DOPAMINE AND THE REGULATION OF MOVEMENTS

- SIGNIFICANCE OF NIGRAL AND STRIATAL DOPAMINE RELEASE IN NORMAL, HEMIPARKINSONIAN AND DYSKINETIC RATS

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Abstract

DOPAMINE AND THE REGULATION OF MOVEMENTS - SIGNIFICANCE OF NIGRAL AND STRIATAL DOPAMINE RELEASE IN NORMAL, HEMIPARKINSONIAN AND DYSKINETIC RATS

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Introduction: The nigrostriatal dopamine (DA) containing neurones are a pivotal component in the basal ganglia, a network that regulates movement. Degeneration of these neurones causes the cardinal symptoms of Parkinson's disease (PD). In addition to releasing DA from terminals in the striatum, these neurones also release DA from cell bodies and dendrites in the substantia nigra (SN). Although, somatodendritic DA release is known to influence motor performance, the mechanisms for this regulation needs to be clarified. PD is predominantly treated with L-DOPA, a precursor of DA. After 4-6 years of L-DOPA-treatment, approximately 40 % of the PD patients develop side effects in the form of abnormal involuntary movements. The reasons for these abnormal movements are not yet fully elucidated, but they are believed to be induced by large pulsatile fluctuations of DA following L-DOPA administration. ***Methods and observations:*** By use of simultaneous nigral and striatal microdialysis combined with motor performance testing, we demonstrate that nigral somatodendritic DA release exerts its influence on motor performance without affecting striatal terminal release. We also show that somatodendritic DA release can functionally compensate for disturbances in striatal DA release and thus partially maintain motor ability. Furthermore, local nigral application of the muscarinic antagonist scopolamine amplifies a previously described motor activity-related increase in somatodendritic DA release, and this amplification partially restores motor performance ability in 6-OHDA-hemilesioned rats. By combining dual probe microdialysis with a rat model of L-DOPA-induced dyskinesias, we demonstrate that the amount of DA formed and released from a given dose of L-DOPA is larger in rats that express dyskinesias than in rats that do not. Furthermore, our data indicate that the larger DA peak in dyskinetic compared to non-dyskinetic animals reflects a denser serotonergic innervation in the former group. We also show that 5-HT autoreceptor agonists attenuate extracellular DA concentrations following L-DOPA and reduce dyskinesias. ***Conclusions:*** The results in this thesis indicate that the principal role of somatodendritic DA release is to modulate basal ganglia output on the level of the substantia nigra, and not to regulate terminal release in the striatum. Moreover, our findings indicate that the amount of DA formed from an L-DOPA dose is the main cause of dyskinesias in rats, and also lend support to previous findings identifying striatal 5-HT neurones as the source of L-DOPA-derived DA.

Keywords: dopamine, substantia nigra, striatum, L-DOPA, dyskinesias, serotonin

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Paper I: **Andersson DR**, Nissbrandt H and Bergquist F. Partial depletion of dopamine in substantia nigra impairs motor performance without altering striatal dopamine neurotransmission. *Eur J Neurosci. 2006 Jul;24(2):617-24.*

Paper II: **Andersson DR**, Bergquist F and Nissbrandt H. Motor activity-induced dopamine release in the substantia nigra is regulated by muscarinic receptors. *Submitted for publication, 2009.*

Paper III: Lindgren HS*, **Andersson DR***, Lagerkvist S, Nissbrandt H and Cenci MA. Serotonergic modulation of striatal and nigral dopamine release in a rat model of L-DOPA-induced dyskinesia *Manuscript, 2009. *shared first authorship*

List of abbreviations

3-MT	3-methoxytyramine
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine, serotonin
6-OHDA	6-hydroxydopamine
ACh	acetylcholine
cAMP	cyclic adenosine monophosphate
COMT	catechol-O-methyltransferase
DA	dopamine
DBS	deep brain stimulation
DOPAC	3, 4-dihydroxyphenylacetic acid
ERK	extracellular signal-related kinase
GABA	gamma-aminobutyric acid
GP	globus pallidus
GPe	globus pallidus, external segment
GPi	globus pallidus, internal segment
HPLC	high performance liquid chromatography
HVA	homovanillic acid
L-DOPA	L-3, 4-dihydroxyphenylalanine
MAO	monoamine oxidase
MPTP	1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine
NA	noradrenaline
PD	Parkinson's disease
PPN	pedunculopontine nucleus
SN	substantia nigra
SNc	substantia nigra, pars compacta
SNr	substantia nigra, pars reticulata
STN	subthalamic nucleus
TH	tyrosine hydroxylase
VIM	ventral intermediate thalamic nucleus
VMAT	vesicular monoamine transporter

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Science is simply common sense at its best; that is, rigidly accurate in observation, and merciless to fallacy in logic.

Thomas Henry Huxley, in "The crayfish", 1879

Introduction

The discovery of dopamine as a neurotransmitter

In the mid 1950s, Arvid Carlsson and Nils-Åke Hillarp described the depletion of catecholamines (noradrenaline (NA) and adrenaline) in the adrenal medulla of rabbits following reserpine treatment (Carlsson and Hillarp 1956). Reserpine had previously been used as an antipsychotic and antihypertensive drug and had been demonstrated to cause depletion of serotonin (5-HT) in the brain as well as in other tissues, but its effects on catecholamines were not previously known (later research showed that reserpine exerts its action by blocking the vesicular monoamine transporter (VMAT) and thus prevents the storage of monoamines in exocytotic vesicles). The finding of reserpine-induced catecholamine depletion was followed by the discovery that the behavioural deficits (an almost complete immobilisation) induced by this drug in rabbits, could be reversed by treatment with DOPA (Carlsson *et al.* 1957), an amino acid which had previously been found to be a precursor in the synthesis of catecholamines. The view at the time was that dopamine (DA) was just an intermediate in the synthesis of NA, but as the initial DOPA-studies failed to show a correlation between behavioural restoration and NA content in the brain, the attention was turned towards DA. After establishing a method of quantifying DA (Carlsson and Waldeck 1958), Carlsson and co-workers found that DA is present in the brain to a similar extent as NA, and that, in contrast to NA, there is a strong correlation between the DA concentration in the brain and the behavioural restoration of reserpine-immobilised animals by DOPA-treatment (Carlsson *et al.* 1957).

In the following years, it was demonstrated that brain DA is mainly located in the basal ganglia (Bertler and Rosengren 1959; Carlsson 1959; Sano *et al.* 1959), and also that DA is reduced in brains of deceased patients suffering from Parkinson's disease (PD, Ehringer and Hornykiewicz 1960). This important finding was followed by clinical trials showing that parkinsonian symptoms are alleviated by treatment with DOPA (Birkmayer and Hornykiewicz 1961; Barbeau 1962). However, in these initial studies, DOPA was administered by intravenous injections and resulted in extensive side effects such as severe nausea and vomiting. Neurologist George Cotzias proposed that the stereoisomeric L-form of DOPA (L-3,4-dihydroxyphenylalanine, L-DOPA) would generate less side effects, and that starting with a small dose and slowly escalating it over several weeks would build tolerance towards side effects. Some years later he published a clinical study clearly demonstrating the beneficial effects and limited side-effects of repeated small doses of an oral preparation of L-DOPA in patients with PD (Cotzias *et al.* 1967). Since this discovery, oral L-DOPA treatment has been the dominating treatment for PD.

Dopamine synthesis and metabolism

DA is synthesised from the amino acid tyrosine, and the initial step in this synthesis is the conversion of tyrosine to DOPA by tyrosine hydroxylase (TH). This conversion is considered to be the rate limiting step in the synthesis as it is generally saturated with its substrate and only 2% of the enzyme population is available for catecholamine synthesis (Cooper *et al.* 1996). The enzyme responsible for the concomitant conversion of DOPA to DA, the aromatic amino acid decarboxylase, is however not saturated with substrate (Bowsher and Henry 1985) and thus has higher activity.

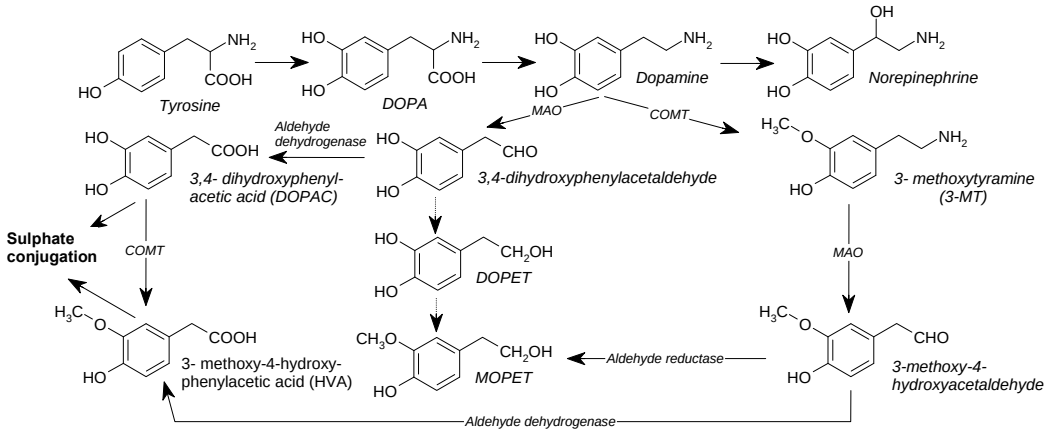

Fig 1. Dopamine (DA) synthesis and metabolism. The synthesis of DA is dependent on two enzymes, tyrosine hydroxylase and aromatic amino acid decarboxylase, and metabolism in turn, is mediated mainly by monoaminooxidase (MAO) and catechol-O-methyltransferase (COMT).

DA breakdown is mediated mainly by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) and through intermediate aldehyde forms. The main metabolites are 3-methoxytyramine (3-MT, Carlsson and Waldeck 1964), 3,4-dihydroxyphenylacetic acid (DOPAC, Rosengren 1960) and 3-methoxy-4-hydroxyphenylacetic acid (HVA, Rutledge and Jonason 1967), which is the terminal metabolite.

The distribution of dopamine in the brain

In parallel with the discovery of DA and its function as a neurotransmitter, sensitive histochemical methods were developed, which made detailed mapping of the distribution of monoamine neurones in the brain possible. The early methods were based on the ability of formaldehyde to react with biogenic amines and form fluorescent compounds. A yellow fluorescence in gut mucosal cells was described as early as the 1930s, and it was later shown to be caused by the presence of 5-HT (Barter and Pearse 1953; Barter and Pearse 1955). Similarly, a green fluorescence in the adrenal glands was proven to originate from NA (Eränkö 1954; Eränkö 1955a; Eränkö 1955b). By using an improved formaldehyde method,

Carlsson and others showed the presence of monoamine-containing neurones also in the brain (Carlsson *et al.* 1962; Falck *et al.* 1962; Corrodi *et al.* 1964); a finding that led to an impressive mapping of monoaminergic cells in the central nervous system as well as the development of more sensitive methods (Dahlström and Fuxe 1964a; Dahlström and Fuxe 1964b; Dahlström and Fuxe 1965; Fuxe 1965a; Fuxe 1965b), later refined by Urban Ungerstedt (Ungerstedt 1971b) and Anders Björklund and Olle Lindvall (Björklund *et al.* 1972; Lindvall and Björklund 1974; Björklund and Lindvall 1975; Lindvall *et al.* 1978).

These early mapping studies identified the major monoaminergic pathways of the brain. In short, the initial description (Dahlström and Fuxe 1964a) defined 12 catecholamine cell clusters named A1-A12, where A1 was the most caudally located (in the medulla oblongata) and A12 in the hypothalamus. It also defined 9 5-HT containing cell clusters named B1-B9 in a similar fashion (with B1 the most caudal). In later studies five additional catecholamine clusters, designated A13-A17, were identified in the more frontal regions of the brain as well as in the retina (Fuxe and Hökfeldt 1969; Björklund and Nobin 1973; Halasz *et al.* 1977; see Lindvall and Björklund 1978).

The DA neurones located in the mesencephalon (midbrain) make up the largest cell body complex of this cell type in the brain, and it is from these cell clusters, designated A8-A10, that the majority of DA-innervated brain regions receive their input. The A9 cluster corresponds largely to the anatomical region of substantia nigra (SN) pars compacta, the dorsal tier of a midbrain structure given its name by its dark colouration caused by intracellular deposits of neuromelanin. The A9 neurones project predominantly to the dorsal parts of the region named striatum, and this projection is therefore referred to as the nigrostriatal pathway. The A10 neurones, located just medially of the SN, correspond to a region known as the ventral tegmental area, and project via the so-called mesocorticolimbic pathway predominantly to the ventral part of striatum (nucleus accumbens), cortical regions, the amygdala and the hippocampus. The A8 cluster is located caudally and dorsally to the A9/A10 complex and contributes to the nigrostriatal and mesocorticolimbic DA pathways. Degeneration of the nigrostriatal system is the main cause of the motor symptoms of PD, which stresses the pivotal role of this pathway in the regulation of movement. The mesocorticolimbic system, on the other hand, is strongly implicated in the mediation of reward, reward-seeking behaviour and cognition, and is consequently implicated in a wide range of illnesses such as drug dependence (e.g. alcoholism) and schizophrenia (Carlsson and Lindqvist 1963; Seeman *et al.* 1976; Engel *et al.* 1988; Wise and Rompre 1989; Koob 1992; Nestler 2001).

The basal ganglia and the regulation of movement

The basal ganglia is the collective term used to describe a network of deep lying cerebral nuclei (the striatum, globus pallidus (GP), SN and the subthalamic nucleus (STN)), that is

intimately engaged in the execution of movement, something which was suggested as early as in the 17th century (see Finger 1994). Lately, it has been recognized that the basal ganglia are of importance for a wide variety of other brain functions such as sensory processing and perception, learning, memory and attention. The basal ganglia is traditionally viewed as a processing and filtering station that regulates and fine-tunes cortical input and then sends signals back to premotor- and motor cortex areas. A simplified scheme of the functional connections within the basal ganglia also showing the main outputs and inputs can be seen in Fig. 2. This type of flow-chart thinking is grossly oversimplified, but can be helpful when trying to explain for instance some of the symptoms of PD (eg. bradykinesia). The model does, however, not readily explain other symptoms, such as tremor, where the probable cause is abnormal oscillations in neuronal activity patterns in the basal ganglia. To understand such dynamic alterations in cellular and network functions, more complex

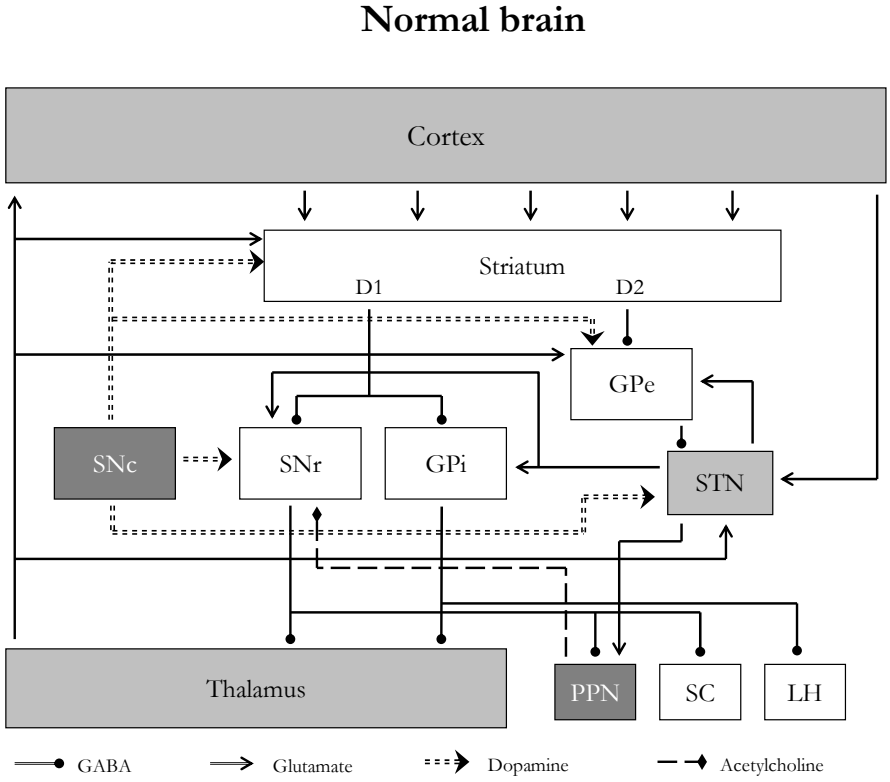

Fig. 2. Simplified scheme of the functional connections of the basal ganglia in a healthy brain. Colouration corresponds to main transmitter output; white, GABA; light grey, glutamate; dark grey, other (dopamine or acetylcholine). Abbreviations: SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; GPi, globus pallidus, internal segment; GPe, globus pallidus, external segment; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; SC, superior colliculus; LH, lateral habenula.

models based on computational modelling of neuronal interactions, can be used (see for instance Bevan *et al.* 2002; Terman *et al.* 2002; Gillies and Willshaw 2004; Gillies and

Willshaw 2007). In addition, the flow-chart models do not easily allow one to draw conclusions with regards to other cellular alterations such as neuronal plasticity or receptor sensitisation/desensitisation.

