EXPERIENTIA

Volume 40/No. 11 Pages 1165–1304 15 November 1984

## Reviews

# The pharmacology of Parkinson's disease: basic aspects and recent advances

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*Summary.* Basic aspects and recent advances in the understanding of the pharmacological mechanism of action of the clinically most used antiparkinson drugs are reviewed. Recent human and animal biochemical investigations clearly confirm and extend previous findings indicating that benserazide is much more potent than carbidopa as peripheral decarboxylase inhibitor. L-DOPA in combination with benserazide or carbidopa constitutes the best available therapy for Parkinson's disease (PD). To reduce peaks and rapid fluctuations of L-DOPA plasma levels (possibly responsible for peak-dose dyskinesias and end-of-dose deterioration) a slow-release formulation of L-DOPA in combination with benserazide or with benserazide plus catechol-O-methyltransferase inhibitors should be developed. In parkinsonian patients under long-term L-DOPA therapy monoamine oxidase inhibitors type B (MAO-B) e.g. (−)deprenyl and direct dopamine receptor agonists (bromocriptine, lisuride, pergolide etc.), due to their L-DOPA-sparing effects, alleviate in some cases L-DOPA-induced side-effects e.g. dyskinesias and on-off phenomena. However, since (−)deprenyl, due to its metabolism to (−)methamphetamine and (−)amphetamine, seem to have indirect sympathomimetic activity, new selective MAO-B inhibitors devoid of indirect sympathomimetic effects should be tested clinically to assess the functional role of pure MAO-B inhibition in the therapy of PD. The auxiliary therapy with direct dopamine receptor agonists of the D-2 subtype represents another valid approach which should be further investigated in order to find novel dopamine agonists, less expensive than bromocriptine, and strictly selective for D-2 receptor sites.

*Key words.* Pharmacology of Parkinson's disease; antiparkinson drugs, benserazide, carbidopa, L-DOPA; dopamine receptor agonists; (−)deprenyl; MAO-B inhibitors.

## *1. Introduction*

The observation that dopamine (DA) in basal ganglia is markedly decreased in Parkinson's disease (PD)[35,46] led to the development of its precursor L-DOPA(L-3,4-dihydroxyphenylalanine), initially alone[2,11,25] and later combined with peripheral decarboxylase inhibitors (e.g. benserazide and carbidopa), as a substitution therapy[5,12,13,19,40,70,76,80,105,109,112]. L-DOPA therapy plays a key role in the treatment of the most disabling symptoms of the disease (tremor, rigidity and bradykinesia)[10,79]. Yet, following a favorable initial therapeutic response lasting for several years, long-term L-DOPA treatment often loses its effectiveness or is increasingly accompanied by various side effects, e.g. dyskinesias and on-off phenomena. The reason for this is not clear. A progressive degeneration of dopaminergic and other neurones[46], a loss of DA receptors or supersensitivity of DA receptors and post-receptor mechanisms may be involved; an obscure long-term toxic effect of L-DOPA has also been suggested[3,4,22,26,36,77,96,113].

One approach to increase efficiency and to reduce the side-effects occurring in parkinsonian patients under L-DOPA therapy consists in the use of (−)deprenyl[9,15,16,28,65,93] and ergot derivatives[20,34,38,67,71–73,92,94] as adjuvants because these drugs allow the dose of L-DOPA to be diminished (L-DOPA sparing effect).

An optimized therapy requires a precise knowledge of the drugs used as well as more insight into the pathology of the progressive disease. The experiments on rats reported below were performed to improve understanding of the actions of the 2 inhibitors of peripheral aromatic L-amino-acid decarboxylase (AAD) used in the treatment of PD, benserazide and carbidopa, as well as those of (−)deprenyl and some ergot derivatives (in particular lisuride).

In other experiments in healthy volunteers we investigated the effect of single oral doses of benserazide and carbidopa on the level of endogenous L-DOPA in plasma as well as the effect of Madopar® 125 on the plasma concentrations of L-DOPA, 3-O-methyl-DOPA and DA.

