition of striatal neurons trans-synaptically activated by nigral stimulation (Fujimoto et al, 1981). It has been shown that the α_2 antagonist yohimbine increases the synthesis and release of dopamine in the striatum, while the agonist clonidine can reverse this effect (Anden and Grabowska, 1976). α_2 presynaptic heteroreceptors also seem to regulate the release of amino acid neurotransmitters such as glutamic acid, aspartic acid, GABA as evaluated with synaptosomes (Bristow and Bennett, 1988, Kamisaki, et al, 1992, Bickler and Hansen, 1996, Pralong and Magistretti, 1995). Immunocytochemical studies reveal that 94% of spiny GABAergic neurons in the striatum contain α_{2C} adrenergic receptors (Holmberg et al, 1999), which are negatively coupled to adenylyl cyclase (Zhang et al, 1999). These α_{2C} receptors are thought to play a regulatory role on the direct and indirect pathways of the basal ganglia by modulating GABA transmission. Recent studies on α_2 receptor knock-out mice indicate that α_{2a} and α_{2C} adrenoceptors are located on different neurons in the striatum, and that striatal GABA release is mediated by the activation of α_{2C} but not α_{2a} adrenoceptor (Zhang & Ordway, 2003). These authors suggest that the effect of α_{2C} on GABA release might be mediated by dopamine.

In the basal ganglia, α adrenoceptors are mainly found in the striatum, globus pallidus, substantia nigra pars compacta SNc and substantia nigra pars reticulata SNr (Unnerstall et al, 1984; Boyajian et al, 1987; Uhlen et al, 1997; Winzer-Srhan et al, 1997).

Noradrenergic pathways might have a significant role in regulating basal ganglia function and thus motor activity by modulating the spontaneous activity of the STN neurons. Accordingly, noradrenaline has been reported to induce stimulation of the firing rate of a

neuronal subpopulation of the subthalamic nucleus, and this stimulation was suggested to be mediated through the activation of α_1 adrenoceptors (Arcos et al, 2003).

The modulation of dopamine neurone firing by the noradrenergic system of the locus coeruleus in the rat has provided further evidence for the role of noradrenaline in regulating the activity of the basal ganglia. Interestingly, noradrenaline has been reported to evoke excitation followed by inhibition of the electrical activity of dopaminergic cells (Grenhoff et al, 1993; Grenhoff et al, 1995).

The SNr represents, with medial segment of globus pallidus, the main output regions of the basal ganglia and therefore, plays a crucial role in movement initiation. The GABAergic neurons in the substantia nigra are spontaneously active and the modulation of their activity would significantly influence the basal ganglia functions. Indeed, there is evidence supporting the regulatory action of noradrenaline upon the neurons of the SNr. Noradrenaline has been demonstrated to increase the tonic firing of principal cells in the SNr (Berretta et al, 2000). On the other hand, we demonstrated the stimulatory effects of both the activation and blockade of α_2 adrenergic receptors on the release of GABA from slices of the SNr. (Alachkar et al, 2006).

6. Noradrenaline- dopamine interaction

The interaction between dopamine and noradrenaline systems has been demonstrated, previously, in the brain. Dopamine, for instance, has long been demonstrated to have stimulatory actions upon noradrenergic neurons in the locus coeruleus (Persson and Waldeck, 1970). On the other hand, noradrenaline has been shown to reduce the spontaneous firing of dopaminergic neurons in the SNc (White & Wang, 1984), although, other workers have reported excitatory responses of the SNc to the stimulation of the locus coeruleus (Grenhoff, 1993). Other studies have provided evidences for the mutual inhibition of dopaminergic and noradrenergic systems (Persson & Waldeck, 1970; Guiard et al, 2008). A number of studies indicate, interestingly, that dopamine is co-released with noradrenaline from noradrenergic neurons in the locus coeruleus (Anden et al, 1973; Devoto et al, 2001).

On the other hand, dopamine may activate α_2 adrenoceptors in more than a region in the brain (Segawa et al, 1998; Cornil et al, 2002; Alachkar et al, 2010a). It is well documented that a molecular relationship exists, at the level of the amino acid sequence, between α_2 and dopamine D2 receptors, in that D2 dopamine receptors are more closely related to α_2 adrenoceptors than to D1 dopaminergic receptors (Harrison et al, 1991).

NA was found to act as a D1 dopaminergic agonist (Kubrusly et al., 2007), and mimic the effect of DA on the DA D2 receptor (Onali et al., 1985). Furthermore, it was demonstrated that NA binds to the human DA D4 receptor with high affinity (Lanau et al., 1997; Newman-Tancredi et al., 1997) and 10% of total D2-like receptors are of the DA D4 receptor located in the caudate putamen (Tarazi et al., 1997).

α_2 adrenoceptor mRNA, type A and C, is present in high levels in the striatum and locus coeruleus (Nicholas et al, 1993; Scheinin et al, 1994, our unpublished results), with receptors binding located in the striatum, and SNr (Rosin et al, 1996; Lee et al, 1998a,b).

The presence of noradrenaline uptake sites in the SNr (Gehlert et al, 1995; Strazielle et al, 1999) indicates noradrenaline release in this nucleus.

The NA could affect the activity of the SNr through their direct noradrenergic projections and their indirect influence by the action of SNc and other parts of basal ganglia.

7. Noradrenaline in Parkinson's disease

In Parkinson's disease, a significant loss of noradrenergic cells of the locus coeruleus and the noradrenergic pathways occurs, in addition to the degeneration of the nigrostriatal dopaminergic pathway, (Hornykiewicz & Kish 1987; Zarow et al., 2003). Moreover, there is a considerable decrease in NA levels in a number of brain structures including the hypothalamus, cerebral cortex, substantia nigra and caudate nucleus in patients with this disease (Fahn et al, 1971; Rinne & Sonninen, 1973; Kish et al, 1984). The significance of the loss of LC cells to Parkinson's disease is still largely unknown. It is possible that noradrenergic depletion contributes to the degeneration of other brain nuclei. Postmortem studies have revealed that the symptoms of depression and dementia in PD were associated with a significant loss of noradrenergic neurons in the LC and NA depletion in the cortex (Zweig et al., 1993; Bosboom et al., 2004; Remy et al., 2005; Ridderinkhof et al., 2004; Ramos and Arnsten, 2007). LC-noradrenergic neurotransmitter system may be involved in the pathogenesis of non-motor symptoms in PD. A decrease in α_2 receptor density in the prefrontal cortex has also been shown in animal models of Parkinson's disease (Mavridis et al, 1991). Administration of α_2 -adrenergic agonist was demonstrated to improve the cognitive impairments in PD patients (Remy et al., 2005; Riekkinen and Riekkinen, 1999).

The great extent to which LC cell loss occurs in PD is emphasized by the study by Zarow et al. who, interestingly, demonstrated that the greatest loss of neurons in PD was found in the LC (83.2%). The degree of cell loss in the LC seemed to be even more extensive than that observed in the substantia nigra (77.8% loss) (Zarow et al. 2003). Significant depletions (>80%) of noradrenaline in the substantia nigra pars compacta and reticulata, of postmortem PD brains have also been described (Taquet et al., 1982).

The NA depletion in the LC was proved to decrease DA release in the striatum (Lategan et al., 1990; Lategan et al., 1992). Furthermore, clinical studies have indicated that some motor symptoms of PD are likely to result from noradrenergic lesions (Grimbergen et al., 2009). These findings suggest the implication of the LC-noradrenergic system in the pathophysiology of PD.

Experimental data suggest that the LC noradrenaline system may have a neuroprotective role on dopaminergic SN neurons (Gesi et al, 2000). For instance, noradrenaline depletion significantly increased MPTP- as well as methylamphetamine-induced striatal dopamine depletion in mice and monkeys (Forani et al, 1995; Marien et al 1993; Archer and Fredriksson, 2006; Nishi et al., 1991). Furthermore, lesions of LC by 6-OHDA in MPTP treated monkeys produced a more significant depletion and greater loss of substantia nigra cell compared to normal controls, and impaired the recovery which usually occurs from the parkinsonian manifestations induced by MPTP (Mavridis et al, 1991; Bing et al, 1994). A potentiation of parkinsonian symptoms following locus coeruleus noradrenaline depletion has been reported in 6-OHDA-lesioned rats (Srinivasan & Schmidt, 2003).

The mechanism by which the locus coeruleus may protect dopaminergic neurons is still unknown. The activation of α_2 adrenoceptors by clonidine, α_2 agonist, has been demonstrated to suppress MPTP-induced reduction of striatal dopamine and tyrosine hydroxylase activity in mice (Bristow and Bennett, 1988; Fornai et al, 1995).

