Noradrenaline in Parkinson's Disease: From Disease Progression to Current Therapeutics

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Abstract: The loss of the neurotransmitter noradrenaline occurs constantly in Parkinson’s disease. This is supposed to worsen disease progression, either by increasing the vulnerability of dopamine-containing neurons or by reducing the recovery once they are damaged. Novel data also show that the loss of noradrenergic innervation facilitates the onset of dyskinesia occurring in Parkinsonian patients during dopamine replacement therapy.

In the first part of the manuscript we review the evidence showing the loss of the noradrenergic system as an early event in the natural history of Parkinsonism. This evidence is discussed in light of novel reports showing the deleterious effects produced by the noradrenergic deficit on the survival of nigral dopamine neurons. In particular, we analyze the biochemical and morphological changes produced in the nigrostriatal system by the loss of endogenous noradrenaline. In a dedicated paragraph we specifically evaluate the cross affinity between dopamine and noradrenaline systems. In fact, this is critical during dopamine/noradrenaline replacement therapy in Parkinson’s disease.

In the last part, we overview novel therapeutic approaches aimed at restoring the activation of noradrenergic receptors to reduce the dyskinesia occurring in the treatment of Parkinson’s disease.

Keywords: Neurodegeneration, dyskinesia, locus coeruleus, L-DOPA, DA agonists, D1 receptors, alpha receptors.

1. NOVEL EVIDENCE INDICATES THAT SEVERE LOSS OF NORADRENALINE OCCURS EARLY IN THE PROGRESSION OF PARKINSON'S DISEASE

Although the anatomical connection between the locus coeruleus (LC) and the substantia nigra pars compacta (SNpc) or the striatum are still poorly understood, a strong functional influence between these areas exists. The role of the LC in Parkinson’s disease (PD) was first recognized at the beginning of the past century. In fact, ranging from earliest pathological reports of Tretiakoff [1] to the biochemical data of Oleh Hornykiewicz and co-workers [2], the loss of noradrenaline (NA)-containing neurons joined with a severe decrease in NA content in a variety of brain areas was clearly established. Nonetheless, these findings were not further explored for several decades. In particular, the relevance of such NA deficiency was never translated into any major clinical outcome, including drug development. However, in the last two decades several reports focused on the need to design novel antiparkinsonian drugs aimed at restoring NA levels in PD [3,4]. In fact, pathological reports confirmed the relevance of NA degeneration and added the concept of a disease-specific pattern of LC damage [5]. In order to evaluate the potential significance of NA loss in parkinsonism we studied the modulation of alpha2-NA receptors on central catecholamine systems [6] and their role in the onset of experimental parkinsonism induced by the neurotoxin 1-methyl-4-phenyl, 1,2,3,6-tetrahydropyridine (MPTP) [7]. As reviewed in the last part of the article, this sub-class of NA receptors is now under clinical evaluation in PD.