The number of nuclei involved in the regulation of movement has recently come to include other regions of the brain, for instance brainstem nuclei such as the inferior and superior colliculus, the pedunculopontine nucleus (PPN), and the periaqueductal grey area, which all provide input to the basal ganglia through the thalamus (Krout and Loewy 2000a; Krout and Loewy 2000b; Krout *et al.* 2001; Krout *et al.* 2002). The basal ganglia, in turn, project back to the brainstem (Deniau and Chevalier 1992; Redgrave *et al.* 1992; Takada *et al.* 1994; Kirouac *et al.* 2004). The basal ganglia-brainstem projections were originally considered to be a route by which the basal ganglia affect brainstem-related motor mechanisms such as for instance oculomotor control, postural control and balance. However, the discovery of brainstem-thalamus projections has led to the suggestions of a separate, subcortical loop system (brainstem-basal ganglia), with the thalamus as the input nucleus to the basal ganglia. This loop system appears capable to in itself regulate motor behaviour, muscle tone, gait and balance without the involvement of cortical areas (Takakusaki *et al.* 2003; Takakusaki *et al.* 2004; Takakusaki *et al.* 2008) These findings, in turn, have led to the proposal that the main function of the basal ganglia is to regulate and discriminate between two separate motor regulatory systems (Redgrave *et al.* 1999; Gurney *et al.* 2001a; Gurney *et al.* 2001b; McHaffie *et al.* 2005), namely the will-controlled cortical motor system and the more autonomic brain stem motor system.

The striatum

The striatum consists of two, anatomically as well as functionally, closely related nuclei (the caudate nucleus and the putamen), and it is viewed as the main input nucleus of the basal ganglia. In addition to the DAergic pathway from the midbrain, it receives an extensive, predominantly excitatory, glutamatergic input topographically distributed from virtually all regions of the cortex (Fonnum *et al.* 1981; Selemon and Goldman-Rakic 1985; Gerfen 1989; Smith and Bolam 1990a; Bolam *et al.* 2000). Other less extensive afferent projections come from 5-HT neurones in the raphe nuclei (Miller *et al.* 1975; Ternaux *et al.* 1977; van der Kooy and Hattori 1980) and NA neurones in the locus coeruleus (Udenfriend and Creveling 1959; Glowinski and Iversen 1966; Ross and Reis 1974; Lategan *et al.* 1990; Lategan *et al.* 1992). Interneurones containing acetylcholine (ACh, Kawaguchi 1993; Di Chiara *et al.* 1994; Graybiel *et al.* 1994; Kawaguchi *et al.* 1995; Koos and Tepper 2002; Sullivan *et al.* 2008) or gamma-aminobutyric acid (GABA, Cowan *et al.* 1990; Kawaguchi 1993; Kawaguchi *et al.* 1995; Berretta *et al.* 1997; Tepper *et al.* 2004; Mallet *et al.* 2005), also have important regulatory roles in the striatum (see Tepper and Bolam 2004).

The rat striatum is comprised of approximately 2.8 million neurones (Oorschot 1996), of which roughly 90-95% are medium spiny projection neurones (Kemp and Powell 1971b). The striatum is anatomically heterogeneous, in that it is organised into so-called striosomes, or "islands" and a surrounding matrix. The striosomes have been shown to have lower TH activity and DA turnover as well as lower density of DA receptors than the matrix (Olson *et al.* 1972; Graybiel 1984; Graybiel *et al.* 1987; Loopuijt *et al.* 1987; Holt *et al.* 1997). There are also differences with regards to innervation, with the striosomes receiving the majority of their input from the prefrontal cortex and project mainly to the SN pars compacta, while the matrix areas receive cortical input from most cortical areas and provide efferents to the reticulate part of the SN and the GPi (see Gerfen 1992).

The substantia nigra

The SN consists of two distinct parts, the pars compacta (SNc) and the pars reticulata (SNr). The cell bodies of DA neurones are almost exclusively located in the SNc, but their dendritic trees infiltrate extensively into the SNr. The SNr is both anatomically and functionally closely related to the GPi, in that it consists mainly of GABAergic output neurones (Besson *et al.* 1986) projecting to the thalamus (Carpenter *et al.* 1976; Ueki 1983; Oertel and Mugnaini 1984). The SNr also sends inhibitory projections to the PPN (Nauta and Mehler 1966; Woolf and Butcher 1986; Semba and Fibiger 1992; Inglis and Winn 1995) and the superior colliculus (Rinvik *et al.* 1976; Hikosaka and Wurtz 1983). The presence of GABAergic neurones projecting from the SNr to the SNc and there exerting an influence on the firing rate of the SNc cells has also been suggested (Hajos and Greenfield 1994; Tepper *et al.* 1995). The SNr receives extensive afferent inputs from various brain regions, such as glutamatergic projections from the STN (Hammond *et al.* 1978; Nakanishi *et al.* 1987), GABAergic projections from the striatum (Kemp and Powell 1971a; Smith and Bolam 1990a) and the external segment of the globus pallidus (GPe, Grofova 1975; Smith and Bolam 1990b; Kita and Kitai 1991; Kita and Kitai 1994), but GABA is also released from local interneurones (Grofova *et al.* 1982; Stanford and Lacey 1996). Modulating inputs to the SNr also exist in the form of 5-HT projections from the raphe nuclei (Dray *et al.* 1976), NA projections from the locus coeruleus (Grenhoff *et al.* 1993; Grenhoff *et al.* 1995) as well as a mixed glutamate/ACh input from the PPN (Scarnati *et al.* 1986; Beninato and Spencer 1987; Clarke *et al.* 1987; Bolam *et al.* 1991; Lavoie and Parent 1994a; Lavoie and Parent 1994b).

Dopamine receptors and their distribution in the striatum and the substantia nigra.

There are two main types of DA receptors, named D1- and D2-like. This subdivision was brought about by observations of differential effects of DA on the intracellular formation of cyclic adenosine monophosphate (cAMP) by the enzyme adenylate cyclase (Roufogalis *et al.* 1976; Garau *et al.* 1978; Spano *et al.* 1978). The findings were summarised by Kebabian and

Calne, who suggested the occurrence of two different types of DA receptors and postulated that the D1-like receptors increase cAMP formation, while the D2-like receptors decrease or do not affect it (Kebabian and Calne 1979). Later, the original classification of two types of DA receptors was broadened by use of molecular cloning techniques, which allowed the identification of five distinguishable subtypes of receptors, named D_1-D_5. The D1-like receptors are D_1 and D_5 (Dearry *et al.* 1990; Monsma *et al.* 1990; Sunahara *et al.* 1991), while D_3-D_4 make up the group referred to as D2-like (Sokoloff *et al.* 1990; Van Tol *et al.* 1991) along with the D_2-receptors, who have been shown to exist in two isoforms (D_2S; short isoform, D_2L; long isoform) (Bunzow *et al.* 1988; Dal Toso *et al.* 1989; Giros *et al.* 1989) with the short form being 29 amino acids shorter (Giros *et al.* 1989; Monsma *et al.* 1989). These two isoforms have different distributions and functions, with the D_2S acting as an autoreceptor regulating DA synthesis and release and the D_2L as a postsynaptic receptor or heteroreceptor on non-DAergic neurones (Usiello *et al.* 2000; Wang *et al.* 2000; Lindgren *et al.* 2003).

The predominant DA receptor subtypes in the striatum are the D_1-receptors, which are located postsynaptically (Krueger *et al.* 1976; Di Chiara *et al.* 1977; Savasta *et al.* 1986; Filloux *et al.* 1987b), and the two isoforms of the D_2-receptor (Filloux *et al.* 1987a; Morelli *et al.* 1987), which are located both pre- and postsynaptically (see above). The postsynaptical receptors (both D_1 and D_2) are mainly located on the medium spiny output neurones, and according to the general model of the basal ganglia, the two types are only rarely present on the same neurone (Surmeier and Kitai 1994; Surmeier *et al.* 1996; Deng *et al.* 2006; Wang *et al.* 2006). This notion, however, is challenged by some studies that indicate a more extensive overlap (Surmeier *et al.* 1992; Aizman *et al.* 2000). Striatal postsynaptic D_2 receptors have been shown to regulate the plasticity of corticostriatal synapses, a key process in adaptive processes such as associative learning and motor plasticity (Calabresi *et al.* 1992; Calabresi *et al.* 1997; Kreitzer and Malenka 2005; see Calabresi *et al.* 2007 for a recent review), and this function appears to be exerted via DA effects on cholinergic interneurones (Wang *et al.* 2006), which also express D_5 receptors (Rivera *et al.* 2002a; Berlanga *et al.* 2005). D_4 receptors are expressed in striatonigral and striatopallidal projection neurones (Ariano *et al.* 1997; Tarazi *et al.* 1998; Rivera *et al.* 2002b), but their functional contribution is poorly understood.

In the SN, the pattern of distribution appears to be similar, with D_1-receptors located mainly postsynaptically (Boyson *et al.* 1986; Savasta *et al.* 1986; Porceddu *et al.* 1987; Beckstead *et al.* 1988) and D_2-receptors presynaptically on DAergic cell bodies acting as autoreceptors (Boyson *et al.* 1986; Bouthenet *et al.* 1987; Morelli *et al.* 1987; Beckstead *et al.* 1988). In addition to D_2-receptors, there are also D_3-receptors present on the DA neurones, but their physiological relevance has not been convincingly demonstrated (Tepper *et al.* 1997; Koeltzow *et al.* 1998; L'Hirondel *et al.* 1998; Zapata *et al.* 2001; Davila *et al.* 2003). The postsynaptic D_1-receptors are mainly located on striatonigral GABA-containing terminals (Kim *et al.* 1971; Fonnum *et al.* 1974), and activation of these receptors has been shown to

facilitate GABA release from these neurones (Reubi *et al.* 1977; Starr 1987; Martin and Waszczak 1994; Timmerman and Westerink 1995; Trevitt *et al.* 2002). There are also indications of D_1 heteroreceptors located on glutamatergic terminals in the SN (Abarca *et al.* 1995; Rosales *et al.* 1997). In addition, there is a postsynaptic population of D_2-type receptors located on cells not expressing TH, such as striatonigral neurones (Sesack *et al.* 1994; Martin and Waszczak 1996) or glutamatergic afferents from the STN (Pickel *et al.* 2002). Also, the existence of both pre- and postsynaptic nigral populations of D_4- and D_5-receptors (Choi *et al.* 1995; Mrzljak *et al.* 1996; Khan *et al.* 2000; Rivera *et al.* 2003) have been demonstrated, but the functional role of these are not known.

Striatal dopamine release and its effects on basal ganglia output

In the striatum, there are two distinct types of output neurones, and DA affects them differentially. The medium spiny projection neurones of striatum have GABA as their primary transmitter (Yoshida and Precht 1971; Fonnum *et al.* 1978; Kita and Kitai 1988) and project either to the main output structures of the basal ganglia (the SNr and the GPi) or to the GPe. The neurones projecting to the SNr and the GPi mainly express the DAergic D_1-receptor and therefore respond excitatory to DA, whereas the ones projecting to the GPe mainly express the inhibitory D_2-receptor and are consequently inhibited by DA (Le Moine *et al.* 1990; Gerfen 1992; Gerfen *et al.* 1995; Le Moine and Bloch 1995). This distinction has resulted in the notion of a "direct" and an "indirect" pathway with opposing effects on net outflow from the basal ganglia onto the thalamus (Albin *et al.* 1989; DeLong 1990; Parent and Hazrati 1995; Galeffi *et al.* 2003). Activation of the direct pathway (D_1-receptor-mediated) results in an inhibition of GABAergic output neurones in the SNr and the GPi and thus results in a reduction of tonic inhibition of the thalamus and consequently an increased outflow of impulses to the motor cortex. Activation of the indirect pathway results in a complex pattern of interactions, mainly between the GPe and the STN, which in turn results in an activation of basal ganglia output structures and therefore generates an inhibition of thalamic excitatory signalling to the motor cortex. As can be concluded from the connection scheme in Fig. 3, a depletion of DA in the striatum (such as in PD) will reduce the activity in the direct pathway and increase the activity in the indirect pathway, and the net effect of this would be reduced excitation of the thalamus and a reduction in outflow of motor impulses. The definition of a direct and an indirect pathway are however challenged by some findings, describing an extensive overlap of D_1- and D_2-receptor expression in the striatal projection neurones, and also that a majority of them project to both segments of the GP and the SNr (Surmeier *et al.* 1992; Aizman *et al.* 2000; Levesque and Parent 2005).

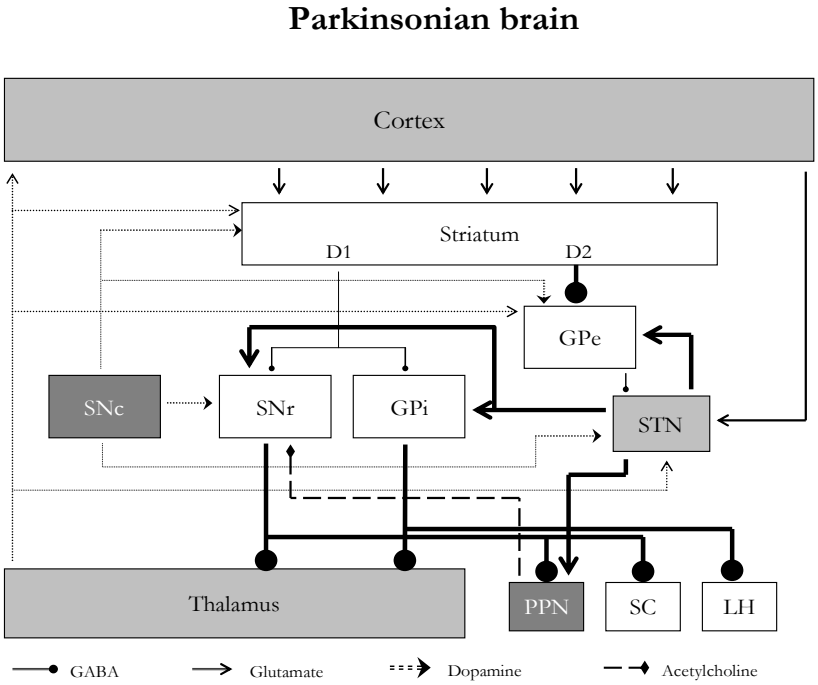

Fig. 3. Schematic representation of signalling pathways within the basal ganglia in the parkinsonian brain. According to the "direct/indirect" model of basal ganglia function, a loss of dopamine in the striatum will shift activity from the "direct" pathway (striatum/D1-SNr/GPi) onto the "indirect" pathway (striatum/D2-GPe-STN-SNr/GPi). This will in turn result in an increased inhibitory outflow from the basal ganglia. Thickness of arrows indicates extent of activity, and several functional connections are omitted for graphic clarity. Abbreviations: SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; GPi, globus pallidus, internal segment; GPe, globus pallidus, external segment; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; SC, superior colliculus; LH, lateral habenula.

Somatodendritic dopamine release and its effects on basal ganglia output

In the first study by Dahlström and Fuxe describing the distribution of monoamines in the brain (Dahlström and Fuxe 1964a), it was concluded that there is a substantial amount of DA in neurones located in the SN. By use of a more sensitive histofluorescence method (Björklund *et al.* 1972; Lindvall and Björklund 1974), it was shown that the nigrostriatal neurones not only contain DA in their cell bodies and striatal terminals, but also in the dendritic tree extending into the SNr (Björklund and Lindvall 1975). Furthermore, the DA-related fluorescence in the dendrites was abolished by reserpine pre-treatment, a finding which made the authors suggest that DA might act as a neurotransmitter locally in the SN, released from cell bodies and dendrites. An active release of DA from dendrites has subsequently been demonstrated by different techniques such as *in vitro* slice preparations (Geffen *et al.* 1976; Paden *et al.* 1976; Hefti and Lichtensteiger 1978; Kant and Meyerhoff 1978; Elverfors *et al.* 1992), voltammetry (Rice *et al.* 1994; Cragg *et al.* 1997; Chen and Rice

2001) and *in vivo*-measurements by push-pull technique (Nieoullon *et al.* 1977) and microdialysis (Robertson *et al.* 1991; Santiago and Westerink 1991a; Elverfors *et al.* 1997; Bergquist *et al.* 1998; Nissbrandt *et al.* 2001). Dendritic DA does not seem to be stored mainly in classic exocytotic vesicles, but in the smooth endoplasmatic reticulum (Wilson et al. 1977; Hattori *et al.* 1979; Groves and Linder 1983). Accordingly, the VMAT is expressed in tubulovesicular structures related to the endoplasmatic reticulum and synaptic vesicles are only rarely detected in dendrites (Nirenberg *et al.* 1996).

The functional importance of nigral DA release for basal ganglia output has not received as much attention as that of DA release in the striatum. Nevertheless, it has been demonstrated that local unilateral nigral infusions of the DA-releasing agent amphetamine activates behaviour in both hemilesioned (Yurek and Hipkens 1993) and intact rats (Timmerman and Abercrombie 1996), and that this behavioural activation is counteracted by simultaneous application of a DA D_1-receptor antagonist. In addition, similar behavioural activation can be triggered by local application of agonists acting at the D_1-receptor (Yurek and Hipkens 1994). Furthermore, injections of both D_1- and D_2- receptor antagonists in the SN increase muscle tone (Double and Crocker 1995; Crocker 1997; Hemsley and Crocker 2001) and D_1-receptor antagonists impair lever pressing when given locally in the SN (Trevitt *et al.* 2001). A previous study from our laboratory (Bergquist *et al.* 2003), demonstrated that antagonism of both D_1/D_5- and D_2/D_3-receptors in the SN has a negative effect on motor performance and that it is possible to improve motor performance in hemilesioned rats by nigral application of the DA receptor agonist apomorphine. In the same study, it was demonstrated for the first time that motor activity increases nigral DA release. Although there are now convincing evidence that nigral DA release can influence motor functions, the functional relation between somatodendritic DA transmission and striatal terminal DA transmission has not been determined.