Noradrenaline may exert its neuroprotective effects by facilitating the release of trophic factors, such as the nerve growth factor NGF; this was suggested to occur through an action on β -adrenoceptors on the glial cells (Mochetti et al, 1989). Noradrenaline may suppress the formation of toxic MPP⁺ from MPTP by inhibiting the production of glial monoamine

oxidase B in the substantia nigra (Stone and Ariano, 1989). Interestingly, the administration of L-threo-3, 4 dihydroxyphenylserine (L-threo-DOPS) an immediate precursor of noradrenaline, seems to alleviate parkinsonian symptoms (Narabayashi et al, 1984). Although L-threo DOPS causes an increase in dopamine as well as noradrenaline levels, its anti-parkinsonian action was inhibited by adrenoceptor antagonists and dopamine β -hydroxylase inhibitors. The α_2 adrenoceptor antagonist R47 243 has been found to reverse some parkinsonian signs in a monkey in which MPTP's effects had been progressive, by a mechanism that is still unknown (Colpaert et al, 1991). On the other hand, blockade of α_2 adrenoceptors counteracted to some extent the development of parkinsonian symptoms and neurochemical alterations in the rotenone model of Parkinson's disease (Alam et al, 2009). In addition Belujon et al have provided behavioral and electrophysiological evidence for the noradrenergic modulation of subthalamic nucleus activity in intact and 6-hydroxydopamine-lesioned rats. The authors have shown that the firing of STN neurons is controlled by noradrenergic system through the activation of α_1 - and α_2 adrenergic receptors (Belujon et al, 2007).

Firing activity of LC-noradrenergic neurons was demonstrated to increase in rats after the SNc lesion (Guiard et al, 2008; Wang et al., 2009), which may imply an overactivity of LC-noradrenergic neurons and enhanced influence of LC in rats with SNc lesion.

On the other hand, lesions of the LC in rat models of PD caused further hyperactivity of SNr neurons implying that LC-noradrenergic system may play a role in decreasing the activity of the output regions of the basal ganglia (wang et al, 2010). Intact noradrenergic neurons of the LC were believed to play a crucial role in the compensational mechanism after the dopaminergic depletion in the SNc (Gesi et al., 2000; Rommelfanger and Weinshenker, 2007).

8. Noradrenaline and L-DOPA-induced dyskinesia

Progressive neurodegeneration of the noradrenergic neurons in the locus coeruleus was suggested to influence the response to dopaminergic replacement (Cotzias et al., 1967), and the pathogenesis of long-term complications of L-DOPA treatment (Bezard et al., 2001; Marsden and Parkes, 1976; Obeso et al., 2000).

The involvement of noradrenergic transmission in L-DOPA-induced dyskinesia has been the focus of several investigations. This was based on the well documented interaction between dopaminergic and noradrenergic system. Early studies on reserpine-treated rats revealed that the hyperkinesia induced by L-DOPA was mediated via activation of the noradrenergic system (Anden et al, 1969; Stromber & Svensson, 1971). A number of studies substantiated evidence that the noradrenergic system may have a modulatory effect on L-DOPA-induced dyskinesia. Gomez-Mancilla and Bedard (1993) investigated the effects of several agents acting on the noradrenergic system in the brain on L-DOPA-induced dyskinesia. They reported that the α_2 adrenergic receptor antagonist, yohimbine, decreased L-DOPA-induced dyskinesia without reducing the anti-parkinsonian action of L-DOPA, in MPTP-treated monkeys. Further studies have reported that the reduction of dyskinesia can be mediated by blocking the actions of α_2 adrenergic receptors, shown using a number of α_2 antagonists (Henry et al 1999, Fox et al 2001; Grondin et al, 2000; Rascol, 2001, Savola et al, 2003; Dekundy et al, 2007). The mechanism by which α_2 antagonists can alleviate L-DOPA-induced dyskinesia is unknown; however, activation of α_2 adrenoceptors on the striatal

output neuron terminals has been suggested to reduce GABA release and inhibition of the lateral segment of the globus pallidus (GPi) in the indirect pathway (Henry et al, 1999). Therefore, blockade at these sites may up-regulate the inhibitory striatopallidal connections and reduce STN inhibition and dyskinesia. The other explanation for the effect of α_2 adrenoceptor antagonists in reducing L-DOPA-induced dyskinesia may be the blockade of the action of noradrenaline synthesised from levodopa on α_{2c} receptors in the basal ganglia (Fox et al, 2001). There is evidence that local administration of NA into the lesioned striatum can induce dyskinetic movements in rats in a similar manner to intrastriatal L-DOPA treatment (Buck & Ferger, 2009).

On the other hand, noradrenaline synthesized from exogenous L-DOPA administered in Parkinson's disease therapy may, in part, be involved in the locomotor activity produced by L-DOPA (Dolphin et al, 1976). This implies that at least some symptoms of LID are mediated through the activation of the noradrenergic system. Therefore, the therapeutic actions of α_2 antagonists may be correlated with this noradrenergic disruption in Parkinson's disease and LID.

Fox et al., have reported that α_2 antagonism reduces L-DOPA-induced dyskinesia but did not affect apomorphine-induced dyskinesia suggesting that L-DOPA-induced dyskinesia but not dopamine agonist-induced dyskinesia, involves activation of adrenoceptors (Fox et al, 2001). The authors suggested that the pharmacological characteristics of the neural mechanisms underlying levodopa-induced dyskinesia and dopamine agonist-induced dyskinesia in parkinsonism are distinct, at least with respect to the involvement of α_2 adrenoceptors.

9. Noradrenergic mechanisms in PD and LID: A theory

9.1 Parkinson's disease PD

We present here a model to explain the mechanism by which noradrenergic system may modulate the activity of the basal ganglia in PD. This model attempts to answer the question of whether noradrenergic abnormalities reflect a response to, or the cause of, the PD. Our scenario is based on the discussion above and most importantly the following three observations:

- Certain evidences support the belief that LC lesion may exacerbate the abnormal activity of basal ganglia in PD, resulting in a further overactivity of the SNr neurons. This implies that LC-noradrenergic system may play a role in decreasing the activity of the output regions of the basal ganglia in PD (wang et al, 2010).
- Further evidence indicates that the firing activity of LC-noradrenergic neurons increases after the SNc lesion (Guiard et al, 2008; Wang et al., 2009), which may imply an overactivity of LC-noradrenergic neurons; and enhanced influence of LC in PD.
- Several studies have described the anti-parkinsonian effects of the blockade of α_2 inhibitory receptors. Although the site of action of these receptors is not known for certain, the data of other several studies conform to a model where alpha-2 antagonists produce their effects in the SNr by interacting with GABAergic transmission.

According to our model, changes in Parkinson's disease that occur in noradrenergic transmission contribute to the mechanism of PD, and partially compensate for the degeneration of the dopaminergic system.

Based on the discussion above, we propose that in Parkinson's disease, the degeneration of 83% of LC neurons and depletion of noradrenaline exacerbate the Parkinsonian symptoms

through increasing the overactivity of the substantia nigra pars reticulata. On the other hand, the destruction of the dopamine-containing cells in the SNc results in a decrease in the inhibition, by dopamine, on the firing of the locus coeruleus and therefore, the remaining intact noradrenergic neurons of the LC are deemed to play a crucial role in the compensational mechanism after the dopaminergic depletion in the SNc (Gesi et al., 2000; Rommelfanger and Weinshenker, 2007). Noradrenaline released from overactive remaining LC neurons is thought to act as an inhibitory transmitter on α_2 adrenoceptors located on the GABAergic striatal projecting neurons, and on the neurons of SNr. This would decrease the firing rate and the activity of the inhibitory GABAergic projection of SNr (which is overactive in PD) to the motor regions of the thalamus, and hence alleviate Parkinsonian symptoms. Accordingly, noradrenaline may contribute to the pathological and the compensational mechanisms in Parkinson's disease. The prevalence of one of these two contradictory effects of noradrenergic system depends mainly on the extent of the degeneration of LC cells. The greater degeneration of LC noradrenergic neurons indicates more extensive abnormalities of the basal ganglia and overactivity of SNr, and thus further potentiation of the Parkinsonian symptoms.

9.2 L-DOPA-induced dyskinesia LID

Administration of L-DOPA with an AADC inhibitor, NSD1015, produced hyperlocomotor activity in reserpine-treated rats (Alachkar et al, 2010b). It seems likely that L-DOPA, or one or more of its metabolites not formed via routes involving direct decarboxylation of L-DOPA, are responsible for the generation of hyperkinesia. Significantly, α_2 receptor antagonist, rauwolscine, reduced centre vertical movement induced by L-DOPA and NSD1015 and shifted the time-course response curve to the left, (i.e. it caused earlier onset of L-DOPA and NSD1015 action). Thus, the behavioural effect of L-DOPA and NSD1015 given together is exerted, at least, in part, by the noradrenergic system.

The prediction, arising from studies on the behavioural effects of L-DOPA, is that manipulation of α_2 or/and dopamine receptors by L-DOPA or its metabolites may result in hyperlocomotor activity. This prediction was tested in a study by radioligand binding in membranes prepared from cell lines expressing α_2 and dopaminergic receptors (Alachkar et al, 2010a). We reported that 3-MT bound to α_{2a} receptors with high affinity compared to α_{2c} adrenoceptors and dopaminergic receptors. The finding in the same study that dopamine bound to α_2 adrenoceptors with relatively high affinities, provides evidence confirming previous reports on the direct activation of α_2 adrenoceptors by dopamine (Cornil et al, 2002; Zhang et al, 1999).

