Pharmacological Reports
2005, 57, 701–712
ISSN 1734-1140

Review

Short review on dopamine agonists: insight into clinical and research studies relevant to Parkinson's disease

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Abstract:
Parkinson's disease (PD) is a chronic and progressive neurological disorder characterized by selective degeneration of dopaminergic neurons (DAergic) in the substantia nigra pars compacta (SNpc) and subsequent decrease in dopamine (DA) levels in the striatum. Although levodopa replacement therapy is initially effective in symptomatic treatment of parkinsonian patients, its effectiveness often declines and various levodopa-related side effects appear after long-term treatment. The disabling side effects of levodopa therapy include motor fluctuations such as the wearing-off or on-off phenomena, dyskinesias and psychiatric symptoms. Nowadays, DA receptor agonists are often regarded as first choice in *de novo* and young parkinsonian patients to delay the onset of levodopa therapy. In advanced stages of the disease, they are also used as adjunct therapy together with levodopa to retard the development of motor complications. DA receptor agonists mimick the endogenous neurotransmitter, dopamine, and act by direct stimulation of presynaptic (autoreceptors) and postsynaptic DA receptors. Next to their clinical role in treating parkinsonian patients, laboratory studies reported antioxidative and neuron-rescuing effects of DA receptor agonists either *in vivo* or *in vitro*. This may involve reduced DA turnover following autoreceptor stimulation and direct free radical scavenging activity. In this review, we focus on and summarize the recently reported effects of the most commonly used DA agonists either in clinical or in research studies relevant to PD treatment.

Key words:
Parkinson's disease, levodopa, dopamine agonists, dopaminergic neurons

Abbreviations: AC – adenylyl cyclase, cAMP – cyclic adenosine monophosphate, DA – dopamine, DAergic – dopaminergic, DAT – dopamine transporter, GPe – globus pallidus pars externa, GPi – globus pallidus pars interna, GSH – glutathione, H_2O_2 – hydrogen peroxide, MAO-B – monoamine oxidase B, MPP^+ – 1-methyl-4-phenylpyridinium, MPTP – 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, NMDA – N-methyl-D-aspartate, 6-OHDA – 6-hydroxydopamine, PD – Parkinson's disease, SNpc – substantia nigra pars compacta, SNpr – substantia nigra pars reticulata, TH – tyrosine hydroxylase

Introduction

Parkinson's disease (PD) is a common progressive neurodegenerative disorder characterized by massive depletion of striatal dopamine (DA) as a result of degeneration of dopaminergic (DAergic) neurons in the substantia nigra. Clinically, the disease is manifested by bradykinesia, resting tremor, rigidity and distur-

bance of posture and gait [99]. To date, the etiopathogenesis of nigral DAergic neuron loss in PD is unclear. However, the presence of ongoing oxidative stress as the result of inefficacious antioxidant defence mechanisms and generation of radical oxygen species in the substantia nigra pars compacta (SNpc) of the parkinsonian brain are important pathogenic mechanisms [2, 60, 142]. It should be noted that part of these free radicals are inevitably produced by dopamine metabolism in the brain either enzymatically through the action of monoamine oxidase-B (MAO-B) or by autooxidation [94]. Other sources of increased radical production may be endogenous neurotoxins occurring in the brain like tetrahydroisoquinolines or exogenously administered neurotoxins like the widely used herbicide paraquat which have similar neurochemical properties like the well-known neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [7, 96]. Moreover, Antkiewicz-Michaluk [7] suggested that PD could be associated with excitotoxicity and apoptosis. Therefore, an effective anti-parkinsonian therapy should not only alleviate the disease-associated symptoms, but should also interfere with the progressive DAergic death in the substantia nigra.