Somatodendritic autoreceptors in the substantia nigra

Nigral D_2-autoreceptors have usually been considered as autoreceptors that affect terminal DA release in the striatum indirectly by modulating the firing rate or firing pattern of the DA neurones. Mechanistically, it is well established from both *in vitro* and *in vivo* studies that pharmacological interference with nigral D_2-autoreceptors alters the firing rate of the nigrostriatal neurones and thereby also affects the release of striatal DA (Groves *et al.* 1975; Aghajanian and Bunney 1977a; Nedergaard *et al.* 1988); (Santiago and Westerink 1991b; Pucak and Grace 1994; Cobb and Abercrombie 2003). However, in the last decade findings have been presented that question the *in vivo* importance of these autoreceptors. Thus, in the previously mentioned study, Bergquist and co-workers (2003) demonstrated that nigral perfusion with the D_2/D_3 antagonist raclopride in a combined microdialysis/rotarod paradigm impairs rotarod performance when the antagonist is administered in a low concentration, which does not affect terminal release of DA in the striatum. When perfusing

with higher concentrations of raclopride, however, motor performance is restored, and this is correlated with an increase of terminal DA release. This suggests that there is a functional population of D_2-receptors in the SN that modulates motor behaviour without altering the activity of DA neurones enough to influence terminal DA release. Other *in vivo* studies also raise some doubt concerning the influence of autoreceptors on firing rate and terminal release. For instance, Engberg and others (Engberg *et al.* 1997) showed that local nigral treatment with GBR 12909, a potent DA reuptake inhibitor, elevated nigral extracellular DA concentrations, but did not affect the firing rate of the DA neurones. In another study (Cobb and Abercrombie 2003), it was demonstrated that local nigral treatment with 5-HT reuptake inhibitors resulted in increased somatodendritic DA release, but terminal release was unaffected. Finally, experiments using antisense knockdown of nigral D_2 receptors were unsuccessful in altering the firing pattern of DA neurones, but resulted in an increase in both nigral and terminal excitability (Tepper *et al.* 1997). It appears that *in vivo*, autoreceptor-induced modulations of electrical activity, leading to altered striatal DA release, can be demonstrated by use of D_2 receptor agonists (or in some cases antagonists), whereas experiments that influence the endogenous somatodendritic release of DA have consistently failed to alter terminal release. Consequently, one must ask under which physiological conditions somatodendritically released DA gives rise to inhibition of terminal release.

Parkinson's disease

In 1817, British politician turned physician James Parkinson published a report on a medical condition he referred to as the shaking palsy or *paralysis agitans* (Parkinson 1817). He described the condition as characterised by "*Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forewards, and to pass from a walking to a running pace: the senses and intellect being uninjured.*" Some forty years later, French neurologist Jean-Marie Charcot discussed the same syndrome, but then referred to it as Parkinson's disease, a name it still holds. The four cardinal symptoms of the disease (resting tremor, rigidity, akinesia and bradykinesia with a subsequent loss of posture) were recognised by the two above mentioned investigators. In 1919, Konstantin Tretiakoff defended his doctoral thesis at the University of Paris, in which he described a marked loss of pigmented neurones in the SN (or *substantia nigra of Sömmering*, as it was then called) of parkinsonian patients (Tretiakoff 1919). In some of the surviving nigral cells he also noted inclusion bodies which he referred to as Lewy bodies, in honour of Friedrich Lewy, who some years earlier had described similar inclusions in the dorsal vagal nerve nuclei of PD sufferers (Lewy 1912). The occurrence of Lewy bodies is since then one of the pathological hallmarks of post mortem diagnosis of sporadic PD.

Symptoms

The term parkinsonism refers to the cardinal symptoms of PD, and it is usually the emergence of parkinsonism that prompts patients to seek medical attention. Parkinsonism is believed to result from abnormalities in basal ganglia function, largely due to the progressive loss of DA neurones in the SN. However, parkinsonism is not restricted to PD alone, but also occurs in other neurodegenerative diseases such as progressive supranuclear palsy, multiple systems atrophy or Lewy body disease. PD also leads to symptoms and pathological findings other than parkinsonism, such as sleep disturbances, sympathetic denervation, olfactory dysfunction, depression and dementia. While the motor symptoms that constitute parkinsonism are directly attributed to the degeneration of nigrostriatal DA neurones and the consequent disturbances within the basal ganglia network, the causes of the other symptoms are less explored, but are tentatively secondary to extrastriatal DA denervation or due to degeneration of other brain regions such as the locus coeruleus, the raphe- and vagal nerve nuclei, the olfactory bulb, and various other brain stem nuclei as well as cortical areas (see Chaudhuri *et al.* 2006, for a recent review on non-motor symptoms of PD).

Etiology

Parkinsonian symptoms can be caused by exposure to environmental factors such as pesticides or other toxins, heavy metals, infections in early life or head trauma (see Logroscino 2005; Elbaz and Tranchant 2007; Elbaz and Moisan 2008, for reviews). In cases where an identified environmental factor has been found responsible for the development of parkinsonian symptoms, the condition is usually referred to as secondary parkinsonism (this term also includes vascular and drug-induced parkinsonism). The causes of sporadic PD, which makes up a majority of cases, are still largely unknown. Post-mortem examinations of the distribution of Lewy bodies in sporadic PD patients and elderly without PD diagnosis but with Lewy bodies has led to a novel theory regarding the progression of sporadic PD (Braak *et al.* 2003). Based on the distribution of Lewy bodies and Lewy spindles, both of which are abnormal aggregations of the normally occurring presynaptic protein α-synuclein, the Braak theory states that the disease process starts in the medulla oblongata (mainly in the dorsal IX/X motor nucleus) and the olfactory bulb and then spreads upwards through the brainstem to the midbrain and from there on into cortical areas. DA neurones are affected relatively late according to this hypothesis, which has had a strong impact on the apprehension of the pathology and etiology of idiopathic PD lately. It has e.g. inspired a "dual hit hypothesis" (Hawkes *et al.* 2007), which suggests an unknown pathogen is responsible for the development of PD by infection through the nasal cavity and digestion system.

There are also several identified variants of PD with Mendelian heredity and identified gene mutations (one, PARK1, being a mutation in the α-synuclein gene, the main constituent of

Lewy bodies), but these forms make up a minority of cases. The long held view has been that sporadic PD is not inherited, but in recent years it has been suggested that hereditary factors are more important than previously thought (Sveinbjornsdottir *et al.* 2000; Maher *et al.* 2002a; Maher *et al.* 2002b; Rocca *et al.* 2004). Environmental risk factors may cause or trigger PD in subjects who are genetically vulnerable. This revised view of PD etiology is supported for example by studies of genetic polymorphisms (McGeer *et al.* 2002; Schulte *et al.* 2002; Sato *et al.* 2005; Bras *et al.* 2007) although a genetic factor common to sporadic PD has not yet been identified.

Treatment of Parkinson's disease

Pharmacological treatments

The standard therapy for PD is pharmacological treatment with L-DOPA (in combination with peripheral decarboxylase inhibitors in order to avoid peripheral side effects), although other pharmacological alternatives such as DA agonists (Calne *et al.* 1974), MAO-inhibitors (Golbe 1988; Golbe *et al.* 1988) and COMT-inhibitors (Rajput *et al.* 1997) are available. DA agonists are often considered to be somewhat more effective against tremor than L-DOPA, but at the cost of less overall efficacy on parkinsonism. Agonists have been advocated as first treatment, particularly in young patients, in order to minimise L-DOPA-treatment, as L-DOPA-usage has been correlated with the development of dyskinesias (see below). MAO- and COMT-inhibitors are commonly used at later stages of the disease to amplify and prolong the effects of a given L-DOPA-dose. Anticholinergic drugs were the first pharmacological treatment with sustained efficacy in PD but current use is limited due to their modest efficacy and the frequent occurrence of unwanted side-effects.

Surgical treatments

When pharmacological treatment loses its efficacy, or is complicated by drug-induced motor complications, surgical treatment with deep brain stimulation (DBS) or pallidotomy can be considered. Pallidotomy has largely been replaced by DBS in the last ten years, but is still used in selected cases, for instance in immunosuppressed patients with HIV infections. DBS is preferred as it is reversible, generates less side effects than pallidotomy when given bilaterally, and also because it permits optimisation of treatment by programming of the electrode (Benabid *et al.* 1998; Krack *et al.* 1998; Koller *et al.* 1999; Olanow *et al.* 2000). The most frequently used target for DBS treatment of PD is the STN. High frequency stimulation there improves virtually all of the parkinsonian symptoms and usually permits reduction of pharmacological therapy. Other targets for DBS in PD are the ventral intermediate thalamic nucleus (VIM) and the internal segment of the globus pallidus (GPi). The beneficial effects of VIM DBS are limited to alleviating tremor, and therefore its use is restricted to the tremor dominant forms of PD, where tremor is handicapping but other

symptoms are well controlled by pharmacological treatment. GPi DBS predominantly effects dyskinesias, but is rarely used (see Limousin and Martinez-Torres 2008, for a review on DBS and choice of target nuclei). It was recently suggested that the PPN can be effectively used as a DBS target (Mazzone *et al.* 2005; Plaha and Gill 2005; Stefani *et al.* 2007), and that it may provide a relief from hypokinesia also in patients not responding to L-DOPA. Clinical trials are under way to determine the usefulness of this target.

Future treatments

Possible future treatments are those based on restoring DA neurotransmission in the striatum or protecting the degenerating nigrostriatal pathway and thus alleviate or eliminate the symptoms. One restorative approach is the implantation of stem cells, but ethical as well as practical issues have slowed progress in this field somewhat, and there have also been discussions regarding clinical efficacy and troublesome side effects (Freed *et al.* 2001; Olanow *et al.* 2003; see Winkler *et al.* 2005 for a review of clinical studies). Another restorative approach, viral vector transfection (where non-DA cells are transfected with enzymes responsible for DA synthesis) is a reasonably new approach and has shown encouraging results in animal models (Mandel *et al.* 1998; Szczypka *et al.* 1999; Kirik *et al.* 2000; Kirik *et al.* 2002; Carlsson *et al.* 2005), but its efficacy in patients is still unknown. Neuroprotection has been attempted by use of agents that reduce oxidative stress, combat excitotoxicity, provide neurotrophic effects, enhance mitochondrial function, counteract inflammation and inhibit apoptosis, but clinical trials have usually shown no or merely modest effects in patients. (see Fahn and Sulzer 2004; LeWitt 2006; Schapira 2008; Voss and Ravina 2008, for reviews).

Animal models of Parkinson's disease

No animal models replicate the entire spectrum of PD (progressive cell degeneration, effects in multiple nuclei, motor impairments and Lewy body pathology with a given distribution). There are, however, models that replicate certain aspects of the disease, such as DA deficiency, oxidative stress and mitochondrial dysfunction or α-synuclein aggregation. Of these, the DA deficiency models are the oldest and most frequently used, and DA depletion can be attained in both rodents and primates by injections of neurotoxins, most commonly 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP). These toxins are specific for catecholamine neurones in general and DA neurones in particular, and they kill cells by generating oxidative damage and mitochondrial dysfunction (Saner and Thoenen 1971; Nicklas *et al.* 1985; Johannessen *et al.* 1986). Recent genetic findings in PD patients has led to the emergence of several genetic animal models, but the genetic variants of the disease are in minority, and the overall concordance of these models with PD is not entirely satisfactory (see Fleming *et al.* 2005, for a review on genetic animal models).

L-DOPA-induced dyskinesias

Dyskinesias in Parkinson's disease

In L-DOPA-treated patients, debilitating adverse events appear in a majority of patients over time, mainly motor fluctuations and abnormal involuntary movements (dyskinesias). Motor fluctuations usually present themselves within a couple of years (see Ahlskog and Muenter 2001) and predominantly in the form of the so-called wearing off-phenomenon, which is a term used to describe a shortening of the time frame for beneficial effects ("on"-state) of a single dose and the consequent re-appearance of symptoms in the latter part of a dose interval ("off"-state). This phenomenon is most likely caused by the progression of the disease, which results in a decline in the number of neurones capable of storing DA. The problem of motor fluctuations is usually addressed by shortening of the dose interval, addition of DA agonists in order to reduce the parkinsonian symptoms at the "off"-state or MAO- or COMT-inhibitors to prolong the effect of L-DOPA.

As motor fluctuations start to occur, there is an increased risk of developing dyskinesias (Rajput *et al.* 2002; Mazzella *et al.* 2005; Hauser *et al.* 2006), and after 4-6 years of L-DOPA-treatment, around 40 % of patients experience dyskinesias (Ahlskog and Muenter 2001). Dyskinesias exist in two distinct forms, peak-dose dyskinesias, that occur when the concentrations of DA in the brain are at their highest, and biphasic dyskinesias that occur when DA concentrations are increasing or decreasing (i.e. before and after the peak of L-DOPA-derived DA). Peak-dose dyskinesias are usually choreiform movements predominantly located to the upper body, but in some cases they also resemble myoclonia or dystonia. Biphasic dyskinesias, on the other hand, are usually more dystonic and often involve the lower extremities. The severity of dyskinesias is related to the dose of L-DOPA, so when they occur without the presence of motor fluctuations they can be reduced by decreasing the dose. However, in patients displaying both motor fluctuations and dyskinesias, this is not possible due to subsequent loss of efficacy, and in these patients dyskinesia may become a severe obstacle for adequate treatment.

The mechanisms of development for L-DOPA-induced dyskinesias is not fully understood but rapid, excessive swings in extracellular DA concentrations following L-DOPA treatment (Chase 1998; Bezard *et al.* 2001; Olanow *et al.* 2004a) is generally considered to contribute by potentiating postsynaptic mechanisms and thereby generating abnormal firing patterns within the basal ganglia. This has resulted in cautiousness with initiating treatment of PD with L-DOPA, as it has been reported that the development of dyskinesias is attenuated when the initial form of treatment is DA agonists (Parkinson Study Group 2000; Rascol *et al.* 2000; Oertel *et al.* 2006). However, DA agonist monotherapy may also result in dyskinesias (Rascol *et al.* 2000; Bracco *et al.* 2004), and furthermore it was recently reported that the beneficial effect of initiating treatment with an agonist is transient, and that patients who

were given L-DOPA as initial therapy had significantly better symptomatic improvement of L-DOPA therapy not only initially, but also later on in the disease (Katzenschlager *et al.* 2008). Thus, the DA agonist approach to prevent the development of dyskinesias comes at the price of symptomatic relief.

Animal models of dyskinesia

Dyskinesias are commonly studied in DA denervated animal models, and there are well established models for quantification of dyskinetic behaviour in both rats, mice and monkeys (Cenci *et al.* 1998; Langston *et al.* 2000; Lundblad *et al.* 2004; Lundblad *et al.* 2005). These models produce quantifiable abnormal motor behaviour as a response to L-DOPA-treatment, and in monkeys in particular these behaviours are very similar to dyskinesias in humans. The 6-OHDA rat model of dyskinesia is the most widely used, due to its cost-effectiveness and high reproducibility. This model has been validated by use of compounds clinically demonstrated to have an antidyskinetic effect (Dekundy *et al.* 2007), and even though the dyskinesias are somewhat different from those seen in patients, the rat model is accepted as a useful tool for preclinical investigations. One should, however, exercise caution when interpreting results of pharmacological interventions from animal models of dyskinesia, as their predictive values of antidyskinetic treatments in humans has been questioned (for review, see Lane and Dunnett 2008), and several strategies of treatment that generated promising results in animal models has failed to live up to expectations when tested in parkinsonian patients.

Findings in animal models of dyskinesia

The emergence of animal models of dyskinesia has initiated extensive research on molecular changes that occur in response to L-DOPA treatment. In particular, a large amount of experimental data points to an association between experimental L-DOPA-induced dyskinesia and D1-type receptor-mediated upregulation of nuclear transcription factors in striatal neurones (see Fig. 4). Thus, in dyskinetic animals D_1-receptor mRNA is upregulated (Konradi *et al.* 2004), D_1 receptor-dependent G-protein activation is increased (Aubert *et al.* 2005) and D_1 receptor-dependent intracellular signalling through the signalling protein DARPP-32 is amplified (Greengard *et al.* 1998; Picconi *et al.* 2003). In addition, D_1 receptor activation in DA denervated striata results in an increase in extracellular signal-related kinases (ERK) 1 and 2 (Gerfen *et al.* 2002), which are both potent upregulators of nuclear transcription factors such as ΔFosB and prodynorphin mRNA. These, in turn, are both upregulated in dyskinetic animals (Cenci *et al.* 1998; Andersson *et al.* 1999; Winkler *et al.* 2002; Lundblad *et al.* 2004). Accordingly, simultaneous L-DOPA and D_1-receptor antagonist treatment attenuates the development of L-DOPA-induced dyskinesias as compared to L-DOPA treatment alone, and this treatment regime also inhibits the upregulations of this intracellular pathway (St-Hilaire *et al.* 2005; Westin *et al.* 2007). Moreover, antagonism of type

5 metabotropic glutamate receptors, which are involved in the regulation of the D_1-dependent intracellular signalling pathway, also blocks the induction of dyskinesias and the increases in ΔFosB-expression and prodynorphin mRNA (Mela *et al.* 2007; Levandis *et al.* 2008).