A mechanism underlying the hyperkinesia induced by L-DOPA following the inhibition of central decarboxylase was suggested. According to these results, L-DOPA is metabolised in two steps leading to the formation of 3-MT, which will cause hyperkinesia (Nakazato & Akiyama, 2002; Nakazato, 2002), possibly through interaction with D1, or α_{2a} adrenoceptors (Alachkar et al, 2010a). The reduction of vertical hyperlocomotor activity by rauwolscine supports that 3-MT interacts with α_2 adrenoceptors (Alachkar et al, 2010b).

In Parkinson's disease, there is a decrease in the activity (Gjedde et al., 1993; Kuwabara et al., 1995) and expression (Ichinose et al., 1994) of the enzyme aromatic amino acid decarboxylase AADC. Interestingly, treatment with L-DOPA produces a further decrease in AADC (Tanaka et al., 1973; Fisher et al, 2000) and an increase of COMT (Liu et al, 2000; Zhao et al, 2001). In view of these observations, we propose that following long-term treatment with L-DOPA, the major portion of exogenous L-DOPA will not be metabolised to

dopamine, instead a large portion of L-DOPA will be methylated to 3-O, methyl dopa. 3-O-methyl dopa has a longer half-life than L-DOPA itself (15 hours vs ½ hour) (Kuruma et al, 1971; Cedarbaum, 1987) and, consequently, 3-O-methyl dopa formed from exogenous L-DOPA accumulates in the plasma and the brain to be subsequently metabolised slowly (Kuruma et al, 1971). The decarboxylation of 3-O-methyl dopa leads to the formation of 3-MT. The significance of methoxy groups in the production of abnormal induced movements was the focus of very early studies (Ericsson et al, 1971). A number of early studies suggested that the occupation of the meta position by a OCH₃ group in the absence of similar groups at the para position caused hyperkinesias in rats (Hornykiewicz, 1966) and induced abnormal movements (Huntington chorea) in humans (Ericsson & Wertman, 1971). More recent studies have confirmed these early finding, as 3-MT was demonstrated to induce hyperactivity in rats (Nakazato & Akiyama, 2002; Nakazato, 2002). As a result, 3-MT seems to be the candidate metabolite to induce dyskinesia following long term treatment with L-DOPA in Parkinson's disease.

Fig. 2. Effect of NSD1015 on the stimulant action of L-DOPA on locomotor activity.

3-MT was found to bind to α_{2a} adrenoceptors with relatively high affinity (Alachkar et al, 2010a). The pharmacological experiments to determine whether 3-MT acts as an agonist or antagonist at α_{2a} adrenoceptors have not yet been undertaken. However, the similarities in the chemical structures between 3-MT and other catecholamines such as α -methylnoradrenaline and epinephrine, which are known to activate α_2 adrenoceptors, suggest that 3-MT may act as

an agonist at these receptors. According to the present scenario, a high concentration of 3-O-methyldopa, and hence 3-MT will occur in Parkinson's disease and following long-term treatment with L-DOPA. The 3-MT will then bind to α_{2a} receptors located presynaptically on the locus coeruleus terminals in the SNr. This hypothesis is supported by the finding of Mela et al. (2007) who demonstrated an increase in extracellular GABA release after administration of L-DOPA in dyskinetic rats in the substantia nigra pars reticulata (Mela et al., 2007).

Fig. 3. **L-DOPA and dopamine metabolic pathways.** Abbreviations: L-DOPA, L-3,4-dihydroxyphenylalanine; DA dopamine; NA noradrenaline; 3-OMD 3-O-methyldopa; 3-MT 3-methoxytyramine; DOPAC dihydroxyphenylacetic acid; HVA homovanillic acid. (1) Esterase or hydrolase; (2) aromatic amino acid decarboxylase AADC; (3) catechol O-methyl transferase COMT; (4) dopamine β -hydroxylase BDH; (5) COMT; (6) monoamine oxidase MAO; (7) unknown; (8) MAO; (9) COMT (Alachkar et al, 2010a).

The activation of α_2 inhibitory autoreceptors would result in an inhibition of noradrenaline release from these terminals and, therefore, a decrease in the inhibitory tone on GABA release from striato-nigral projection to the SNr. This leads to the increase of the activity of the GABAergic direct pathway, resulting in an increase of the inhibition of the output regions of the basal ganglia, counteracting the underactivity of this structure, which is the key pathological mechanism of LID. Thus, the abnormalities in noradrenergic transmission may contribute to, or facilitate, the development of LID.

Previous experimental studies have demonstrated that α_2 adrenoceptor antagonists such as yohimbine reduce L-DOPA-induced dyskinesia in rodent (Lundblad et al., 2002; Dekundy et al., 2007) as well as primate models (Gomez-Mancilla and Bedard, 1993). Moreover, some α_2 adrenoceptor antagonists like idazoxan and fipamezole have shown antidyskinetic efficacy without compromising the anti-parkinsonian action of L-DOPA in monkey studies (Grondin et al., 2000; Fox et al., 2001; Savola et al., 2003) and clinical trials.

A series of behavioural studies have demonstrated the therapeutic benefits of non-selective α_2 antagonists in reducing LID in animal models of Parkinson's disease (Henry et al, 1999; Gomez-mancilla & Bedard, 1993). The anti-dyskinetic effects of the α_{2a} selective antagonist fipamezole in non-human primate model of PD have been demonstrated (Savola et al, 2003). It was suggested in this study that in LID, the activation of α_2 adrenoceptors that regulate the activity of the direct pathway, by L-DOPA or its metabolites, may facilitate LID (Savola et al, 2003). Although the exact site of α_2 adrenoceptor antagonist was not determined in the study by Savola et al, the authors have reached a similar conclusion by suggesting the involvement of the direct pathway in the mechanism of α_2 adrenoceptor antagonists.

According to the previous discussion, the anti-dyskinetic effect of α_2 adrenoceptors can be simply explained by the blockade, by the antagonist, of the effect of 3-MT at the inhibitory presynaptic α_{2a} in the terminals of locus coeruleus projection to the substantia nigra, resulting in facilitation of noradrenaline release. Noradrenaline, subsequently, exerts an inhibitory action on the GABAergic projection in the direct pathway, counteracting the overactivity of this pathway.

10. Conclusion

In conclusion, the discussions presented in this review demonstrate a potential role for noradrenergic system in Parkinson's disease and LID. Several lines of evidence suggest that the noradrenergic system regulates the activity of the direct pathway of the basal ganglia, through presynaptic α_2 receptors located in the SNr, and the indirect pathway through pre- and postsynaptic α_2 in the striatum, and α_2 and α_2 in the subthalamic nucleus. The model presented here suggests that the degeneration of noradrenergic neurons contributes to the pathophysiology and symptomatology of PD, and that the remaining intact noradrenergic neurons exert a compensatory mechanism in PD. Furthermore, we suggest a role for L-DOPA metabolites in the mechanism of LID; this role might be mediated through the activation of α_2 adrenoceptors. According to this model, the anti-dyskinetic action of α_2 antagonists might be mediated by the blockade of α_{2a} adrenoceptors located in the terminals of locus coeruleus projection to the SNr.

11. References

- Ader, J.P., P. Room, F. Postema, J. Korf, Bilaterally diverging axon collaterals and contralateral projections from rat locus coeruleus neurons, demonstrated by fluorescent retrograde double labeling and norepinephrine metabolism, J. Neural Transm. 49 (1980) 207–208. ISSN: 0300-9564
- Agid, Y., F. Javoy-Agid, M. Ruberg (1987). "Biochemistry of neurotransmitters in Parkinson's disease In: Marsden CD, Fahn S, eds. Movement Disorders. New York: Butterworth & Co. 1987;166-230.