The use of levodopa in PD

Treatment with levodopa

Since its introduction by Birkmayer and Hornykiewicz [15] levodopa remained the central pillar and the most effective drug for the symptomatic treatment of PD. Its prescription for parkinsonian patients is primarily based on its ability as a DA precursor to compensate for the decrease of DA in the brain. Although the initial use of levodopa replacement therapy is effective in symptomatic treatment of PD, the clinical efficacy often declines after long-term therapy and additionally disabling side-effects appear, most notably motor fluctuation such as the wearing-off or on-off phenomena and dyskinesia [23, 34]. These motor response complications appear in most patients with advanced PD treated with levodopa [23]. The precise mechanisms for the appearance of these treatment-related fluctuations are not clear. Nutt [91] reported that the long-duration response that characterizes the first few years of levodopa use in parkinsonian patients appeared to depend on the integrity of remaining DAergic nerve terminals in the striatum which retained the capacity to synthesize, release, reuptake and store newly synthesized DA. After long-term use of levodopa and with progression of the disease, the short-duration response to levodopa and appearance of motor fluctuations are paralleled with more advanced DAergic denervation and loss of release and reuptake capacity [80]. Nonphysiological pulsatile stimulation of DA receptors seems to induce the development of motor fluctuations and dyskinesias whereas a more continuous stimulation might be associated with less fluctuation [136].

Effect of levodopa on dopaminergic cells

However DA replacement therapy with levodopa is successful to improve PD symptoms, it does not inhibit the progressive degeneration of DA neurons in SN [66]. Levodopa is not only ineffective against death of DAergic cells in PD patients, but there is also serious concern about possible toxic actions of levodopa on the remaining DAergic neurons. It has been reported that it was toxic to cultured DAergic neurons [4, 21, 46, 74, 90]. On the other hand, there is some evidence indicating that large doses of levodopa did not induce DA neuron degeneration in humans or normal mice and rats [101, 105]. In parkinsonian patients, it was speculated that the remaining DAergic neurons in the patient's brain could be particularly vulnerable to levodopa toxicity since they are hyperactive as a consequence of compensatory mechanisms [143]. In contrast, Dziewczapolski et al. [32] and Murer et al. [87] reported that treatment of rats with different degree of nigrostriatal damage for 6 months with oral levodopa was not toxic for the remaining DAergic neurons. Even when levodopa administration is started during an active degenerative process of DAergic neurons after intrastriatal 6-hydroxydopamine (6-OHDA) treatment, no aggravation of toxicity was found [40].

However, it is discussed that levodopa can enter other DAergic neurons, particularly of the mesolimbic pathway, which may result in psychotic symptoms and mood disturbance in some patients [141].

Mechanisms underlying levodopa toxicity

It was reported that increasing oxidative stress *via* autooxidation of levodopa plays an important role in levodopa toxicity. Spina and Cohen [120] and Fahn and Cohen [35] reported that the autooxidation and metabolism of levodopa can give rise to potentially

harmful free radical species, hydrogen peroxide (H_2O_2) and quinones. H_2O_2 played the most crucial role in the cascade of oxidative events induced by DA or levodopa towards SH-SY5Y cells [70]. Quinones were suggested to be responsible in part for the degeneration of non-DAergic neurons [97]. Pardo et al. [97] reported that the levels of quinones positively correlated with the severity of cell death in human neuroblastoma NB69 cells and at the same time the damage of DA neurons took place early before the rising of quinones. In addition to generation of H_2O_2 and quinone formation, levodopa-induced cell death may result from induction of apoptosis as evidenced by the increase in caspase-3 activity in Neuro-2A cells [100]. Taken together, levodopa-induced toxicity is related primarily to DA production. Excessive dopamine metabolism by high-dose levodopa therapy may promote oxidative stress and thereby accelerate the rate of neuronal degeneration either *in vivo* or *in vitro*. Interestingly, Muriel et al. [88, 89] observed that levodopa treatment of control and 6-OHDA-lesioned rats altered the localization of the D_1 DA receptor from the plasma membrane into the cytoplasm. They also reported that this effect was probably the result of D_1 DA receptor activation rather than that of DAergic denervation as such changes were observed on the lesioned and unlesioned side of the striatum of 6-OHDA-lesioned rats. The altered localization of D_1 receptors may participate in the occurrence of the side effects of levodopa therapy such as dyskinesia and fluctuations in motor performance.

