Amino Acids (2005) 28: 157–164
DOI 10.1007/s00726-005-0162-4

Amino Acids
Printed in Austria

Peculiarities of L-DOPA treatment of Parkinson's disease

Review Article

R. M. Kostrzewa[1], **P. Nowak**[2], **J. P. Kostrzewa**[1], **R. A. Kostrzewa**[1], and **R. Brus**[2]

[1] Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee, U.S.A.
[2] Department of Pharmacology, Medical University of Silesia, Zabrze, Poland

Received August 5, 2003
Accepted August 1, 2004
Published online March 9, 2005;

Summary. L-Dihydroxyphenylalanine (L-DOPA), the anti-parkinsonian drug affording the greatest symptomatic relief of parkinsonian symptoms, is still misunderstood in terms of its neurotoxic potential and the mechanism by which generated dopamine (DA) is able to exert an effect despite the absence of DA innervation of target sites in basal ganglia. This review summaries important aspects and new developments on these themes. On the basis of L-DOPA therapy in animal models of Parkinson's disease, it appears that L-DOPA is actually neuroprotective, not neurotoxic, as indicated by L-DOPA's reducing striatal tissue content of the reactive oxygen species, hydroxyl radical ($HO^{\bullet}$), and by leaving unaltered the extraneuronal *in vivo* microdialysate level of $HO^{\bullet}$. In addition, the potential beneficial anti-parkinsonian effect of L-DOPA is actually increased because of the fact that the basal ganglia are largely DA-denervated. That is, from *in vivo* microdialysis studies it can be clearly demonstrated that extraneuronal *in vivo* microdialysate DA levels are actually higher in the DA-denervated vs. the intact striatum of rats – owing to the absence of DA transporter (i.e., uptake sites) on the absent DA nerve terminal fibers in parkinsonian brain. In essence, there are fewer pumps removing DA from the extraneuronal pool. Finally, the undesired motor dyskinesias that commonly accompany long-term L-DOPA therapy, can be viewed as an outcome of L-DOPA's sensitizing DA receptors (D_1–D_5), an effect easily replicated by repeated DA agonist treatments (especially agonist of the D_2 class) in animals, even if the brain is not DA-denervated. The newest findings demonstrate that L-DOPA induces BDNF release from corticostriatal fibers, which in-turn enhances the expression of D_3 receptors; and that this effect is associated with motor dyskinesias (and it is blocked by D_3 antagonists). The recent evidence on mechanisms and effects of L-DOPA increases our understanding of this benefical anti-parkinsonian drug, and can lead to improvements in L-DOPA effects while providing avenues for reducing or eliminating L-DOPA's deleterious effects.

Keywords: L-DOPA – Dopamine – Parkinson's disease – Volume transmission – Basal ganglia – Striatum

Abbreviations: 5-HT, serotonin; 5-OH-Trp, 5-hydroxytryptophan; 6-OHDA, 6-hydroxydopamine; AADC, aminoacid decarboxylase; COMT, catechol-*O*-methyltransferase; DA, dopamine; DAT, dopamine transporter; DDC, dopa decarboxylase; L-DOPA, L-3,4-dihydroxyphenylalanine; DOPAC, 3,4-dihydroxyphenylacetic acid; Fe^{2+}, ferrous ion; Fe^{3+}, ferric ion; H^+, hydrogen ion; $HO^{\bullet}$, hydroxyl radical; HO^-, hydroxyl ion; H_2O_2, hydroxygen peroxide; HPLC, high performance liquid chromatography; MAO, monoamine oxidase; NH_3, ammonia; PD, Parkinson's disease; ROS, reactive oxygen species; TOH, tyrosine hydroxylase; Trp, tryptophan; TrpOH, tryptophan hydroxylase

Introduction

The discovery by Hornykiewicz that L-dihydroxyphenylalanine (L-DOPA) could successfully treat Parkinson's disease (PD) in humans (Ehringer and Hornykiewicz, 1960; Birkmeyer and Hornykiewicz, 1961), has been hailed as the first neurological disorder that can be treated by pharmacologically replacing a 'missing' neurotransmitter [dopamine (DA)] – otherwise lacking because of spontaneous degeneration of pars compacta dopaminergic neurons in substantia nigra, thereby resulting in nigrostriatal axonal loss with accompanying DA denervation of basal ganglia. While this is all true, the dynamics involved in restoring the missing DA is complicated and not well understood. The purpose of the review article is to highlight the intricacies involved in successful L-DOPA therapy of PD.