*2. Inhibition of AAD by benserazide and carbidopa*

It is well established that appropriate doses of benserazide and carbidopa inhibit extracerebral but not cerebral AAD[6,7]. The co-administration of these inhibitors with L-DOPA therefore prevents the formation of DA in peripheral tissues without interfering with the decarboxylation of L-DOPA in the CNS[8]. The selective inhibition of peripheral AAD allows some typical side-effects of L-DOPA administration, e.g. nausea and vomiting, to be reduced to a minimum and, at the same time, the amount of L-DOPA shunted into the brain to be increased[87].

*2.1. Extracerebral vs striatal AAD inhibition in rats after oral benserazide.* As shown in figure 1, there is a clear dissociation between inhibition of peripheral and striatal AAD after oral administration of benserazide to rats. Indeed, already 1 h after 10 mg (34 μmoles)/kg benserazide p.o., AAD in liver and kidney was maximally inhibited, whereas AAD activity in the striatum was virtually unaffected even after 50 mg/kg of the drug. Only doses of benserazide as high as 250 mg/kg inhibited the striatal enzyme (by about 60%).

In agreement with previous findings[7,8], our results indicate that benserazide at very high doses inhibits both extracerebral and cerebral AAD, whereas with carbidopa essentially no AAD inhibition in the brain is detected even after doses as high as 1000 mg/kg[7].

*2.2. Benserazide vs carbidopa: time-course of inhibition of peripheral AAD.* Studies of the time-course of effect of oral benserazide (30 μmoles [8.8 mg]/kg) and carbidopa (300 μmoles[73.3 mg]/kg) show that maximal AAD inhibition is achieved very rapidly with both compounds (1 h after drug administration) in rat liver and kidney. The duration of action of the two AAD inhibitors is relatively long, i.e. more than 24 h (fig. 2 and fig. 3). Our experiments indicate (as did studies by other investigators[8,63,87]) that benserazide is more potent than carbidopa in inhibiting AAD activity in peripheral tissues.

*2.3. Time-course of the effects of benserazide and carbidopa on endogenous L-DOPA levels in human plasma.* Normally, L-DOPA is present in very low concentrations in human plasma (1.5–2.5 ng/ml); hence, changes in this concentration could be measured reliably only after the recent development of highly sensitive radioenzymatic methods[114].

The data in table 1 show that both benserazide (1.5 mg/

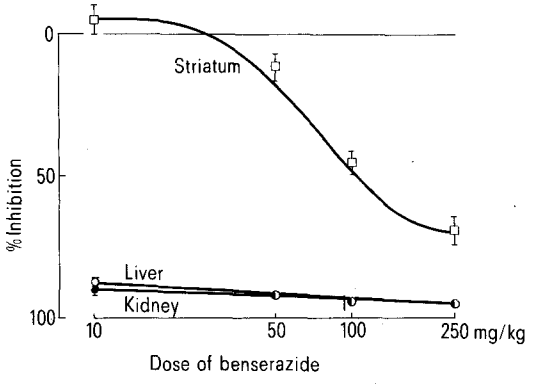


Figure 1. Inhibition of aromatic L-aminoacid decarboxylase (AAD) in striatum, liver and kidney of rats 1 h after oral administration of various single doses of benserazide. The enzyme activity was measured by the $^{14}CO_2$ trapping method[33]. The tissues were homogenized in distilled water: striatum (1:5 w/v), liver and kidney (1:30 w/v). The reaction mixture consisting of 60 μl tissue homogenate and 240 μl potassium phosphate buffer (0.1 M, pH 7.1) contained pyridoxal-5'-phosphate and $^{14}$C-DOPA at the final concentration of $10^{-5}$ M and $10^{-3}$ M, respectively. Four animals per dose were used. Points are means ± SEM of determinations in triplicate for each rat. Absolute AAD activity (untreated animals) for striatum, liver and kidney = 5.7 ± 0.2, 60.7 ± 3.5 and 58.1 ± 1.6 μmoles/mg fresh tissue/h, respectively.