Dopamine receptors and dopamine receptor agonists

Dopamine receptors

In brief, DA receptors belong to two classes of G protein-coupled receptors, the D_1 and D_2 classes. The classification of DA receptors was primarily based on their effects on adenylyl cyclase (AC) activity and cyclic adenosine monophosphate (cAMP) accumulation in the cells [63]. The D_1 receptor subtypes promote, whereas the D_2 subtypes inhibit AC activity and cAMP synthesis [84]. However, it has been reported that the D_2 receptors are mainly responsible for modulating the activity of voltage-sensitive Ca^{2+} and K^+ channels [119]. Moreover, molecular cloning confirmed that D_1 and D_2 receptors constituted two different classes of DA subtypes. In mammals, two receptor subtypes have been assigned to the D_1 receptor class (D_{1A}/D_1 and D_{1B}/D_5), but other types (D_{1C} and D_{1D}) exist in nonmammalian vertebrates [62] and similarly three types (D_2, D_3 and D_4) of the D_2 class have been isolated [20]. DA receptor subtypes share similar sequences and structure [20]. Each type of DA receptors contains seven transmembrane domains with a unique binding site formed by the external loops of the protein [115].

The D_1 and D_2 receptors constitute the major DA receptor subtypes and they are differentially expressed in various regions of the human brain. The D_1 receptors are the most widespread receptors and are mainly expressed in the striatum, nucleus accumbens, olfactory tubercle, cerebral cortex and amygdala. It has also been detected in the island of Calleja and in the subthalamic nucleus [57, 58, 127]. The D_2 receptors are also mainly expressed in the striatum, nucleus accumbens and olfactory tubercle, but additionally in the SNpc and in the ventral tegmental area, where they presumably function as autoreceptors [58, 117, 127]. In the SNpr, binding of D_1-specific ligands was demonstrated, but no mRNA was detected. Probably D_1 receptors are synthesized in the striatal neurons that project to the substantia nigra [58, 127]. Generally, D_1 receptors are mainly post-synaptic, while D_2 receptors are found post- and pre-synaptically (autoreceptor function) [57]. Functionally, there is some evidence that striatal D_1 receptors are expressed selectively by medium spiny neurons projecting to the globus pallidus pars interna (GPi) (direct pathway) [43, 53], while D_2 receptors are expressed by striatal medium spiny neurons projecting to the globus pallitus pars externa (Gpe) (indirect pathway) [43, 53] as well as by both striatal cholinergic interneurons and dopaminergic nigrostriatal neurons (autoreceptors) [79, 85]. In accordance, occupation of D_1 receptors by DA or D_1 receptor agonists stimulates AC activity and stimulates the direct pathway. On the other hand, D_2 receptor occupation by DA or D_2 receptor agonists suppresses AC activity and inhibits neurons projecting from the striatum to GPe [3].

The D_5 receptor is localized in the SNpc, hypothalamus, striatum, cerebral cortex, nucleus accumbens and olfactory tubercle [64]. Also, it was reported that the D_5 receptor displayed higher affinity for DA than the D_1 subtype [49, 121]. The high affinity of the D_5 receptor for DA and its presence in the areas of DA pathways suggests that the D_5 receptor may participate in some activities of DAergic neurotransmission [67].

The D_3 receptor is localized in the forebrain limbic areas [119] and the largest receptor densities occur in granule cells of the islands of Calleja and in medium-sized spiny neurons of the rostral and ventromedial shell of the nucleus accumbens [29, 71]. D_3 receptor expression is low in the striatum. It is also expressed in the ventral pallidum, SNpc, the ventral tegmental area, mediodorsal thalamus, cerebral cortex, the cerebellum and amygdala in the rat brain [19, 29, 30]. There are some evident links between the alteration in dopamine D_3 receptor function and the etiology of a variety of CNS disorders, including schizophrenia and PD [75].