- Alachkar, A., Brotchie, J. M., Jones, O. (2006). "alpha2-Adrenoceptor-mediated modulation of the release of GABA and noradrenaline in the rat substantia nigra pars reticulata." *Neurosci Lett* 395(2): 138-42. ISSN: 0304-3940
- Alachkar, A., Brotchie, J. M., Jones, O. (2010a) "Binding of dopamine and 3-methoxytyramine as L-DOPA metabolites to human alpha(2)-adrenergic and dopaminergic receptors." *Neurosci Res* 67(3): 245-9. ISSN: 1872-8111
- Alachkar, A., Brotchie, J. M., Jones, O. (2010b) "Locomotor response to L-DOPA in reserpine-treated rats following central inhibition of aromatic L-amino acid decarboxylase: further evidence for non-dopaminergic actions of L-DOPA and its metabolites." *Neurosci Res* 68(1): 44-50. ISSN: 1872-8111
- Alam, M., W. Danysz, Schmidt, W. J. Dekundy, A. (2009). "Effects of glutamate and alpha2-noradrenergic receptor antagonists on the development of neurotoxicity produced by chronic rotenone in rats." *Toxicol Appl Pharmacol* 240(2): 198-207. ISSN: 1096-0333
- Albin, R. L., J. W. Aldridge, A. B. Young, S. Gilman (1989). "Feline subthalamic nucleus neurons contain glutamate-like but not GABA-like or glycine-like immunoreactivity." *Brain Res* 491(1): 185-8. ISSN: 0006-8993
- Altar, C. A. and M. R. Marien (1989). "Preservation of dopamine release in the denervated striatum." *Neurosci Lett* 96(3): 329-34. ISSN: 0304-3940
- Anden, N. and M. Grabowska (1976). "Pharmacological evidence for a stimulation of dopamine neurons by noradrenaline neurons in the brain." *Eur J Pharmacol* 39(2): 275-82. ISSN: 0014-2999
- Anden, N. E., A. Carlsson, J. Haggendal, (1969). "Adrenergic mechanisms." *Annu Rev Pharmacol* 9: 119-34. ISSN: 0066-4251
- Anden, N. E., C. V. Atack, T. H. Svensson, (1973). "Release of dopamine from central noradrenaline and dopamine nerves induced by a dopamine-beta-hydroxylase inhibitor." *J Neural Transm* 34(2): 93-100. ISSN: 0300-9564
- Aoki, C., Beta-adrenergic receptors: astrocytic localization in the adult visual cortex and their relation to catecholamine axon terminals as revealed by electron microscopic immunocytochemistry, *J. Neurosci.* 12 (1992) 781-792. ISSN: 0270-6474
- Arai, H., K. Kosaka, R. Izuka (1984). "Changes of biogenic amines and their metabolites in postmortem brains from patients with Alzheimer-type dementia." *J Neurochem* 43(2): 388-93. ISSN: 0022-3042
- Archer, T., Fredriksson, A., 2006. Influence of noradrenaline denervation on MPTP-induced deficits in mice. *J. Neural Transm.* 113, 1119-1129. ISSN: 0300-9564
- Arcos, D., A. Sierra, A. Nunez, G. Flores, J. Aceves, J. A. Arias-Montano (2003). "Noradrenaline increases the firing rate of a subpopulation of rat subthalamic neurons through the activation of alpha1-adrenoceptors." *Neuropharmacology* 45(8): 1070-9. ISSN: 0028-3908
- Aston-Jones, G. and F. E. Bloom (1981). "Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle." *J Neurosci* 1(8): 876-86. ISSN: 0270-6474
- Aston-Jones, G., C. Chiang, T. Alexinsky (1991). "Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance." *Prog Brain Res* 88: 501-20. ISSN: 0079-6123

- Autret, A., M. Minz, T. Beillevaire, H. P. Cathala, H. Schmitt (1977). "Effect of clonidine on sleep patterns in man." *Eur J Clin Pharmacol* 12(5): 319-22. ISSN: 0031-6970
- Baker, K.G., I. Tork, J.P. Hornung, P. Halasz, The human locus coeruleus complex: an immunohistochemical and three dimensional reconstruction study, *Exp. Brain Res.* 77 (1989) 257– 270. ISSN: 0014-4819
- Barolin, G. S. and O. Hornykiewicz (1967). "[On the diagnostic value of homovanillic acid in the cerebrospinal fluid]." *Wien Klin Wochenschr* 79(44): 815-8. ISSN: 0043-5325
- Beaudet, A., L. Descarries, The monoamine innervation of rat cerebral cortex: synaptic and nonsynaptic axon terminals, *Neuroscience* 3 (1978) 851–860. ISSN: 0306-4522
- Belujon, P., Bezard, E., Taupignon, A., Bioulac, B., Benazzouz, A., 2007. Noradrenergic modulation of subthalamic nucleus activity: behavioral and electrophysiological evidence in intact and 6-hydroxydopamine-lesioned rats. *J. Neurosci.* 27, 9595–9606. ISSN: 1529-2401
- Berretta, N., G. Bernardi, N. B. Mercuri (2000). "Alpha(1)-adrenoceptor-mediated excitation of substantia nigra pars reticulata neurons." *Neuroscience* 98(3): 599-604. ISSN: 0306-4522
- Bezard, E., P. Ravenscroft, C. E. Gross, A. R. Crossman, J. M. Brotchie (2001). "Upregulation of striatal preproenkephalin gene expression occurs before the appearance of parkinsonian signs in 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine monkeys." *Neurobiol Dis* 8(2): 343-50. ISSN: 0969-9961
- Bickler, P. E. and B. M. Hansen (1996). "Alpha 2-adrenergic agonists reduce glutamate release and glutamate receptor-mediated calcium changes in hippocampal slices during hypoxia." *Neuropharmacology* 35(6): 679-87. ISSN: 0028-3908
- Bing, G., Y. Zhang, Y. Watanabe, B. S. McEwen, E. A. Stone (1994). "Locus coeruleus lesions potentiate neurotoxic effects of MPTP in dopaminergic neurons of the substantia nigra." *Brain Res* 668(1-2): 261-5. ISSN: 0006-8993
- Bosboom, J., Stoffers, D., Wolters, E., 2004. Cognitive dysfunction and dementia in Parkinson's disease. *J. Neural Transm.* 111, 1303–1315. ISSN: 0300-9564
- Boyajian, C. L., S. E. Loughlin, F. M. Leslie (1987). "Anatomical evidence for alpha-2 adrenoceptor heterogeneity: differential autoradiographic distributions of [3H]rauwolscine and [3H]idazoxan in rat brain." *J Pharmacol Exp Ther* 241(3): 1079-91. ISSN: 0022-3565
- Bristow, L. J. and G. W. Bennett (1988). "Biphasic effects of intra-accumbens histamine administration on spontaneous motor activity in the rat; a role for central histamine receptors." *Br J Pharmacol* 95(4): 1292-302. ISSN: 0007-1188
- Brotchie, J., A. Crossman, I. Mitchell, S. Duty, C. Carroll, A. Cooper, B. Henry, N. Hughes, Y. Maneuf (1993). "Chemical signalling in the globus pallidus in parkinsonism." *Prog Brain Res* 99: 125-39. ISSN: 0079-6123
- Buck, K. and B. Ferger (2009). "Comparison of intrastriatal administration of noradrenaline and L-DOPA on dyskinetic movements: a bilateral reverse in vivo microdialysis study in 6-hydroxydopamine-lesioned rats." *Neuroscience* 159(1): 16-20. ISSN: 0306-4522
- Bungo, T., M. Shimojo, Y. Masuda, Y. H. Choi, D. M. Denbow, M. Furuse (1999). "Induction of food intake by a noradrenergic system using clonidine and fusaric acid in the neonatal chick." *Brain Res* 826(2): 313-6. ISSN: 0006-8993

- Caffe, A. R., F. W. van Leeuwen, R. M. Buijs, G. J. de Vries, M. Geffard, (1985). "Coexistence of vasopressin, neurophysin and noradrenaline immunoreactivity in medium-sized cells of the locus coeruleus and subcoeruleus in the rat." *Brain Res* 338(1): 160-4. ISSN: 0006-8993
- Carpenter, M. B., S. C. Carleton, J. T. Keller, P. Conte (1981). "Connections of the subthalamic nucleus in the monkey." *Brain Res* 224(1): 1-29. ISSN: 0006-8993
- Cedarbaum, J. M. (1987). "Clinical pharmacokinetics of anti-parkinsonian drugs." *Clin Pharmacokinet* 13(3): 141-78. ISSN: 0312-5963
- Charney, D. S., G. R. Heninger, D. E., Redmond, Jr. (1983). "Yohimbine induced anxiety and increased noradrenergic function in humans: effects of diazepam and clonidine." *Life Sci* 33(1): 19-29. ISSN: 0024-3205
- Colpaert, F. C., A. D. Degryse, H. V. Van Craenendonck (1991). "Effects of an alpha 2 antagonist in a 20-year-old Java monkey with MPTP-induced parkinsonian signs." *Brain Res Bull* 26(4): 627-31. ISSN: 0361-9230
- Cornil, C. A., J. Balthazart, P. Motte, L. Massotte, V. Seutin, (2002). "Dopamine activates noradrenergic receptors in the preoptic area." *J Neurosci* 22(21): 9320-30. ISSN: 1529-2401
- Cotzias, G. C., M. H. Van Woert, L. M. Schiffer (1967). "Aromatic amino acids and modification of parkinsonism." *N Engl J Med* 276(7): 374-9. ISSN: 0028-4793
- Coyle, J. T. and D. Henry (1973). "Catecholamines in fetal and newborn rat brain." *J Neurochem* 21(1): 61-7. ISSN: 0022-3042
- Crespi, F. (2009). "Anxiolytics antagonize yohimbine-induced central noradrenergic activity: a concomitant in vivo voltammetry-electrophysiology model of anxiety." *J Neurosci Methods* 180(1): 97-105. ISSN: 1872-678X
- Crossman, A. R. (1990). "A hypothesis on the pathophysiological mechanisms that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment." *Mov Disord* 5(2): 100-8. ISSN: 0885-3185
- Dekundy A, Lundblad M, Danysz W, Cenci MA (2007) Modulation of L-DOPA-induced abnormal involuntary movements by clinically tested compounds: further validation of the rat dyskinesia model. *Behav Brain Res* 179(1):76-89. ISSN: 0166-4328
- Devoto, P., G. Flore, L. Pira, M. Diana, L. Gessa, (2002). "Co-release of noradrenaline and dopamine in the prefrontal cortex after acute morphine and during morphine withdrawal." *Psychopharmacology (Berl)* 160(2): 220-4. ISSN: 0033-3158
- Dolphin, A., P. Jenner, C. D. Marsden (1976). "Noradrenaline synthesis from L-DOPA in rodents and its relationship to motor activity." *Pharmacol Biochem Behav* 5(4): 431-9. ISSN: 0091-3057
- Endroczi, E., I. Marton, Z. Radnai, J. Biro (1978). "Effect of the depletion on brain noradrenaline on the plasma FSH and growth hormone levels in ovariectomized rats." *Acta Endocrinol (Copenh)* 87(1): 55-60. ISSN: 0001-5598
- Ericsson, A. D. and B. G. Wertman (1971). "Sensitivity studies of L-dopa metabolites in reserpinized rats and their clinical significance." *Neurology* 21(11): 1129-33. ISSN: 0028-3878