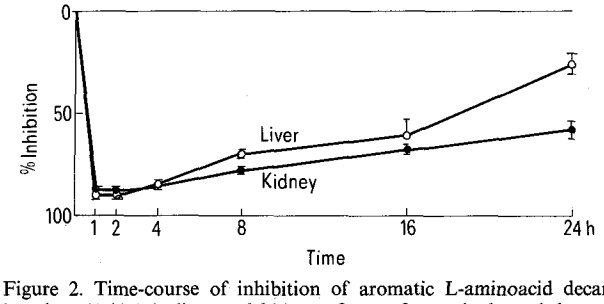


Figure 2. Time-course of inhibition of aromatic L-aminoacid decarboxylase (AAD) in liver and kidney of rats after a single oral dose of benserazide (30 μmoles [8.8 mg]/kg). Four animals for each time point were used. Values are means ± SEM of determinations in triplicate for each rat. Absolute AAD activity (untreated animals) for liver and kidney = 55.7 ± 6.2 and 62.1 ± 3.8 μmoles/mg fresh tissue/h, respectively. Experimental conditions as in figure 1.

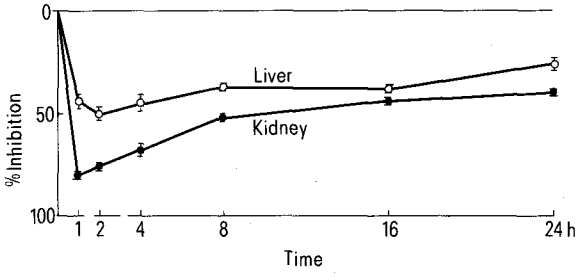


Figure 3. Time-course of inhibition of aromatic L-aminoacid decarboxylase (AAD) in liver and kidney of rats after a single oral dose of carbidopa (300 μmoles [73.3 mg]/kg). Four animals for each time point were used. Values are means ± SEM of determinations in triplicate for each rat. Experimental conditions as in figure 1.

Table 1. Time-course of changes in the endogenous free L-DOPA in human plasma after equimolar doses of benserazide and carbidopa (5.1 μmoles/kg p.o.)

| Drug | Levels in percent of control (=100) Hours after administration | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.5 | 1 | 2 | 3 | 4 | 8 | 24 |
| Benserazide (1.5 mg/kg p.o.) | 281 ± 31 | 532 ± 35 | 874 ± 81 | 897 ± 80 | 831 ± 84 | 602 ± 65 | 265 ± 24 |
| Carbidopa (1.25 mg/kg p.o.) | 132 ± 13 | 193 ± 18 | 274 ± 18 | 307 ± 25 | 308 ± 25 | 260 ± 31 | 147[a] ± 25 |

L-DOPA concentrations are means ± SEM, n = 5 healthy male subjects (30–50 years of age). Absolute values of L-DOPA (ng/ml plasma ± SEM, n = 5) before benserazide and carbidopa administration were 1.88 ± 0.1 and 2.65 ± 0.3, respectively.

The same subjects were given first benserazide and, after a drug-free interval of 7 days, carbidopa.

The compounds were dissolved in water shortly before oral administration. Statistical significance vs pre-drug values, at least $p < 0.01$ (Student's t-test). Statistical significance benserazide vs carbidopa values, at least $p < 0.05$ (Student's t-test).

kg p.o.) and an equimolar dose of carbidopa significantly increase endogenous L-DOPA levels in the plasma of healthy volunteers. Already after 30 min, endogenous L-DOPA was significantly elevated with both inhibitors, and peak concentrations were attained about 3 h later. The rise of L-DOPA in the plasma persisted for at least 24 h; however, at all times investigated, the plasma L-DOPA levels were significantly higher after benserazide than after carbidopa (table 1). On the whole, these findings support the view that, also in man, benserazide is more potent than carbidopa in inhibiting peripheral AAD.