The D_4 receptor level is low in the basal ganglia and higher in the frontal cortex, medulla, amygdala, hypothalamus, hippocampus and mesencephalon [57].

In the rat central nervous system, the relative abundance of the DA receptors is $D_1 > D_2 > D_3 > D_5 > D_4$ [57].

Development of DA therapy with receptor agonists for treating PD

DA receptor agonists play an important role in anti-parkinsonian therapy and have become increasingly popular since the introduction of bromocriptine by Donald Calne and colleagues in 1974 [41]. Their development aimed at reducing the disabling motor complications produced by levodopa therapy [61]. More recently, DA receptor agonists are being used in the initial treatment of patients with *de novo* PD either as monotherapy or combined with low doses of levodopa [108]. Moreover, DA receptor agonists are advantageous in several aspects. They do not require carrier-mediated transport in the gut or brain. They act directly on the DA receptors without the need for metabolic modification, release or storage. They also have longer half-lives than levodopa and, therefore, they produce more persistent DA receptor stimulation than levodopa. Their metabolism does not generate free radicals which are considered one of the most important hazards in levodopa treatment particularly on DAegic neurons [46]. The most important DA receptor agonists which are currently approved and gained access into the clinical and research studies are ergoline derivatives such as bromocriptine, lisuride, pergolide, cabergoline and α-dihydroergocriptine as well as the non-ergoline derivatives like rotigotine, pramipexole, ropinirole and apomorphine. Ergolines, derivatives of ergot alkaloids, have a longer history in anti-parkinsonian therapy and are as effective as non-ergolines, which were developed in the hope that they might provide the benefits of the ergoline agents without their side effects [17]. However, recently valvular heart disease was presented as a new complication of ergot derivative DA receptor agonists [55, 107, 118, 133] but non-ergot DA receptor agonists cannot be excluded at present due to lack of sufficient reliable pharmacoepidemiological data [24]. Partly, the individual DA receptor agonists show significant variation in their receptor affinity [44].

General effects of DA receptor agonists

DA receptor agonists are initially prescribed at the early stage of parkinsonism to postpone the onset of levodopa therapy. They are co-administered with low doses of levodopa to delay the development and to minimize the severity of levodopa-associated treatment complications [12, 110]. There is great evidence that stimulation of D_2 receptors at the post-synaptic level is primarily involved in alleviating levodopa-induced motor fluctuations. Additionally, direct receptor activation with an agonist might be expected to elicit more specific and controllable effects than those produced by the transmitter precursor levodopa, in patients with a damaged extrapyramidal system [41]. More recently, there is increasing evidence in the literature that DA agonists are not only beneficial to postpone levodopa therapy in early parkinsonism or to counteracting its complications after long-term use but they have also been suggested to be neuroprotective particularly in experimental models [72, 103]. The mechanisms and processes underlying the neuroprotective actions of DA receptor agonists appear to be interlaced. They spare levodopa, thereby reducing the formation of oxidative radicals from levodopa metabolism, act as radical scavengers, reduce DA synthesis, release and metabolism *via* activating presynaptic autoreceptors, ameliorate excitotoxicity by suppressing subthalamic nucleus overactivity and exert antiapoptotic effects [113].

Interestingly, DA receptor agonists have been reported to play an important neurogenic modulatory role in the central nervous system (CNS) development [129]. In line with this, Höglinger et al. [54] observed that experimental depletion of dopamine in rodents decreased precursor cell proliferation in both subependymal and subgranular zones in the adult. The highly proliferative precursors in subependymal zone

express DA receptors and receive DAergic afferents. More specifically, DA D_3 receptor mRNA expression in CNS occurs quite early in development and is predominantly found in the proliferative neuroepithelium [31]. In addition to *in vivo* reports, *in vitro* studies have shown that DA increased ^{3}H thymidine incorporation (a marker of cell proliferation) in a neuroblastoma-glioma hybrid cell line transfected with the human D_3 receptor [102]. In contrast to the involvement of D_3 receptor early in neurogenesis, D_2 and D_1 receptor mRNAs occur later in the development and appear predominantly in migrating and differentiating neurons [31]. Moreover, in neurosphere cultures prepared from neural precursors in the adult subependymal zone, activation of dopamine D_2-like receptors directly increased the proliferation of these precursors [54].