The loss of the NA system arising from the LC received a special attention when a variety of pre-clinical studies demonstrated the deleterious influence of such a loss on the survival of DA neurons. This evidence was first shown in primates by Mavridis et al. [8], who suggested that a previous damage to NA neurons impaired the recovery of the nigrostriatal DA pathway following a neurotoxic lesion produced by MPTP. Further studies, using catecholamine assay or nigral cell counts confirmed this detrimental effect [9,10] respectively. These studies led to hypothesize that, the detrimental influence of NA loss consisted in increasing the susceptibility, rather then decreasing the recovery of DA neurons belonging to the SNpc. In fact, in 1997, we found that, the damage to LC-NA neurons did not alter the spontaneous recovery of nigral DA cells following MPTP, but instead, it produced an increased vulnerability for nigral DA neurons [11]. This concept was strengthened by the evidence that, an increased NA stimulation was neuroprotective against MPTP toxicity [12]. A few years before, it was found that an increased DA vulnerability was not dependent on the specific neurotoxin (i.e. MPTP), but it was rather a general effects extending to a variety of conditions. Thus, we found that, in the absence of the physiological NA innervation, the DA damage produced by the drug of abuse methamphetamine was magnified [13]. This phenomenon was shown to be the consequence of an increased vulnerability which develops within DA neurons in the absence of NA [14]. More recently, increased DA vulnerability was demonstrated for the neurotoxin 6-hydroxydopamine, when it was administered to LC-lesioned rodents [15]. The strength of these pre-clinical findings led investigators to re-assess the natural history of PD, and to evaluate in humans the role of LC in the progression of the disorder. Thus, based on pioneer studies, showing that the LC was impaired very early in the course of the disorder, it was suggested that such a lesion plays a causative role in the natural progression of PD (for a review, see Gesi et al. [16]). Such working hypothesis is now substantiated by facts, as shown very recently in humans by an extensive biochemical analysis carried out by Tong and co-workers [4], who consistently found a negative correlation between the richness of NA innervation and the occurrence of DA loss in a variety of brain areas. These findings led the authors to hypothesize a facilitating effect of LC damage to the subsequent DA degeneration, as postulated in the experimental models reported above. Thus, the loss of NA is now a critical point in the natural history of PD. This is also confirmed by recent neuropathological findings obtained in a large number of newly autopsied PD patients joined with retrospective cases. Altogether these cases demonstrated that the loss of NA neurons of the LC is at least as severe, as the death of DA cells in the SNpc [17]. This was in line with the extensive neuropathological re-assessment of the PD by Braak and co-workers [18,19,20]. These authors found that, in a number of PD patients, disease progression starts from lower brainstem regions (including the LC) and later extends to more rostral areas including the mesencephalic SNpc. Altogether, findings obtained within pre-clinical settings, and in PD patients, by using a neuropathological and biochemical
approach, converge to suggest the need of a NA-based therapy in PD, in order to slow-down disease progression. This urge is now evident to clinicians, as elegantly posied by Rye and DeLong [3], who assessed the need “to focus on the locus”, and by Tong et al. [4], who suggested to consider the need of a NA-replacement therapy in the course of treatment of PD patients.

2. THE ROLE OF THE NORADRENERGIC SYSTEM ARISING FROM THE LOCUS COERULEUS IN THE LONG-TERM TREATMENT OF PARKINSON’S DISEASE.

The presence of damage to LC-NA neurons, in the course of PD, is not limited to produce an increased susceptibility for DA neurons, but it is likely to extend to the long-term complications of the DA-substitution therapy. In particular, the integrity of LC has been recently related with the onset of L-DOPA induced dyskinesia. These consist of abnormal involuntary movements (AIMs), and represent a severe complication during the course of an intermittent DA-replacement therapy (mainly, L-DOPA) in PD patients [21,22,23].

These movements are currently thought to derive from behavioural sensitisation, which develops following chronic, intermittent administration of DA-replacement therapy [24]. The onset of this drug-triggered movement disorder has been recently characterized in term of plastic changes [25], due to an abnormal activation of D1 DA receptors (D1R). In fact, chronic pulses of L-DOPA in a DA-denervated striatum produce an altered D1R signalling [26,27], both in parkinsonian rats and primates [28,29], as well as in humans [30]. This is in line with an elegant model proposed by Gerfen [31], on the role of altered metabolic pathways, placed downstream to the D1R binding site, which are triggered when the DA-depleted striatum is challenged by peaks of exogenous L-DOPA. This phenomenon is partly sustained by an abnormal interplay between D1R and glutamate receptors and occurs through the recruitment of abnormal transduction mechanisms [32]. In fact, both receptors cause similar activation of transduction pathways which leads to behavioural sensitisation responsible for AIMs. For instance, phosphorylation of CREB and DARPP-32 depends on the activation of D1R as shown by Hotte et al. [33]. In line with this, Edwards et al. [34] found that the D1R-induced phosphorylation of intracellular proteins also involves the NMDA glutamate receptor. On the other hand, Nishi et al. [35] demonstrated that, activation of NMDA receptors promotes the phosphorylation of DARPP-32 in the striatum, thus creating a reciprocal enhancement between glutamate receptor activation and D1R activity. This hypothesis might explain the ability of both D1R and NMDA antagonists to reduce L-DOPA-induced dyskinesia. This cross-talk between glutamate and D1R is likely to sustain the strengthening of synaptic connections in medium spiny neurons of the striatum. In fact, both glutamatergic input (from cortex) and DA input (from SNpc) converge on the same medium-size spiny neurons. Recent evidence shows a dimerization of D1R and glutamate receptor subunits to form receptor hybrids, which move out from the synaptic area during L-DOPA-induced dyskinesia [26,36]. These data add further evidence on the synergism between D1R and glutamate receptor during synaptic plasticity induced by pulses of L-DOPA, suggesting the D1R/NMDA dimers as novel targets to treat dyskinesia [36].