It is well known that benserazide inhibits catechol-O-methyltransferase (COMT) activity in vitro more potently than carbidopa[18,44]. However, since in vivo inhibition of this enzyme in rats has only been shown with extremely high doses of benserazide (879 mg/kg)[17], the increase of L-DOPA levels observed in man (more marked for benserazide than for carbidopa, see table 1), is probably not due to inhibition of COMT.

*2.4. Plasma levels of L-DOPA, 3-O-methyl-DOPA, and total DA after Madopar® in man.* The changes in time of the plasma levels of L-DOPA, 3-O-methyl-DOPA, and total DA after a single tablet of Madopar® 125 (100 mg L-DOPA plus 25 mg benserazide) are shown in figure 4. These data show a rapid, but short-lasting, increase of the L-DOPA level (estimated half-life about 1 h). In contrast, 3-O-methyl-DOPA increased less rapidly than L-DOPA and, unlike its parent compound, remained elevated for several hours. This is in line with the findings of other authors who have shown that the plasma half-life of 3-O-methyl-DOPA is longer than that of DOPA (15 and 1 h, respectively)[8].

The question arises whether the massive transformation of L-DOPA into 3-O-methyl-DOPA may interfere with the availability of the remaining L-DOPA in brain. In fact, it has been reported that 3-O-methyl-DOPA does interfere with the utilization of L-DOPA in rat brain[37,89]. It is, however, not clear whether the concentration of 3-O-methyl-DOPA occurring in parkinsonian patients under chronic L-DOPA treatment is able to reduce the therapeutic effect of L-DOPA by hampering the utilization of the latter compound in the brain.

As far as plasma DA is concerned, figure 4 shows that the level of total DA (free plus 3-O-sulphated DA) was much less increased than those of L-DOPA and 3-O-methyl-DOPA, indicating that, in healthy humans, marked inhibition of the peripheral AAD occurred after administration of Madopar® 125. It should be noted that the bulk (about 98%) of the plasma DA measured in our experiment consists of the sulphoconjugated amine, a DA derivative with low, if any, biological activity. This probably explains the low incidence of peripheral side-effects (e.g. nausea and vomiting) observed in parkinsonian patients treated with Madopar®[95].

### *3. (−)Deprenyl: a MAO-B inhibitor with monoamine releasing properties*

(−)Deprenyl is considered to be a preferential inhibitor of the monoamine oxidase (MAO) type B since it inhibits more markedly the deamination of phenylethylamine (PEA) than that of 5-hydroxytryptamine (5-HT)[58]. In contrast to the MAO-A inhibitors, (−)deprenyl has the advantage of not eliciting hypertensive crises when co-administered with L-DOPA in parkinsonian patients[15,16,59,60,100]. Since in human brain DA is considered to be deaminated predominantly by MAO-B[41], the blockade of this enzyme by (−)deprenyl, impairing the degradation of DA, reduces the amount of L-DOPA required to maintain optimal DA levels in the parkinsonian brain[59,60,91]. This L-DOPA-sparing effect seems to have the benefit of curtailing the incidence of on-off phenomena in patients on L-DOPA therapy[9,15,16,28,29,65,93].

Although it is well established that low doses of (−)deprenyl (0.5–1 mg/kg i.p.) preferentially inhibit type B MAO in rats[32], the compound seems to interfere with the monoaminergic system by several additional mechanisms. For instance, it was reported that in the isolated cat nictitating membrane (−)deprenyl inhibits the uptake of NA, DA and tyramine[59]. On the other hand, *in vivo* experiments in rats have shown that (−)deprenyl, at doses higher than those needed for se-