Ergoline DA receptor agonists

Bromocriptine

Bromocriptine is the first DA receptor agonist that has been approved for anti-parkinsonian therapy since 1974 [41]. It was first used as adjunct therapy to levodopa in patients experiencing motor fluctuations and later was recommended as monotherapy in the early stage of the disease [134]. Bromocriptine has been shown to protect mice and DAergic cells against 6-OHDA and MPTP, and levodopa-induced cell loss, respectively. It also attenuated DA depletion in mouse striatum in response to methamphetamine [68, 92, 122]. The neuroprotective effect of bromocriptine is dependent on both, its action as a D_2 receptor agonist and its antioxidant capacity. In this context, it has been reported that bromocriptine is able to scavenge hydroxyl and superoxide radicals *in vitro* [92, 138] and to inhibit hydroxyl radical formation and lipid peroxidation *in vivo* [92].

Pergolide

Pergolide, a semi-synthetic ergoline derivative, is a potent DA receptor agonist used as adjunct to levodopa therapy to slow the clinical progression of PD or to prevent the levodopa-associated motor complications [47, 59]. However, its clinical use is already of minor importance now, since it was recently shown to be associated with the development of restrictive valvular heart disease [10, 55, 128]. Pergolide is absorbed rapidly following oral dosing reaching peak plasma concentration within 2–3 h, has a long half-life of about 21 h and is completely eliminated within 4–5 days [16]. Accordingly, it should produce a more physiological and continuous stimulation of DA receptors avoiding or delaying the induction of dyskinesia [16]. The neuroprotective effect of pergolide has been observed either *in vivo* or *in vitro*. For instance, chronic administration of pergolide preserved the integrity of nigrostriatal neurons in the aging rat's brain [38] and protected against reduction of striatal DA and its metabolites after 6-OHDA injection in mice [9]. Using cell culture models, pergolide has been shown to promote the survival of DAergic neurons, to exhibit partial protection against 1-methyl-4-phenylpyridinium iodide (MPP^+) toxicity and to increase ^{3}H-dopamine uptake by cultured cells after levodopa treatment [46]. Moreover, pergolide had protective effect against H_2O_2 in SH-SY5Y neuroblastoma cells [126]. The neuroprotective effect of pergolide has been shown to be mediated by free radical scavenging activity particularly hydroxyl radicals and nitric oxide and by decreasing phospholipid peroxidation [48, 95], suppressing apoptotic pathways through inhibiting of NF-κB nuclear translocation [125] and stabilizing the mitochondrial function [46]. In clinical trials pergolide was shown to reduce the long-term decline of striatal fluorodopa uptake compared to levodopa treatment, however, without reaching significance [116].

α-Dihydroergocriptine

α-Dihydroergocriptine is a synthetic hydrogenated ergot derivative with a strong dopamino-mimetic activity *in vivo* and *in vitro* [104]. It showed high efficacy and tolerance in treatment of PD [12, 13, 18, 77, 83] and revised PD-like symptoms in experimental models [27]. It was shown that α-dihydroergocriptine reduced abnormal motor behavior and neuronal degeneration induced by MPTP in monkeys [14], protected mice against convulsions induced by intracerebroventricular injection of glutamate and incresed the survival time in mice submitted to total cerebral ischemia induced by $MgCl_2$ [27]. In cellular models, α-dihydroergocriptine protected cultured rat cerebral granule cells against age-dependent and glutamate-induced neuronal cell death [37] and increased the survival of primary cultured DAergic cells when co-administered with either levodopa or DA [45]. The neuroprotective