- Ericsson, A. D., B. G. Wertman, K. M. Duffy (1971). "Reversal of the reserpine syndrome with L-dopa metabolites in reserpinized rats." *Neurology* 21(10): 1023-9. ISSN: 0028-3878
- Fahn, S., L. R. Libsch, R. W. Cutler (1971). "Monoamines in the human neostriatum: topographic distribution in normals and in Parkinson's disease and their role in akinesia, rigidity, chorea, and tremor." *J Neurol Sci* 14(4): 427-55. ISSN: 0022-510X
- Fearnley JM, Lees AJ. 1991. Ageing and Parkinson's disease: Substantia nigra regional selectivity. *Brain* 114:2283–2301.
- Fisher, A., C. S. Biggs, O. Eradiri, M. S. Starr (2000). "Dual effects of L-3,4-dihydroxyphenylalanine on aromatic L-amino acid decarboxylase, dopamine release and motor stimulation in the reserpine-treated rat: evidence that behaviour is dopamine independent." *Neuroscience* 95(1): 97-111. ISSN: 0306-4522
- Foote, S. L., G. Aston-Jones, F. E. Bloom (1980). "Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal." *Proc Natl Acad Sci U S A* 77(5): 3033-7. ISSN: 0027-8424
- Fornai, F., L. Bassi, et al. (1995). "Norepinephrine loss exacerbates methamphetamine-induced striatal dopamine depletion in mice." *Eur J Pharmacol* 283(1-3): 99-102. ISSN: 0014-2999
- Fox, S. H., B. Henry, M. P. Hill, D. Peggs, A. R. Crossman, J. M. Brotchie, (2001). "Neural mechanisms underlying peak-dose dyskinesia induced by levodopa and apomorphine are distinct: evidence from the effects of the alpha(2) adrenoceptor antagonist idazoxan." *Mov Disord* 16(4): 642-50. ISSN: 0885-3185
- Franowicz, J. S. and A. F. Arnsten (1998). "The alpha-2a noradrenergic agonist, guanfacine, improves delayed response performance in young adult rhesus monkeys." *Psychopharmacology (Berl)* 136(1): 8-14. ISSN: 0033-3158
- Franowicz, J. S., L. E. Kessler, C. M. Borja, B. K. Kobilka, L. E. Limbird, Arnsten, A. F. (2002). "Mutation of the alpha2A-adrenoceptor impairs working memory performance and annuls cognitive enhancement by guanfacine." *J Neurosci* 22(19): 8771-7. ISSN: 1529-2401
- Fujimoto, S., M. Sasa, S. Takaori (1981). "Inhibition from locus coeruleus of caudate neurons activated by nigral stimulation." *Brain Res Bull* 6(3): 267-74. ISSN: 0361-9230
- Fuxe, K. (1965). "Evidence for the Existence of Monoamine Neurons in the Central Nervous System. Iv. Distribution of Monoamine Nerve Terminals in the Central Nervous System." *Acta Physiol Scand* 64: SUPPL 247:37+. ISSN: 0302-2994
- Gehlert, D. R., S. L. Gackenhimer, D. W. Robertson (1993). "Localization of rat brain binding sites for [3H]tomoxetine, an enantiomerically pure ligand for norepinephrine reuptake sites." *Neurosci Lett* 157(2): 203-6. ISSN: 0304-3940
- Gerlach, M., D. Ben-Shachar, P. Riederer, M. B. Youdim (1994). "Altered brain metabolism of iron as a cause of neurodegenerative diseases?" *J Neurochem* 63(3): 793-807. ISSN: 0022-3042
- German, D.C., B.S. Walker, K. Manaye, W.K. Smith, D.J. Woodward, A.J. North, The human locus coeruleus: computer reconstruction of cellular distribution, *J. Neurosci.* 8 (1988) 1776– 1788. ISSN: 0270-6474
- Gesi M, Soldani P, Giorgi FS, Santinami A, Bonaccorsi I, Fornai F. The role of the locus coeruleus in the development of Parkinson's disease. *Neurosci Biobehav Rev* 2000;24:655–68. ISSN: 0149-7634

- Gibbs, M. E. and R. J. Summers (2002). "Role of adrenoceptor subtypes in memory consolidation." *Prog Neurobiol* 67(5): 345-91. ISSN: 0301-0082
- Gjedde, A., G. C. Leger, P. Cumming, Y. Yasuhara, A. C. Evans, M. Guttman, H. Kuwabara (1993). "Striatal L-dopa decarboxylase activity in Parkinson's disease in vivo: implications for the regulation of dopamine synthesis." *J Neurochem* 61(4): 1538-41. ISSN: 0022-3042
- Glowinski, J. and L. Iversen (1966). "Regional studies of catecholamines in the rat brain. 3. Subcellular distribution of endogenous and exogenous catecholamines in various brain regions." *Biochem Pharmacol* 15(7): 977-87. ISSN: 0006-2952
- Goldman, C. K., L. Marino, S. F. Leibowitz (1985). "Postsynaptic alpha 2-noradrenergic receptors mediate feeding induced by paraventricular nucleus injection of norepinephrine and clonidine." *Eur J Pharmacol* 115(1): 11-9. ISSN: 0014-2999
- Gomez-Mancilla, B. and P. J. Bedard (1993). "Effect of nondopaminergic drugs on L-dopa-induced dyskinesias in MPTP-treated monkeys." *Clin Neuropharmacol* 16(5): 418-27. ISSN: 0362-5664
- Graeff, F. G. (1994). "Neuroanatomy and neurotransmitter regulation of defensive behaviors and related emotions in mammals." *Braz J Med Biol Res* 27(4): 811-29. ISSN: 0100-879X
- Grant, S. J. and D. E. Redmond, Jr. (1984). "Neuronal activity of the locus ceruleus in awake *Macaca arctoides*." *Exp Neurol* 84(3): 701-8. ISSN: 0014-4886
- Grenhoff, J., M. Nisell, S. Ferre, G. Aston-Jones, T. H. Svensson (1993). "Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat." *J Neural Transm Gen Sect* 93(1): 11-25. ISSN: 0300-9564
- Grenhoff, J., R. A. North, S. W. Johnson (1995). "Alpha 1-adrenergic effects on dopamine neurons recorded intracellularly in the rat midbrain slice." *Eur J Neurosci* 7(8): 1707-13. ISSN: 0953-816X
- Grimbergen, Y., Langston, J., Roos, R., Bloem, B., 2009. Postural instability in Parkinson's disease: the adrenergic hypothesis and the locus coeruleus. *Expert. Rev. Neurother.* 9, 279–290. ISSN: 1744-8360
- Grondin, R., A. Hadj Tahar, V. D. Doan, P. Ladure, P. J. Bedard (2000). "Noradrenoceptor antagonism with idazoxan improves L-dopa-induced dyskinesias in MPTP monkeys." *Naunyn Schmiedebergs Arch Pharmacol* 361(2): 181-6. ISSN: 0028-1298
- Guiard, B. P., M. El Mansari, P. Blier (2008) "Cross-talk between dopaminergic and noradrenergic systems in the rat ventral tegmental area, locus coeruleus, and dorsal hippocampus." *Mol Pharmacol* 74(5): 1463-75. ISSN: 1521-0111
- Guiard, B. P., M. El Mansari, Z. Merali, P. Blier (2008) "Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions." *Int J Neuropsychopharmacol* 11(5): 625-39. ISSN: 1461-1457
- Guiliano, F., O. Rampin, G. Benoit, A. Jardin (1997). "[The peripheral pharmacology of erection]." *Prog Urol* 7(1): 24-33. ISSN: 1166-7087
- Harrison, J. K., D. D. D'Angelo, D. D. D'Angelo, D. W. Zeng, K. R. Lynch, (1991). "Pharmacological characterization of rat alpha 2-adrenergic receptors." *Mol Pharmacol* 40(3): 407-12. ISSN: 0026-895X
- Henry, B., S. H. Fox, D. Peggs, A. R. Crossman, J. M. Brotchie, (1999b). "The alpha2-adrenergic receptor antagonist idazoxan reduces dyskinesia and enhances anti-