Within this context, the potential role of the NA system in conditioning the treatment of PD emerged in the last decade.

In particular, Ruckert et al. [37] examined the effects of a bilateral lesion of the LC, and found that the antiparkinsonian effects of both the DA precursor L-DOPA, and the NMDA antagonist dizocline were markedly attenuated in the presence of damage to LC neurons. The role of the NA system extends to the behavioral sensitization, as shown in a recent paper by Fulceri et al. [38].

In this work it is shown that the loss of NA activity dramatically worsens the severity, and accelerates the onset of L-DOPA-induced dyskinesia. This is demonstrated in rats possessing, either a pure DA, or a combined DA+NA lesion and undergoing chronic L-DOPA administration according to the protocol of Cenci et al. [39]. Hemiparkinsonian rodents, receiving chronic L-DOPA administration, in the absence of LC innervation, developed rapidly dyskinesia, which were more severe compared with DA-lesioned, NA-intact rodents. In keeping with this, there is a negative correlation between the amount of brain NA and the severity of L-DOPA-induced dyskinesia [38]. This indicates a modulatory role of NA activity in the DA-dependent behavioural sensitisation. This effect is not surprising when considering the powerful influence of LC neurons in brain plasticity and gene expression (see for instance the paper by Cirelli and Tononi [40]). In fact, the activity of LC is critical in modulating those immediate early genes [41], which are also affected by chronic L-DOPA administration [42], or in general by DA-releasing drugs [43]. In a way, it seems that those intracellular cascades, promoted by DA-stimulating agents, are counteracted by sustained LC activity, while they are enhanced in the absence of NA innervation. This hypothesis is substantiated by very recent data showing that the co-transmitter galanin released by LC axons attenuates CREB phosphorylation in striatal neurons [44], which is increased following L-DOPA [45]. At present, this effect is thought to be a major drive for the onset of dyskinesia [46], and to sustain behavioural sensitization following a variety of DA stimulating drugs [47]. In line with this, Shank et al. [48] found an increased locomotor activation following cocaine administration in mice deficient for the gene coding for DA-beta-hydroxylase, which is the enzyme responsible for NA synthesis. Again, Alttoa et al. [49] found that, a similar effect is produced for the locomotor sensitisation following methamphetamine administration.

In keeping with a potential role of the NA system in modulating the long-term complications of DA substitution therapy, recent studies demonstrated that drugs increasing NA activity (by acting at alpha2-NA receptors, improve L-DOPA-induced AIMs, in a variety of animals species including rodents [50], non human primates [51], and PD patients [52]. For these reasons, Brown et al. [53] suggested NA drugs as a novel approach to treat L-DOPA-induced dyskinesia. These effects of NA ligands can be partly explained by the role of the NA system on the plasticity of the DA meso-striatal pathway, as shown by pioneer and very recent embryological findings, which indicate a strong trophic effect of the coeruleus-nigral pathway on mesencephalic DA neurons [54,55,56]. In line with this, following a loss of LC-NA terminals an increased sensitivity of striatal DA receptors has been demonstrated [57]. At the same time, cross-reactivity between NA and DA at receptor level, may also sustain the influence of NA during long-term, L-DOPA-induced dyskinesia.