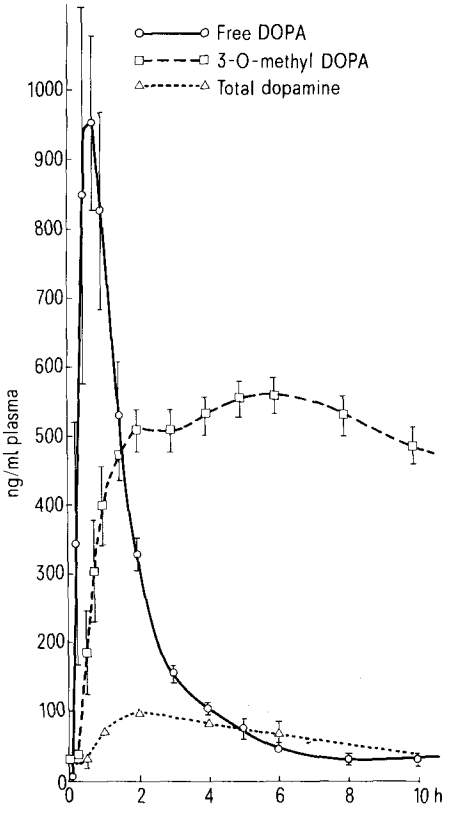


Figure 4. Plasma levels of free DOPA, free 3-O-methyl-DOPA and total (free plus sulphoconjugated) dopamine in 9 healthy volunteers receiving a single capsule of Madopar® 125 (100 mg L-DOPA plus 25 mg benserazide) immediately after the first blood sampling (time 0). Values are means ± SEM of single determinations (N = 9). Pre-drug values (ng/ml plasma): L-DOPA = 1.9 ± 0.1; 3-O-methyl-DOPA = 30 ± 7; total dopamine = 4.0 ± 0.5.
3-O-Methyl-DOPA was measured concomitantly with DOPA by high-performance liquid chromatography with electrochemical detection. A liquid chromatograph (LC-304), equipped with a TL-5 glassy carbon electrode (Bioanalytical System) was used. DOPA values lower than 100 ng/ml plasma were detected by a highly sensitive radioenzymatic method[114]. Total dopamine was measured radioenzymatically[30] after sulphatase-catalyzed hydrolysis[50].

lective MAO-B inhibition, releases NA in the peripheral sympathetic system[32, 107]. The fact that (−)deprenyl can be converted *in vivo* to (−)amphetamine supports the view that the amine releasing properties of (−)deprenyl are essentially linked to (−)amphetamine formation[90].
In order to obtain more insight into the mechanisms by which (−)deprenyl acts on the central dopaminergic system, we performed experiments in rats lesioned unilaterally in the nigro-striatal dopaminergic tract[110].

*3.1. (−)Deprenyl-induced circling in rats with unilateral lesion in the nigro-striatal pathway.* In these experiments the dopaminergic nigro-striatal pathway of rats was unilaterally destroyed by stereotaxic injection of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle (MFB)[85]. This animal model, characterized by a decreased function of the dopaminergic nigro-striatal neurones, is quite suitable for studying the effect of drugs that stimulate brain DA receptors directly or indirectly[111].
In these animals direct DA agonists, such as apomorphine and ergot derivatives (see below), cause circling towards the intact side (contralateral circling) by stimulation of the supersensitive DA receptors located on the lesioned side. In contrast, DA-releasing drugs, like amphetamine, induce circling movements of the rat towards the lesioned side (ipsilateral circling) by releasing DA in the striatum of the intact side[85, 111]. As shown in table 2, (−)deprenyl induced dose-dependent, ipsilateral circling, whereas pargyline, in spite of being a preferential inhibitor of type B MAO, was virtually ineffective. The data in table 2 show also that (−)deprenyl-induced circling was markedly diminished by inhibition of the DA-$\beta$-hydroxylase and by $\alpha$-adrenoceptor blockade. Thus, the decrease of NA synthesis by FLA-63 and the impairment of NA transmission by blockade of the $\alpha$-receptors with prazosin markedly reduced the intensity of this circling behavior.
In previous experiments we were able to antagonize the (−)deprenyl-induced circling behavior with the DA receptor blocker haloperidol[32], indicating that the circling was mainly due to dopaminergic activation. However, the fact that (−)deprenyl-induced circling was also counteracted by reducing noradrenergic neurotransmission (e.g. after FLA-63 and prazosin) suggests a modulatory (synergistic) role of NA in the circling. Several other pharmacological and behavioral studies also point to the existence of a NA-DA link in which NA neurones facilitate dopaminergic activity[1, 62, 88].
Based on these data, the claimed beneficial effect of (−)deprenyl as L-DOPA adjuvant in PD could be related both to MAO-B inhibiting properties as well as to enhanced noradrenergic transmission, which in turn increases dopaminergic activity[47].