Dopamine synthesis

a. In untreated non-Parkinsonian DA neurons

Tyrosine –TOH→ L-DOPA –AADC→ DA

In dopaminergic neurons, DA is synthesized, packaged, released and recovered in the following way. The essential

aminoacid tyrosine is accumulated in the nerve by facilitated diffusion. The rate-limiting enzyme in DA synthesis, namely tyrosine hydroxylase (TOH) then adds an *ortho*-phenolic group to form L-DOPA. In the final step in DA synthesis, the abundant enzyme aminoacid decarboxylase (AADC), also known as dopa decarboxylase (DDC), removes the carboxyl group to form DA.

Fate of intraneuronal DA. DA is rapidly accumulated by synaptic vesicles (i.e., chromaffin granules) via the vesicular monoamine transporter (VMT) located in the vesicle's outer membrane. As VMT is coupled to a proton-antiporter, for every molecule of DA that is accumulated, a molecule of hydrogen ion (H^+) is also accumulated. Because DA is a primary amine with a pK $\sim$ 8.5, DA thus becomes protonated and essentially ion-trapped in the vesicle. The intravesicular pH is about 5.5, and the vesicle can achieve a gradient of DA of about 135,000:1 vs. cytoplasm (i.e., 135,000 times more DA in the vesicle vs. cytoplasm). A single vesicle stores $\sim 3 \times 10^6$ DA molecules (Feldman et al., 1997), and there are thousands of vesicles in every nerve terminal.

Recycling of DA in nerves. When a DA nerve is stimulated, passage of an axon potential across the plasma membrane promotes fusion of vesicles with the outer nerve membrane, whereby DA and other vesicular contents are released and thereby act on other cells. As much as 85% of released DA is reaccumulated by DA nerves via a DA transporter (DAT) linked with an ATPase in the outer plasma membrane. Inside the nerve the reaccumulated DA is repackaged in the vesicles. DA may cycle in this way, in and out (and in again) in the nerve, multiple times. Some of the released DA merely diffuses from the site, and some is catabolized by monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT). In the nerve, only MAO is present, cleaving the amino group from cytoplasmic DA.

b. In untreated DA neurons in PD

Tyrosine –TOH→ L-DOPA –AADC→ DA

The same manner of processing of DA occurs in DA nerves in PD. However, because approximately 80% or more of DA innervation is lost to basal ganglia, the dynamics involved in DA metabolism and recycling is altered. In essence, the remaining 20% of DA neurons attempt to compensate for the missing 80% of DA nerves. Consequently, turnover of DA is much more rapid, plus less DA actually recycles. In PD, there are fewer DA nerve endings which also means that there are fewer DATs in the outer membrane. Therefore, fewer DA molecules reenter DA nerves. Accordingly, in the schema just a few lines above, tyrosine, L-DOPA and DA are smaller font than in the original schema, indicating less of these molecules in DA nerves in untreated PD.

c. In DA neurons after L-DOPA treatment of PD

Tyrosine –TOH→ L-DOPA **–AADC→ DA**
(Endogenous)
↑ ↑ ↑ ↑ ↑ ↑
L-DOPA
(Exogenous)

In treated parkinsonians, exogenous L-DOPA, if given alone, must be administered in gram amount per day in order to produce a therapeutic effect. In reality, L-DOPA is typically administered in combination with a selective AADC inhibitor that is unable to cross the blood-brain barrier. When given as such combination therapy, L-DOPA is largely unmetabolized by AADC in muscle, liver, kidney, etc. – so that most of an administered L-DOPA is able to enter the brain and undergo conversion to DA in nerve cells. In the schema, a large exogenous amount of L-DOPA is shown to enter the endogenous (intraneuronal) pool, generating a high intraneuronal L-DOPA content. AADC converts large amounts of L-DOPA to DA, thereby elevating intraneuronal DA (shown as a larger font size).

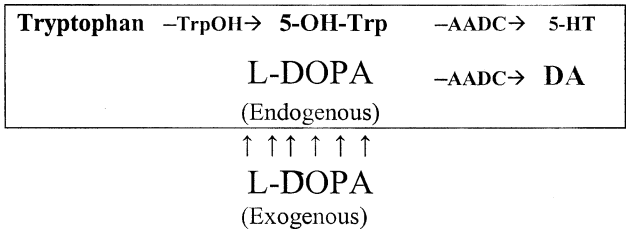
d. In non-DA neurons (e.g., 5-HT neurons) before L-DOPA treatment of PD

Tryptophan –TrpOH→ 5-OH-Trp –AADC→ 5-HT

Below, L-DOPA will be shown to enter non-dopaminergic nerves and undergo conversion to DA in these non-dopaminergic nerves. In the present example, a serotonin (5-HT) neuron is shown to normally convert the substrate tryptophan to 5-hydroxytryptophan (5-OH-Trp) via the enzymatic action of tryptophan hydroxylase (TrpOH). 5-OH-Trp is subsequently converted to the neurotransmitter 5-HT via action of AADC, of identical molecular

structure as the AADC in DA neurons. 5-HT neurons do not normally synthesize DA, as 5-HT neurons lack tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis.