3. STRUCTURE-ACTIVITY RELATIONSHIP: THE CROSS AFFINITY BETWEEN DOPAMINE AND NORADRENERGIC

The description of cross-affinity, between DA and NA, for the same receptors dates back from the 70’s [58], when the ergot derivative, DA agonist dihydriocgryptine (DHEC) was shown to bind with high affinity to various classes of NA receptors. In fact, the binding of [3H] dihydriocgryptine to rat liver membranes was originally used by Neville [59] to discover the class of alpha-NA receptors. The compound DHEC is presently considered by clinicians as a typical DA agonist [60]. However, as mentioned above, structure-activity studies carried out in the late 70’s, already showed a wide spectrum affinity for various classes of NA receptors. In particular, competition of the binding of DHEC with various pharmacological agents produces the typical alpha-adrenergic
potency series being the (-)-isomers are more potent than (+)-isomers.

In the last 30 years, DA agonists have been considered more and more helpful for PD, leading the clinical use of DHEC as a typical DA agonist agent. Thus, it is not surprising that, when considering the efficacy of DHEC, the powerful NA effects reported above are missed out.

Since the early 90’s, the use the DA agonists emerged as a primary therapy for PD based on the chance to delay the onset of AIDs during long term L-DOPA syndrome (LTS) [61]. The concept of DA agonists as neuroprotective drugs initially was based on the direct stimulation of DA receptors, thus by-passing the degenerating nigrostriatal neurons and their metabolic machinery [62]. This consideration was confirmed by the direct evidence of a protective effect in experimental models [63], which was further sustained in the last decade [64,65,66,67, 68] up to recent PET and SPECT succedaneum evidence for a delayed disease progression induced by DA agonists, which is presently under debate [69,70]. In all these studies showing the variety of effects produced by DA agonists, the focus on structure-activity studies, showing a binding pattern for NA receptors did note receive enough attention.

This is, in our opinion, a classic example on how the therapeutic potential of NA drugs is not just difficult to prove, but in a way, it can be missed out, due to vicious thoughts in term of PD as a disease due to a pure DA deficiency. Although Boissier et al. [71] were considering DHEC as a typical DA agonist, other pioneer studies during the same year [72] were already emphasizing its strong affinity for alpha-NA receptors, and this is the case for other DA agonists.

Sometime, the awareness of NA binding properties for this class of DA agonists led to a mere explanation of a few potential side-effects related to systemic NA activity. However, to our knowledge, no study properly investigated the chance that symptomatic relief in PD patients might have been related, at least in part to powerful NA effects. Although their mechanisms of action at striatal DA post-synaptic receptor have been extensively studied, equally plausible NA changes in the basal ganglia have been all but ignored. This not surprising when considering that, even a few effects produced by DA are mediated by its affinity for various classes of NA receptors, including alpha 3,74] and alpha 4 NA receptors [75]. In view of what reported in the previous paragraph, it is likely that part of the antidyskinetic effects of these drugs may ultimately involve the activation of NA receptors.