- parkinsonian actions of L-dopa in the MPTP-lesioned primate model of Parkinson's disease." *Mov Disord* 14(5): 744-53. ISSN: 0885-3185
- Hoehn-Saric, R., A. F. Merchant, M. L. Keyser, V. K. Smith (1981). "Effects of clonidine on anxiety disorders." *Arch Gen Psychiatry* 38(11): 1278-82. ISSN: 0003-990X
- Holmberg, M., M. Scheinin, H. Kurose, R. Miettinen (1999). "Adrenergic α_2 -receptors reside in rat striatal GABAergic projection neurons: comparison of radioligand binding and immunohistochemistry." *Neuroscience* 93(4): 1323-33. ISSN: 0306-4522
- Hornykiewicz, O. (1966). "Dopamine (3-hydroxytyramine) and brain function." *Pharmacol Rev* 18(2): 925-64. ISSN: 0031-6997
- Hornykiewicz, O. (1973). "Parkinson's disease: from brain homogenate to treatment." *Fed Proc* 32(2): 183-90. ISSN: 0014-9446
- Hornykiewicz, O. and S. J. Kish (1987). "Biochemical pathophysiology of Parkinson's disease." *Adv Neurol* 45: 19-34. ISSN: 0091-3952
- Ichinose, H., T. Ohye, K. Fujita, F. Pantucek, K. Lange, P. Riederer, T. Nagatsu, (1994). "Quantification of mRNA of tyrosine hydroxylase and aromatic L-amino acid decarboxylase in the substantia nigra in Parkinson's disease and schizophrenia." *J Neural Transm Park Dis Dement Sect* 8(1-2): 149-58. ISSN: 0936-3076
- Jellinger, K. (1990). "New developments in the pathology of Parkinson's disease." *Adv Neurol* 53: 1-16. ISSN: 0091-3952
- Jellinger, K. A. (1991). "Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway." *Mol Chem Neuropathol* 14(3): 153-97. ISSN: 1044-7393
- Kamisaki, Y., T. Hamada, K. Maeda, M. Ishimura, T. Itoh, (1993). "Presynaptic α_2 adrenoceptors inhibit glutamate release from rat spinal cord synaptosomes." *J Neurochem* 60(2): 522-6. ISSN: 0022-3042
- Kish, S. J., K. S. Shannak, A. H. Rajput, J. J. Gilbert, O. Hornykiewicz (1984). "Cerebellar norepinephrine in patients with Parkinson's disease and control subjects." *Arch Neurol* 41(6): 612-4. ISSN: 0003-9942
- Kish, S. J., K. Shannak, O. Hornykiewicz (1988). "Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications." *N Engl J Med* 318(14): 876-80. ISSN: 0028-4793
- Koda, L.Y., J.A. Schulman, F.E. Bloom, Ultrastructural identification of noradrenergic terminals in rat hippocampus: unilateral destruction of the locus coeruleus with 6-hydroxydopamine, *Brain Res.* 145 (1978) 190-195. ISSN: 0006-8993
- Kubrusly RC, Ventura AL, de Melo Reis RA, Serra GC, Yamasaki EN, Gardino PF, de Mello MC, de Mello FG (2007) Norepinephrine acts as D1-dopaminergic agonist in the embryonic avian retina: late expression of beta1-adrenergic receptor shifts norepinephrine specificity in the adult tissue. *Neurochem Int* 50(1):211-218. ISSN: 0197-0186
- Kumar, V. M. (2003). "Role of noradrenergic fibers of the preoptic area in regulating sleep." *J Chem Neuroanat* 26(2): 87-93. ISSN: 0891-0618
- Kuruma, I., G. Bartholini, R. Tissot, A. Pletscher (1971). "The metabolism of L-3-O-methyldopa, a precursor of dopa in man." *Clin Pharmacol Ther* 12(4): 678-82. ISSN: 0009-9236
- Kuwabara, H., P. Cumming, Y. Yasuhara, G. C. Leger, M. Guttman, M. Diksic, A. C. Evans, A. Gjedde, (1995). "Regional striatal DOPA transport and decarboxylase activity in Parkinson's disease." *J Nucl Med* 36(7): 1226-31. ISSN: 0161-5505

- Lanau F, Zenner MT, Civelli O, Hartman DS (1997) Epinephrine and norepinephrine act as potent agonists at the recombinant human dopamine D4 receptor. *J Neurochem* 68(2):804–812. ISSN: 0022-3042
- Lategan, A., Marien, M., Colpaert, F., 1990. Effects of locus coeruleus lesions on the release of endogenous dopamine in the rat nucleus accumbens and caudate nucleus as determined by intracerebral microdialysis. *Brain Res.* 523, 134–138. ISSN: 0006-8993
- Lategan, A., Marien, M., Colpaert, F., 1992. Suppression of nigrostriatal and mesolimbic dopamine release in vivo following noradrenaline depletion by DSP-4: a microdialysis study. *Life Sci.* 50, 995–999. ISSN: 0024-3205
- Lee, A., A. E. Wissekerke, D. L. Rosin, K. R. Lynch (1998a). "Localization of alpha2C-adrenergic receptor immunoreactivity in catecholaminergic neurons in the rat central nervous system." *Neuroscience* 84(4): 1085-96. ISSN: 0306-4522
- Lee, A., D. L. Rosin, E. J. Van Bockstaele (1998b). "alpha2A-adrenergic receptors in the rat nucleus locus coeruleus: subcellular localization in catecholaminergic dendrites, astrocytes, and presynaptic axon terminals." *Brain Res* 795(1-2): 157-69. ISSN: 0006-8993
- Lin, M. T., J. J. Jou, W. C. Ko (1981). "Effects of intracerebroventricular injection of clonidine on metabolic, respiratory, vasomotor and temperature responses in the rabbit." *Naunyn Schmiedebergs Arch Pharmacol* 315(3): 195-201. ISSN: 0028-1298
- Liu, X. X., K. Wilson, C. G. Charlton (2000). "Effects of L-dopa treatment on methylation in mouse brain: implications for the side effects of L-dopa." *Life Sci* 66(23): 2277-88. ISSN: 0024-3205
- Loughlin, S. E., S. L. Foote, F. E. Bloom (1986). "Efferent projections of nucleus locus coeruleus: topographic organization of cells of origin demonstrated by three-dimensional reconstruction." *Neuroscience* 18(2): 291-306. ISSN: 0306-4522
- Lundblad M, Andersson M, Winkler C, Kirik D, Wierup N, Cenci MA. Pharmacological validation of behavioural measures of akinesia and dyskinesia in a rat model of Parkinson's disease. *Eur J Neurosci* 2002;15:120–32. ISSN: 0953-816X
- Mallick, B. N., S. Majumdar, M. Faisal, V. Yadav, V. Madan, D. Pal (2002). "Role of norepinephrine in the regulation of rapid eye movement sleep." *J Biosci* 27(5): 539-51. ISSN: 0250-5991
- Mann, D., The locus coeruleus and its possible role in ageing and degenerative disease of the human central nervous system, *Mech. Ageing Dev.* 23 (1983) 73– 94. ISSN: 0047-6374
- Mann, D.M., P.O. Yates, J. Hawkes, The pathology of the human locus ceruleus, *Clin. Neuropathol.* 2 (1983) 1 –7. ISSN: 0722-5091
- Marien, M., M. Briley, F. Colpaert (1993). "Noradrenaline depletion exacerbates MPTP-induced striatal dopamine loss in mice." *Eur J Pharmacol* 236(3): 487-9. ISSN: 0014-2999
- Marrs, W., Kuperman, J., Avedian, T., Roth, R. H., Jentsch, J. D. (2005). "Alpha-2 adrenoceptor activation inhibits phencyclidine-induced deficits of spatial working memory in rats." *Neuropsychopharmacology* 30(8): 1500-10. ISSN: 0893-133X
- Marsden, C. D. (1990). "Parkinson's disease." *Lancet* 335(8695): 948-52. ISSN: 0140-6736
- Marsden, C. D. and J. D. Parkes (1976). ""On-off" effects in patients with Parkinson's disease on chronic levodopa therapy." *Lancet* 1(7954): 292-6. ISSN: 0140-6736