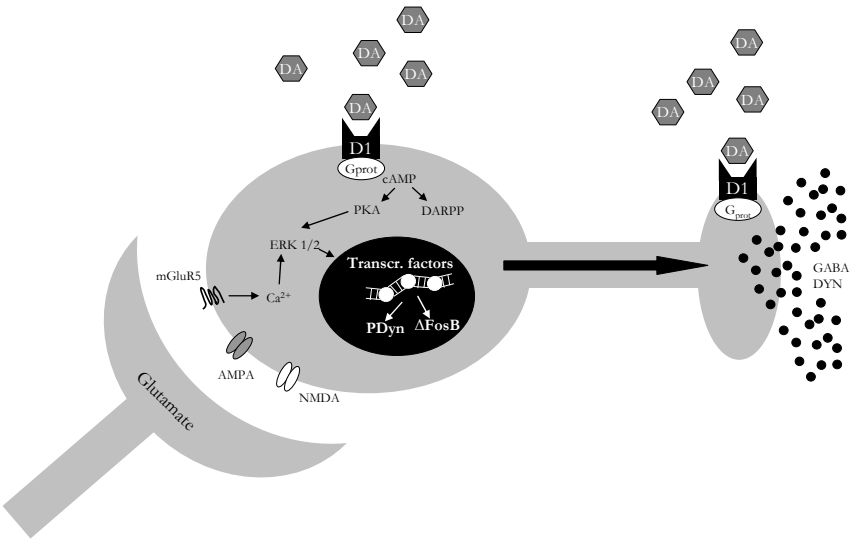

Fig 4. Schematic representation of a medium spiny neurone and the subcellular signalling pathways implicated in the development of dyskinesias in animal models. D_1-receptor activation as well as mGluR5-activation is believed to be crucial to an upregulation of nuclear transcription factors that result in an increased expression of ΔFosB and prodynorphin, which in turn drive the expression of late-response genes, leading to an abnormal sensitivity to incoming signalling and to alterations in GABA/DYN output from the neurone. Adapted from Cenci and Lundblad (2006) and Cenci and Lindgren (2007).

Dyskinetic animals lack the ability to reverse long term potentiation of corticostriatal synapses (Picconi *et al.* 2003), a finding which implicates that abnormalities in synaptic plasticity are of importance for the development of dyskinesias. Furthermore, dyskinetic animals have altered intracellular trafficking of NMDA receptors (Fiorentini *et al.* 2006; Gardoni *et al.* 2006) and increased phosphorylation of AMPA receptors (Santini *et al.* 2007) in striatal medium spiny neurones, pointing towards a hyperglutamatergic influence on striatal neurones. Corticostriatal synaptic plasticity has been suggested to be a pivotal component in the formation of motor memories (Graybiel *et al.* 1994; Packard and Knowlton 2002; Yin and Knowlton 2006; see Kreitzer and Malenka 2008), and the glutamatergic dysfunction seen in dyskinetic could be a central component in the establishment of dyskinetic motor patterns (Chase and Oh 2000; Bezard *et al.* 2001; Picconi *et al.* 2003). This notion has initiated the suggestion that NMDA- and AMPA-receptor antagonists may prevent the development of dyskinesias (Bibbiani *et al.* 2005; see Brotchie

2005, for discussion). Studies in animal models have also identified the receptors of opioid peptides, endocannabinoids as well as adenosine as potential targets for antidyskinetic treatment (Johansson *et al.* 2001; Xiao *et al.* 2006; Aubert *et al.* 2007; Morgese *et al.* 2007). Notably, an increase in opioid receptor binding has been found in dyskinetic patients (Piccini *et al.* 1997).

Alterations in postsynaptic sensitivity and corticostriatal synaptic plasticity dysfunction are, however, not necessarily the only factors of importance for the development of dyskinesias. In 6-OHDA-lesioned rats, there is a large surge in extracellular DA following L-DOPA-injection (Abercrombie *et al.* 1990), and a recent study in parkinsonian patients demonstrated that the amount of striatal DA release following L-DOPA is positively correlated with the severity of dyskinesias (Pavese *et al.* 2006). Also, patients who had experienced motor fluctuations had elevated striatal DA turnover in a post-mortem analysis as compared to patients who had no motor fluctuations (Rajput *et al.* 2004).

A study by Carta and co-workers (Carta *et al.* 2006) indicates that L-DOPA concentrations may increase more in dyskinetic than in non-dyskinetic in response to L-DOPA-treatment, but overall little is known about the role of presynaptic mechanisms in the animal models of dyskinesia. It is therefore not clear if altered intracerebral L-DOPA and DA kinetics is a universal phenomenon in dyskinesia, and factors explaining the observed variability in DA release in dyskinetic patients remain unexplored. Determining the role of intracerebral DA kinetics for the development and expression of dyskinesias could potentially shed light on the question of why dyskinesias are expressed to various extents in both animal models and human patients.

Aim of thesis

The overall aim of this thesis is to characterise the influence of dopamine transmission in the substantia nigra and the striatum on motor functions in both normal rats and in rat models of Parkinson's disease and L-DOPA-induced dyskinesia.

Specific aims

1) To investigate the relative importance of nigral and striatal dopamine release for motor performance by inducing local blockade or depletion of dopamine release in the respective nuclei.
2) To characterize in what way nigral somatodendritic dopamine release modulates striatal axon terminal release, and vice versa, under near physiological conditions.
3) To investigate the possible regulatory action of cholinergic projections to the substantia nigra on the motor activity-induced increase of somatodendritic dopamine release.
4) To characterise release and metabolism of dopamine in the striatum and the substantia nigra in response to an L-DOPA-provocation in parkinsonian animals primed for L-DOPA-induced dyskinesias, and to investigate if the intracerebral dopamine kinetics differs between dyskinetic and non-dyskinetic animals.

Materials and methods

Ethical considerations

All experiments in this thesis were approved by the local ethical committees in Göteborg and Lund and carried out in accordance with the European Communities Council Directive of November 24th 1986. All efforts were made in order to minimise the number of animals in the studies as well as their suffering.

Materials

Animals

Female Sprague Dawley rats from B&K Universal, Sollentuna, Sweden (papers I and II) or Harlan Netherlands (paper III) weighing between 200-250 grams on arrival were used. Animals were housed under controlled environmental conditions (12-h light–dark cycle, 26°C, 60–65% humidity) in cages of four animals in each until microdialysis probe implantation and from then on separately for no more than 48 hours until microdialysis experiments.

Drugs and anaesthetics

Drugs and chemicals used in reverse dialysis experiments:

Drug	Vendor
Tetrabenazine (paper I)	1) Tocris Bioscience, Bristol, UK and 2) gift from Carlsson Research AB, Göteborg, Sweden
Scopolamine (paper II)	Sigma-Aldrich, Germany
Mecamylamine (paper II)	Sigma-Aldrich, Germany
Tetrodotoxin (paper III)	Tocris Bioscience, Bristol, UK

Drugs and chemicals used for systemic treatment:

Drug	Vendor
3,4-dihydroxyphenylalanine (L-DOPA, paper III)	Sigma-Aldrich, Germany
Benserazide (paper III)	Sigma-Aldrich, Germany
8-OH-DPAT (paper III)	Tocris Bioscience, Bristol, UK
CP-94253 (paper III)	Tocris Bioscience, Bristol, UK
Dexamphetamine (paper III)	Apoteksbolaget AB, Sweden

Drugs and chemicals used for intracerebral injections:

Drug	Vendor
6-hydroxydopamine (6-OHDA, papers II and III)	Sigma-Aldrich, Sweden

Drugs and chemicals used for anaesthesia and postsurgical analgesia:

Drug	Vendor
Isoflurane (papers I, II and III)	Abbot Scandinavia AB, Solna, Sweden
Ketoprofen (papers I, II and III)	Merial, Lyon, France
Buprenorphine (paper III)	Apoteksbolaget AB, Sweden

Methods

The common methodology employed in paper I-III is the combination of behavioural testing (rotarod or abnormal involuntary movement rating) with measurements of neurotransmission by intracerebral microdialysis sampling.

Intracerebral microdialysis

The microdialysis technique for sampling neurotransmitters or other small molecules from brain tissue in living animals was developed in the early 1980s (Brodin *et al.* 1983; Johnson and Justice 1983). Microdialysis sampling of molecules in the extracellular space is based on the principle of concentration-driven diffusion across a semipermeable membrane. A hollow semipermeable membrane fibre is implanted into a target structure in the brain and perfused with a physiological salt solution resembling cerebrospinal fluid. Neurotransmitters from the surrounding tissue will diffuse across the membrane and be removed by the perfusion flow. The perfusion fluid is then collected and the concentrations of neurotransmitters and other small molecules can be determined online or offline by biochemical analysis.

Probe implantation (papers I, II and III)

In-house produced microdialysis probes (see Elverfors *et al.* 1997) were washed with approximately 100 µl of ethanol (70%) followed by 100 µl of Ringer solution (3 µl/minute). The tubing was then heat-sealed and probes were stored with the membranes in Ringer solution for no more than a couple of hours until implantation. Animals were anaesthetised with isoflurane delivered from a rodent inhalation anaesthesia system (Univentor 400 Anaesthesia Unit, Univentor Ltd., Zejtun, Malta). The level of anaesthesia was monitored by observing the breathing frequency and the absence of response to tail-pinching, and the isoflurane concentration was adjusted accordingly. The rats were placed in a stereotactic frame (David Kopf Instruments, Tujunga, CA, USA) with the skull plane in a level position (bregma and lambda in a horizontal plane), a skin incision was made and holes were drilled at the following coordinates relative to bregma (for probes aimed at SN: 5.3 mm caudal, 2.2

mm lateral; or at striatum: 1.0 mm rostral, 2.6 mm lateral in paper I and II, 0.6 mm rostral, 3.5 mm lateral in paper III). Two additional holes were drilled for screws used to anchor the probes. The dura mater was carefully opened by a hooked needle, and the probes were lowered down into the target structure (for SN: 8.6 mm from brain surface; for striatum 6.2 mm (papers I and II) or 6.0 mm (paper III). Dental cement was used to fix the probes to the skull and the anchoring screws. Normal body temperature was maintained by a heating pad, and postsurgical analgesia was attained by administering ketoprofen (5 mg/kg, s.c.). The animals were also fitted with a plastic collar for later connection to the swivelled perfusion arm.

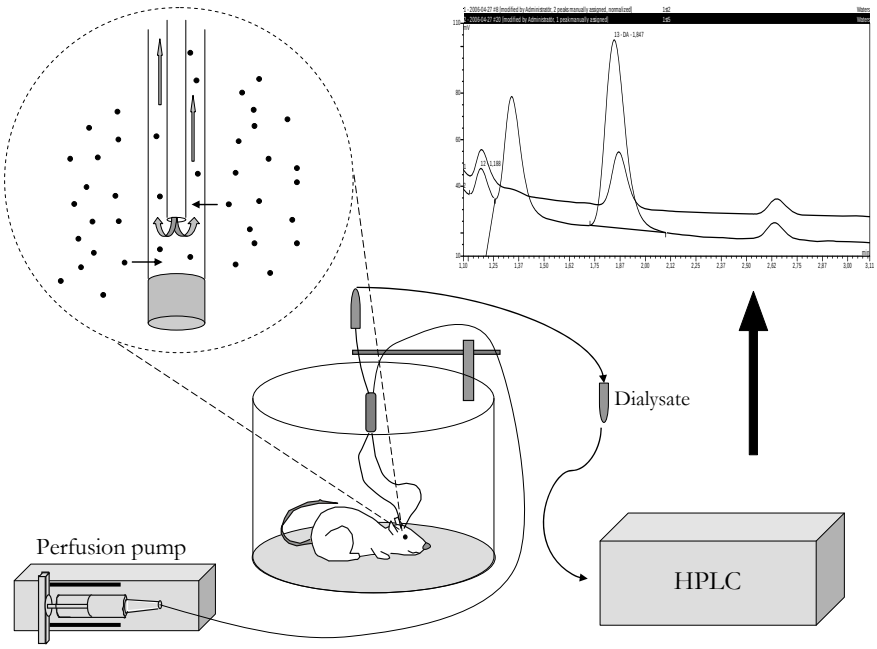

Fig. 5. The setup in a microdialysis experiment. A perfusion flow passes by a semipermeable membrane implanted into the brain of the experimental subject. The perfusion fluid is collected in sample vials, and these vials are then placed in an HPLC, where the dialysate concentration of neurotransmitters and metabolites is determined.

Microdialysis experiments

On the day of experiments (40-48 hours after surgery), animals were connected by their neck collar to a swivelled arm, which allowed them to move freely in the cage. During combined microdialysis/rotarod experiments, cages were placed alongside the rotarod equipment, and the swivelled arms could then be swung over the rod when the animal was tested and back over the cage in between sessions. Approximately 5 minutes after rats being connected to the arms, the microdialysis probes were connected to the perfusion system. In rotarod experiments in paper I and II, a rotarod session (Acc10-test or 15 minutes at 10 rpm) was performed before initiation of perfusion. Probes were then perfused with Ringer solution

(140 mM NaCl, 1.2 mM $CaCl_2$, 3.0 mM KCl and 1.0 mM $MgCl_2$) for one hour of equilibration at 3.0 µL/min (paper I), 2.8 µL/min (paper II) or 2.0 µL/min (papers II and III), after which baseline sampling began. Two or three baseline samples were then used to determine baseline concentrations of analysed substances, and alterations in dialysate concentrations during pharmacological modulation and/or behavioural testing were monitored during the remainder of the experiments. Sample volumes were 30 µL (paper I and II), 42 µL (paper II) or 40 µL (paper III). Following completion of experiments, animals were euthanized and probe location was confirmed by vibratome slicing. Animals with probes located outside of the target structure or with intracranial haemorrhages were excluded. In tetrabenazine-treated animals for determination of DA depletion (paper I), the striatum and the SN on both sides were dissected and rapidly placed on dry ice for later biochemical analysis. In 6-OHDA-lesioned animals, the SN (paper III) and the striatum (papers II and III) on both sides were also dissected for later determination of extent of lesion. In paper II, probe placement in the SN was verified as above, while probe placement and absence of haemorrhages was confirmed in the remaining midbrain segments following dissection in paper III.

6-OHDA lesions (papers II and III)

In paper II, the nigrostriatal DA system in the right side of the brain was lesioned by intracerebral injection of 6-OHDA in the medial forebrain bundle. Isoflurane anaesthesia was attained as previously described and a burr hole was made over the right median forebrain bundle (4.4 mm caudal, 1.2 lateral, with reference to bregma, and 7.8 mm below brain surface, tooth bar set at -2.4). A stainless steel cannula with an outer diameter of 0.55 mm was used to stereotactically inject 7.5 µg of 6-OHDA dissolved in 0.02% ascorbate/saline solution (2.5 µl, 1 µl/min). Ketoprofen (5 mg/kg, s.c.) was given for postsurgical analgesia and the skin wound was closed with metal clips. In paper III, the surgical procedure was the same as in paper II, but the animals were also injected with 6-OHDA (6 µg in 2.0 µl 0.02% ascorbate/saline, 1 µl/min) in the ventral tegmental area (4.0 mm caudal and 0.8 mm lateral to bregma, and 8.0 mm below brain surface, tooth bar set at +3.4). After surgery, the animals were given the opioid buprenorphine (0.167 mg/kg s.c.) for postsurgical analgesia.

Behavioural evaluation of lesions (papers II and III)

Two weeks after 6-OHDA surgery, the extent of lesions was evaluated by the amphetamine rotation test (paper III). The test measures the number of ipsilateral turns that the hemilesioned animals does in response to amphetamine treatment (2.5 mg/kg, i.p.). Rotations are measured over 90 minutes in an automated rotometer. Rats rotating more than five full ipsilateral turns per minute, which predicts a DA lesion of more than 90% (Winkler *et al.* 2002; Carta *et al.* 2006), were selected for further studies. In paper II, where the

objective of 6-OHDA-lesioning was to generate impairment in rotarod performance, an Acc10-test was performed four weeks after the 6-OHDA lesion, and animals with Acc10-performance of less than 60% of pre-lesion performance were selected for microdialysis experiments.

Rotarod training and testing (papers I and II)

The rotarod test determines overall motor performance and does not discriminate between different aspects of it (such as coordination, balance and motivation). In this thesis, motor performance was measured by the so-called Acc10-test (see Bergquist *et al.* 2003), which consists of four consecutive acceleration trials (during which the rod accelerates from 4 to 40 rpm in 10 minutes), with 5 minutes of rest in between trials. The Acc10 performance is

Table 1. Training procedures for rotarod motor performance measurements (top) and continuous motor activity experiments (bottom).

Training for Acc10 performance measurements						
Day	CS7 (minutes)	CS10 (minutes)	AccelerationN (number of)	Acceleration5 (number of)	Acceleration10 (number of)	ORP (number of)
1	3x5 min					
2	5 min	2x5 min	2	1	1	
3		2x5 min		2	2	
4		1x5 min		1	1	1
5		2x5 min			4 (Acc10-test)	
Training for continuous motor activity experiments						
Day	CS7 (minutes)	CS10 (minutes)	AccelerationN (number of)	Acceleration5 (number of)	Acceleration10 (number of)	ORP (number of)
1	3x5 min					
2		2x5 min 3x10 min				
3		2x5 min 2x10 min			2	
4		2x5 min 2x15 min			2	
5		2x15 min				1

Abbreviations: CS7, CS10 = constant speed, 7 and 10 rpm, respectively; AccelerationN = acceleration without fall, where the rod speed increases from 4 to 40 rpm in 2 minutes, but the session is halted just before the animal falls off; Acceleration5 and 10 = acceleration session where the rod speed increases from 4 to 40 rpm in 5 and 10 minutes, respectively. ORP = overall rod performance test, where 10, 15, 20 and 30 rpm is tried for five minutes or until the animal falls off.

the mean time spent on the rod in the four trials. In one set of experiments in paper II, the objective was to use the rotarod equipment to provide a period of continuous motor activity, and in this case, the animals were walking on the rod for 15 minutes at 10 rpm. To obtain stable and reliable measurements from rotarod experiments, animals have to be trained in advance. Before the first Acc10 performance measurement, animals are put through a five day training regime starting at a low constant speed (5-7 rpm), and progressing to higher constant speeds and acceleration trials over the course of the training period. The training for continuous motor activity experiments in paper II consisted mainly of constant speed sessions of increasing length. Training schedules for both performance experiments and continuous motor activity experiments can be seen in Table 1.

Abnormal involuntary movement (AIMs) rating (paper III)

Animals that had been lesioned by more than 90% as indicated by the amphetamine rotation test received daily injections of L-DOPA (6 mg/kg, s.c) and benserazide (12 mg/kg, s.c.) to induce abnormal involuntary movements (AIMs), the rat model equivalence of dyskinesias in L-DOPA-treated patients. After 14 days of this treatment, the majority of animals develop AIMs. Every three days of the AIMs induction period, rats were placed in individual cages, and the severity of AIMs was assessed for one minute every twenty minutes over the first three hours after an L-DOPA injection. Rat AIMs are classified into three subtypes based on how they are expressed: 1) axial AIMs, i.e. dystonic postures or choreiform twisting of the neck and upper body towards the side contralateral to the lesion; 2) limb AIMs, i.e. abnormal, purposeless movements of the forelimb and digits contralateral to the lesion; 3) orolingual AIMs, i.e. empty jaw movements and tongue protrusions towards the contralateral side. Each of these three subtypes is scored on a severity scale from 0 to 4, and the amplitude of AIMs is also assessed. A global AIMs score is calculated for each monitoring period by multiplying the basic severity score with the amplitude score for each AIM subtype at each time point, and the sum of all time points constitute the global AIMs score. The criteria for each level of severity and amplitude are given in Table 2.

Biochemical analysis

The microdialysis samples were analysed for contents of amine neurotransmitters and their metabolites (and in study III also L-DOPA) by high performance liquid chromatography followed by electrochemical detection (HPLC-ED). In studies I and II, we used a split fraction system that detects DA and 5-HT on one column and, DOPAC, 5-hydroxy indole acetic acid (5-HIAA) and HVA on another (Lagerkvist 1991). Two chromatographic systems shared a common auto- injector with two sample loops (20 μ l for DA and 5-HT, 9 μ l for the metabolites) for simultaneous injection on the two separate analysis systems. DA and

Table 2. Criteria for severity and amplitude of abnormal involuntary movements (AIMs).

Severity rating	Criteria
0	Absent
1	Present less than 50 % of time
1.5	Present 50 % of time
2	Present more than 50 % of time
2.5	Present during most of the time, but with very short non-dyskinetic episodes
3	Present all of the time, but interrupted by external stimulus
3.5	Present all of the time, but only sometimes interrupted by external stimulus
4	Present all of the time, and not interrupted by external stimulus

Amplitude rating	Criteria for limb AIMs
1	Tapping or tiny oscillatory movements of forelimb/forepaw around a fixed point
2	Low amplitude movements with some involvement of distal and proximal muscles
3	Movements involving the entire forelimb with visible contraction of shoulder muscles
4	Vigorous circular forelimb and shoulder movements of maximal amplitude
Amplitude rating	Criteria for axial AIMs
1	Sustained lateral deviation of upper body with approximately 30° angle
2	Sustained lateral deviation of upper body with 30°-60° angle
3	Sustained lateral deviation of upper body with 60°-90° angle
4	Sustained lateral deviation of upper body with more than 90° angle, and consequent loss of balance
Amplitude rating	Criteria for orolingual AIMs
1	Twitching of facial muscles accompanied by small masticatory movements without jaw opening
2	Twitching of facial muscles accompanied by noticeable masticatory movements, occasional jaw opening
3	Movements with broad involvement of facial muscles and masticatory muscles. Frequent jaw opening with occasional tongue protrusion
4	All of the above muscle muscle categories involved to the maximum possible degree

Severity and amplitude is rated during one minute every twenty minutes for three hours, and the severity is multiplied by the amplitude. The AIMs score is calculated as the total sum of the (severity x amplitude) of each subtypes of AIMs for each time point, and a global AIMs score is calculated as the total sum of AIMs for all time points. Adapted from Cenci and Lundblad (2007).

5-HT were separated on a reverse phase column (Prodigy 3 µ ODS(3) 100A, Phenomenex, Torrance, CA, USA) by isocratic eluation with 30% methanol, 3.0 mM citric acid, 10 mM sodium citrate, 0.275 mM 1-decanesulphonic acid and 0.012 mM of Na_2EDTA. The amines were oxidised using an amperometric detector working at +0.61 V (Waters 460, Millipore Waters, Milford, MA, USA). The metabolites DOPAC, 5-HIAA and HVA were separated on a reverse phase column (Nucleosil 3 µ C_{18} 100A, Phenomenex, Torrance, CA, USA) by

isocratic eluation with 0.010 M K_2HPO_4, 0.040 M citric acid, 0.012 mM Na_2EDTA and 5% methanol and oxidised on another amperometric detector operated at +0.80 V (Decade, Antec Leyden, Leiden, Netherlands). The resulting currents were recorded in separate channels and analysed on a desktop PC equipped with Dionex Chromeleon® chromatography software (Dionex, Sunnyvale, CA, USA).

In paper III, the monoamine transmitter substances (DA, 5-HT) as well as their amine (3-MT) and acid (DOPAC, 5-HIAA, HVA) metabolites and DOPA were quantified in a split fraction, two-dimensional HPLC-ED system. Separation and detection of acids (DOPAC, 5-HIAA, HVA and DOPA) was done by a method similar to the one used in papers I and II, but with octyl sulphate (0.04 %) included in the mobile phase. Octyl sulphate is an ion pair binder that improves retention of charged substances (in this case DOPA) in reverse phase chromatography. The acids were detected by a coulometric detector operated at +0.40 V (ESA coulochem II). The amines (DA, 5-HT and 3-MT) were separated by column-switching chromatography with reverse phase followed by reverse phase with ion pairing. Electrochemical detection was performed as described above with an amperometric detector operated at +0.61 V (Waters 460, Millipore Waters, Milford, MA, USA). The two-dimensional chromatography configuration improves the selective separation of amines and shortens the necessary eluation times, both resulting in improved detection limits.

Biochemical analysis of tissue samples.

Tissue samples were homogenised (Sonifier Cell Disruptor B30; Branson Sonic Power Co.) in a solution of 0.1 M perchloric acid, 4.5 mM EDTA and 1.6 mM glutathione (paper I) or 0.1 M perchloric acid and 2.5 mM EDTA (papers II and III), centrifuged (10000 rpm, 10 minutes), and the supernatant was then injected into the detection systems, as above.

Results and discussion

Paper I: Partial depletion of dopamine in substantia nigra impairs motor performance without altering striatal dopamine neurotransmission

Background

An influence of nigral DA release on motor behaviour and muscle tone has previously been established in experiments using local nigral treatment with DA antagonists as well as amphetamine (Yurek and Hipkens 1993; Yurek and Hipkens 1994; Timmerman and Abercrombie 1996; Crocker 1997; Trevitt *et al.* 2001; Bergquist *et al.* 2003). Furthermore, local nigral perfusion with the unspecific DA agonist apomorphine partially restores motor performance in 6-OHDA-hemilesioned rats (Bergquist *et al.* 2003). However, the importance of somatodendritic DA release in relation to the more extensive terminal release in the striatum has not been investigated. The existence of somatodendritic DA autoreceptors is well established, but their influence under physiological conditions is not as clear (see the chapter on somatodendritic autoreceptors in the introduction). It is for example not known if autoreceptors in the SN actually modulate the activity of DA neurones and the resulting striatal DA release under physiological conditions. This study was undertaken to shed light on the relative contribution of somatodendritic DA release to the performance of motor tasks and to investigate the effects of local nigral DA depletion on terminal release.

Experimental design

The VMAT-inhibitor tetrabenazine (TBZ) was administered by reverse dialysis to the SN and/or the striatum of rats before and during Acc10-testing (for experimental timeline, see Fig.6). Dialysate concentrations of DA, 5-HT and their metabolites were monitored by HPLC-ED. The effects of TBZ perfusion on DA dialysis concentrations and whole tissue contents of the neurotransmitters and metabolites were also investigated in a control group that were not put through motor performance testing.

Findings and discussion

Nigral TBZ-treatment significantly decreased nigral dialysate DA concentrations, but did not affect DA dialysis concentrations in the striatum. Local nigral TBZ-perfusion also resulted in a significant impairment in motor performance, as compared to untreated controls. Measurements of whole tissue DA contents demonstrated that nigral TBZ-perfusion reduced DA tissue content by approximately 60% as compared to the untreated side. But this depletion did not alter striatal DA release, even during motor performance testing. The

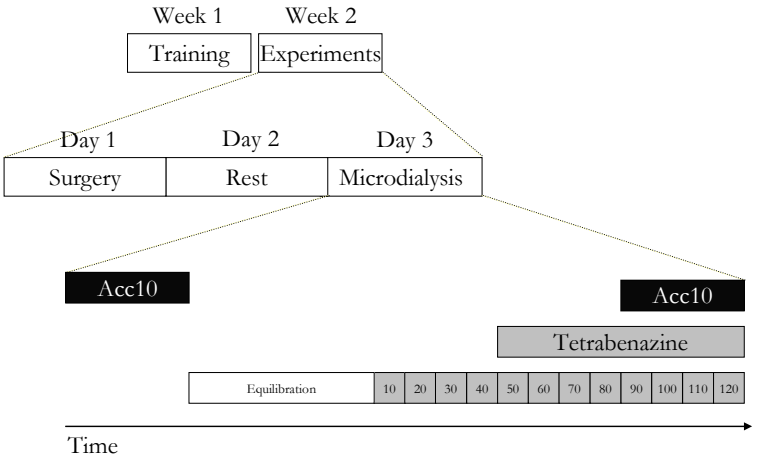

Fig 6. Experimental design in paper I. Animals were trained on the rotarod during week 1, and during week 2 microdialysis probes were implanted. During microdialysis experiments baseline Acc10-measurements of motor performance and dialysis concentrations were performed, and TBZ perfusion was then initiated in the SN, the striatum of both. A second Acc10-test was performed during the last 40 minutes of the experiment.

existence of compensatory mechanisms mediated by other receptors than nigral D_2 autoreceptors can not be excluded, but even so, this finding indicates that endogenous activation of nigral D_2 receptors does not modulate striatal release during physiologically relevant conditions, such as motor activity.

Dialysate DA concentrations in the striatum were similarly decreased by local perfusion with TBZ, but in contrast to TBZ perfusion in SN, this was not accompanied by impaired motor performance. Striatal whole tissue DA contents were not significantly altered by local perfusion, which may be explained by the larger volume of striatum; its higher DA content; or theoretically that whole tissue DA contents are maintained by a compensatory upregulation of DA synthesis and release in striatal regions that are located outside the direct influence of the local TBZ perfusion.

However, the substantial increase in somatodendritic DA release during striatal TBZ-perfusion and motor performance testing argues against the conclusion that striatal TBZ-treatment affects too small a part of the striatum to affect motor functions. A possible explanation to the lack of effect of striatal TBZ-treatment on motor performance may be that striatal TBZ-perfusion creates a functional imbalance within the basal ganglia, but that the increased somatodendritic DA release to some extent counteracts this imbalance and

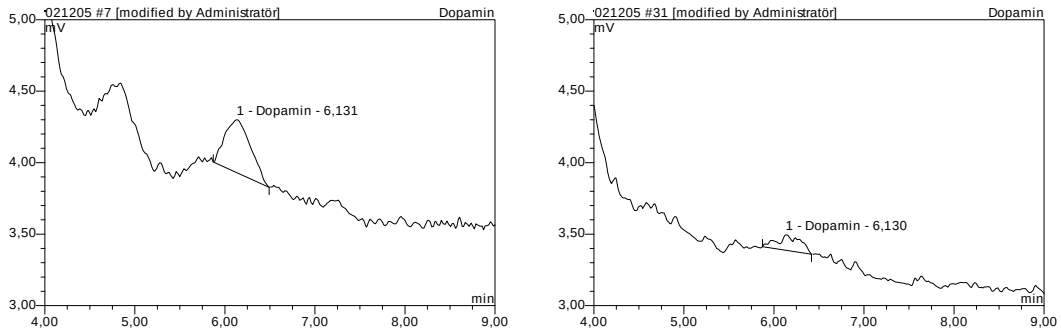

Fig. 7. Typical chromatograms of DA measurements in the SN of a rat at baseline (left) and after 40 minutes of TBZ perfusion (right). DA concentration measurements corresponding to DA peaks seen above were 0.2895 fmol/µl for the baseline sample and 0.0778 fmol/µl for TBZ-treated sample.

thereby maintains motor performance. This hypothesis is supported by the observation that when somatodendritic DA release was also prevented, by simultaneous TBZ-perfusion in the SN in addition to the striatum, motor performance was significantly impaired both in relation to controls and to animals receiving only striatal TBZ.

Overall, this study provides further support for an important function of nigral somatodendritic DA release in motor functions, and also shows that this effect is not mediated through regulation of terminal release in the striatum. Furthermore, it also suggests that compromised DA transmission in the striatum may be compensated for by increases in DA release in the SN.

Paper II: Motor activity-induced dopamine release in the substantia nigra is regulated by muscarinic receptors

Background

The SN receives inputs from many different sources. One of those, the PPN, is a brain structure that has received considerable attention in recent years (Lee *et al.* 2000; Mena-Segovia *et al.* 2008; Stein 2009). Several different functions have been ascribed this nucleus, and among those, sleep regulations and locomotion is of particular relevance for PD. Stimulation of the PPN promotes locomotion and lesions have been suggested to result in akinesia (Eidelberg *et al.* 1981; Garcia-Rill *et al.* 1987; Kojima *et al.* 1997; Aziz *et al.* 1998; Jenkinson *et al.* 2006; Kuo *et al.* 2008; for review, see Stein 2009). The efferent parts of the PPN consist mainly of glutamate and Ach neurones, and the SN is the nucleus in the brain that is most densely innervated by cholinergic fibres from the PPN. The PPN was recently introduced as a potential target for DBS in PD and other similar neurodegenerative diseases (Pahapill and Lozano 2000; Nandi *et al.* 2002; Mazzone *et al.* 2005; Plaha and Gill 2005; Stefani *et al.* 2007; Lozano and Snyder 2008) and notably, drugs blocking cholinergic receptors are efficacious for relieving some symptoms of PD. This study was undertaken to

test the hypothesis that cholinergic modulation of neurotransmission in the SN influences nigral and/or striatal DA release and that this is of importance for motor functions. We reasoned that the previously observed increase in somatodendritic DA release during motor activity (Bergquist *et al.* 2003; Andersson *et al.* 2006) ought to be the result of altered activity of afferent neurotransmitter release in the SN, and a main neurotransmitter candidate for augmenting nigral DA release during motor activity is ACh. Therefore, we decided to investigate the possible effects of nigral administration of ACh receptor antagonists on DA release in the SN and the striatum as well as on motor performance, in both intact and hemilesioned rats.

Experimental design

Appropriate concentrations of the muscarinic receptor antagonist scopolamine and the nicotinic receptor antagonist mecamylamine were determined in separate dose-response experiments. This was done to find the highest concentration that did not alter DA release in the SN during resting conditions, assuming that it would still alter motor activity-evoked nigral DA release if the stimulation of the addressed receptors is increased during motor activity. In subsequent experiments, the chosen antagonist concentrations were perfused in the SN for 45 minutes before and 30 minutes after continuous motor activity (15 minutes at 10 rpm) and extracellular DA concentrations in the SN and the striatum were measured

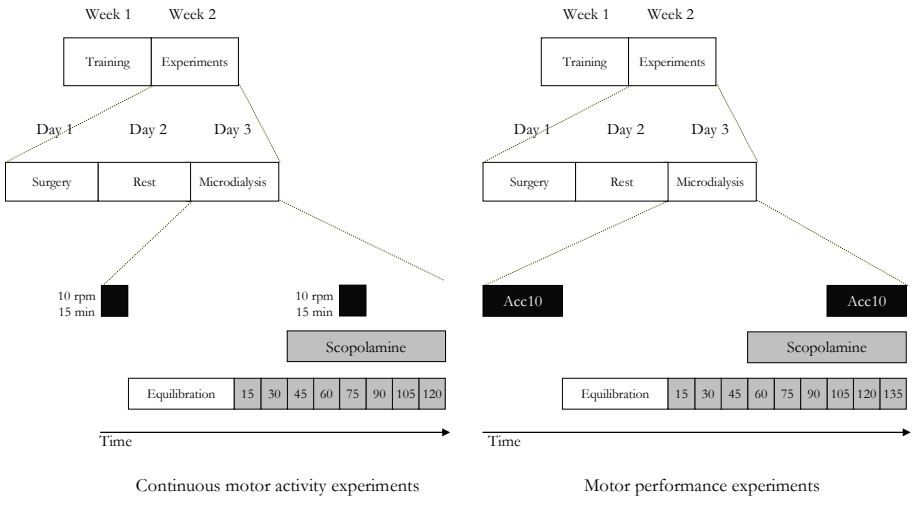

Fig. 8. Experimental setup for dialysis experiments with continuous motor activity (left) and motor performance testing through the Acc10-test (right). In experiments with 6-OHDA-hemilesioned rats, the week of training was followed by lesion surgery, and animals were allowed to recover for four weeks before performing another Acc10-test, and microdialysis probes were then implanted.

simultaneously (see Fig. 8 for basic experimental design). The effect of nigral muscarine receptor blockade on motor performance was investigated by perfusing the SN with scopolamine before and during the accelerating rod test (Acc10) in normal and 6-OHDA hemilesioned animals.

Findings and discussion

The main finding in this paper is that nigral perfusion with the muscarinic receptor antagonist scopolamine amplifies the motor activity-evoked increase in somatodendritic DA release and improves motor performance in 6-OHDA hemilesioned rats.

In the continuous motor activity experiments, scopolamine perfusion generated a significant and long-lasting augmentation of motor activity evoked nigral DA release, while mecamylamine perfusion did not alter DA dialysate concentrations during motor activity. Previously it has been shown that local injections of scopolamine into the SN decrease striatal DA release (Miller and Blaha 2005), and also that nigral scopolamine administration attenuates an increase in striatal DA release evoked by PPN stimulation (Forster and Blaha 2003). Together, these findings indicate that nigral muscarinic receptors have a tonic excitatory effect on nigrostriatal neurones, and that they also mediate PPN activity-induced regulation of terminal release. In our experiments, however, we did not observe any significant changes in striatal DA release (although there was a tendency towards a decrease) in response to nigral scopolamine treatment. This may to some extent be explained by the considerably lower amount of scopolamine delivered to the SN in the present study; the reverse microdialysis during 90 min totally perfused the probe with 5.5 μg (90 min x 2 μL x 100 μM x MW scopolamine =303) of which only a small percentage will reach the brain tissue, as compared to the local injection of 200 μg (Forster and Blaha 2003; Miller and Blaha 2005). The dose of scopolamine used in motor activity experiments in this study was chosen because of its lack of effects on baseline somatodendritic DA, and it may therefore be too small to significantly affect terminal release of DA. The dose-response experiments in

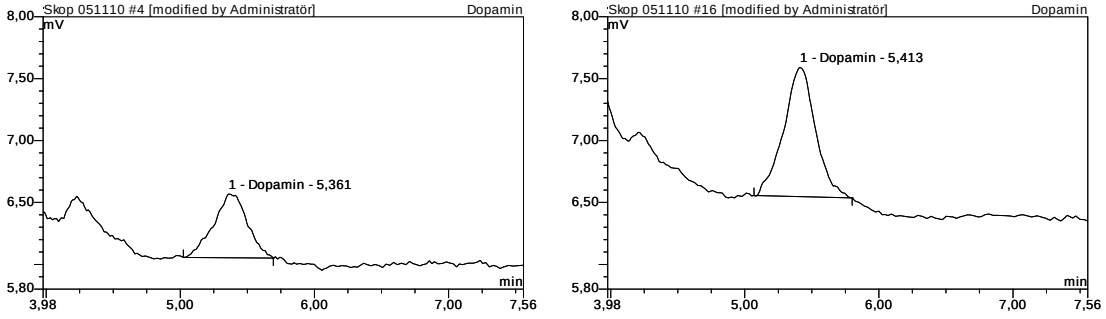

Fig. 9. Typical chromatograms of DA measurements in the SN of a rat at baseline (left) and after 15 minutes of continuous rotarod activity (10 rpm). DA concentration measurements corresponding to DA peaks seen above were 0.3635 fmol/μl for the baseline sample and 0.6932 fmol/μl for TBZ-treated sample.

this paper indicates that nigral treatment with higher doses of scopolamine increase somatodendritic DA release even at rest, and therefore, the inhibitory effects on terminal DA release seen during treatment with higher scopolamine doses may, apart from blocking direct excitatory effects of ACh, also involve activation of inhibitory nigral DA autoreceptors.

We are not the first to report an increase in somatodendritic DA release as a consequence of local muscarinic receptor antagonism (Izurieta-Sanchez *et al.* 2000), but the explanation for this counterintuitive response to blockade of excitatory cholinergic receptors is not evident. The activity of the PPN is increased in 6-OHDA-hemilesioned rats (Carlson *et al.* 1999; Breit *et al.* 2006; Zhang *et al.* 2008) and in MPTP lesioned primates (Gomez-Gallego *et al.* 2007) and given that PPN stimulation increases striatal terminal release of DA (Forster and Blaha 2003), the overactivity of the PPN is most likely beneficial for the outflow of motor impulses from the basal ganglia. Furthermore, muscarinic receptor activation in the SN excites nigrostriatal neurones, so our findings seem to be the opposite of what one would expect. However, one possible explanation is that local nigral scopolamine administration blocks muscarinic inhibitory autoreceptors located on the cholinergic terminals from the PPN, and thereby increases Ach release which in turn excites dendrites locally and stimulates nigral DA release by postsynaptic nicotine receptors. Another possibility is that local nigral DA release is stimulated by an increase in glutamatergic neurotransmission, tentatively from neurones originating in the PPN; glutamate in the SN is previously known to increase nigral DA release (Campusano *et al.* 2002; Cobb and Abercrombie 2002; Bustos *et al.* 2004). The mechanism for increased glutamate release could involve blockade of muscarinic inhibitory heteroreceptors located on glutamate axon terminals in the SN (Grillner *et al.* 1999; Zheng and Johnson 2003; Michel *et al.* 2004; Miller and Blaha 2005). This suggestion finds some support in the dialysate glutamate measurements, where an increase, although not statistically significant, was observed in response to scopolamine treatment during motor activity

As increased nigral DA activity can improve, or compensate, motor performance in DA depleted animals (Bergquist *et al* 2003, Andersson *et al* 2006), we were interested to see if scopolamine-induced enhancement of DA release would also improve motor functions in DA-hemilesioned rats. The effect of nigral perfusion with scopolamine was therefore investigated in rats that had previously been unilaterally lesioned with 6-OHDA. In these animals, scopolamine treatment both increased nigral DA release and improved motor functions. Our study does not, however, exclude the possibility that the motor improvement observed during nigral scopolamine treatment is the result of alterations in nigral neurotransmission other than dopaminergic. Striatal DA release, however, remained unaffected during the entire experiment, which makes it unlikely that the scopolamine induced motor improvement is mediated by altered striatal DA release. In particular because the expected effect of nigral scopolamine treatment would be inhibition of striatal DA

release (Miller and Blaha 2005). The scopolamine-induced enhancement of somatodendritically released DA did not alter motor performance as measured by the Acc10 test in intact rats. The reason for this inability in intact rats could be that in normal rats the motor performance is already optimal and no further increase in performance can be achieved.

Overall, this paper points to a cholinergic modulation of the somatodendritic DA release, in particular during motor activity, and this modulation may in part explain the beneficial effects of anticholinergic treatment of PD. The findings in this paper also indicate that cholinergic neurotransmission in the SN is important for the regulation of motor performance, as well as they strengthen the notion of a nigral dopaminergic regulation of motor activity/performance, independent of striatal DA release.

Paper III: Serotonergic modulation of striatal and nigral dopamine release in a rat model of L-DOPA-induced dyskinesia

Background

The emergence of validated animal models of L-DOPA induced dyskinesias has led to the identification of several postsynaptic abnormalities in dyskinetic animals, but investigations on possible presynaptic factors are scarce. In parkinsonian patients, a correlation between putaminal release of DA following L-DOPA-treatment and severity of dyskinesias has been demonstrated (de la Fuente-Fernandez *et al.* 2004; Pavese *et al.* 2006), and this indicates that presynaptic factors leading to a difference in DA formation and release may either contribute to the development of dyskinesias, to the expression of dyskinesias, or to both. In the 6-OHDA rat model, a relationship between the amounts of DA formed following high dose (20-25 mg/kg) L-DOPA-treatment and the severity of dyskinesias has been demonstrated (Meissner *et al.* 2006; Lee *et al.* 2008), which is in coherence with clinical studies. These studies, however, did not include non-dyskinetic animals, and the reasons for their resistance towards developing dyskinesias are still unknown. A study using microdialysis has shown that dyskinetic rats have higher DOPA-concentrations in striatal microdialysates following systemic L-DOPA administration than non-dyskinetic rats (Carta *et al.* 2006), and another study describes endothelial proliferation and increased blood-brain barrier permeability in dyskinetic rats (Westin *et al.* 2006). However, it is not known whether or not this leads to a difference in DA kinetics.

L-DOPA can be taken up and converted into DA by 5-HT neurones (Arai *et al.* 1995; Tanaka *et al.* 1999), and in a recent study it was demonstrated that L-DOPA induced dyskinesias in 6-OHDA-hemilesioned rats were reduced following neurotoxic lesions of the 5-HT system (Carta *et al.* 2007). The same study showed that dyskinesias were reduced when

L-DOPA was given following pre-treatment with 5-HT-autoreceptor agonists, which inhibit neurotransmitter release from 5-HT neurones. This led the authors to suggest that dysregulated DA release from 5-HT terminals in the striatum is the prime cause of dyskinesias in the rat model. However, that hypothesis was not verified by measuring DA release or metabolism. The objective of this study was to investigate if the kinetics of the DA response to an L-DOPA challenge is different in dyskinetic and non-dyskinetic rats, and to further clarify the role of 5-HT neurones for the expression of L-DOPA-induced dyskinesias.

Experimental design

6-OHDA-hemilesioned rats with a DA lesion in excess of 90%, as determined by the amphetamine rotation test were selected for the study. The rats were treated with subcutaneous L-DOPA- (6 mg/kg) and benserazide (12 mg/kg) injections for 14 days and microdialysis probes were then implanted in the SN and the striatum ipsilateral to the lesion. On the day of experiment, animals were given a subcutaneous injection of L-DOPA, and the effects on behaviour as well as dialysis concentrations of DA, 5-HT, HVA, DOPAC, 5-HIAA and DOPA were determined. In a second experiment, the effects of pre-treatment with a combination of the 5-HT_{1A} receptor agonist 8-OHDPAT and the 5-HT_{1B} receptor agonist CP-94253 were investigated, as were the effects of microdialysis probe perfusion

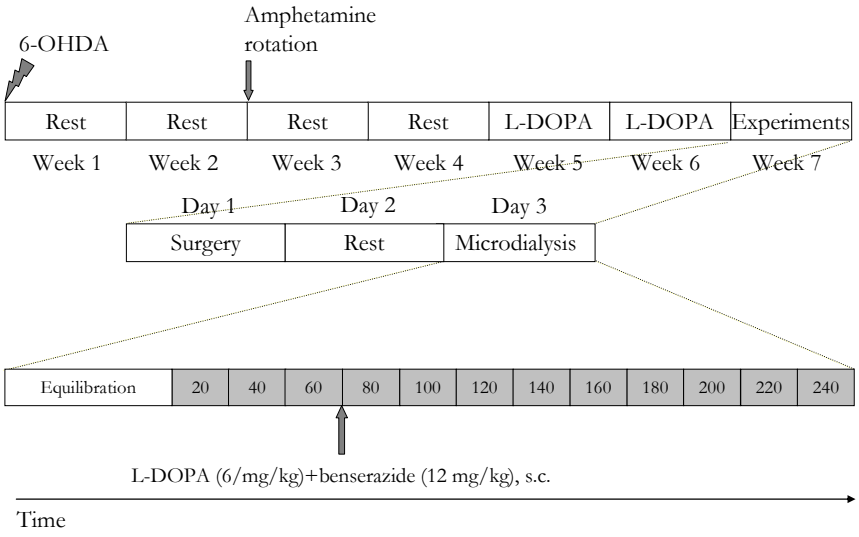

Fig. 10. Experimental design in paper III. On the day of experiments a subcutaneous dose of L-DOPA was administered and followed by dialysis sampling for three hours. In 5-HT-agonist studies, a subcutaneous injection of the two agonists was administered five minutes before L-DOPA, and in the combined 5-HT-agonist/TTX experiments, TTX perfusion was initiated one hour before L-DOPA administration.

with the fast sodium-channel blocker tetrodotoxin (TTX) during L-DOPA+5-HT-agonist therapy. The experimental setup is described in Fig. 10.

Findings and discussion

Microdialysis measurements following L-DOPA-injection revealed that dyskinetic rats respond to a given L-DOPA dose with a larger surge in extracellular DA concentrations than non-dyskinetic, in both the striatum and the SN. This difference could not be ascribed to different uptake of L-DOPA into the CNS, as DOPA dialysis concentrations were similar in dyskinetic and non-dyskinetic rats. Nor could it be explained by differences in DA catabolism, as dialysis concentrations of DA metabolites and DA turnover were similar in dyskinetic and non-dyskinetic rats.

Biochemical analysis of tissue contents of DA, 5-HT and 5-HIAA revealed that while there was no difference in the extent of striatal DA lesions between dyskinetic and non-dyskinetic rats, there was a substantial difference in striatal tissue contents of 5-HT, with non-dyskinetic rats having more extensive lesions, and a similar difference was also found for tissue concentrations of 5-HIAA. Also, striatal baseline dialysis concentrations of 5-HT and 5-HIAA were both higher in dyskinetic rats than in non-dyskinetic, which further underlines a difference in the striatal 5-HT system between groups. In the SN, no difference in the extent of DA lesions could be observed, and nigral 5-HT tissue concentrations were not significantly altered compared to the intact side, even though a trend towards lower 5-HT concentrations could be seen in both dyskinetic and non-dyskinetic rats. The relatively modest effect on nigral tissue concentrations of 5-HT is probably due to the fact that the 5-HT innervation of the SN does not travel through the medial forebrain bundle, and will therefore be less affected by the 6-OHDA lesion procedure than the 5-HT innervation of the striatum.

We did not find a significant difference in striatal peak dialysis concentrations of L-DOPA between dyskinetic and non-dyskinetic animals, although a slight tendency towards higher concentrations in dyskinetic animals was observed in both regions. This stands in stark contrast to the previously reported approximately five-fold difference reported by Carta and co-authors (2006). The reasons for this discrepancy are unclear, but several methodological differences exist between the studies. In our study, we used subcutaneous injections of L-DOPA, as intraperitoneal injections of L-DOPA are associated with a higher frequency of so-called "dose failures" due to misplacement of injections into the intestines (Lindgren *et al.* 2007). Furthermore, HPLC analysis of dialysates in our study was performed immediately, which precludes the possibility of time-related effects (i.e. breakdown) on dialysate concentrations.

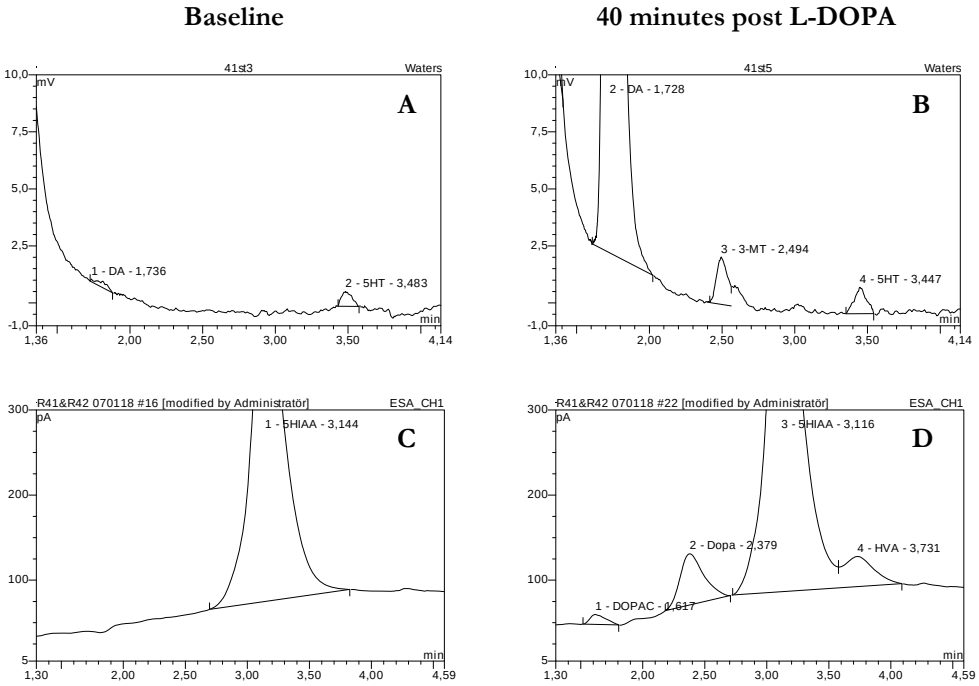

Fig. 11. Typical chromatograms showing dialysis concentrations of DA, 5-HT, DOPAC, DOPA, 5-HIAA and HVA in the striatum of a 6-OHDA-hemilesioed dyskinetic rat at baseline (A and C) and 40 minutes post an s.c. injection of L-DOPA (B and D). The concentration measurements corresponding to peaks were at baseline; DA: 0.0295 fmol/µl, 5-HT: 0.0531 fmol/µl, and 5-HIAA: 95.919 fmol/µl. DOPAC and HVA were not detectable. At 40 minutes post L-DOPA; DA: 10.9681 fmol/µl, 5-HT: 0.1103 fmol/µl, DOPAC: 5.4863 fmol/µl, DOPA: 41.4193 fmol/µl, 5-HIAA: 118.5773 fmol/µl, HVA: 11.2874 fmol/µl.

Our finding, that dyskinetic animals have more 5-HT terminals in the striatum than non-dyskinetic animals, can explain the greater surges in extracellular DA concentrations in dyskinetic rats, if most of the conversion of L-DOPA to DA in DA-depleted animals takes place in 5-HT-neurones. To further test the hypothesis that dyskinesias are caused by dysregulated DA release from 5-HT terminals, a second set of experiments was performed, where we administered the 5-HT_{1A} receptor agonist 8-OHDPAT and the 5-HT_{1B} receptor agonist CP-94253 five minutes before administration of L-DOPA. The 5-HT_{1A} receptor is expressed on the soma and dendrites of 5-HT neurones and the 5-HT_{1B} receptor is expressed on the terminals. Both receptors act as autoreceptors by reducing firing rate (5-HT_{1A}) and terminal release of from 5-HT neurones (5-HT_{1B}). Inhibiting 5-HT neurone activity in this fashion resulted in a significant decrease in L-DOPA-induced dyskinesias and in reduced microdialysis DA concentrations, as compared to controls. Our findings verify those of Carta and co-authors (2007), and they also indicate that the number of 5-HT terminals in the striatum may be a major determinant for the expression of dyskinesias.

However, 5-HT agonist treatment did not completely abolish DA from microdialysis samples, so we wanted to investigate if the remainder of dialysate DA was derived from any other neuronal source or from 5-HT terminals not completely inhibited by agonist treatment. This was done by giving L-DOPA+5-HT-agonists while simultaneously perfusing the dialysis probes with TTX, which potently blocks action-potential dependent neurotransmitter release. Adding local TTX-treatment to the systemic 5-HT agonist treatment resulted in a slight attenuation of the amounts of DA in dialysates, although this did not reach statistical significance. In previous studies, TTX infusion reduced L-DOPA-induced DA release by approximately 60-80% (Miller and Abercrombie 1999; Sarre *et al.* 2004), which can be compared to the approximately 50% reduction in DA dialysis concentrations brought about by 5-HT-agonist treatment in our study. Thus, in DA depleted animals the conversion of DOPA to DA in 5-HT neurones appears to be a dominating mechanism for DA formation in response to L-DOPA treatment, even though a substantial extra neuronal formation also exists.

The findings of this study demonstrate that there is a significant difference in the amount of DA formed following L-DOPA treatment between rats that express dyskinesias and rats that do not. This difference is most likely explained by a difference in the extent of damage to striatal 5-HT-innervation. Thus, an intact 5-HT system seems to be a major determinant of dyskinesias in this animal model, and future clinical studies investigating the integrity of the 5-HT system in parkinsonian patients with and without dyskinesias are highly warranted. Also, the potential use of a combination of 5-$HT_{1A/1B}$ receptor agonists as antidyskinetic therapy should be explored.

Methodological considerations

Microdialysis

In these studies we have exploited some of the most prominent advantages of the microdialysis sampling method: to be able to sample the extracellular environment in alert unrestricted animals while causing minimal disturbance of the intracerebral environment, and thereby investigate the effects of physical activity on neurotransmission and vice versa. It was also used to administer drugs by reverse dialysis to the immediate surrounding of the microdialysis probe and to simultaneously measure what effects the drugs had on neurotransmission, as well as behaviour. Other strengths of the microdialysis method are that the composition of microdialysis samples directly reflects the extracellular milieu (even though it does not provide absolute extracellular concentrations), and that the individual compounds can be separated and quantified by sensitive and specific analytical methods, such as HPLC, immuno-assays etc. The number of compounds that can be determined in the same sample is only restricted by the separation capacities and sensitivity of the biochemical analysis method. It is often possible to measure several neurotransmitters as well as their metabolites in one single sample.

A main consideration regarding the microdialysis technique is the tissue damage resulting from implantation. This has been characterised by both histological and biochemical methods (Benveniste and Diemer 1987; Santiago and Westerink 1990; Ballarin *et al.* 1991; Grabb *et al.* 1998). Measurements of extracellular transmitters within the first hour after implantation predominantly reflect leakage from damaged tissue, but on the other hand, chronically implanted probes are subjected to extensive gliosis, which may hamper accuracy of measurements and perhaps also affect the physiological properties of the investigated tissue (Grabb *et al.* 1998). In this thesis, microdialysis experiments were performed two days after implantation, as a time window of 24-48 hours after surgery has been suggested to be optimal with regards to transmitter release and gliosis formation (see Westerink and Timmerman 1999). All papers in this thesis incorporated behavioural studies, and therefore microdialysis experiments were performed two days after surgery and not one, allowing a full day's rest following surgery in order to allow the best behavioural recovery possible without jeopardising the accuracy of measurements.

Other possible drawbacks of the microdialysis method are its relatively low temporal resolution (usually several minutes) and the size of the dialysis probe (usually Ø 0.2-0.5 mm), which makes measurements in small nuclei difficult. One should also note that due to the size of the microdialysis probe, dialysate measurements do not directly reflect synaptic signalling but instead reflect the extrasynaptic environment. This is an important property of the microdialysis method, and raises some concern with regards to measurements of fast synaptic transmitters such as glutamate, GABA and ACh. These fast transmitters are usually

released from tightly arranged synapses and also have highly effective systems for reuptake and enzymatic breakdown. Therefore, microdialysis measurements of these fast transmitters may reflect synaptic signalling to a lesser extent than it does for modulatory transmitters like DA and 5-HT, which to a larger extent exert their effects via volume transmission and have target receptors distant from the site of release (Vizi 1982; Fuxe *et al.* 1989; Agnati *et al.* 1995; Cragg *et al.* 2001; Rice and Cragg 2008).

Rotarod

There is a wide variety of tests for the evaluation of separate motor functions, such as stepping test, lever pressing tests, staircase tests and several different balance tests. The rotarod test offers the possibility of assessing the overall motor performance of rodents, is easily managed and highly reproducible. The incorporation of several different aspects of motor functions into the rotarod test can be seen both as its strength and its weakness, as it is able to detect dysfunctions in balance, stepping, motor coordination and motivation, but is unable to discriminate between them. Rotarod testing is frequently used in the medical industry as a screening tool for adverse drug reactions affecting motor coordination, and rotarod testing in PD animal models was initially introduced in the form of the so-called overall rod performance (ORP) test, which is comprised of several sessions of constant speed, but with higher speed for each session (Rozas and Labandeira Garcia 1997). The Acc10-test, used by Bergquist and co-authors (2003) is less time consuming than the ORP test, and therefore more suitable to use in combination with microdialysis. Also, motor performance values derived from acceleration testing vary less than values from constant speed testing (Bogo *et al.* 1981). In animal models of PD, rotarod testing provides an indication of the extent of DA depletion (Rozas *et al.* 1997), and may therefore be of use as a screening tool. If animals are repeatedly subjected to testing over the first weeks following DA lesions, they tend to recover some of their rod performance (Tillerson *et al.* 2002; Goldberg *et al.* 2003). In order to minimise recovery of rotarod performance in the 6-OHDA-hemilesioned rats in paper II, rotarod testing was restricted to just one Acc10 test prior to microdialysis surgery, and only rats showing a performance impairment of 40 % or more in this test were selected for dialysis experiments.

The 6-OHDA-model of dyskinesia

Since its introduction (Ungerstedt 1968; Ungerstedt 1971a), the 6-OHDA-hemilesion model has become the most widely used rodent model of parkinsonism. It provides a model of permanent dopaminergic depletion selective to the region of choice, and is highly reproducible and cost-effective. The resulting motor deficit is by large restricted to a somewhat reduced contralateral limb ability and some postural bias, and does therefore not affect the general well-being of animals to any greater extent. The 6-OHDA model is a useful tool for studying motor disabilities related to DA depletion, but it does not reproduce

other features of PD, such as for instance brain stem nuclei degeneration and Lewy body formation, and it shows no progressive degeneration. 6-OHDA is a non-specific catecholaminergic toxin, but more selective dopaminergic degeneration can be achieved by simultaneous administration of NA reuptake inhibitors, most commonly desipramine. Judging from the measurements of striatal tissue contents of 5-HT in paper III, if the desire is to study DA depletion alone, it would perhaps be of use to also protect 5-HT neurones, as they too seem to be affected by 6-OHDA, and in a highly variable extent.

The L-DOPA-induced dyskinesia model in 6-OHDA-hemilesioned rats was introduced in the late 1990s (Cenci *et al.* 1998), and is today extensively characterised and widely used. Its predictive qualities with regards to dyskinesias in humans have been questioned (see Bezard *et al.* 2001; Cenci *et al.* 2002 for reviews), but it has been pharmacologically validated with drugs demonstrated as having clinical efficacy on dyskinesias (Dekundy *et al.* 2007). Given that rats are quadrupeds, their different musculoskeletal system and movement pattern may at least so some extent explain the differences in their dyskinetic movements, as compared those in PD patients and primate models. 6-OHDA-hemilesioned rats chronically treated with L-DOPA develop AIMs of three distinct types (orolingual, axial and limb dyskinesias), all of which resemble dyskinetic behaviour in humans. It also produces contralateral rotations, however, and these lack a human equivalent. Rotational behaviour also appears to have a different regional origin within the striatum than orolingual, axial and limb dyskinesias, as these are correlated with upregulation of molecular markers in the caudal-lateral striatal regions, while rotational behaviour is linked to rostral and dorsal striatal regions (Kirik *et al.* 1998; Andersson *et al.* 1999), and the same regional difference is observed in dyskinesias derived from intrastriatal grafts (Carlsson *et al.* 2006; Carlsson *et al.* 2007). For these reasons, rotational behaviour is not included in the assessment of AIMs.

General discussion

Somatodendritic dopamine release

Ramon y Cajal´s original theory of the neurone defined them as being unidirectional, i.e. receiving signals into the dendrites and propagating them via axons to terminals, from where signalling to other neurones takes place. The concept of dendritic release of neurotransmitters was introduced in the mid 1960s, and since then a physiological role for somatodendritic transmitter release has been demonstrated in many different types of neurones. Dendrites are now seen not only as input structures, but also as important sources of neurotransmission and neuromodulation, and somatodendritic neurotransmitter release may in some cases be independent of terminal release as well as the electrical activity of the neurone.

Somatodendritic DA release in the SN was demonstrated in the late 1970s, but its functional importance in relation to terminal release has not yet been fully clarified. Among the first findings that indicated a role for somatodendritically released DA was the regulation of DA neurone firing by somatodendritic D_2 autoreceptors (Aghajanian and Bunney 1977b). *In vivo* studies on motor effects of agonists/antagonists/DA releasers applied locally in the SN all indicate that nigral DA release facilitates motor functions. At the same time, nigral DA release should under some circumstances inhibit terminal DA release by activating autoreceptors, and thus impair motor abilities. So the question arises; what is the dominating physiological function of somatodendritic DA release?

This thesis demonstrates that nigral VMAT-inhibition (paper I) impairs motor functions, and in agreement with a previous study (Bergquist *et al.* 2003), such impairments can occur without altered striatal DA release. In paper I, we show that a 60% depletion of nigral tissue concentrations of DA impairs motor performance but generates no effects on striatal DA release. In paper II, we show that local muscarinic antagonism amplifies motor induced somatodendritic DA release, this too without any significant effects in the striatum. Increased somatodendritic DA release appears to be important for motor performance, and as shown in paper I it also appears to be able to functionally compensate, to some extent, for lost striatal DA release. If the increase in motor activity-related somatodendritic DA release is pharmacologically inhibited, motor performance is impaired (paper I), and if the increase is amplified, motor performance is improved when it has previously been impaired by 6-OHDA-hemilesions (paper II). Somatodendritic D_2-autoreceptor-mediated inhibition of terminal release has been observed in several studies, but the physiological conditions under which it occurs has not been determined. Our studies indicate that normal physiological activity does not activate autoreceptors enough to cause inhibition of terminal release, not even when somatodendritic DA release is amplified by pharmacological manipulation by scopolamine. Our findings clearly indicate that the regulatory effects of

somatodendritic DA release on motor functions occur without affecting striatal DA release, and thus, nigral DA release may be functionally dissociated from striatal terminal release under physiological conditions.

The concept of dissociation between somatodendritic release and terminal release in a single neurone is not entirely controversial, as it has been suggested in other neuronal systems. The best documented example of dissociated somatodendritic and terminal release is the oxytocin- and vasopressin-containing magnocellular neurones (MCNs) of the hypothalamic supraoptic nucleus and the paraventricular nuclei. These neurones are unique in the sense that they release transmitters into two anatomically and functionally separated compartments (the central nervous system and the peripheral blood stream), and almost no axon collaterals project back to the MCN nuclei. These features have permitted the dendritic release of peptides from MCNs to be characterised to a greater extent than that of other neurotransmitters. In MCNs, there is a well documented dissociation of terminal and somatodendritic release of peptides; in that electrical activity in cell bodies can release peptides from nerve terminals without dendritic release, and some stimuli (such as for instance stress) induce dendritic peptide release without affecting electrical activity or secretion from nerve terminals (Wotjak *et al.* 1998; Engelmann *et al.* 1999; Ludwig *et al.* 2002; Sabatier *et al.* 2003; de Kock *et al.* 2004).

Another example of a neuronal system that may display dissociation between somatodendritic and terminal neurotransmitter release is the 5-HT-neurones in the raphe nuclei. The electrical activity of 5-HT neurones is strongly regulated by inhibitory 5-HT_{1A} autoreceptors on somata and dendrites of raphe neurones (Sprouse and Aghajanian 1986; Sprouse and Aghajanian 1987; Arborelius *et al.* 1994; Starkey and Skingle 1994). However, it appears that somatodendritic 5-HT-release is strongly regulated by 5-HT_{1D}-receptors, and that this regulation is independent of the electrical activity of raphe neurones (Starkey and Skingle 1994; Pineyro *et al.* 1995; el Mansari and Blier 1996; Pineyro and Blier 1996). It is also possible to induce somatodendritic release of 5-HT from raphe neurones by local activation of NMDA-receptors, and this release occurs without generation of action potentials, indicating that somatodendritic 5-HT release may be completely independent of axon terminal release (de Kock *et al.* 2006).

Our findings in paper I and II lead us to conclude that somatodendritic DA release may also be independent of terminal release, at least under physiologically relevant conditions such as motor activity. Although somatodendritic autoreceptors can regulate terminal release of DA in the striatum, this does evidently not happen during the type of motor activity that we have studied, and it remains to determine under which, if any, physiological conditions endogenous somatodendritic DA release acts autoinhibitory. We propose that the main function of nigral somatodendritic DA release is to act as a "gatekeeper", regulating the outflow of motor impulses from the basal ganglia by local nigral effects on the outflow of

motor impulses, and that autoreceptor-mediated effects on striatal terminal release may be of less importance under physiological conditions.

L-DOPA-induced dyskinesias

L-DOPA treatment is the standard treatment for PD, with good symptomatic effect, especially in the early years of treatment. The emergence of dyskinesias is a prominent drawback, however, and treatments preventing the development of dyskinesias would be a welcome addition to the therapeutic arsenal. The animal models of dyskinesia provide a useful tool for identifying the pathophysiological mechanisms leading to dyskinesia as well as for evaluating new treatment strategies. In paper III, we identify a difference in DA response to L-DOPA between rats that have developed dyskinesias in response to chronic L-DOPA treatment and rats that have not. We also present data indicating that the cause of this difference in DA response is a larger striatal degeneration of 5-HT-terminals in non-dyskinetic rats.

A positive correlation between the amounts of DA formed by L-DOPA and the severity of dyskinesias has previously been demonstrated in both humans (de la Fuente-Fernandez *et al.* 2004; Pavese *et al.* 2006) and rats (Meissner *et al.* 2006; Lee *et al.* 2008), but none of these studies included non-dyskinetic subjects. In the 6-OHDA-hemilesioned rat model, approximately 20 % of rats do not develop dyskinesias during chronic intermittent treatment with L-DOPA in doses (6-10 mg/kg) considered to be equivalent to those used clinically in PD patients (see Cenci 2007). The reasons for their resistance towards developing dyskinesias are unknown, but our findings indicate that the number of striatal 5-HT terminals may be a determinant of dyskinesias through governing the amount of extracellular DA formed from L-DOPA, and this motivates investigations of the 5-HT system in PD patients. Currently, only one study investigating the possible relationship between dyskinesias and striatal 5-HT innervation has been published, and in that study no significant difference between dyskinetic and non-dyskinetic PD patients was found (Kish *et al.* 2008). One should note, however, that the number of patients was small, and this precludes definitive conclusions.