Table 2. Effect of FLA-63 and prazosin on (−)deprenyl-induced ipsilateral circling in rats unilaterally lesioned in the nigrostriatal dopaminergic system (N = 10)

| Drugs (mg/kg i.p.) | Cumulative turns (h) | % |
|---|---|---|
| Pargyline (3) | 40 (3) | |
| Pargyline (30) | 75 (3) | |
| (−)Deprenyl (0.3) | 120 (2) | |
| (−)Deprenyl (1) | 425 (3) | |
| (−)Deprenyl (3) | 815 (4) | |
| (−)Deprenyl (10) | 1095 (4) | 100 |
| FLA-63 (20) + (−)Deprenyl (10) | 425 (4) | 39 |
| Prazosin (5) + (−)Deprenyl (10) | 274 (4) | 25 |

The experiments were performed in female rats with unilateral lesion of the medial forebrain bundle (6-hydroxydopamine, 3.5 µg base/4 µl) injected at least 2 weeks before testing (for details see ref. 85). FLA-63 and prazosin were injected 4 and 1 h before (−)deprenyl, respectively.

*4. Ergot derivatives directly acting on dopaminergic receptors*

DA receptor agonists, in particular bromocriptine and, more recently, pergolide and lisuride, have been proposed for the therapy of patients exhibiting a declining response to L-DOPA[20, 34, 38, 67–69, 71–73, 94, 99]. These compounds, in fact, should prove beneficial even in cases with advanced degeneration of the nigro-striatal dopaminergic system, by direct stimulation of post-synaptic DA receptors in the striatum.
Among the multiple DA-binding sites found in brain tissue (for review see ref.[27, 103]) only the D-2 sites (which, in contrast to D-1 sites, are not linked with adenylate cyclase activity)[52] show properties related to dopaminergic behavioral and endocrinological responses, and therefore, may be considered as true receptors[21, 53, 64, 108]. Symptoms observed in PD are most likely related to reduced tonic stimulation of dopaminergic D-2 receptors located on intrastriatal cholinergic neurones[101, 104]. Indeed, stimulation of D-2 receptors by ergot derivatives relieves parkinsonism, whereas blockade of D-2 receptors (e.g. by molindone) exacerbates parkinsonian symptoms[108]. A serious limitation to the clinical use of ergot derivatives lies in the fact that these compounds induce peripheral (mainly nausea and vomiting) as well as central (psychotomimetic reactions) side-effects[10]. The observed lack of selectivity of these compounds, which interact also with other subtypes of DA receptors (e.g. D-1)[43, 102] as well as with serotoninergic and noradrenergic receptors[23, 24, 39, 54–57, 75, 83, 84], could represent an additional disadvantage for their therapeutic use. Up to date, pergolide, a long-acting ergot derivative which stimulates DA receptors without affecting 5-HT neurones[39, 43, 61], seems to be the most promising ergot compound for clinical use. In fact, in parkinsonian patients after 1-year treatment, pergolide showed longterm and stable therapeutic effects with only transient side-effects (e.g. nausea, orthostatic hypotension and hallucinations)[42, 74].
In the following, we present results on the DA-agonistic activity of some ergot derivatives, as assessed by rat circling behavior. Furthermore, some biochemical experiments will show the multiplicity of the effects of lisuride on the monoaminergic systems of the rat brain.