e. In non-DA neurons (e.g., 5-HT neurons) before L-DOPA treatment of PD



It is significant that 5-HT neurons and other types of neurons can accumulate L-DOPA. If this occurs, L-DOPA will be converted via AADC to DA and thereby become a 'false transmitter' in the 5-HT- or other type of neuron. In the schema accompanying this paragraph, exogenously administered L-DOPA is shown to enter 5-HT neurons to undergo conversion to DA which will be stored in vesicles in 5-HT neurons. This is so, because the VMT in vesicles in 5-HT nerves is identical to the VMT in vesicles in DA nerves. Accordingly, DA will displace some 5-HT, as indicated by reduced 5-HT content of striatal tissue following L-DOPA treatment of an animal model of PD (Kostrzewa et al., 2000). In the above schema, the smaller font size for 5-HT in the presence of DA is intended to indicate a lowered 5-HT content.

In phenotypically different neurons in which DA is unable to be stored, DA might simply diffuse out of the nerve, independent of nerve activity.

Volume transmission – a crucial process for successful L-DOPA therapy

There are two major types of chemical neurotransmission: synaptic transmission and volume transmission.

a. Description of synaptic transmission

In synaptic transmission the neurotransmitter (e.g., DA) enters a small space and is virtually trapped. As such, the transmitter acts locally on the post-synaptic cell and then is largely reaccumulated by the pre-synaptic nerve, or it diffuses, or it is degraded by enzymes. Neuromuscular transmission, involving release of acetylcholine by a motor nerve onto the motor endplate, is classically 'synaptic transmission'. Minor amounts of the neurotransmitter enter the extraneuronal milieu outside the synaptic space.

b. Description of volume transmission

In volume transmission the neurotransmitter is released in paracrine fashion, a reasonably large distance from its site of action on other nerves. For DA neurotransmission, DA would diffuse to a site that is distant from the DA nerve ending. Consequently, only small amounts of DA so-released would return to the DA nerve for reaccumulation by the DAT. In other words, most of the released DA would remain extraneuronal.

What are the consequences of this? In this situation basal extraneuronal levels of DA would be reasonably high. Although DA nerves would not 'recapture' DA, the turnover rate for DA can be less because of the high extraneuronal level.

c. Implications of volume transmission on L-DOPA treatment of PD

If DA acted largely via synaptic transmission, much DA would be reaccumulated by nerve endings in the vicinity of DA receptors. Because DA functions largely by volume transmission, not only endogenously released DA has a long half-life extraneuronally, but DA formed by exogenously administered L-DOPA also has a long half-life after being released by (or diffusing from) nerves.

Measured extraneuronal levels of DA following L-DOPA treatment

Because this type of assessment involves invasive methods, studies described here are from animal experiments.

Basal extraneuronal level of striatal DA in intact and lesioned rats

As shown by Abercrombie et al. (1990) the basal striatal *in vivo* microdialysate level (i.e., extraneuronal level) of DA was unaltered when rat striatum was DA-depleted by 10–80%. This indicates that there are major compensatory mechanisms (i.e., safety factor) to maintain normal function even in the presence of a major disruption to the DA system. However, in rats in which the striatum was DA-depleted by >80%, the basal *in vivo* microdialysate level was reduced by nearly 80%. This indicates that

physiologic compensatory mechanisms fail when there is major damage to the DA system.

L-DOPA treatment of control rats with full DA innervation of striatum

When intact control rats pretreated with the peripherally restricted AADC inhibitor RO4-4602 received a low dose of L-DOPA (25 or 50 mg/kg), there was a brief decline in the striatal *in vivo* microdialysate levels (i.e., extraneuronal levels) of DA. Because L-DOPA can acutely have this effect on activity (i.e., firing rate) of DA neurons *in vitro* (Bunney et al., 1973), the noted *in vivo* effect possibly is attributable to action of newly formed DA on DA neuronal autoreceptors to inhibit DA nerve activity and associated release of DA from vesicles (Abercrombie et al., 1990; Wachtel and Abercrombie, 1994). In contrast, a high dose of L-DOPA (100 or 200 mg/kg) produced a prolonged elevation in the *in vivo* microdialysate level of DA in these rats (Zetterstrom et al., 1986; Abercrombie et al., 1990; Wachtel and Abercrombie, 1994; Miller and Abercrombie, 1999). The striatal tissue level of DA was not appreciably changed by acute carbidopa-L-DOPA (60 mg/kg) treatment (Kostrzewa et al., 2000).