If the ability to bind NA receptors for drugs which are considered as classic DA agonists needs to be taken into account, also the ability of NA to bind sub-types of DA receptors is now emerging. Such an effect may further help to clarify the significance of NA loss in term of physiopathology of the DA system in PD. For instance, NA may act as an agonist at D 1 receptor [76]. In a recent study, Czermak and co-workers [77] found that both NA and adrenaline were able to stimulate the human dopamine D 1 receptor expressed in different polymorphic variants (hD4.2, hD4.4 and hD4.7) in CHO-K1 cells. In particular, the authors demonstrated that DA was differentially stimulating the three variants (being 1.7 fold more sensitive than the hD4.4 and 2.5 fold more sensitive than the hD4.2.), while NA and adrenaline had a similar efficacy for the three forms of D 1 receptor. These data add further evidence to the original study of Lanau et al. [78] who demonstrated that NA possesses a high affinity for D 2 receptors (only 4 fold less than DA). In addition, Kubrusly et al. [76] demonstrated that NA can activate, at least during specific developmental stages, D 2R. This concept assumes a variety of implications if one considers that, an abnormal activation of D 2R is now regarded as a leading pathway for the onset of dyskinesias [30,79]. The similarity in the binding structure between these receptors is confirmed by the recent findings that the selective D 2R ligand, SKF 83959, binds with equal affinity to D 1R and alpha NA receptors (pKi=6.72, and 6.41, respectively) [80]. These authors demonstrated that this compound produces its anti Parkinsonian effect not in virtue of DA agonist activity but rather as a consequence of a slight increase in DA and NA release due to an interaction with pre-synaptic receptors. At the same time, benzazepine is able to block the NA transporter (NET), thus further increasing extra cellular NA levels [80]. The cross-affinity between DA receptors and the NET represents another feature to be taken into account when considering the effects of DA ligands. This is the case of zotepine, which binds to DA receptors, while produces an elevation of extra cellular NA due to the blockade of NET [81]. Only in a few cases DA agonists are routinely screened for their affinity for the NET and the DAT despite the great homology between these transporters [82] and the similarities with domains of DA receptors. Thus, the ability of many DA drugs to elevate extra cellular NA remains a constant feature in their mechanism of action. Again, the interaction between NA and DA might become more evident, as shown by Devoto et al. [83], since DA release can be triggered from NA terminals by inhibiting pre-synaptic alpha 2 adrenoceptors. Within this context, the therapeutic potential we discussed above for alpha 2 antagonists in PD may extend to promote DA release.

Altogether these data indicate further cross-reactivity among NA and DA systems, and intrigue the puzzle on the variety of mechanisms by which the integrity of the NA system is important for the progression of PD.

**CONCLUSIONS**

The recent interest on the damage of the NA system in the progression of PD, called for novel therapeutic approaches aimed at restoring the physiological activity of both DA and NA systems. This represents a part of the so-called class of non-DA drugs which recently represents an expanding therapeutic field in PD [84,85]. In line with this, novel NA drugs have been developed aimed at curing both motor and non-motor symptoms in PD, as well as for reducing the side-effects induced by classic DA replacement therapies. Among these, pre-clinical and clinical studies reported several compounds with powerful NA effects. Among these the most commonly used are the NA precursor three-DOPS [86,87,88] which provided some symptomatic relief in advanced PD patients in relation with freezing and postural hypotension. However, this compound was neither evaluated in pre-clinical or clinical studies for a potential benefit in disease progression and nigrostriatal damage, nor in L-DOPA-induced dyskinesia. On the other hand, dyskinesia are improved by drugs enhancing NA release by acting at pre-synaptic NA receptors. This is the case of alpha-2 antagonists like ephedroxan or idoxoxan which have been used both in experimental models and PD patients [50-53]. Again, since PD patients suffer very often from depression, it would very interesting to administer pure NA-uptake blockers such as reboxetine.

Thus, a novel therapeutic approach based on NA-substitution therapy, which was urged by recent studies, is already started in PD. Nonetheless, the critical re-assessment of the pharmacological properties of classic DA drugs reveals unexpected properties towards the NA neurons. Therefore, the NA substitution therapy in PD was probably begun a while ago, on empirical basis without the awareness of NA-stimulating properties possessed by drugs classically defined as DA agonists. On the other hand, such an empirical approach represents the routine more than the exception in drug development. In this way, the antidyskinetic effects of specific DA agonists as well as their suspected neuroprotective potential may already represent a combined DA+NA-based therapy of PD.
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LIST OF ABBREVIATIONS

DA = dopamine
DAT = Dopamine transporter
DHEC = Dihydroxyecrgocryptine
DOPA = dihydroxyphenylalanine
NA = noradrenaline
NET = noradrenaline transporter
LC = Locus Coeruleus
PD = Parkinson's disease
SNpc = Substantia nigra pars compacta
AIMs = abnormal involuntary movements

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