- Mason, S.T., H.C. Fibiger, Regional topography within noradrenergic locus coeruleus as revealed by retrograde transport of horseradish peroxidase, *J. Comp. Neurol.* 187 (1979) 703–724. ISSN: 0021-9967
- Mavridis, M., F.C. Colpaert, M.J. Millan, Differential modulation of (+)-amphetamine-induced rotation in unilateral substantia nigra-lesioned rats by alpha 1 as compared to alpha 2 agonists and antagonists, *Brain Res.* 562 (1991) 216–224. ISSN: 0006-8993
- McGeer, P. L., S. Itagaki, B. E. Boyes, E. G. McGeer (1988). "Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains." *Neurology* 38(8): 1285-91. ISSN: 0028-3878
- Melamed, E., F. Hefti, V. Bitton, M. Globus (1984). "Suppression of L-dopa-induced circling in rats with nigral lesions by blockade of central dopa-decarboxylase: implications for mechanism of action of L-dopa in parkinsonism." *Neurology* 34(12): 1566-70. ISSN: 0028-3878
- Mocchetti, I., M. A. De Bernardi, A. M. Szekely, H. Alho, G. Brooker, E. Costa, (1989). "Regulation of nerve growth factor biosynthesis by beta-adrenergic receptor activation in astrocytoma cells: a potential role of c-Fos protein." *Proc Natl Acad Sci U S A* 86(10): 3891-5. ISSN: 0027-8424
- Moore, R. Y. and F. E. Bloom (1979). "Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems." *Annu Rev Neurosci* 2: 113-68. ISSN: 0147-006X
- Morales, A., M. Condra, J. A. Owen, D. H. Surridge, J. Fenemore, C. Harris, (1987). "Is yohimbine effective in the treatment of organic impotence? Results of a controlled trial." *J Urol* 137(6): 1168-72. ISSN: 0022-5347
- Morrison, J. H., M. E. Molliver, R. Grzanna, J. T. Coyle (1979). "Noradrenergic innervation patterns in three regions of medial cortex: an immunofluorescence characterization." *Brain Res Bull* 4(6): 849-57. ISSN: 0361-9230
- Morrison, J. H., S. L. Foote, D. O'Connor, F. E. Bloom (1982). "Laminar, tangential and regional organization of the noradrenergic innervation of monkey cortex: dopamine-beta-hydroxylase immunohistochemistry." *Brain Res Bull* 9(1-6): 309-19. ISSN: 0361-9230
- Mouradian, M. M., I. J. Heuser, F. Baronti, M. Giuffra, K. Conant, L. Davis, T. Chase, T. N. (1991). "Comparison of the clinical pharmacology of (-)NPA and levodopa in Parkinson's disease." *J Neurol Neurosurg Psychiatry* 54(5): 401-5. ISSN: 0022-3050
- Mouradian, M. M., J. L. Juncos, G. Fabbrini, J. Schlegel, J. J. Bartko, T. N. Chase, (1988). "Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, Part II." *Ann Neurol* 24(3): 372-8. ISSN: 0364-5134
- Mura, A., D. Jackson, M. S. Manley, S. J. Young, P. M. Groves (1995). "Aromatic L-amino acid decarboxylase immunoreactive cells in the rat striatum: a possible site for the conversion of exogenous L-DOPA to dopamine." *Brain Res* 704(1): 51-60. ISSN: 0006-8993
- Nakazato, T. (2002). "The medial prefrontal cortex mediates 3-methoxytyramine-induced behavioural changes in rat." *Eur J Pharmacol* 442(1-2): 73-9. ISSN: 0014-2999
- Nakazato, T. and A. Akiyama (2002). "Behavioral activity and stereotypy in rats induced by L-DOPA metabolites: a possible role in the adverse effects of chronic L-DOPA treatment of Parkinson's disease." *Brain Res* 930(1-2): 134-42. ISSN: 0006-8993

- Narabayashi, H., T. Kondo, T. Nagatsu, A. Hayashi, T. Suzuki, (1984). "DL-threo-3,4-dihydroxyphenylserine for freezing symptom in parkinsonism." *Adv Neurol* 40: 497-502. ISSN: 0091-3952
- Newman-Tancredi A, Audinot-Bouchez V, Gobert A, Millan MJ (1997) Noradrenaline and adrenaline are high affinity agonists at dopamine D4 receptors. *Eur J Pharmacol* 319(2-3):379-383. ISSN: 0014-2999
- Nicholas, A. P., V. Pieribone, T. Hokfelt (1993). "Distributions of mRNAs for alpha-2 adrenergic receptor subtypes in rat brain: an in situ hybridization study." *J Comp Neurol* 328(4): 575-94. ISSN: 0021-9967
- Nishi, K., Kondo, T., Narabayashi, H., 1991. Destruction of norepinephrine terminals in 1-methyl-4-phenyl-1236-tetrahydropyridine (MPTP)-treated mice reduces locomotor activity induced by L-DOPA. *Neurosci. Lett.* 123, 244-247. ISSN: 0304-3940
- Obeso JA, Olanow CW, Nutt JG. Levodopa motor complications in Parkinson's disease. *Trends Neurosci* 2000; 23:S2-7. ISSN: 0166-2236
- Onali P, Olanas MC, Gessa GL (1985) Characterization of dopamine receptors mediating inhibition of adenylate cyclase activity in rat striatum. *Mol Pharmacol* 28(2):138-145. ISSN: 0026-895X
- Opacka-Juffry, J. and D. J. Brooks (1995). "L-dihydroxyphenylalanine and its decarboxylase: new ideas on their neuroregulatory roles." *Mov Disord* 10(3): 241-9. ISSN: 0885-3185
- Parent, A. and L. N. Hazrati (1995). "Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry." *Brain Res Brain Res Rev* 20(1): 128-54. PMID: 7711765
- Parnavelas, J.G., G.C. Papadopoulos, The monoaminergic innervations of the cerebral cortex is not diffuse and nonspecific, *Trends Neurosci.* 12 (1989) 315- 319. ISSN: 0166-2236
- Persson, T. and B. Waldeck (1970). "Further studies on the possible interaction between dopamine and noradrenaline containing neurons in the brain." *Eur J Pharmacol* 11(3): 315-20. ISSN: 0014-2999
- Pralong, E. and P. J. Magistretti (1995). "Noradrenaline increases K-conductance and reduces glutamatergic transmission in the mouse entorhinal cortex by activation of alpha 2-adrenoreceptors." *Eur J Neurosci* 7(12): 2370-8. ISSN: 0953-816X
- Quinn, N. P., P. Luthert, M. Honavar, C. D. Marsden (1989). "Pure akinesia due to lewy body Parkinson's disease: a case with pathology." *Mov Disord* 4(1): 85-9. ISSN: 0885-3185
- Ramos, B., Arnsten, A., 2007. Adrenergic pharmacology and cognition: focus on the prefrontal cortex. *Pharmacol. Ther.* 113, 523-536. ISSN: 0163-7258
- Rascol, O., I. Arnulf, H. Peyro-Saint Paul, C. Brefel-Courbon, M. Vidailhet, C. Thalamas, A. M. Bonnet, S. Descombes, B. Bejjani, N. Fabre, J. L. Montastruc, Y. Agid (2001). "Idazoxan, an alpha-2 antagonist, and L-DOPA-induced dyskinesias in patients with Parkinson's disease." *Mov Disord* 16(4): 708-13. ISSN: 0885-3185
- Remy, P., Doder, M., Lees, A., Turjanski, N., Brooks, D., 2005. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 128, 1314-1322. ISSN: 1460-2156
- Ridderinkhof, K., Ullsperger, M., Crone, E., Nieuwenhuis, S., 2004. The role of the medial frontal cortex in cognitive control. *Science* 306, 443-447. ISSN: 1095-9203

- Riekkinen, M., Riekkinen, P.J., 1999. Alpha2-adrenergic agonist clonidine for improving spatial working memory in Parkinson's disease. *J. Clin. Psychopharmacol.* 19, 444–449. ISSN: 0271-0749
- Rinne, U. K. and V. Sonninen (1973). "Brain catecholamines and their metabolites in Parkinsonian patients. Treatment with levodopa alone or combined with a decarboxylase inhibitor." *Arch Neurol* 28(2): 107-10. ISSN: 0003-9942
- Rollema, H., (1992). "Indole-N-methylation of beta-carbolines: the brain's bioactivation route to toxins in Parkinson's disease?" *Ann N Y Acad Sci* 648: 263-5. ISSN: 0077-8923
- Rommelfanger KS, Weinshenker D (2007) Norepinephrine: The redheaded stepchild of Parkinson's disease. *Biochem Pharmacol* 74(2):177–190. ISSN: 0006-2952
- Room, P., F. Postema, J. Korf, Divergent axon collaterals of rat locus coeruleus neurons: demonstration by a fluorescent double labeling technique, *Brain Res.* 221 (1981) 219– 230. ISSN: 0006-8993
- Rosin, D. L., E. M. Talley, A. Lee, R. L. Stornetta, B. D. Gaylinn, P. G. Guyenet, K. R. Lynch (1996). "Distribution of alpha 2C-adrenergic receptor-like immunoreactivity in the rat central nervous system." *J Comp Neurol* 372(1): 135-65. ISSN: 0021-9967
- Ruffolo, R. R., Jr., A. J. Nichols, Hieble (1991). "Metabolic regulation by alpha 1- and alpha 2-adrenoceptors." *Life Sci* 49(3): 171-83. ISSN: 0024-3205
- Sallinen, J., R. E. Link, A. Haapalinna, T. Viitamaa, M. Kulatunga, B. Sjöholm, E. Macdonald, M. Peltö-Huikko, T. Leino, G. S. Barsh, B. K. Kobilka, M. Scheinin (1997). "Genetic alteration of alpha 2C-adrenoceptor expression in mice: influence on locomotor, hypothermic, and neurochemical effects of dexmedetomidine, a subtype-nonspecific alpha 2-adrenoceptor agonist." *Mol Pharmacol* 51(1): 36-46. ISSN: 0026-895X
- Savola, J. M., M. Hill, M. Engstrom, H. Merivuori, S. Wurster, S. G. McGuire, S. H. Fox, A. R. Crossman, J. M. Brotchie (2003). "Fipamezole (JP-1730) is a potent alpha2 adrenergic receptor antagonist that reduces levodopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson's disease." *Mov Disord* 18(8): 872-83. ISSN: 0885-3185
- Schapiro, A., 2008. Progress in Parkinson's disease. *Eur. J. Neurol.* 15, 1. ISSN: 1468-1331
- Scheinin, M., J. W. Lomasney, D. M. Hayden-Hixson, U. B. Schambra, M. G. Caron, R. J. Lefkowitz, R. T. Fremeau, Jr. (1994). "Distribution of alpha 2-adrenergic receptor subtype gene expression in rat brain." *Brain Res Mol Brain Res* 21(1-2): 133-49. ISSN: 0169-328X
- Scherman, D., C. Desnos, F. Darchen, P. Pollak, F. Javoy-Agid, Y. Agid (1989). "Striatal dopamine deficiency in Parkinson's disease: role of aging." *Ann Neurol* 26(4): 551-7. ISSN: 0364-5134
- Schramm, N. L., M. P. McDonald, L. E. Limbird (2001). "The alpha(2a)-adrenergic receptor plays a protective role in mouse behavioral models of depression and anxiety." *J Neurosci* 21(13): 4875-82. ISSN: 1529-2401
- Segawa, T., H. Ito, Inoue, K. Wada, H. Minatoguchi, S. Fujiwara, H. (1998). "Dopamine releases endothelium-derived relaxing factor via alpha 2-adrenoceptors in canine vessels: comparisons between femoral arteries and veins." *Clin Exp Pharmacol Physiol* 25(9): 669-75. ISSN: 0305-1870
- Snyder, G. L. and M. J. Zigmond (1990). "The effects of L-dopa on in vitro dopamine release from striatum." *Brain Res* 508(2): 181-7. ISSN: 0006-8993