L-DOPA treatment of rats with DA-denervated striatum (i.e., Parkinsonian rats)

In rats in which striatal DA was depleted by >80%, L-DOPA (100 mg/kg; RO4-4602 pretreatment) produced a marked increase in the striatal *in vivo* microdialysate level of DA. In these rats, with the striatum largely DA-denervated, the extraneuronal DA level after L-DOPA was about 5-times higher than in L-DOPA-treated intact rats (Zetterstrom et al., 1986; Abercrombie et al., 1990). This outcome is reflective of the importance of volume transmission for maintaining high levels of extraneuronal DA, particularly if numbers of nerve endings with DATs are reduced in number. One can see how this would be particularly advantageous in using L-DOPA therapy in Parkinsonian patients in which there is >80% loss of nigrostriatal fibers (and accompanying DA-denervation of basal ganglia. The striatal tissue level of DA was increased several-fold by acute carbidopa-L-DOPA (60 mg/kg) treatment, thereby partly restoring low tissue DA content (Kostrzewa et al., 2000). The dramatic elevation in the striatal *in vivo* microdialysate level of DA in largely DA-denervated rat striatum is illustrated in Fig. 1. While

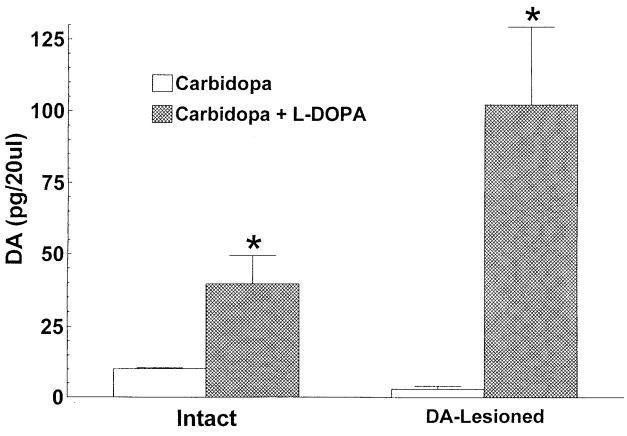


Fig. 1. Effect of acute L-DOPA treatment of the *in vivo* microdialysate level of dopamine (DA) in intact rat striatum and (largely) DA-denervated rat striatum. L-DOPA (60 mg/kg IP) + carbidopa (12.5 mg/kg IP) was administered to rats approximately 1 h prior to sampling and analysis of the *in vivo* microdialysate at or near the peak L-DOPA effect in freely moving rats in which a microdialysis probe had been implanted on the previous day. Intact rats were treated at 3 days after birth with desipramine HCl (20 mg/kg IP) and vehicle [saline (0.85%)-ascorbic acid (0.1%), intracerebroventicularly (ICV)], while DA-denervation of striatum was produced by treatment with 6-hydroxydopamine (134 μg ICV, base form; desipramine pretreatment). Neonatal 6-OHDA treatment consistently produces >97% reduction in striatal tissue DA content, assessed in adulthood

the basal striatal extraneuronal level of DA is reduced by only about 65% despite the 99% reduction in striatal tissue content, acute IP L-DOPA (60 mg/kg)-carbidopa (12.5 mg/kg) treatment elevates the extraneuronal content (*in vivo* microdialysate level) to a much greater extent in the largely DA-denervated striatum. It is this phenomenon of a multiplication in L-DOPA effect in DA-denervated striatum that is largely responsible for the effectiveness of L-DOPA as a therapy for PD.

L-DOPA effect on reactive oxygen species (ROS)

An ongoing debate over the past decade relates to the concern of whether L-DOPA promotes reactive species (ROS) formation in brain, and thereby possibly accelerating the progression of PD. The basis of this is the following. For every molecule of DA that is metabolized by monoamine oxidase (MAO), one molecule of H_2O_2 is formed. As the striatum and substantia nigra are rich in iron (Fe^{2+}), hydroxyl radical ($HO^{\bullet}$) will subsequently be generated via the Fenton reaction.

$$DA + O_2 + H_2O - MAO \rightarrow H_2O_2 + DOPAC + NH_3$$

$$H_2O_2 + Fe^{2+} \rightarrow HO^{\bullet} + Fe^{3+} + HO^{-}$$

One assumption is that DA turnover would be increased after L-DOPA therapy and that generation of ROS would be increased. However, in an earlier study, quite the contrary was shown. In rats in which striatal DA content had been reduced by about 99%, acute L-DOPA treatment (60 mg/kg; carbidopa, 12.5 mg/kg IP) actually reduced striatal tissue content of $HO^{\bullet}$, assessed by HPLC analysis of dihydroxybenzoic acids (2,3- and 2,5-DHBA) – spin trap products of salicylate (Kostrzewa et al., 2000). Thus, it is more likely that L-DOPA is neuroprotective rather than neurotoxic.

L-DOPA priming of DA receptors

In Parkinsonians treated long-term with L-DOPA, motor dyskinesias commonly develop. As DA receptor supersensitization has been invoked as one of the likely processes underlying this disturbing outcome of L-DOPA therapy (Groppetti et al., 1990; Hossain and Weiner, 1993; Carey et al., 1994; Cole et al., 1994; Hume et al., 1995; Opacka-Juffry et al., 1998), we describe some aspects of this phenomenon.

L-DOPA priming of DA receptors

In adult rats in which the striatum was largely DA-denervated shortly after birth, an assortment of exaggerated stereotypic and locomotor activities were produced by L-DOPA – even after initial treatment (Breese et al., 1984). Breese and colleagues showed that DA D_1 receptors were largely involved in many of these effects, but that D_1 agonists did not produce similarly exaggerated behavioral effects in the DA-lesioned rats until after the third dose. The delayed development of receptor supersensitivity, produced by repeated agonist treatment, was termed 'priming'. The Breese group showed also that repeated D_2 agonist treatment would similarly prime D_1 receptors. Therefore, D_1 receptor priming could be homotypic (D_1 agonist-induced) or heterotypic (D_2 agonist-induced). L-DOPA was considered to prime receptors during its initial effects (Breese et al., 1985, 1987; Criswell et al., 1989).

Subsequently, it was shown that further sensitization of the D_1 receptor could be produced in neonatally DA-lesioned rats by ontogenetic postnatal D_1 agonist treatments (Gong et al., 1993, 1994) or ontogenetic postnatal D_2 agonist treatments (Brus et al., 2003).

Although DA D_2 receptors were also sensitized in this animal model, the behavioral effects of D_2 agonist treatments were not nearly so dramatic as those observed with D_1 agonist treatments (Breese et al., 1985, 1987; Criswell et al., 1989). Moreover, ontogenetic D_2 agonist treatments did not further sensitize D_2 receptors in the lesioned rats, at least not appreciably (Brus et al., 2003).

Despite the dramatic D_1 receptor supersensitivity in the above series of studies, there were no obvious intracellular or biochemical processes that could be clearly linked to receptor supersensitivity (Johnson et al., 1992; Duncan et al., 1993; Gong et al., 1994). However, in rats that were DA-lesioned, enhanced DA-induced adenylyl cyclase activity was reported (Gropetti et al., 1990), as well as up-regulated striatal DA-induced phosphorylation of the cAMP-response element-binding protein (Cole et al., 1994), and increased D_2 receptor number (Hume et al., 1995; Opacka-Juffry et al., 1998).

DA-denervation-supersensitivity of DA D_2 receptors

Ungerstedt and Arbuthnott showed in 1970 that in rats with a unilateral lesion of the nigrostriatal tract that amphetamine or apomorphine produces rotational motor activity in the direction of the lesioned side. As these agonist-induced effects are blocked by D_2 receptor antagonists, it is apparent that D_2 receptors become supersensitized in this particular instance.

D_2 agonist priming of D_2 receptors

In intact rats treated repeatedly with quinpirole, a preferential D_2 agonist, D_2 receptors become supersensitized (Kostrzewa et al., 1990, 1991, 1993a, b; Kostrzewa and Brus, 1991; Kostrzewa, 1995), as evidenced by exaggerated quinpirole-induced stereotypies (vertical jumping, paw treading, rearing, digging), which develop gradually in relation to the number of treatments (Eilam and Szechtman, 1989, 1990; Szechtman et al., 1994). Although the effect is most notable in rats that are quinpirole-primed during postnatal ontogeny, quinpirole-priming in adult rats also occurs (Szechtman et al., 1994; Brus et al., 1998). Once quinpirole-priming has been induced, it tends to persist and can be life-long (Brus et al., 1998; Oświęcimska et al., 2000). The so-called ''super'' sensitization of D_2 receptors may be a misnomer, in that primed receptors may actually be ''sub'' sensitive autoreceptors in the ventral tegmental area or in the substantia nigra. Support for this hypothesis is marshaled from the findings of Nowak et al. (2002) who showed that acute amphetamine treatment produced a 5-fold increase

in the striatal microdialysate level of DA in primed vs. control rats. Subsensitivity of D_2 autoreceptors would account for less feedback inhibition of extraneuronal DA following the indirect-acting agonist, amphetamine.

L-DOPA, BDNF, induction of D_3 receptors and behavioral sensitization

In unilaterally 6-OHDA-lesioned rats, repeated L-DOPA treatments induce the overexpression of D_3 receptors in the shell of the nucleus accumbens and in the striatum (Bordet et al., 1997). Because L-DOPA-induced rotational activity is blocked by a D_3 receptor antagonist, it appears that behavioral sensitization to L-DOPA is dependent on D_3 receptor expression (Bordet et al., 1997). In fact, a partial D_3 agonist promotes rotational activity (Pilla et al., 1999). Presumably, these effects of L-DOPA are the result of DA action (from decarboxylation of L-DOPA) on DA D_1 and/or D_5 receptors in cortical layers V and VI, thereby enhancing BDNF synthesis and release by corticostriatal neurons (Guillin et al., 2001).

L-DOPA-induced motor dyskinesias and D_3 receptors

In MPTP-treated parkinsonian monkeys (Morissette et al., 1998) and in post-mortem human Parkinsonians there is reduced D_3 receptor expression in the brain (Ryoo et al., 1998); and its reversal by repeated L-DOPA treatment (Bezard et al., 2003) coincides with the onset and worsening of motor dyskinesias (Sokoloff et al., 2002).

Summary of L-DOPA therapy and treatment effects

L-DOPA, when administered to intact or DA-lesioned rats, is decarboxylated to DA in nerves of the DA phenotype and in nerves of a non-DA phenotype, with the latter being of much greater importance following nigrostriatal DA-denervation (i.e., parkinsonian animal model). Extraneuronal levels of DA (i.e., as in *in vivo* microdialysates) in basal ganglia (i.e., striatum in the rat) is surprisingly much higher in the parkinsonian than in the control. This outcome of L-DOPA treatment is related to 1) DA being a volume transmitter in striatum, and also 2) the absence of DA transporters in the parkinsonian brain (i.e., absence of DA nerve terminals on which DA transporters are located). These latter phenomena are largely responsible for the beneficial therapeutic effects of L-DOPA therapy of PD.

L-DOPA secondarily acts at both DA D_1 and DA D_5 receptors on coticostriatal neurons which release BDNF in striatum and thereby promote expression of D_3 receptors. L-DOPA also 'primes' (sensitizes) receptors of the D_1 class (D_1, D_5 receptors) and D_2 class (D_2, D_3, D_4 receptors), thereby producing exaggerated behavioral effects. These effects add to the receptor supersensitivity accompanying dopaminergic fiber denervation *per se* (Herrera-Marschitz et al., 1985a, b). Apparently the so-called supersensitization may represent overt subsensitization of DA D_2 autoreceptors – as this would produce identical exaggerated behavioral effects. Finally, the overall summation of L-DOPA's secondary effects, on priming receptors and on inducing expression of D_3 receptors *per se*, accounts for the undesired motor dyskinesias commonly associated with long-term L-DOPA therapy.

Future objectives are to maximize the beneficial symptomatic effects of L-DOPA while limiting the priming effects of DA receptors. Partial D_3 agonists represent a viable approach towards achieving this goal.

Acknowledgments

This work was supported by NINDS grant number NS39272 (RMK) and by NN-2-007/03 (RB).

References

Abercrombie ED, Bonatz AE, Zigmond MJ (1990) Effects of L-dopa on extracellular dopamine in striatum of normal and 6-hydroxydopamine-treated rats. Brain Res 525: 36–44

Bezard E, Ferry S, Mach U, Stark H, Leriche L, Boraud T, Gross C, Sokoloff P (2003) Attenuation of levodopa-induced dyskinesia by normalizing dopamine D_3 receptor function. Nature Med 9(6): 762–767

Birkmeyer W, Hornykiewicz O (1961) Der L-3,4-Dioxyphenylalanin (=DOPA)-Effekt bei der Parkinson-Akinese. Wien Klin Wochenschr 73: 787–788

Bordet R, Ridray S, Carboni S, Diaz J, Sokoloff P, Schwartz J-C (1997) Induction of dopamine D_3 receptor expression as a mechanism of behavioral sensitization to levodopa. Proc Natl Acad Sci USA 94: 3363–3367

Breese GR, Baumeister AA, McCown TJ, Emerick SG, Frye GD, Crotty K, Mueller RA (1984) Behavioral differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. J Pharmacol Exp Ther 231: 343–354

Breese GR, Baumeister A, Napier TC, Frye GD, Mueller RA (1985) Evidence that D-1 dopamine receptors contribute to the supersensitive behavioral responses induced by L-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine. J Pharmacol Exp Ther 235: 287–295

Breese GR, Duncan GE, Napier TC, Bondy SC, Iorio LC, Mueller RA (1987) 6-hydroxydopamine treatments enhance behavioral responses to intracerebral microinjection of D1- and D2-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding. J Pharmacol Exp Ther 240: 167–176

Brus R, Szkilnik R, Nowak P, Kasperska A, Oświęcimska J, Kostrzewa RM, Shani J (1998) Locomotor sensitization of dopamine receptors by their agonists quinpirole and SKF-38393, during maturation and aging in rats. Pharmacol Reviews and Commun 10: 25–30

Brus R, Kostrzewa RM, Nowak P, Kostrzewa JP, Perry KW (2003) Ontogenetic quinpirole treatments fail to prime for D_2 agonist-enhancement of locomotor activity in 6-hydroxydopamine-lesioned rats. Neurotoxicity Res 5: 329–338

Bunney BS, Aghajanian GK, Roth RH (1973) Comparison of effects of L-DOPA, amphetamine and apomorphine on firing rate of rat dopaminergic neurons. Nature 245: 123–325

Carey RJ, Pinheiro-Carrera M, Tomaz C, Huston JP (1994) Early L-dopa treatment initially retards but later enhances dopamine receptor supersensitivity following unilateral dopamine denervation. Brain Res 658: 145–154

Cole DG, Kobierski LA, Konradi C, Hyman SE (1994) 6-Hydroxydopamine lesions of rat substantia nigra up-regulate dopamine-induced phosphorylation of the cAMP-response element-binding protein in striatal neurons. Proc Natl Acad Sci USA 91: 9631–9635

Criswell H, Mueller RA, Breese GR (1989) Priming of D1-dopamine receptor responses: long-lasting behavioral supersensitivity to a D1-dopamine agonist following repeated administration to neonatal 6-OHDA-lesioned rats. J Neurosci 9: 125–133

Duncan GE, Breese GR, Criswell HE, Johnson KB, Schambra UB, Mueller RA, Caron MG, Fremeau RT Jr (1993) D1 dopamine receptor binding and mRNA levels are not altered after neonatal 6-hydroxydopamine treatment: evidence against dopamine-mediated induction of D1 dopamine receptors during postnatal development. J Neurochem 61: 1255–1262

Ehringer H, Hornykiewicz O (1960) Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin Wochenschr 38: 1236–1239

Eilam D, Szechtman H (1989) Biphasic effect of D-2 agonist quinpirole on locomotion and movements. Eur J Pharmacol 161: 151–157

Eilam D, Szechtman H (1990) Dosing regimen differentiates sensitization of locomotion and mouthing to D2 agonist quinpirole. Pharmacol Biochem Behav 36: 989–991

Feldman RS, Meyer JS, Quenzer LF (1997) Principles of neuropsychopharmacology. Sinauer Associated Inc., Sunderland, Massachusetts

Gong L, Kostrzewa RM, Brus R, Fuller RW, Perry KW (1993) Ontogenetic SKF 38393 treatments sensitize dopamine D1 receptors in neonatal 6-OHDA-lesioned rats. Brain Res Dev Brain Res 76: 59–65

Gong L, Kostrzewa RM, Li C (1994) Neonatal 6-hydroxydopamine and adult SKF 38393 treatments alter dopamine D1 receptor mRNA levels: absence of other neurochemical associations with the enhanced behavioral responses of lesioned rats. J Neurochem 63: 1282–1290

Groppetti A, Ceresoli G, Mandelli V, Parenti M (1990) Role of opiates in striatal D-1 dopamine receptor supersensitivity induced by chronic L-dopa treatment. J Pharmacol Exp Ther 253: 950–956

Guillin O, Diaz J, Carroll P, Griffon N, Schwartz J-C, Sokoloff P (2001) Bdnf controls dopamine D_3 receptor expression and triggers behavioural sensitization. Nature 411: 86–89

Herrera-Marschitz M, Forster C, Ungerstedt U (1985a) Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats. I: Comparison between systemic and intrastriatal injections. Acta Physiol Scand 125: 519–527

Herrera-Marschitz M, Forster C, Ungerstedt U (1985b) Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats. II: The striatum of the rat is heterogeneously organized for rotational behaviour. Acta Physiol Scand 125(3): 529–535

Hossain MA, Weiner N (1994) Dopaminergic functional supersensitivity: effects of chronic L-dopa and carbidopa treatment in an animal model of Parkinson's disease. J Pharmacol Exp Ther 267: 1105–1111

Hume SP, Opacka-Juffry J, Myers R, Ahier RG, Ashworth S, Brooks DJ, Lammertsma AA (1995) Effect of L-dopa and 6-hydroxydopamine lesioning on [^{11}C]raclopride binding in rat striatum, quantified using PET. Synapse 21: 45–53