activity of α-dihydroergocriptine may be based on activation of dopamine D_2 receptors, interaction with excitatory amino acids, influencing the glutathione redox index, improving of cellular energy metabolism, decreasing of lipoperoxidative cellular degeneration, radical scavenging activity, and enhancement of antioxidant enzymes [27, 36, 45, 78]. Moreover, α-dihydroergocriptine increased the number of astrocytes in monkeys after MPTP treatment. Astrocyte activation is important for restoration of neuronal function by enhancing neuronal survival and axon growth in injured areas [86].

Cabergoline

Cabergoline, an ergoline DA receptor agonist, has a relatively long average elimination half-life of 65–110 h as estimated by data on urinary excretion rates in healthy volunteers and in parkinsonian patients, compared with other DA receptor agonists [137]. It was reported that cabergoline is well tolerated and effective in controlling parkinsonism particularly in the early stage of the disease. When combined with levodopa therapy, it was highly effective in improving motor disability without inducing hyperactivity or dyskinesia in cynomolgus monkeys [8]. Like other ergot derivative DA receptor agonists, cabergoline showed neuroprotective potential. It was reported that cabergoline protected nigrostriatal DAergic neurons against 6-OHDA in mice [139]. Activation of GSH, catalase, superoxide dismutase, direct free radical scavenging activity and stimulation of neurotrophic factors are important in mediating the neuroprotective action of cabergoline [93, 139].

Non-ergoline dopamine receptor agonists

Pramipexole

Pramipexole, a synthetic amino-benzothiazole derivative, has a potent agonist activity for D_2 and D_3 receptors [81, 82]. The rank order of receptor affinity of pramipexole within the D_2 subfamily is $D_3 > D_2$ according to saturation binding experiments [44]. On the other hand, pramipexole is lacking affinity for DA D_1 and D_5 receptors [67].

Clinically, it was reported that the safety profile of pramipexole is similar to that of the ergot-derived compounds and it was effective as monotherapy in early parkinsonism and as adjunct therapy with levodopa in advanced stages of the disease [109]. Pramipexole has been found to slow the rate of loss of striatal dopamine transporter (DAT) density as measured in PD patients with the single photon emission computed tomography ligand ^{123}Iβ-carbomethoxy-3β(4-iodophenyltropane) [76, 98]. Furthermore, there are some clinical trials suggesting that pramipexole not only ameliorated motor symptoms, but also the depressive symptoms in PD [109].

Beside the effective role of pramipexole in treating parkinsonian symptoms, it showed a variety of neuroprotective effects in *in vivo* and *in vitro* experimental paradigms [6, 22, 39, 73, 132]. For example, pramipexole inhibited the depletion of striatal DA content in mice [106] and after MPTP treatment. In *in vitro* systems, it has been shown that pramipexole increased the survival of rat mesencephalic cells exposed to levodopa [21], protected SHSY-5Y neuroblastoma cells against MPP^+ and rotenone [51] and rescued cerebellar granule cells from levodopa toxicity [131]. The neuroprotective effect of pramipexole seemed to be derived from different mechanisms. Several reports claimed that the neuroprotective effects of pramipexole are the result of the antioxidant properties [39, 73, 130, 144], inhibition of apoptotic pathways [1, 22, 65] and induction of neurotrophic factors [67]. Moreover, Carvey et al. [21] suggested that the neuroprotective effect of pramipexole may be mediated, in part, by interaction with the D_3 receptor. This hypothesis was further investigated *in vivo* by Ramirez et al. [106]. They reported that pramipexole was apparently less effective in inhibiting striatal DA depletion as a result of MPTP treatment in D_3 receptor knockout mice than in mice expressing the receptor. Moreover, the D_3 receptor antagonist, A-437203, was found to partially inhibit the protective effect of pramipexole against MPTP-induced striatal DA. Conclusively, D_3 receptor-dependent and -independent mechanisms seem to play a role against MPTP toxicity in this model.