*4.1. Contralateral circling induced by ergot derivatives in rats with unilateral lesions of the nigro-striatal pathway.* As shown in table 3, bromocriptine, pergolide and lisuride elicited a circling response contralateral to the lesioned side in 6-OHDA-lesioned rats. The fact that this circling is qualitatively similar to that induced by apomorphine (a typical DA receptor agonist) and that it is blocked by neuroleptics provides good evidence that ergot derivatives stimulate DA receptors[32, 86]. In this be-

Table 3. Contralateral circling elicited by various dopaminergic agonists in rats lesioned by 6-OHDA injected unilaterally into the medial forebrain bundle (N = 5–10).

| Compound | Dose (mg/kg i.p.) | Latency of onset (min) | Cumulative turns | Duration (h) |
|---|---|---|---|---|
| Apomorphine | 0.1 | 1 | 450 | 0.75 |
| Bromocriptine | 1 | 90 | 1850 | 5 |
| Pergolide | 0.1 | 12 | 5030 | 6 |
| Lisuride | 0.05 | 5 | 5850 | 6 |

For details see legend to table 2.

havioral test bromocriptine and, especially, pergolide and lisuride proved to be particularly efficacious DA agonists, since they elicited a much stronger and longer-lasting rotation than apomorphine. The latency of rotation onset was very short for all compounds tested with the exception of bromocriptine which, due to its peptide moiety, probably penetrates slowly into the brain.

In intact rats all these compounds unequivocally induced signs of DA receptor stimulation consisting of stereotypies (e.g. sniffing, gnawing and biting)[48, 49, 61, 106, 108]. Only lisuride elicited, in addition to DA-linked stereotypies, signs of 5-HT receptor stimulation ('serotonin behavioral syndrome'), as well as typical masculine mounting behavior in grouped rats[31, 57, 106]. Since those ergot derivatives which are virtually devoid of 5-HT agonistic activities (e.g. bromocriptine and pergolide) are as effective as lisuride in PD[68, 72], there is no reason to assume that a modulation of serotoninergic mechanisms has therapeutic relevance for this neurological disorder.

*4.2. Neurochemical effects of lisuride on the monoaminergic systems in rat brain.* Lisuride at relatively low doses (0.1 mg/kg i.p.) induces only minimal changes of the DA and 5-HT levels, while it reduces the NA level in the rat brain[54, 56, 83, 84]. The reduction of homovanillic acid (HVA) as well as that of 5-hydroxyindoleacetic acid (5-HIAA) observed after lisuride supports the view that the compound stimulates both DA and 5-HT receptors. We have provided experimental evidence that presynaptic as well as postsynaptic DA[56, 57, 86] and 5-HT receptors[56, 84] are activated by lisuride. Therefore, the decrease of HVA and 5-HIAA is probably mediated by both mechanisms.

Other experiments have shown that in whole rat brain the 5-HIAA decrement remained approximately the same over a wide dose range (up to 10 mg/kg i.p.)[57]. In contrast, HVA was decreased after low doses (0.01–0.05 mg/kg i.p.) but was unchanged or even slightly increased after high doses (1–10 mg/kg i.p.) of lisuride. This biphasic effect on the HVA level could be related to the mixed agonist/antagonist properties of lisuride at DA recreptors[57].