- Srinivasan, J. and W. J. Schmidt (2003). "Potentiation of parkinsonian symptoms by depletion of locus coeruleus noradrenaline in 6-hydroxydopamine-induced partial degeneration of substantia nigra in rats." *Eur J Neurosci* 17(12): 2586-92. ISSN: 0953-816X
- Stone, E. A. and M. A. Ariano (1989). "Are glial cells targets of the central noradrenergic system? A review of the evidence." *Brain Res Brain Res Rev* 14(4): 297-309. PMID: 2560410
- Strazielle, C., R. Lalonde, C. Hebert, T. A. Reader (1999). "Regional brain distribution of noradrenaline uptake sites, and of alpha1-alpha2- and beta-adrenergic receptors in PCD mutant mice: a quantitative autoradiographic study." *Neuroscience* 94(1): 287-304. ISSN: 0306-4522
- Stromberg, U. and T. H. Svensson (1971). "L-DOPA induced effects on motor activity in mice after inhibition of dopamine-beta-hydroxylase." *Psychopharmacologia* 19(1): 53-60. ISSN: 0033-3158
- Swanson, L. W. and B. K. Hartman (1975). "The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-beta-hydroxylase as a marker." *J Comp Neurol* 163(4): 467-505. ISSN: 0021-9967
- Tanaka, M., M. Yoshida, H. Emoto, H. Ishii (2000). "Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies." *Eur J Pharmacol* 405(1-3): 397-406. ISSN: 0014-2999
- Tanaka, M., T. Oshima, S. Hayashi, C. Ishibashi, S. Kobayashi (1973). "Enhancement of the pharmacological action of 3,4-dihydroxy-L-phenylalanine(L-dopa) and reduction of dopa decarboxylase activity in rat liver after chronic treatment with L-dopa." *Eur J Pharmacol* 22(3): 360-2. ISSN: 0014-2999
- Taquet, H., F. Javoy-Agid, F. Cesselin, M. Hamon, J.C. Legrand, Y. Agid, Microtopography of methionine-enkephalin, dopamine and noradrenaline in the ventral mesencephalon of human control and Parkinsonian brains, *Brain Res.* 235 (1982) 303-314. ISSN: 0006-8993
- Tarazi FI, Kula NS, Baldessarini RJ (1997) Regional distribution of dopamine D4 receptors in rat forebrain. *Neuroreport* 8(16): 3423-3426. ISSN: 0959-4965
- Tejani-Butt, S. M., Yang, J., Zaffar, H. (1993). "Norepinephrine transporter sites are decreased in the locus coeruleus in Alzheimer's disease." *Brain Res* 631(1): 147-50. ISSN: 0006-8993
- Timofeeva, O. A. & Levin E. D. (2008). "Idazoxan blocks the nicotine-induced reversal of the memory impairment caused by the NMDA glutamate receptor antagonist dizocilpine." *Pharmacol Biochem Behav* 90(3): 372-81. ISSN: 0091-3057
- Uhlen, S., J. Lindblom, A. Johnson, J. E. Wikberg (1997). "Autoradiographic studies of central alpha 2A- and alpha 2C-adrenoceptors in the rat using [3H]MK912 and subtype-selective drugs." *Brain Res* 770(1-2): 261-6. ISSN: 0006-8993
- Unnerstall, J. R., T. A. Kopajtic, M. J. Kuhar (1984). "Distribution of alpha 2 agonist binding sites in the rat and human central nervous system: analysis of some functional, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents." *Brain Res* 319(1): 69-101. ISSN: 0006-8993
- Valet, P., M. Taouis, M. A. Tran, P. Montastruc, M. Lafontan, M. Berlan (1989). "Lipomobilizing effects of procaterol and yohimbine in the conscious dog:

- comparison of endocrinological, metabolic and cardiovascular effects." *Br J Pharmacol* 97(1): 229-39. ISSN: 0007-1188
- Wang, T., Zhang, Q.J., Liu, J., Wu, Z.H., Wang, S., 2009. Firing activity of locus coeruleus noradrenergic neurons increases in a rodent model of Parkinsonism. *Neurosci. Bull.* 25, 15-20. ISSN: 1673-7067
- Wang, Y., Q. J. Zhang, Liu, J. Ali, U. Gui, Z. H. Hui, Y. P. Chen, L. Wu, Z. H. Li, Q. (2010). "Noradrenergic lesion of the locus coeruleus increases apomorphine-induced circling behavior and the firing activity of substantia nigra pars reticulata neurons in a rat model of Parkinson's disease." *Brain Res* 1310: 189-99. 1872-6240
- Weiss, G. F. and S. F. Leibowitz (1985). "Efferent projections from the paraventricular nucleus mediating alpha 2-noradrenergic feeding." *Brain Res* 347(2): 225-38. ISSN: 0006-8993
- White, F. J. and R. Y. Wang (1984). "A10 dopamine neurons: role of autoreceptors in determining firing rate and sensitivity to dopamine agonists." *Life Sci* 34(12): 1161-70. ISSN: 0024-3205
- Winzer-Serhan, U. H., H. K. Raymon, R. S. Broide, Y. Chen, F. M. Leslie (1997). "Expression of alpha 2 adrenoceptors during rat brain development--I. Alpha 2A messenger RNA expression." *Neuroscience* 76(1): 241-60. ISSN: 0306-4522
- Zarow, C., S.A. Lyness, J.A. Mortimer, H.C. Chui, Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases, *Arch. Neurol.* 60 (2003) 337-341. ISSN: 0003-9942
- Zhang, W. and G. A. Ordway (2003). "The alpha(2C)-adrenoceptor modulates GABA release in mouse striatum." *Brain Res Mol Brain Res* 112(1-2): 24-32. ISSN: 0169-328X
- Zhang, W., V. Klimek, J. T. Farley, M. Y. Zhu, G. A. Ordway (1999). "alpha2C adrenoceptors inhibit adenylyl cyclase in mouse striatum: potential activation by dopamine." *J Pharmacol Exp Ther* 289(3): 1286-92. ISSN: 0022-3565
- Zhao, W. Q., L. Latinwo, X. X. Liu, E. S. Lee, N. Lamango, C. G. Charlton (2001). "L-dopa upregulates the expression and activities of methionine adenosyl transferase and catechol-O-methyltransferase." *Exp Neurol* 171(1): 127-38. ISSN: 0014-4886
- Zweig, R., Cardillo, J., Cohen, M., Giere, S., Hedreen, J., 1993. The locus ceruleus and dementia in Parkinson's disease. *Neurology* 43, 986-991. ISSN: 0028-3878

IntechOpen

Mechanisms in Parkinson's Disease - Models and Treatments

Edited by Dr. Juliana Dushanova

ISBN 978-953-307-876-2

Hard cover, 582 pages

Publisher InTech

Published online 08, February, 2012

Published in print edition February, 2012

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Amal Alachkar (2012). Noradrenergic Mechanisms in Parkinson's Disease and L-DOPA-Induced Dyskinesia: Hypothesis and Evidences from Behavioural and Biochemical Studies, *Mechanisms in Parkinson's Disease - Models and Treatments*, Dr. Juliana Dushanova (Ed.), ISBN: 978-953-307-876-2, InTech, Available from: <http://www.intechopen.com/books/mechanisms-in-parkinson-s-disease-models-and-treatments/noradrenergic-mechanisms-in-parkinson-s-disease-and-l-dopa-induced-dyskinesia-hypothesis-and-evidenc>

INTeCH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen