REVIEW

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Enhancing Aromatic L-amino Acid Decarboxylase Activity: Implications for L-DOPA Treatment in Parkinson's Disease

Maria Hadjiconstantinou & Norton H. Neff

Division of Molecular Neuropsychopharmacology, Departments of Psychiatry and Pharmacology, College of Medicine, Ohio State University, Columbus, OH, USA

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Correspondence
Maria Hadjiconstantinou, M.D., Division of Molecular Neuropsychopharmacology, Department of Psychiatry, College of Medicine, Ohio State University, 333 West Tenth Avenue, Columbus, OH 43210, USA.
Tel: +614-292-6168;
Fax: +614-292-7232;
E-mail: neff.6@osu.edu

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Aromatic L-amino acid decarboxylase (AAAD) is an essential enzyme for the formation of catecholamines, indolamines, and trace amines. Moreover, it is a required enzyme for converting L-DOPA to dopamine when treating patients with Parkinson's disease (PD). There is now substantial evidence that the activity of AAAD in striatum is regulated by activation and induction, and second messengers play a role. Enzyme activity can be modulated by drugs acting on a number of neurotransmitter receptors including dopamine (D1–4), glutamate (NMDA), serotonin (5-HT_{1A}, 5-HT_{2A}) and nicotinic acetylcholine receptors. Generally, antagonists enhance AAAD activity; while, agonists may diminish it. Enhancement of AAAD activity is functional, as the formation of dopamine from exogenous L-DOPA mirrors activity. Following a lesion of nigrostriatal dopaminergic neurons, AAAD in striatum responds more robustly to pharmacological manipulations, and this is true for the decarboxylation of exogenous L-DOPA as well. We review the evidence for parallel modulation of AAAD activity and L-DOPA decarboxylation and propose that this knowledge can be exploited to optimize the formation of dopamine from exogenous L-DOPA. This information can be used as a blue print for the design of novel L-DOPA treatment adjuvants to benefit patients with PD.

Introduction

It is more than 70 years since the discovery of aromatic L-amino acid decarboxylase (AAAD, EC 4.1.1.28, synonyms include: DOPA decarboxylase; tryptophan decarboxylase; 5-hydroxytryptophan decarboxylase) in mammalian tissue [1]. Its strategic importance in medicine was recognized when it was demonstrated that its substrate L- DOPA alleviated the clinical symptoms of Parkinson's disease (PD) [2–4] by replacing lost dopamine from nigrostriatal neurons. Indeed, L-DOPA has been the gold standard for PD patients' treatment since these first clinical studies. Prolonged therapy with L-DOPA, however, is associated with diminishing effectiveness and motor complications. L-DOPA pharmacokinetics, continual degeneration of dopamine containing neurons, and changes of dopamine receptors and their signaling might be the underlying causes. Although, there has been a long-standing discussion as to why and how L-DOPA looses effectiveness, the enzyme that forms dopamine from L-DOPA and AAAD has received minimal consideration. Perhaps this is because to many investigators AAAD is an uninteresting enzyme; it is relatively nonspecific, it is rather widely distributed, and it is normally not rate-limiting for dopamine synthesis [5]. Unfortunately, this dogmatic and erroneous viewpoint still persists despite the newer developments in AAAD neurochemistry and its implications for L-DOPA treatment for PD. There is now substantial evidence that the activity of AAAD, the second enzyme in the pathway leading to the biosynthesis of dopamine, is regulated and L-DOPA decarboxylation mirrors enzyme regulation. Decarboxylation of L-DOPA by AAAD is the controlling step for the formation of dopamine in Parkinsonian patients, and altered enzyme activity and regulation might contribute to the decreasing therapeutic response of L-DOPA. The reviewed preclinical evidence advances the concept that AAAD is a potential target for pharmacological

intervention in PD, and that drugs that modulate AAAD activity could be considered as a potential adjuvant when developing strategies for L-DOPA treatment augmentation.

AAAD is a Regulated Enzyme

AAAD is regulated *in vivo* and *in vitro,* and regulation involves both enzyme activation and induction. Activation *in vivo* occurs in response to the acute action of physiological stimuli, drugs that act at neurotransmitter receptors, or modulation of the activity of endogenous kinases/phosphatases [6–16]. In striatum and retina, kinetic activation of AAAD is rapid, short-lasting, and characterized by changes in the apparent Vmax for both the substrate and the cofactor pyridoxal-5′-phosphate, suggesting partial phosphorylation of the enzyme [6,7]. Indeed, phosphorylation appears to play a role in the activation of the enzyme *in vivo*. Injection of either forskolin [12] or phorbol-12,13-myristic acid (PMA) [11] intracerebroventricularly (icv) increases the activity of AAAD in striatum, a response that can be blocked by selective inhibitors of protein kinase A (PKA) or protein kinase C (PKC). In addition, okadaic acid, a protein phosphatase PP1 and PP2A inhibitor, exaggerates the response to PMA [11]. Notably, diminished serine phosphorylation and AAAD activity has been described in dopaminergic cells that overexpress α-synuclein, attributed to enhanced PP2A activity [17]. *In vitro* studies with recombinant and brain (striatum and midbrain) AAAD demonstrated that the enzyme is phosphorylated and activated by PKA, but not PKC [18], indicating that the effect of PKC activators *in vivo* is apparently indirect. Additionally, *in vitro* evidence suggests that recombinant and brain AAAD can be phosphorylated by protein kinase G (PKG), but its biological role remains to be elucidated (personal observation).

The early activation of AAAD is followed by a late, longer lasting (hours) response, which is accompanied by an increase in AAAD mRNA and protein [7,13,19]. Prolonged induction of AAAD (days) also occurs after chronic administration of neuroactive drugs [20]. Although the transcription of AAAD in neuronal cells is not fully explored, the presence of putative regulatory elements on the promoter [21–23] (Genbank AY37370) and the observation that pharmacological agents, hormones, and trophic factors change the abundance of AAAD mRNA [13,19,24–31] imply that the transcriptional regulation of the enzyme is possible. The finding that icv forskolin induces a late increase of AAAD activity and mRNA in midbrain neurons suggests that cyclic-AMP might regulate the transcription of AAAD *in vivo* [10].

Even if AAAD is a regulated enzyme, there is no evidence supporting a rate limiting action for the synthesis of dopamine under normal circumstances. Despite commonalities in regulatory mechanisms and responses [10,19,24,28,32], often the pharmacological regulation of AAAD and tyrosine hydroxylase, the rate limiting enzyme for dopamine synthesis, in the striatum is discordant [13,20,31] suggesting (i) that AAAD might serve additional function(s); and/or (ii) that AAAD regulation might, in part, occur in extra-dopaminergic sites in striatum. Indeed, AAAD is the rate-limiting enzyme for the synthesis of trace amines [5]; it is present in serotonergic and noradrenergic neurons and in a subset of $AAAD^+$ neurons in striatum [33–35]; and AAAD mRNA increases in the locus coeruleus and raphe nuclei, in addition to substantia nigra pars compacta and ventral tegmental area, after pharmacological manipulations [19].

Receptors and Regulation of Striatal AAAD

Dopamine Receptors

Cumulative evidence suggests that acute or chronic blockade of D1- and D2-like receptors increase the activity of AAAD in rodent striatum (Table 1). Selec-

Table 1 Drugs acting at dopamine receptors and AAAD activity

Receptor type	Drug	AAAD activity		References
		Acute	Chronic	
D1-like				
Agonists	SKF 38393	↔	↑↔	7,13,20
Antagonists	SCH 23390	↑	↑	7,13,20,9,36
D2-like				
Agonists	Bromocryptine	↓	↓	7,13,20,36
	Quinpirole	↔	↓	7,13,20,36
	7-OH-DPAT	↓	↔	13,20
Antagonists	Haloperidol	↑	↑	7,13,20
	Sulpiride	↑	↑	7
	Spiperone*	↑	↑	13,20
	Flupenthixol	↑	ND	36
	Pimozide	↑	ND	9
	Remoxipride	↑	ND	36
	Clozapine*	↑	ND	19
	L-745,870	↑	ND	19
Dopamine receptors				
Indirect agonists	L-DOPA	↓	↓	7,16
	Clorgyline	↓	ND	31
	Pargyline	↓	ND	31

Effect of acute or chronic treatment with dopamine receptor agonists or antagonists on AAAD activity in the striatum: ↓ = decrease AAAD activity; ↑ = increase of AAAD activity; ↔ = No change of activity.
*5-HT2A antagonist action; ND = not determined.

tive or mixed D1, D2, D3 or D4 antagonists administered acutely, all elevate striatal AAAD activity, and a similar effect has been observed with multireceptor drugs displaying affinity for D2-like receptors, such as spiperone and clozapine [7,9,13,19,36]. In general, there is an early transient activation and a late induction, and the latter is accompanied by a rise in enzyme mRNA in midbrain and protein content in the striatum [7,13]. Similarly, chronic blockade of D1- and D2-like receptors results in a prolonged increase of AAAD activity in striatum and mRNA in brain and midbrain nigrostriatal neurons [20,37], and similar results are observed after icv administration of a D2 receptor antisense oligodeoxynucleotide [29]. In the same line, PET studies measuring ^{18}F-L-DOPA uptake have shown suppressed AAAD activity in the ventral striatum of drug-free schizophrenics, which is increased with typical or atypical antipsychotic treatment [38]. Finally, depletion of dopamine by reserpine increases AAAD activity in striatum [7,39,40].

Studies with agonists suggest that dopamine receptor activation decreases enzyme activity, but the responses are variable and modest. In rodents, acute or chronic administration of D_2-like agonists, particularly bromocryptine, suppresses the activity of AAAD in striatum; while, the effect of D1-like agonists SKF 38393 is inconsistent [7,13,16,20,36]. Correspondingly, acute or chronic administration of L-DOPA [7,16] and inhibition of MAO A which raises synaptic dopamine [31,41] also decreases AAAD activity in striatum. Deprenyl attenuates AAAD activity in striatum at doses that inhibit both MAO B and MAO A [31] and elevates mRNA in the substantia nigra pars compacta and ventral tegmental area [27]. In agreement with the neurochemical studies, enhancement of AAAD activity following flupenthixol and diminution by apomorphine has been observed by following [^{3}H]DOPA conversion to [^{3}H]dopamine in the rat striatum *in vivo* [42]. Moreover, PET studies have documented an increase in AAAD activity in the human and porcine striatum after haloperidol [43,44], and a decrease in AAAD activity in the macaque striatum after MAO B inhibition [45]. In humans, AAAD activity appears to be genetically determined, as healthy subjects carrying the A1 allele of the human D2 receptor gene have increased enzyme activity in striatum, presumably due to decreased D2 autoreceptor function [46].

Other Receptors

Even though the majority of the studies have focused on the regulation of AAAD by dopamine receptors, a notable body of evidence suggests that the enzyme is subjected to regulation by other neurotransmitter receptors as well (Table 2). The emerging picture supports the idea that serotonergic, glutamatergic, and nicotinic receptors (Table 2) modulate AAAD activity; whereas, involvement of alpha adrenergic, muscarinic, and GABA receptors appears less likely in brain. For example, the 5-HT_{2A}/5-HT_{2C} antagonist ketanserin, the 5-HT_{1A}/5-HT_{2A} antagonist metergoline, and the 5-HT_{1A} selective antagonist Way 100635 all increase AAAD activity in striatum after acute administration, while selective antagonists of 5-HT_{2C} and 5-HT_3 receptors do not influence enzyme activity [19]. Acute blockade of the glutamate NMDA ionotropic receptors by the noncompetitive antagonist MK-801 enhances the activity of AAAD in striatum [30], and similar observations have been made for other NMDA channel blockers, phencyclidine, budipine, amantadine, memantine, and dextromethorphan [14–16]. Unlike NMDA competitive antagonists, antagonists acting at the glycine or polyamine site, and AMPA noncompetitive antagonists have little effect [14,15]. AAAD in dopaminergic and nondopaminergic neurons might be regulated by NMDA receptors, as acute administration of MK-801 increases the expression of AAAD mRNA in midbrain [30]; whereas, chronic administration of phencyclidine has been shown to augment AAAD mRNA in striatum [47] indicating possible regulation in AAAD$^+$ neurons of the region. Acute, intermittent, or chronic administration of nicotine has no effect on AAAD activity (unpublished personal observations). In contrast, mecamylamine, a noncompetitive nicotine receptor antagonist, increases enzyme activity (unpublished personal observations). Alpha$_1$- and alpha$_2$-adrenergic and muscarinic receptors do not appear to play a role in the acute regulation of AAAD in striatum [19], and we have made similar observations for $GABA_A$ and $GABA_B$ receptors (unpublished personal observations). In the retina in contrast to the striatum, blockade of alpha$_2$-adrenergic receptors increases, while activation of the receptor decreases enzyme activity [8]. Perhaps in different regions of the nervous system the biochemical mechanisms and receptors for regulating AAAD activity vary.

Taken together, the dopaminergic, glutamatergic, and setotonergic system have been identified as candidate targets for pharmacological regulation of AAAD via selective receptors (Table 2). Apparently in nigrostriatal neurons AAAD is under dopaminergic control, and dopamine receptors regulate enzyme activity via presynaptic (D2, D3) and post-synaptic (D1, D2) mechanisms [13]. Collectively, the studies reviewed so far imply that under normal conditions, dopamine exerts tonic inhibition of AAAD activity in dopaminergic neurons via autoreceptors. Glutamate, NMDA, and serotonin, 5-HT_{1A} and 5-HT_{2A}, receptors modulate dopaminergic neuron firing, dopamine synthesis and release (for reviews see [48–51]) and their respective antagonists could affect AAAD

Table 2 Drugs acting on various neurotransmitter receptors and AAAD activity

Receptor type	Drug	AAAD activity	Reference
Alpha adrenergic			
Alpha 1 agonist	Methoxamine	↔	a
Alpha 1 antagonist	Prazosin	↔	19
Alpha 2 agonist	Clonidine	↔↑	a,30
Alpha 2 antagonist	Yohimbine	↔	19
Cholinergic			
nAChR agonist	Nicotine	↔	a
nAChR antagonist	Mecamylamine	↑	a
mAChR agonist	Oxotremorine	↔	a
mAChR antagonist	Atropine	↔	19,30
Serotonergic			
5-HT_{1A} antagonist	Way 100635	↑	19
	Metergoline	↑	19
5-HT_{2A} antagonist	Ketanserin	↑	19
	Spiperone*	↑	19
	Clozapine*	↑	19
5-HT_{2C} antagonist	SB-242084	↔	19
5-HT_3 antagonist	Tropiserton	↔	19
GABAergic			
GABAA antagonist	Bicuculine	↔	a
GABAB antagonist	SCH 50911	↔	a
Glutamatergic			
NMDA channel blockers	MK-801	↑	30,14,15
	Phencyclidine	↑	14
	Amantadine	↑	14,15,16
	Memantine	↑	14,15,16
	Dextromethorphan	↑	13,14
	Budipine	↑	14,15,16,40
NMDA polyamine site antagonist	Eliprodil	↔	14,15
NMDA glycine site antagonist	R-HA 966	↔	14,15
NMDA competitive antagonist	CGP 40116	↔	14,15
AMPA noncompetitive antagonist	NBQX	↔	14,15

Antagonist drugs were administered acutely and AAAD activity estimated in striatum: ↓ = decrease AAAD activity; ↑ = increase of AAAD activity; ↔ = No change of activity.

*D2-like antagonist action; a = unpublished personal results.

activity, at least in part, by disinhibiting dopaminergic control. Although studies exploring the regulation of AAAD in serotonergic neurons are lacking, we speculate that in analogy with dopaminergic neurons, AAAD in serotonergic neurons is under the control of serotonin and 5-HT_{1A}, antagonists could regulate AAAD expression in raphe nuclei [19] via somatodendritic autoreceptors [50].

Receptors and L-DOPA Decarboxylation

Support for the notion that elevated AAAD is associated with enhanced conversion of L-DOPA to dopamine under physiological conditions was first provided in studies of retina dopaminergic neurons. Exposing rats to environmental light, which increases AAAD activity in retina, enhances the conversion of exogenous L-DOPA to dopamine [52]. Subsequent studies in the striatum demonstrated that moderate changes in AAAD activity appear to be functionally responsive to exogenous L-DOPA. Indeed, dopamine formation, release, and metabolism from exogenous L-DOPA are enhanced following treatment with drugs that increase AAAD activity. Systemic administration of the D1 antagonist SCH 23390 and the multireceptor (including D2-like and 5-HT_{2A}) antagonist clozapine prior to exogenous L-DOPA causes an about 40% increase in L-DOPA decarboxylation product formation and a doubling of dopamine turnover rate in striatum [19,53]. The noncompetitive NMDA antagonist budipine enhances dopamine and DOPAC released

Table 3 AAAD regulation and L-DOPA decarboxylation in PD models

Drug	AAAD	L-DOPA product	Animal model	Reference
DA receptors antagonists				
SCH 23390	↑	↑ (tissue DA + DOPAC)	MPTP	53
Sulpiride	↑	↑ (dialysate DA + DOPAC)	Reserpine	40
Clozapine	↑	↑ (tissue DA + DOPAC)	MPTP	19
GLU receptor antagonists				
Budipine	↑	↑ (dialysate DA + DOPAC)	Reserpine	40,54
MK-801	↑	↑ (dialysate DA)	6-OHDA	65
Amantadine	↑	↑ (dialysate DA)	6-OHDA	66

L-DOPA and antagonists were administered systemically and dopamine (DA) and DOPAC formation measured in striatum.

by exogenous L-DOPA in striatum, studied by *in vivo* microdialysis, suggesting increased dopamine availability in the synapse [54]. Furthermore, the decarboxylation rate of radiolabeled L-DOPA is augmented in the striatum following treatment with MK-801 [55]. Potentiation of L-DOPA decarboxylation by AAAD inducers depends on and is proportional to AAAD activity [19,53], and reflects an increase in the magnitude and duration of the response [19,53,54]. More importantly, the effect is most evident with low doses of L-DOPA. Augmented L-DOPA decarboxylation in striatum apparently occurs in dopaminergic neurons, since increased dopamine formation, release, and metabolism have also been observed in the substantia nigra of animals treated with L-DOPA and drugs that induce AAAD activity [53,54]. Support, albeit limited, for these preclinical studies has been provided by a report that following treatment of humans with amantadine, the rate of conversion of [^{18}F]DOPA to [^{18}F]dopamine is accelerated in striatum consistent with enhanced AAAD activity and L-DOPA decarboxylation [56].

Taken together, it appears that the drugs that increase AAAD activity in striatum have the potential to enhance dopamine formation from exogenous L-DOPA, and accordingly antagonists of dopamine (D1–4), serotonin (5-HT$_{2A;}$5-HT$_{1A}$), glutamate (NMDA), and nicotinic receptors (Tables 1 and 2) are expected to act as L-DOPA decarboxylation enhancers. While in theory agonists could attenuate L-DOPA decarboxylation, the impact of reduced AAAD activity on dopamine formation from exogenous L-DOPA is unexplored. L-DOPA decarboxylation in striatum occurs in dopaminergic as well as nondopaminergic sites [33–35,57–63], questioning whether neuronal-phenotype selective modulation of L-DOPA decarboxylation is feasible. We will argue that the number of neurotransmitter receptors shown to regulate AAAD in striatum and the finding that enzyme expression in raphe nuclei and locus coeruleus [19] is elevated by clozapine favor such a probability. The ability to pharmacologically manage AAAD activity and L-DOPA decarboxylation in dopaminergic, serotonergic, noradrenergic, or AAAD$^+$ neurons is of strategic importance for the treatment of PD.

AAAD Activity and L-DOPA Decarboxylation in PD Models

AAAD activity in nigrostriatal neurons appears to be upregulated soon after a MPTP lesion [64] implying the involvement of compensatory or altered regulatory mechanisms. In MPTP-treated mice, AAAD in the denervated striatum responds more robustly to D1- and D2-like antagonists [7], and the same appears to be true for clozapine, a broad spectrum receptor antagonist (Table 3) [19]. We have termed this exaggerated responsiveness of AAAD after a lesion of the nigrostriatal neurons "presynaptic supersensitivity," and it is manifested by a shift of the time- and dose–response curves to the left and upward; that is, AAAD activity is more pronounced and observed earlier and with lower antagonist doses. Altered posttranslational modification of AAAD after MPTP and/or altered receptor/second messenger signaling cascades secondary to the dopaminergic lesion might underlie this phenomenon. Indeed, the magnitude of exogenous PKA-induced AAAD phosphorylation is greater in homogenates prepared from striatum and midbrain of MPTP-lesioned mice, with the response increasing with time following the lesion (unpublished observations), and icv administration of forskolin in MPTP-mice amplifies the activation of the enzyme and causes an earlier induction of AAAD mRNA [10,12]. In contrast, MPTP treatment shortens the duration of AAAD activation by icv administered PMA, and abolishes the PMA-induced late rise of AAAD mRNA [10,11].

The "supersensitive" response of AAAD to pharmacological enhancers in the MPTP-mouse is mirrored by the rate of L-DOPA decarboxylation. The response to dopamine receptor antagonism by SCH 23390 and clozapine is striking, with a doubling in total decarboxylation product formation and dopamine turnover rate in both striatum and midbrain, estimated in tissue homogenates, and the response being AAAD-dependent and proportional to the magnitude of enzyme induction [19,53]. These data imply that the enzyme activity is closely associated with substrate response and is a determining factor for the formation of dopamine. It should be stressed that neither the lesion nor SCH 23390 [53] or clozapine (unpublished personal observations) alter the levels of DOPA in the striatum following exogenous L-DOPA administration.

Unlike the tissue L-DOPA decarboxylation studies summarized above, *in vivo* dialysis measurements of extracellular dopamine are influenced by the formation, storage, release, transport, and metabolism of the amine, and although they provide an approximate index for the intrasynaptic availability of dopamine, they are not reliable estimators of L-DOPA decarboxylation. Notwithstanding, *in vivo* dialysis studies investigating the effect of NMDA receptor blockade on L-DOPA decarboxylation in reserpine treated and 6-OHDA-lesioned rats have provided in general supportive results. Systemic administration or local infusion of budipine markedly increases the magnitude and duration of L-DOPA-stimulated dopamine release in the striatum and substantia nigra of rats treated with reserpine [39,40,54], and AAAD inhibition blocks the response [40]. Likewise, systemic administration of MK-801 or amantadine enhances the L-DOPA-induced dopamine release in the 6-OHDA denervated striatum [65,66]. Whether NMDA antagonists can produce AAAD "supersensitive responses" in animals with compromised dopaminergic neurotransmission needs exploration; while budipine appears to increase AAAD activity about the same in the striatum of control and reserpine treated rats [14], CGP 40116 and HA 966, that are ineffective in control animals [14], markedly augment enzyme activity [16].

Imaging studies using ^{18}F-DOPA [67,68] have shown that the PD process differentially affects AAAD in various brain regions and within the striatum over time [69–73], and have estimated a relative upregulation of striatal AAAD by comparison to other neurochemical, neuroanatomical, and imaging dopaminergic markers [74–77]. Although this has been attributed to a compensatory increase of AAAD activity in the remaining dopaminergic neurons, serotonergic, noradrenergic, and intrinsic striatal neurons contribute to the AAAD measurements and enzyme activity in striatum [71,73] and might add to the calculated AAAD "upregulation" [77] as well. Regardless, radiotracer imaging studies have strengthened our original proposal that AAAD is a regulated enzyme [6,7] and provided clues supporting the idea that AAAD can be subjected to pharmacological manipulation in PD. For example, therapeutic infusion of L-DOPA or apomorphine caused a small decrease in L-[^{11}C]DOPA influx in the striatum with early but not advanced PD [78,79]; while, oral administration of 100 mg of L-DOPA had no measurable effect on ^{18}F-DOPA uptake [80]. Reported [81] decreases in putamen AAAD activity following a 2-year treatment with L-DOPA, –20.3%, or a D2 agonist, –13.4%, are intriguing but difficult to interpret, as there is enzyme activity loss over time [72,76,82]. However, the study was performed over 12 h following drug removal, a time that AAAD activity is decreased in rodent striatum [7,20], and the decrease of putamen AAAD activity in PD has been calculated between 7% and 10% annually [72,82–85].

To complete our understanding of AAAD regulation after a dopaminergic lesion, studies investigating the effect of L-DOPA and dopamine agonists on AAAD and L-DOPA decarboxylation in PD models are needed. Progressive loss of presynaptic dopaminergic control might alter enzyme regulation under basal conditions and following receptor stimulation. Finally, it should be stressed that depending on the progression of dopaminergic loss, L-DOPA decarboxylation in striatum is expected to increasingly take place in nondopaminergic sites. While this possibility has been much talked about, little is known as to how AAAD and L-DOPA decarboxylation are regulated outside the dopaminergic neurons and the contribution of such a regulation to the formation of dopamine from exogenously administered L-DOPA in the dopaminergically denervated striatum.

Clinical Implications

When treating PD patients with exogenous L-DOPA, AAAD becomes the rate-limiting step for the formation of dopamine and the potential to modulate the activity of the enzyme by pharmacological means should not be disregarded. We propose that enhancing and stabilizing AAAD activity might be an alternative approach to achieve and maintain optimal dopaminergic transmission with L-DOPA treatment, and AAAD inducers may prove to be useful L-DOPA adjuncts. Drugs that increase AAAD activity in the striatum enhance the formation of dopamine from L-DOPA, and are expected to decrease the dose of L-DOPA, smooth the rise and fall of striatal dopamine following intermittent administration of

L-DOPA, and maintain relatively constant levels of intrasynaptic dopamine resulting, thus, to a more physiological receptor stimulation. Hence, L-DOPA decarboxylation enhancers could meet two important tenets for successful L-DOPA therapy: (i) to use the least amount of drug that improves disability and (ii) to achieve a relatively continuous stimulation of dopamine receptors [86–88]. High doses of L-DOPA are associated with an increased risk of motor complications [89,90], and continuous dopaminergic stimulation in early PD is believed to reduce this risk [87,88,91].

AAAD enhancement strategies are envisioned to initially aim at the residual nigrostriatal dopaminergic neurons, where physiological L-DOPA decarboxylation occurs and tonic release of dopamine is therapeutically desirable. As the disease advances and L-DOPA decarboxylation shifts to nondopaminergic neurons, however, it is sensible that AAAD in these neurons be targeted as well. Ostensibly, such strategy requires the development of neuronal-phenotype selective AAAD inducers, and a better understanding of how L-DOPA decarboxylation in nondopaminergic neurons is regulated and newly formed dopamine is stored and released. It has been estimated that a decrease of 30–50% in putamen AAAD might represent the threshold for the onset of motor symptoms in PD [77]. Given that the annual decline rate of AAAD activity in Parkinsonian patients has been estimated between 7% and 10% in putamen and 3% and 7% in caudate [72,82–85,92], we surmise that stabilizing AAAD activity about or over the estimated threshold might be most favorable for maintaining physiological dopaminergic neurotransmission under standard intermittent oral L-DOPA treatment. Preclinical studies predict that this strategy would appreciably reduce the daily dose of L-DOPA and elevate the striatal levels of dopamine during the periods of low L-DOPA troughs in the plasma.

Clinical studies provide implicit support for the translational inferences we made afore. The L-DOPA adjuvants amantadine, budipine and memantine, increase AAAD activity and L-DOPA decarboxylation in experimental animals [14–16], improve Parkinsonian symptoms [93–98] and reduce motor complications [98,99]. In L-DOPA treated patients, the atypical antipsychotic clozapine moderately improves motor performance [100–107] and reduces motor fluctuations and dyskinesias [99,107–113], while in a PD model, it augments AAAD activity and L-DOPA decarboxylation [19]. Finally, the antidepressants mianserin, nefazodone, and ritanserin improve Parkinsonian symptoms [114–116] and the blockade of 5-HT_{2A} receptors enhances AAAD activity in the striatum of mice [19]. These observations call for further studies to understand the role of AAAD in L-DOPA treatment and adjuvant L-DOPA therapies. From the emerging pharmacological profile, it is obvious that AAAD induction may not be the exclusive property of L-DOPA decarboxylation enhancers, and other independent pharmacological actions may be advantageous for treating PD psychomotor abnormalities not responding to L-DOPA, for example, tremor, dementia, depression, etc, and/or L-DOPA-associated side effects. Available NMDA and 5-HT_{2A} antagonists appear to meet these criteria, and further preclinical studies are recommended. Adenosine A_{2A} receptor antagonists are another interesting group of drugs, as they enhance L-DOPA decarboxylation in animals [117] and potentiate the anti-Parkinson effect of L-DOPA [118], apparently via an association with D2 receptors [119] that are known to regulate AAAD [7,9]. Preclinical studies have indicated that L-DOPA decarboxylation enhancers can encompass a broad class of neuroactive drugs targeting AAAD expression in various neuronal populations in striatum, and the translational challenge ahead is to identify them. Selective and rational use of such drugs during the various stages of PD could improve therapeutic outcome and prolong the efficacy of L-DOPA treatment with regard to Parkinsonian symptoms, and as a consequence delay/reduce unwanted motor complications.

Conflict of Interest

The authors have no conflicts of interest.

References

1. Holtz P, Heise R, Ludtke K. Fermentativer Abbau von L-Dioxyphenylalanin (Dopa) durch Niere. *Naunyn Schmiedeberg's Arch exp Path Pharmak* 1938;**191**:87–118.
2. Birkmayer W, Hornykiewicz O. [The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia.]. *Wien Klin Wochenschr* 1961;**73**:787–788.
3. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of Parkinsonism. *N Engl J Med* 1967;**276**:374–379.
4. Yahr MD, Duvoisin RC, Schear MJ, Barrett RE, Hoehn MM. Treatment of Parkinsonism with levodopa. *Arch Neurol* 1969;**21**:343–354.
5. Berry MD, Juorio AV, Li XM, Boulton AA. Aromatic L-amino acid decarboxylase: A neglected and misunderstood enzyme. *Neurochem Res* 1996;**21**:1075–1087.
6. Hadjiconstantinou M, Rossetti Z, Silvia C, Krajnc D, Neff NH. Aromatic L-amino acid decarboxylase activity of the rat retina is modulated in vivo by environmental light. *J Neurochem* 1988;**51**:1560–1564.
7. Hadjiconstantinou M, Wemlinger TA, Sylvia CP, Hubble JP, Neff NH. Aromatic L-amino acid decarboxylase

activity of mouse striatum is modulated via dopamine receptors. *J Neurochem* 1993;**60**:2175–2180.
8. Rossetti Z, Krajnc D, Neff NH, Hadjiconstantinou M. Modulation of retinal aromatic L-amino acid decarboxylase via alpha 2 adrenoceptors. *J Neurochem* 1989;**52**:647–652.
9. Zhu MY, Juorio AV, Paterson IA, Boulton AA. Regulation of aromatic L-amino acid decarboxylase by dopamine receptors in the rat brain. *J Neurochem* 1992;**58**:636–641.
10. Young EA, Duchemin AM, Neff NH, Hadjiconstantinou M. Parallel modulation of striatal dopamine synthetic enzymes by second messenger pathways. *Eur J Pharmacol* 1998;**357**:15–23.
11. Young EA, Neff NH, Hadjiconstantinou M. Phorbol ester administration transiently increases aromatic L-amino acid decarboxylase activity of the mouse striatum and midbrain. *J Neurochem* 1994;**63**:694–697.
12. Young EA, Neff NH, Hadjiconstantinou M. Evidence for cyclic AMP-mediated increase of aromatic L-amino acid decarboxylase activity in the striatum and midbrain. *J Neurochem* 1993;**60**:2331–2333.
13. Cho S, Neff NH, Hadjiconstantinou M. Regulation of tyrosine hydroxylase and aromatic L-amino acid decarboxylase by dopaminergic drugs. *Eur J Pharmacol* 1997;**323**:149–157.
14. Fisher A, Biggs CS, Starr MS. Differential effects of NMDA and non-NMDA antagonists on the activity of aromatic L-amino acid decarboxylase activity in the nigrostriatal dopamine pathway of the rat. *Brain Res* 1998;**792**:126–132.
15. Fisher A, Biggs CS, Starr MS. Effects of glutamate antagonists on the activity of aromatic L-amino acid decarboxylase. *Amino Acids* 1998;**14**:43–49.
16. Fisher A, Starr MS. Opposite effects of glutamate antagonists and antiparkinsonian drugs on the activities of DOPA decarboxylase and 5-HTP decarboxylase in the rat brain. *Brain Res* 2000;**868**:268–274.
17. Tehranian R, Montoya SE, van Laar AD, Hastings TG, Perez RG. Alpha-synuclein inhibits aromatic amino acid decarboxylase activity in dopaminergic cells. *J Neurochem* 2006;**99**:1188–1196.
18. Duchemin AM, Berry MD, Neff NH, Hadjiconstantinou M. Phosphorylation and activation of brain aromatic L-amino acid decarboxylase by cyclic AMP-dependent protein kinase. *J Neurochem* 2000;**75**:725–731.
19. Neff NH, Wemlinger TA, Duchemin AM, Hadjiconstantinou M. Clozapine modulates aromatic L-amino acid decarboxylase activity in mouse striatum. *J Pharmacol Exp Ther* 2006;**317**:480–487.
20. Cho S, Duchemin AM, Neff NH, Hadjiconstantinou M. Tyrosine hydroxylase, aromatic L-amino acid decarboxylase and dopamine metabolism after chronic treatment with dopaminergic drugs. *Brain Res* 1999;**830**:237–245.
21. Aguanno A, Lee MR, Marden CM, Rattray M, Gault A, Albert VR. Analysis of the neuronal promoter of the rat aromatic L-amino acid decarboxylase gene. *J Neurochem* 1995;**65**:1944–1954.
22. Hahn SL, Hahn M, Kang UJ, Joh TH. Structure of the rat aromatic L-amino acid decarboxylase gene: Evidence for an alternative promoter usage. *J Neurochem* 1993;**60**:1058–1064.
23. O'Malley KL, Harmon S, Moffat M, Uhland-Smith A, Wong S. The human aromatic L-amino acid decarboxylase gene can be alternatively spliced to generate unique protein isoforms. *J Neurochem* 1995;**65**:2409–2416.
24. Wessel TC, Joh TH. Parallel upregulation of catecholamine-synthesizing enzymes in rat brain and adrenal gland: Effects of reserpine and correlation with immediate early gene expression. *Brain Res Mol Brain Res* 1992;**15**:349–360.
25. Li XM, Juorio AV, Boulton AA. NSD-1015 alters the gene expression of aromatic L-amino acid decarboxylase in rat PC12 pheochromocytoma cells. *Neurochem Res* 1993;**18**:915–919.
26. Li XM, Juorio AV, Boulton AA. Induction of aromatic L-amino acid decarboxylase mRNA by interleukin-1 beta and prostaglandin E2 in PC12 cells. *Neurochem Res* 1994;**19**:591–595.
27. Li XM, Juorio AV, Paterson IA, Zhu MY, Boulton AA. Specific irreversible monoamine oxidase B inhibitors stimulate gene expression of aromatic L-amino acid decarboxylase in PC12 cells. *J Neurochem* 1992;**59**:2324–2327.
28. Kim KT, Park DH, Joh TH. Parallel up-regulation of catecholamine biosynthetic enzymes by dexamethasone in PC12 cells. *J Neurochem* 1993;**60**:946–951.
29. Hadjiconstantinou M, Neff NH, Zhou LW, Weiss B. D2 dopamine receptor antisense increases the activity and mRNA of tyrosine hydroxylase and aromatic L-amino acid decarboxylase in mouse brain. *Neurosci Lett* 1996;**217**:105–108.
30. Hadjiconstantinou M, Rossetti ZL, Wemlinger TA, Neff NH. Dizocilpine enhances striatal tyrosine hydroxylase and aromatic L-amino acid decarboxylase activity. *Eur J Pharmacol* 1995;**289**:97–101.
31. Cho S, Duchemin AM, Neff NH, Hadjiconstantinou M. Modulation of tyrosine hydroxylase and aromatic L-amino acid decarboxylase after inhibiting monoamine oxidase-A. *Eur J Pharmacol* 1996;**314**:51–59.
32. Baptista MJ, O'Farrell C, Daya S, Ahmad R, Miller DW, Hardy J, Farrer MJ, Cookson MR. Co-ordinate transcriptional regulation of dopamine synthesis genes by alpha-synuclein in human neuroblastoma cell lines. *J Neurochem* 2003;**85**:957–968.
33. Tashiro Y, Kaneko T, Sugimoto T, Nagatsu I, Kikuchi H, Mizuno N. Striatal neurons with aromatic L-amino acid

decarboxylase-like immunoreactivity in the rat. *Neurosci Lett* 1989;**100**:29–34.
34. Eaton MJ, Gudehithlu KP, Quach T, Silvia CP, Hadjiconstantinou M, Neff NH. Distribution of aromatic L-amino acid decarboxylase mRNA in mouse brain by in situ hybridization histology. *J Comp Neurol* 1993;**337**:640–654.
35. Meredith GE, Farrell T, Kellaghan P, Tan Y, Zahm DS, Totterdell S. Immunocytochemical characterization of catecholaminergic neurons in the rat striatum following dopamine-depleting lesions. *Eur J Neurosci* 1999;**11**:3585–3596.
36. Zhu MY, Juorio AV, Paterson IA, Boulton AA. Regulation of striatal aromatic L-amino acid decarboxylase: Effects of blockade or activation of dopamine receptors. *Eur J Pharmacol* 1993;**238**:157–164.
37. Buckland PR, O'Donovan MC, McGuffin P. Changes in dopa decarboxylase mRNA but not tyrosine hydroxylase mRNA levels in rat brain following antipsychotic treatment. *Psychopharmacology (Berl)* 1992;**108**:98–102.
38. Elkashef AM, Doudet D, Bryant T, Cohen RM, Li SH, Wyatt RJ. 6-(18)F-DOPA PET study in patients with schizophrenia. Positron emission tomography. *Psychiatry Res* 2000;**100**:1–11.
39. Biggs CS, Fisher A, Starr MS. The antiparkinsonian drug budipine stimulates the activity of aromatic L-amino acid decarboxylase and enhances L-DOPA-induced dopamine release in rat substantia nigra. *Synapse* 1998;**30**:309–317.
40. Fisher A, Biggs CS, Eradiri O, Starr MS. Dual effects of L-3,4-dihydroxyphenylalanine on aromatic L-amino acid decarboxylase, dopamine release and motor stimulation in the reserpine-treated rat: Evidence that behaviour is dopamine independent. *Neuroscience* 2000;**95**:97–111.
41. Cumming P, Kuwabara H, Ase A, Gjedde A. Regulation of DOPA decarboxylase activity in brain of living rat. *J Neurochem* 1995;**65**:1381–1390.
42. Cumming P, Ase A, Laliberte C, Kuwabara H, Gjedde A. In vivo regulation of DOPA decarboxylase by dopamine receptors in rat brain. *J Cereb Blood Flow Metab* 1997;**17**:1254–1260.
43. Vernaleken I, Kumakura Y, Cumming P, Buchholz HG, Siessmeier T, Stoeter P, et al. Modulation of [18F]fluorodopa (FDOPA) kinetics in the brain of healthy volunteers after acute haloperidol challenge. *Neuroimage* 2006;**30**:1332–1339.
44. Danielsen EH, Smith D, Hermansen F, Gjedde A, Cumming P. Acute neuroleptic stimulates DOPA decarboxylase in porcine brain in vivo. *Synapse* 2001;**41**:172–175.
45. DeJesus OT, Flores LG, Roberts AD, Dick DW, Bartlett RM, Murali D, et al. Aromatic L-amino acid decarboxylase (AAAD) activity in rhesus macaque striatum after MAO-B inhibition by Ro 16-6491. *Synapse* 2005;**56**:54–56.
46. Laakso A, Pohjalainen T, Bergman J, Kajander J, Haaparanta M, Solin O, et al. The A1 allele of the human D2 dopamine receptor gene is associated with increased activity of striatal L-amino acid decarboxylase in healthy subjects. *Pharmacogenet Genomics* 2005;**15**:387–391.
47. Buckland PR, Marshall R, Watkins P, McGuffin P. Does phenylethylamine have a role in schizophrenia?: LSD and PCP up-regulate aromatic L-amino acid decarboxylase mRNA levels. *Brain Res Mol Brain Res* 1997;**49**:266–270.
48. Zigmond MJ, Castro SL, Keefe KA, Abercrombie ED, Sved AF. Role of excitatory amino acids in the regulation of dopamine synthesis and release in the neostriatum. *Amino Acids* 1998;**14**:57–62.
49. David HN, Ansseau M, Abraini JH. Dopamine-glutamate reciprocal modulation of release and motor responses in the rat caudate-putamen and nucleus accumbens of "intact" animals. *Brain Res Brain Res Rev* 2005;**50**:336–360.
50. Alex KD, Pehek EA. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacol Ther* 2007;**113**:296–320.
51. Bustos G, Abarca J, Campusano J, Bustos V, Noriega V, Aliaga E. Functional interactions between somatodendritic dopamine release, glutamate receptors and brain-derived neurotrophic factor expression in mesencephalic structures of the brain. *Brain Res Brain Res Rev* 2004;**47**:126–144.
52. Xu JA, Hadjiconstantinou M, Neff NH. Exposure to light accelerates the formation of dopamine from exogenous L-dopa in the rat retina. *J Ocul Pharmacol* 1985;**1**:177–181.
53. Neff NH, Wemlinger TA, Hadjiconstantinou M. SCH 23390 enhances exogenous L-DOPA decarboxylation in nigrostriatal neurons. *J Neural Transm* 2000;**107**:429–443.
54. Biggs CS, Starr MS. Microdialysis study of the effects of the antiparkinsonian drug budipine on L-DOPA-induced release of dopamine and 5-hydroxytryptamine by rat substantia nigra and corpus striatum. *Synapse* 1999;**34**:36–46.
55. Reith J, Cumming P, Gjedde A. Enhanced [3H]DOPA and [3H]dopamine turnover in striatum and frontal cortex in vivo linked to glutamate receptor antagonism. *J Neurochem* 1998;**70**:1979–1985.
56. Deep P, Dagher A, Sadikot A, Gjedde A, Cumming P. Stimulation of dopa decarboxylase activity in striatum of healthy human brain secondary to NMDA receptor antagonism with a low dose of amantadine. *Synapse* 1999;**34**:313–318.
57. Melamed E, Hefti F, Wurtman RJ. Nonaminergic striatal neurons convert exogenous L-dopa to dopamine in Parkinsonism. *Ann Neurol* 1980;**8**:558–563.
58. Tison F, Mons N, Geffard M, Henry P. The metabolism of exogenous L-dopa in the brain: An immunohistochemical study of its conversion to

dopamine in non-catecholaminergic cells of the rat brain. *J Neural Transm Park Dis Dement Sect* 1991;**3**:27–39.
59. Mura A, Jackson D, Manley MS, Young SJ, Groves PM. Aromatic L-amino acid decarboxylase immunoreactive cells in the rat striatum: A possible site for the conversion of exogenous L-DOPA to dopamine. *Brain Res* 1995;**704**:51-60.
60. Brown WD, Taylor MD, Roberts AD, Oakes TR, Schueller MJ, Holden JE, et al. FluoroDOPA PET shows the nondopaminergic as well as dopaminergic destinations of levodopa. *Neurology* 1999;**53**:1212–1218.
61. Lopez A, Munoz A, Guerra MJ, Labandeira-Garcia JL. Mechanisms of the effects of exogenous levodopa on the dopamine-denervated striatum. *Neuroscience* 2001;**103**:639–651.
62. Lopez-Real A, Rodriguez-Pallares J, Guerra MJ, Labandeira-Garcia JL. Localization and functional significance of striatal neurons immunoreactive to aromatic L-amino acid decarboxylase or tyrosine hydroxylase in rat Parkinsonian models. *Brain Res* 2003;**969**:135–146.
63. Maeda T, Nagata K, Yoshida Y, Kannari K. Serotonergic hyperinnervation into the dopaminergic denervated striatum compensates for dopamine conversion from exogenously administered l-DOPA. *Brain Res* 2005;**1046**:230–233.
64. Hadjiconstantinou M, Neff NH. Differential recovery of dopamine synthetic enzymes following MPTP and the consequences of GM1 ganglioside treatment. *Eur J Pharmacol* 1990;**181**:137–139.
65. Jonkers N, Sarre S, Ebinger G, Michotte Y. MK801 influences L-DOPA-induced dopamine release in intact and hemi-Parkinson rats. *Eur J Pharmacol* 2000;**407**:281–291.
66. Arai A, Kannari K, Shen H, Maeda T, Suda T, Matsunaga M. Amantadine increases L-DOPA-derived extracellular dopamine in the striatum of 6-hydroxydopamine-lesioned rats. *Brain Res* 2003;**972**:229–234.
67. Heiss WD, Hilker R. The sensitivity of 18-fluorodopa positron emission tomography and magnetic resonance imaging in Parkinson's disease. *Eur J Neurol* 2004;**11**:5–12.
68. Ravina B, Eidelberg D, Ahlskog JE, Albin RL, Brooks DJ, Carbon M, et al. The role of radiotracer imaging in Parkinson disease. *Neurology* 2005;**64**:208–215.
69. Kuwabara H, Cumming P, Yasuhara Y, Leger GC, Guttman M, Diksic M, et al. Regional striatal DOPA transport and decarboxylase activity in Parkinson's disease. *J Nucl Med* 1995;**36**:1226–1231.
70. Morrish PK, Sawle GV, Brooks DJ. Clinical and [18F] dopa PET findings in early Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1995;**59**:597–600.
71. Rakshi JS, Uema T, Ito K, Bailey DL, Morrish PK, Ashburner J, et al. Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [(18)F]dopa-PET study. *Brain* 1999;**122**(Pt 9):1637–1650.
72. Bruck A, Aalto S, Nurmi E, Vahlberg T, Bergman J, Rinne JO. Striatal subregional 6-[18F]fluoro-L-dopa uptake in early Parkinson's disease: A two-year follow-up study. *Mov Disord* 2006;**21**:958–963.
73. Moore RY, Whone AL, Brooks DJ. Extrastriatal monoamine neuron function in Parkinson's disease: An 18F-dopa PET study. *Neurobiol Dis* 2008;**29**:381–390.
74. Lee CS, Samii A, Sossi V, Ruth TJ, Schulzer M, Holden JE, et al. In vivo positron emission tomographic evidence for compensatory changes in presynaptic dopaminergic nerve terminals in Parkinson's disease. *Ann Neurol* 2000;**47**:493–503.
75. Tedroff J, Ekesbo A, Rydin E, Langstrom B, Hagberg G. Regulation of dopaminergic activity in early Parkinson's disease. *Ann Neurol* 1999;**46**:359–365.
76. Whone AL, Moore RY, Piccini PP, Brooks DJ. Plasticity of the nigropallidal pathway in Parkinson's disease. *Ann Neurol* 2003;**53**:206–213.
77. Brooks DJ, Piccini P. Imaging in Parkinson's disease: The role of monoamines in behavior. *Biol Psychiatry* 2006;**59**:908–918.
78. Torstenson R, Hartvig P, Langstrom B, Westerberg G, Tedroff J. Differential effects of levodopa on dopaminergic function in early and advanced Parkinson's disease. *Ann Neurol* 1997;**41**:334–340.
79. Ekesbo A, Rydin E, Torstenson R, Sydow O, Laengstrom B, Tedroff J. Dopamine autoreceptor function is lost in advanced Parkinson's disease. *Neurology* 1999;**52**:120–125.
80. Ceravolo R, Piccini P, Bailey DL, Jorga KM, Bryson H, Brooks DJ. 18F-dopa PET evidence that tolcapone acts as a central COMT inhibitor in Parkinson's disease. *Synapse* 2002;**43**:201–207.
81. Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. *Ann Neurol* 2003;**54**:93–101.
82. Rakshi JS, Pavese N, Uema T, Ito K, Morrish PK, Bailey DL, et al. A comparison of the progression of early Parkinson's disease in patients started on ropinirole or L-dopa: An 18F-dopa PET study. *J Neural Transm* 2002;**109**:1433–1443.
83. Morrish PK, Sawle GV, Brooks DJ. An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. *Brain* 1996;**119**(Pt 2):585–591.
84. Nurmi E, Ruottinen HM, Bergman J, Haaparanta M, Solin O, Sonninen P, et al. Rate of progression in Parkinson's disease: A 6-[18F]fluoro-L-dopa PET study. *Mov Disord* 2001;**16**:608–615.
85. Nurmi E, Bergman J, Eskola O, Solin O, Vahlberg T, Sonninen P, et al. Progression of dopaminergic

hypofunction in striatal subregions in Parkinson's disease using [18F]CFT PET. *Synapse* 2003;**48**:109–115.
86. Koller WC. Treatment of early Parkinson's disease. *Neurology* 2002;**58**:S79–S86.
87. Olanow W, Schapira AH, Rascol O. Continuous dopamine-receptor stimulation in early Parkinson's disease. *Trends Neurosci* 2000;**23**:S117–S126.
88. Chase TN. The significance of continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Drugs* 1998;**55**(Suppl. 1):1–9.
89. Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. *Brain* 2000;**123**(Pt 11):2297–2305.
90. Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004;**351**:2498–2508.
91. Stocchi F, Olanow CW. Continuous dopaminergic stimulation in early and advanced Parkinson's disease. *Neurology* 2004;**62**:S56–S63.
92. Morrish PK, Rakshi JS, Bailey DL, Sawle GV, Brooks DJ. Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [18F]dopa PET. *J Neurol Neurosurg Psychiatry* 1998;**64**:314–319.
93. Jellinger K, Bliesath H. Adjuvant treatment of Parksinson's disease with budipine: A double-blind trial versus placebo. *J Neurol* 1987;**234**:280–282.
94. Merello M, Nouzeilles MI, Cammarota A, Leiguarda R. Effect of memantine (NMDA antagonist) on Parkinson's disease: A double-blind crossover randomized study. *Clin Neuropharmacol* 1999;**22**:273–276.
95. Rabey JM, Nissipeanu P, Korczyn AD. Efficacy of memantine, an NMDA receptor antagonist, in the treatment of Parkinson's disease. *J Neural Transm Park Dis Dement Sect* 1992;**4**:277–282.
96. Przuntek H, Bittkau S, Bliesath H, Buttner U, Fuchs G, Glass J, et al. Budipine provides additional benefit in patients with Parkinson disease receiving a stable optimum dopaminergic drug regimen. *Arch Neurol* 2002;**59**:803–806.
97. Crosby N, Deane KH, Clarke CE. Amantadine in Parkinson's disease. *Cochrane Database Syst Rev* 2003:CD003468.
98. Goetz CG, Poewe W, Rascol O, Sampaio C. Evidence-based medical review update: Pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. *Mov Disord* 2005;**20**:523–539.
99. Fabbrini G, Brotchie JM, Grandas F, Nomoto M, Goetz CG. Levodopa-induced dyskinesias. *Mov Disord* 2007;**22**:1379–1389;quiz 523.
100. Factor SA, Brown D. Clozapine prevents recurrence of psychosis in Parkinson's disease. *Mov Disord* 1992;**7**:125–131.
101. Linazasoro G, Marti Masso JF, Suarez JA. Nocturnal akathisia in Parkinson's disease: Treatment with clozapine. *Mov Disord* 1993;**8**:171–174.
102. Bennett JP, Jr, Landow ER, Dietrich S, Schuh LA. Suppression of dyskinesias in advanced Parkinson's disease: Moderate daily clozapine doses provide long-term dyskinesia reduction. *Mov Disord* 1994;**9**:409–414.
103. Wagner ML, Defilippi JL, Menza MA, Sage JI. Clozapine for the treatment of psychosis in Parkinson's disease: Chart review of 49 patients. *J Neuropsychiatry Clin Neurosci* 1996;**8**:276–280.
104. Trosch RM, Friedman JH, Lannon MC, Pahwa R, Smith D, Seeberger LC, et al. Clozapine use in Parkinson's disease: A retrospective analysis of a large multicentered clinical experience. *Mov Disord* 1998;**13**:377–382.
105. Ellis T, Cudkowicz ME, Sexton PM, Growdon JH. Clozapine and risperidone treatment of psychosis in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2000;**12**:364–369.
106. Goetz CG, Blasucci LM, Leurgans S, Pappert EJ. Olanzapine and clozapine: Comparative effects on motor function in hallucinating PD patients. *Neurology* 2000;**55**:789–794.
107. Morgante L, Epifanio A, Spina E, Di Rosa AE, Zappia M, Basile G, et al. Quetiapine versus clozapine: A preliminary report of comparative effects on dopaminergic psychosis in patients with Parkinson's disease. *Neurol Sci* 2002;**23**(Suppl. 2):S89–S90.
108. Arevalo GJ, Gershanik OS. Modulatory effect of clozapine on levodopa response in Parkinson's disease: A preliminary study. *Mov Disord* 1993;**8**:349–354.
109. Bennett JP Jr, Landow ER, Schuh LA. Suppression of dyskinesias in advanced Parkinson's disease. II. Increasing daily clozapine doses suppress dyskinesias and improve Parkinsonism symptoms. *Neurology* 1993;**43**:1551–1555.
110. Durif F, Vidailhet M, Assal F, Roche C, Bonnet AM, Agid Y. Low-dose clozapine improves dyskinesias in Parkinson's disease. *Neurology* 1997;**48**:658–662.
111. Pierelli F, Adipietro A, Soldati G, Fattapposta F, Pozzessere G, Scoppetta C. Low dosage clozapine effects on L-dopa induced dyskinesias in Parkinsonian patients. *Acta Neurol Scand* 1998;**97**:295–299.
112. Morgante L, Epifanio A, Spina E, Zappia M, Di Rosa AE, Marconi R, et al. Quetiapine and clozapine in Parkinsonian patients with dopaminergic psychosis. *Clin Neuropharmacol* 2004;**27**:153–156.
113. Waters C. Other pharmacological treatments for motor complications and dyskinesias. *Mov Disord* 2005;**20**(Suppl. 11):S38–S44.
114. Henderson J, Yiannikas C, Graham JS. Effect of ritanserin, a highly selective 5-HT2 receptor antagonist, on Parkinson's disease. *Clin Exp Neurol* 1992;**29**:277–282.
115. Ikeguchi K, Kuroda A. Mianserin treatment of patients with psychosis induced by antiparkinsonian drugs. *Eur Arch Psychiatry Clin Neurosci* 1995;**244**:320–324.

116. Avila A, Cardona X, Martin-Baranera M, Maho P, Sastre F, Bello J. Does nefazodone improve both depression and Parkinson disease? A pilot randomized trial. *J Clin Psychopharmacol* 2003;**23**:509–513.
117. Golembiowska K, Dziubina A. Striatal adenosine A(2A) receptor blockade increases extracellular dopamine release following l-DOPA administration in intact and dopamine-denervated rats. *Neuropharmacology* 2004;**47**:414–426.
118. Bara-Jimenez W, Sherzai A, Dimitrova T, Favit A, Bibbiani F, Gillespie M, et al. Adenosine A(2A) receptor antagonist treatment of Parkinson's disease. *Neurology* 2003;**61**:293–296.
119. Hillion J, Canals M, Torvinen M, Casado V, Scott R, Terasmaa A, et al. Coaggregation, cointernalization, and codesensitization of adenosine A2A receptors and dopamine D2 receptors. *J Biol Chem* 2002;**277**:18091–10897.