Ropinirole

Ropinirole is a non-ergoline DA receptor agonist that exhibits a high affinity for the D_2 and D_3 receptors but little or no affinity for the D_1 receptor [25, 33]. Ropinirole is rapidly absorbed and well tolerated after oral administration [69]. Symptomatically, it was reported that ropinirole was as effective as bromocriptine in reducing motor complications and decreas-

ing levodopa dose without increasing adverse events including dyskinesia [26]. Also, ropinirole monotherapy was effective in treating resting tremor in early PD [114], in reducing periodic leg movements and in improving sleep efficiency in patients with restless legs syndrome [5, 25]. These positive effects of ropinirole in PD are believed to be due to stimulation of the post-synaptic dopamine D_2-type receptor [33]. In experimental models for PD, it has been found that ropinirole reversed the motor and behavioral deficits induced by MPTP in marmosets [33] and showed neuroprotective effect against 6-OHDA in mice [56]. Activation of GSH and GSH-regulating enzymes such as glutathione peroxidase, glutathione reductase and glutathione transferase as well as activation of catalase and superoxide dismutase were principal neuroprotective mechanisms mediated by ropinirole [123]. In clinical trials ropinirole reduced the long-term decline of striatal fluorodopa uptake compared to levodopa therapy indicating a preserving effect on terminal function of DAergic neurons [135].

Apomorphine

Apomorphine, a non-ergoline DA receptor agonist, is a short-acting and non-selective dopamine D_1/D_2 receptor agonist [28]. It was the first DA receptor agonist used for treating PD [28]. It has been recently reported that subcutaneous intermittent injections or continuous infusions of apomorphine are currently used for the management of sudden, unexpected and refractory levodopa-induced "off" states in fluctuating PD [28]. Like other DA receptor agonists, there is some evidence in the literature describing the neuroprotective potential of apomorphine in experimental models. It has been shown that apomorphine exhibited neuroprotection against DA depletion in 6-OHDA lesioned-rats [142] and MPTP-treated mice [50]. Furthermore, Battaglia et al. [11] and Yuan et al. [142] reported that continuous subcutaneous infusion of apomorphine rescued striatal DAergic terminals and increased the TH and DAT immunoreactivity against toxicity induced by MPTP in mice and enhanced the number of TH^+ cells in the ventral tegmental area in partially 6-OHDA-lesioned rats, respectively. It has been observed that apomorphine increased the survival of cultured mesencephalic DAergic cells [52]. These findings provided an evidence for trophic effects of apomorphine either *in vivo* or *in vitro*. The neuroprotective effect of apomorphine could be a consequence of antioxidant activity [42, 112], potent iron chelating action [124], inhibition of lipid peroxidation [140], induction of neurotrophic factors [111] and anti-inflammatory effects [50].

Concluding remarks

Since the introduction of bromocriptine in 1974, great attention has been paid to DA receptor agonists for treating PD. They are successfully used in the initial treatment of patients with *de novo* PD either as monotherapy or combined with low doses of levodopa. The beneficial effects of DA receptor agonists as anti-parkinsonian drugs is based on their ability to produce direct and continuous stimulation of both presynaptic (autoreceptors) and postsynaptic DA receptors. More recently, DA receptor agonists have been shown to produce neuroprotective activites in experimental models either *in vivo* or *in vitro*. However, there is shortage in the literature concerning the neuroprotective role of DA receptor agonists in parkinsonian patients as there is no objective method to check thoroughly for DAergic cell death. Taken together, we can say that there is no drug that has been unequivocally proven to be neuroprotective in the parkinsonian patient until now. On the other hand, DA receptor agonists are promising in this respect and ongoing research with more accurate neuroimaging devices should decrease the distance between the data obtained from experimental models and clinical studies.

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Received:
February 10, 2005; in revised form: October 5, 2005.