Johnson KB, Criswell HE, Jensen KF, Simson PE, Mueller RA, Breese GR (1992) Comparison of the D1-dopamine agonists SKF-38393 and A-68930 in neonatal 6-hydroxydopamine-lesioned rats: behavioral effects and induction of c-fos-like immunoreactivity. J Pharmacol Exp Ther 262: 855–865

Kostrzewa RM (1995) Dopamine receptor supersensitivity. Neurosci Biobehav Rev 19: 1–17

Kostrzewa RM, Brus R (1991) Ontogenic homologous supersensitization of quinpirole-induced yawning in rats. Pharmacol Biochem Behav 39: 517–519

Kostrzewa RM, Hamdi A, Kostrzewa FP (1990) Production of prolonged supersensitization of dopamine D_2 receptors. Eur J Pharmacol 183: 1411–1412

Kostrzewa RM, Brus R, Kalbfleisch J (1991) Ontogenetic homologous sensitization to the antinociceptive action of quinpirole in rats. Eur J Pharmacol 209: 157–161

Kostrzewa RM, Brus R, Rykaczewska M, Plech A (1993a) Low dose quinpirole ontogenically sensitizes to quinpirole-induced yawning in rats. Pharmacol Biochem Behav 44: 487–489

Kostrzewa RM, Guo J, Kostrzewa FP (1993b) Ontogenetic quinpirole treatments induce vertical jumping activity in rats. Eur J Pharmacol 239: 183–187

Kostrzewa RM, Kostrzewa JP, Brus R (2000) Dopaminergic denervation enhances susceptibility to hydroxyl radicals in rat neostriatum. Amino Acids 19: 183–199

Miller DW, Abercrombie ED (1999) Role of high-affinity dopamine uptake and impulse activity in the appearance of extracellular dopamine in striatum after administration of exogenous L-DOPA: studies in intact and 6-hydroxydopamine-treated rats. J Neurochem 72: 1516–1522

Morissette M, Goulet M, Grondin R, Blanchet P, Bedard PJ, Di Paolo T, Levesque D (1998) Associative and limbic regions of monkey striatum express high levels of dopamine D_3 receptors: effects of MPTP and dopamine agonist replacement therapies. Eur J Neurosci 10: 2565–2573

Nowak P, Brus R, Kostrzewa RM (2001) Amphetamine-induced enhancement of neostriatal *in vivo* microdialysate dopamine content in rats, quinpirole-primed as neonates. Pol J Pharmacol 53: 319–329

Opacka-Juffry J, Ashworth S, Ahier RG, Hume SP (1998) Modulatory effects of L-DOPA on D_2 dopamine receptors in rat striatum, measured using *in vivo* microdialysis and PET. J Neural Transm 105: 349–364

Oświęcimska J, Brus R, Szkilnik R, Nowak P, Kostrzewa RM (2000) 7-OH-DPAT, unlike quinpirole, does not prime a yawning response in rats. Pharmacol Biochem Behav 67: 11–15

Pilla M, Perachon S, Sautel F, Garrido F, Mann A, Wermuth CG, Schwartz J-C, Everitt BJ, Sokoloff P (1999) Selective inhibition of cocaine-seeking behaviour by a partial dopamine D_3 receptor agonist. Nature 400: 371–375

Ryoo HL, Pierrotti D, Joyce JN (1998) Dopamine D_3 receptor is decreased and D_2 receptor is elevated in the striatum of Parkinson's disease. Mov Disord 13: 788–797

Sokoloff P, Guillin O, Diaz J, Carroll P, Griffon N (2002) Brain-derived neurotrophic factor controls dopamine D_3 receptor expression: implications for neurodevelopmental psychiatric disorders. Neurotoxicity Res 4: 671–678

Szechtman H, Dai H, Mustafa S, Einat H, Sullivan RM (1994) Effects of dose and interdose interval on locomotor sensitization to the dopamine agonist quinpirole. Pharmacol Biochem Behav 48: 921–928

Ungerstedt U, Arbuthnott GW (1970) Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. Brain Res 24: 485–493

Wachtel SR, Abercrombie ED (1994) L-3,4-dihydroxyphenylalanine-induced dopamine release in the striatum of intact and 6-hydroxy-dopamine-treated rats: differential effects of monoamine oxidase A and B inhibitors. J Neurochem 63: 108–117

Zetterstrom T, Herrera-Marschitz M, Ungerstedt U (1986) Simultaneous measurement of dopamine release and rotational behaviour in 6-hydroxydopamine denervated rats using intracerebral dialysis. Brain Res 376: 1–7

Authors' address: Richard M. Kostrzewa, Ph.D., Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, PO Box 70,577, VA Bldg. #1, Rm. 1-44, Johnson City, TN 37614-0577, U.S.A.,

Fax: + 1 423 439-8773, E-mail: Kostrzew@etsu.edu