The increase of 3-methoxy-4-hydroxyphenylethyleneglycol sulphate (MOPEG-$SO_4$) indicates that lisuride also possesses $\alpha$-adrenoceptor blocking properties[56, 57, 83]. This view is further supported by the fact that the lisuride-elicited increase of MOPEG-$SO_4$ was completely abolished by the $\alpha_2$-adrenoceptor agonist clonidine[57]. On the whole, the neurochemical effects induced by lisuride on the monoaminergic systems of the rat brain seem to be qualitatively similar to those observed after bromocriptine[24, 55, 75] and pergolide[39], as far as DA and NA synthesis is concerned. On the other hand, it seems that bromocriptine, in contrast to lisuride, increases 5-HT turnover[75], whereas pergolide leaves it unaffected[39]. In view of the fact that the antiparkinsonian action of the ergot derivatives seems to be due essentially to their stimulating properties on DA (D-2 subtype) receptors, the development of better tailored and less expensive analogues should lead to compounds with selective agonistic activities on D-2 receptors lacking, at the same time, any effect on 5-HT and NA neurones.

## *5. Concluding remarks*

The combination of L-DOPA with a peripheral AAD inhibitor, such as benserazide (Madopar®), leads to an impressive alleviation of parkinsonian symptoms and greatly improves the quality of life of parkinsonian patients.

Substitution therapy with L-DOPA is the treatment of choice of PD, even though the drug often progressively loses its effectiveness and distressing difficulties (e.g. dyskinesias and on-off phenomena) arise with continuous administration.

Some problems occurring with chronic L-DOPA therapy are probably due to overdosage, since the control of parkinsonian symptoms may often be reestablished by giving more frequent but smaller doses of the L-DOPA-benserazide or -carbidopa combination[66, 78].

Since, in healthy subjects, the intestinal absorption of L-DOPA is rapid and consistent all over the upper part of the small intestine[45], it is conceivable that slow-release formulations of L-DOPA in combination with peripheral decarboxylase inhibitors might reduce both peak-dose dyskinesias and end-of-dose deterioration.

The benefit of the L-DOPA substitution therapy could be further enhanced and more finely tuned by preventing the transformation of L-DOPA into 3-O-methyl-DOPA using COMT inhibitors[37]. For this purpose new COMT inhibitors of higher potency and low toxicity are required.

(−)Deprenyl, by its L-DOPA sparing effect, seems to be useful as adjuvant in the therapy of parkinsonian patients with deteriorating response and/or on-off phenomena. The reported reduction in total disability in PD after (−)amphetamine[82] and the changes in the urinary concentrations of catecholamines, PEA, m- and p-tyramine measured in parkinsonian patients on (−) deprenyl and L-DOPA therapy[51] suggest that the biotransformation of (−)deprenyl into (−)methamphetamine and (−)amphetamine[91] may play a role in the therapeutic action of (−)deprenyl in parkinsonism. However, since withdrawal symptoms after L-DOPA plus peripheral decarboxylase inhibitors and (−)deprenyl have been observed neither in PD nor in depressive patients following (−)deprenyl plus (−)phenylalanine[14], the therapeutic relevance of (−)deprenyl metabolites (e.g. (−)methamphetamine and (−)amphetamine) is still rather controversial. Thus, the beneficial effect of MAO-B inhibition in PD should be further assessed by developing new potent and selective MAO-B inhibitors devoid of amine-releasing properties.

The stimulation of dopaminergic receptors by ergot derivatives offers an additional therapeutic approach in parkinsonism. In fact, their use as adjuvants to chronic L-DOPA therapy may decrease the required dose of L-DOPA and alleviate the side-effects of L-DOPA. Moreover, since there is still a sufficient number of striatal DA receptors susceptible to direct stimulation in patients with deteriorating response to L-DOPA[97,98,103], agents that mimic the action of DA, such as bromocriptine, pergolide and lisuride, could play a major role in parkinsonism when other therapies have lost their efficacy[42,68,69,73,74,99].

However, the ergot derivatives available are not entirely satisfactory with respect to their pharmacological profile and may offer only limited advantages in parkinsonian patients with low density of striatal D-2 receptors[67,81,98]. Nevertheless, considering the solid rationale of this therapeutic approach, it would be desirable to develop novel direct-acting DA agonists with long-lasting and selective pharmacological actions, restricted to the D-2 receptors.


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