Our findings also lend support to previous findings demonstrating that a combination of 5-$HT_{1A/1B}$ receptor agonists is a promising candidate for a clinical study in dyskinetic patients. A low-dose combination of these agonists have been shown to attenuate L-DOPA-induced dyskinesia in both rats and monkeys, and also to prevent the development of dyskinesias and the upregulation of FosB, which is increased in dyskinetic rats (Carta *et al.* 2007; Munoz *et al.* 2008). We show that a combination of the 5-HT_{1A} agonist 8-OH-DPAT and the 5-HT_{1B} agonist CP94253 attenuates dyskinetic movements. In addition, the treatment was associated with a reduction of L-DOPA-induced extracellular DA. The 5-HT_{1A} receptor agonists sarizotan and buspirone have been evaluated as monotherapies against dyskinesias, but

several clinical studies have shown a lack of effect and even a worsening of parkinsonian symptoms (Hammerstad *et al.* 1986; Ludwig *et al.* 1986; Olanow *et al.* 2004b; Goetz *et al.* 2007). Simultaneous administration of subthreshold doses of 8-OH-DPAT and CP94253 in rats have been shown to result in a synergistic potentiation of antidyskinetic effects, and also specificity for presynaptic receptors, thus limiting side effects related to activation of postsynaptic receptors (Carta *et al.* 2007).

Meissner and co-authors (2006) demonstrate that L-DOPA produces a larger striatal DA efflux in 6-OHDA-hemilesioned rats that have been chronically treated with L-DOPA than rats that have not. This implies that the cause underlying extracellular swings in DA is progressively increasing its capacity. The results from our study and others identify striatal 5-HT terminals as the main source of DA release in DA depleted animals, and it may therefore be important to understand the mechanisms that determine the amount of 5-HT terminals in the striatum. 6-OHDA-lesions has been reported to increase the 5-HT innervation of the stiatum (Zhou *et al.* 1991; Guerra *et al.* 1997; Maeda *et al.* 2005), and investigating if this process is amplified by chronic L-DOPA-treatment could improve the understanding of how 5-HT neurones influence the development and expression of L-DOPA induced dyskinesias in PD.

Another issue that needs clarification is the role of the SN in dyskinesias. In paper III, we show that the amount of DA formed in the SN following L-DOPA administration is higher in dyskinetic than in non-dyskinetic rats. This difference could not be explained by a difference in 5-HT innervation or by differences in DA metabolism. A recent study

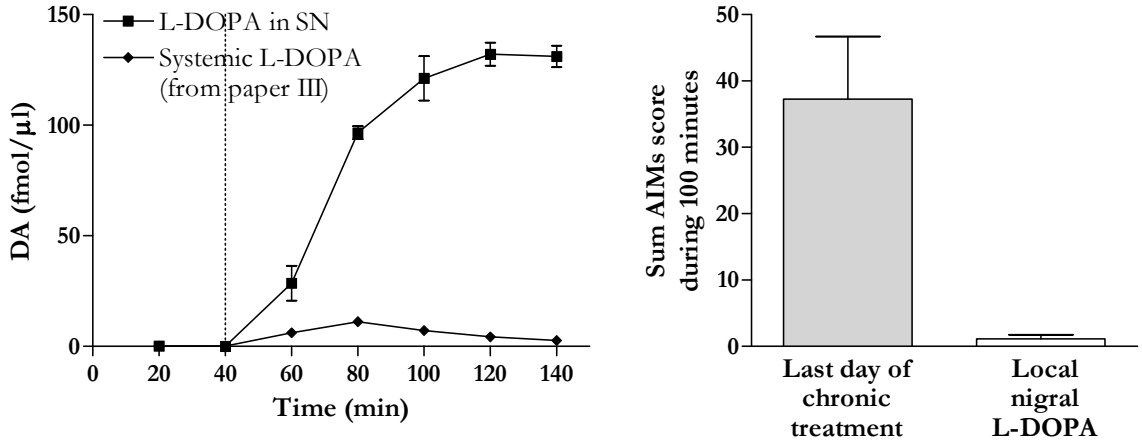

Fig. 12. Preliminary data showing the nigral response in DA (left) and response in AIMs (right) to local nigral perfusion of 1 mM of L-DOPA in rats previously made dyskinetic by chronic systemic L-DOPA-treatment (n=4). Microdialysis data from dyskinetic rats in paper III are added as comparison.

(Prescott *et al.* 2008) describes alterations in nigral LTP in PD patients, indicating that synaptic plasticity in PD is altered not only in the striatum (Picconi *et al.* 2003).

The possible contribution of DA transmission in the SN to the development and expression of dyskinesias has to our knowledge not been determined. However, preliminary data from our lab indicate that it is not possible to trigger the expression of dyskinesias by local nigral infusion of L-DOPA in rats that have previously been made dyskinetic by chronic L-DOPA-treatment (see Fig 12). Reverse dialysis with 1 mM of L-DOPA in the SN resulted in an increase in extracellular DA concentrations approximately ten times that of dyskinetic rats given a systemic injection of 6 mg/kg of L-DOPA as in paper III. Local striatal perfusion with L-DOPA is known to induce AIMs (Carta *et al.* 2006; Buck and Ferger 2008), but in spite of the massive DA response to L-DOPA-perfusion of the SN, no dyskinesias could be seen.

Concluding remarks and future prospects

In this thesis we investigate the impact of central DA neurotransmission under normal conditions as well as under pathological (i.e. parkinsonian and dyskinetic). We conclude that nigral DA release regulates motor functions mainly by local nigral mechanisms during physiological conditions, and we demonstrate that both extracellular fluctuations of DA and expression of dyskinesias following L-DOPA treatment in 6-OHDA hemilesioned rats can be explained by unregulated DA release from 5-HT terminals in the striatum.

The role of nigral somatodendritic DA may be to modulate output signals in order to fine-tune basal ganglia output, and as such it could be an important function not only under normal but also under pathological conditions, such as parkinsonism. Therefore, treatments aimed at restoring DA transmission in PD patients should perhaps also incorporate a strategy of normalising DA release and metabolism in the SN.

To this date, there is no treatment available that prevents the development of L-DOPA-induced dyskinesias in PD patients. Such a treatment would be useful, as dyskinesias may impose severe restrictions on therapy aimed at symptomatic relief. The findings in paper III strongly support the notion that the 5-HT-system is the main site of L-DOPA conversion into DA in the 6-OHDA-model of parkinsonism and dyskinesia, and also highlights the need for further investigations on the 5-HT system in PD patients. The release of DA from 5-HT neurones is most likely unregulated due to lack of DA autoreceptors and uptake systems. Introducing an artificial feedback regulation by administering the 5-HT agonists 8-OH-DPAT and CP94253 may be a useful strategy of alleviating L-DOPA-induced dyskinesias in PD patients.

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References

Abarca, J., K. Gysling, R. H. Roth and G. Bustos (1995). "Changes in extracellular levels of glutamate and aspartate in rat substantia nigra induced by dopamine receptor ligands: in vivo microdialysis studies." Neurochem Res **20**(2): 159-69.

Abercrombie, E. D., A. E. Bonatz and M. J. Zigmond (1990). "Effects of L-dopa on extracellular dopamine in striatum of normal and 6-hydroxydopamine-treated rats." Brain Res **525**(1): 36-44.

Aghajanian, G. K. and B. S. Bunney (1977a). "Dopamine"autoreceptors": pharmacological characterization by microiontophoretic single cell recording studies." Naunyn Schmiedebergs Arch Pharmacol **297**(1): 1-7.

Aghajanian, G. K. and B. S. Bunney (1977b). "Pharmacological characterization of dopamine "autoreceptors" by microiontophoretic single-cell recording studies." Adv Biochem Psychopharmacol **16**: 433-8.

Agnati, L. F., M. Zoli, I. Stromberg and K. Fuxe (1995). "Intercellular communication in the brain: wiring versus volume transmission." Neuroscience **69**(3): 711-26.

Ahlskog, J. E. and M. D. Muenter (2001). "Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature." Mov Disord **16**(3): 448-58.

Aizman, O., H. Brismar, P. Uhlen, E. Zettergren, A. I. Levey, H. Forssberg, P. Greengard and A. Aperia (2000). "Anatomical and physiological evidence for D1 and D2 dopamine receptor colocalization in neostriatal neurons." Nat Neurosci **3**(3): 226-30.

Albin, R. L., A. B. Young and J. B. Penney (1989). "The functional anatomy of basal ganglia disorders." Trends Neurosci **12**(10): 366-75.

Andersson, D. R., H. Nissbrandt and F. Bergquist (2006). "Partial depletion of dopamine in substantia nigra impairs motor performance without altering striatal dopamine neurotransmission." Eur J Neurosci **24**(2): 617-24.

Andersson, M., A. Hilbertson and M. A. Cenci (1999). "Striatal fosB expression is causally linked with l-DOPA-induced abnormal involuntary movements and the associated upregulation of striatal prodynorphin mRNA in a rat model of Parkinson's disease." Neurobiol Dis **6**(6): 461-74.

Arai, R., N. Karasawa, M. Geffard and I. Nagatsu (1995). "L-DOPA is converted to dopamine in serotonergic fibers of the striatum of the rat: a double-labeling immunofluorescence study." Neurosci Lett **195**(3): 195-8.

Arborelius, L., B. B. Hook, U. Hacksell and T. H. Svensson (1994). "The 5-HT1A receptor antagonist (S)-UH-301 blocks the qR)-8-OH-DPAT-induced inhibition of serotonergic dorsal raphe cell firing in the rat." J Neural Transm Gen Sect **96**(3): 179-86.

Ariano, M. A., J. Wang, K. L. Noblett, E. R. Larson and D. R. Sibley (1997). "Cellular distribution of the rat D4 dopamine receptor protein in the CNS using anti-receptor antisera." Brain Res **752**(1-2): 26-34.

Aubert, I., C. Guigoni, K. Hakansson, Q. Li, S. Dovero, N. Barthe, B. H. Bioulac, C. E. Gross, G. Fisone, B. Bloch and E. Bezard (2005). "Increased D1 dopamine receptor signaling in levodopa-induced dyskinesia." Ann Neurol **57**(1): 17-26.

Aubert, I., C. Guigoni, Q. Li, S. Dovero, B. H. Bioulac, C. E. Gross, A. R. Crossman, B. Bloch and E. Bezard (2007). "Enhanced preproenkephalin-B-derived opioid transmission in striatum and subthalamic nucleus converges upon globus pallidus internalis in L-3,4-dihydroxyphenylalanine-induced dyskinesia." Biol Psychiatry **61**(7): 836-44.

Aziz, T. Z., L. Davies, J. Stein and S. France (1998). "The role of descending basal ganglia connections to the brain stem in parkinsonian akinesia." British Journal of Neurosurgery **12**(3): 245-9.

Ballarin, M., B. B. Fredholm, S. Ambrosio and N. Mahy (1991). "Extracellular levels of adenosine and its metabolites in the striatum of awake rats: inhibition of uptake and metabolism." Acta Physiol Scand **142**(1): 97-103.

Barbeau, A. (1962). "The pathogenesis of Parkinson's disease: a new hypothesis." Can Med Assoc J **87**: 802-7.

Barter, R. and A. G. Pearse (1953). "Detection of 5-hydroxytryptamine in mammalian enterochromaffin cells." Nature **172**(4383): 810.

Barter, R. and A. G. Pearse (1955). "Mammalian enterochromaffin cells as the source of serotonin (5-hydroxytryptamine)." J Pathol Bacteriol **69**(1-2): 25-31.

Beckstead, R. M., G. F. Wooten and J. M. Trugman (1988). "Distribution of D1 and D2 dopamine receptors in the basal ganglia of the cat determined by quantitative autoradiography." J Comp Neurol **268**(1): 131-45.

Benabid, A. L., A. Benazzouz, D. Hoffmann, P. Limousin, P. Krack and P. Pollak (1998). "Long-term electrical inhibition of deep brain targets in movement disorders." Mov Disord **13 Suppl 3**: 119-25.

Beninato, M. and R. F. Spencer (1987). "A cholinergic projection to the rat substantia nigra from the pedunculopontine tegmental nucleus." Brain Res **412**(1): 169-74.

Benveniste, H. and N. H. Diemer (1987). "Cellular reactions to implantation of a microdialysis tube in the rat hippocampus." Acta Neuropathol **74**(3): 234-8.

Bergquist, F., J. Jonason, E. Pileblad and H. Nissbrandt (1998). "Effects of local administration of L-, N-, and P/Q-type calcium channel blockers on spontaneous dopamine release in the striatum and the substantia nigra: a microdialysis study in rat." J Neurochem **70**(4): 1532-40.

Bergquist, F., H. N. Shahabi and H. Nissbrandt (2003). "Somatodendritic dopamine release in rat substantia nigra influences motor performance on the accelerating rod." Brain Res **973**(1): 81-91.

Berlanga, M. L., T. K. Simpson and A. A. Alcantara (2005). "Dopamine D5 receptor localization on cholinergic neurons of the rat forebrain and diencephalon: a potential neuroanatomical substrate involved in mediating dopaminergic influences on acetylcholine release." J Comp Neurol **492**(1): 34-49.

Berretta, S., H. B. Parthasarathy and A. M. Graybiel (1997). "Local release of GABAergic inhibition in the motor cortex induces immediate-early gene expression in indirect pathway neurons of the striatum." J Neurosci **17**(12): 4752-63.

Bertler, A. and E. Rosengren (1959). "Occurrence and distribution of dopamine in brain and other tissues." Experientia **15**(1): 10-1.

Besson, M. J., M. L. Kemel, C. Gauchy, J. A. Girault, U. Spampinato, N. Lantin, M. Desban and J. Glowinski (1986). "In vivo measurement of [3H]GABA release: an approach to the study of the regulation of GABA-containing neurons in the basal ganglia and associated structures in the cat and the rat." Ann N Y Acad Sci **473**: 475-88.

Bevan, M. D., P. J. Magill, D. Terman, J. P. Bolam and C. J. Wilson (2002). "Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network." Trends Neurosci **25**(10): 525-31.

Bezard, E., J. M. Brotchie and C. E. Gross (2001). "Pathophysiology of levodopa-induced dyskinesia: potential for new therapies." Nat Rev Neurosci **2**(8): 577-88.

Bibbiani, F., J. D. Oh, A. Kielaite, M. A. Collins, C. Smith and T. N. Chase (2005). "Combined blockade of AMPA and NMDA glutamate receptors reduces levodopa-induced motor complications in animal models of PD." Exp Neurol **196**(2): 422-9.

Birkmayer, W. and O. Hornykiewicz (1961). "[The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia.]." Wien Klin Wochenschr **73**: 787-8.

Björklund, A. and O. Lindvall (1975). "Dopamine in dendrites of substantia nigra neurons: suggestions for a role in dendritic terminals." Brain Res **83**(3): 531-7.

Björklund, A., O. Lindvall and L. A. Svensson (1972). "Mechanisms of fluorophore formation in the histochemical glyoxylic acid method for monoamines." Histochemie **32**(2): 113-31.

Björklund, A. and A. Nobin (1973). "Fluorescence histochemical and microspectrofluorometric mapping of dopamine and noradrenaline cell groups in the rat diencephalon." Brain Res **51**: 193-205.

Bogo, V., T. A. Hill and R. W. Young (1981). "Comparison of accelerod and rotarod sensitivity in detecting ethanol- and acrylamide-induced performance decrement in rats: review of experimental considerations of rotating rod systems." Neurotoxicology **2**(4): 765-87.

Bolam, J. P., C. M. Francis and Z. Henderson (1991). "Cholinergic input to dopaminergic neurons in the substantia nigra: a double immunocytochemical study." Neuroscience **41**(2-3): 483-94.

Bolam, J. P., J. J. Hanley, P. A. Booth and M. D. Bevan (2000). "Synaptic organisation of the basal ganglia." J Anat **196 (Pt 4)**: 527-42.

Bouthenet, M. L., M. P. Martres, N. Sales and J. C. Schwartz (1987). "A detailed mapping of dopamine D-2 receptors in rat central nervous system by autoradiography with [125I]iodosulpride." Neuroscience **20**(1): 117-55.

Bowsher, R. R. and D. P. Henry (1985). "Aromatic L-amino acid decarboxylase. Biochemistry and functional significance. In: Boulton AA, Baker GB, Yu PH, editors. Neuromethods, Series 1: Neurochemistry. New Jersey: Humana Press, Clifton." 33-78.

Boyson, S. J., P. McGonigle and P. B. Molinoff (1986). "Quantitative autoradiographic localization of the D1 and D2 subtypes of dopamine receptors in rat brain." J Neurosci **6**(11): 3177-88.

Braak, H., K. Del Tredici, U. Rub, R. A. de Vos, E. N. Jansen Steur and E. Braak (2003). "Staging of brain pathology related to sporadic Parkinson's disease." Neurobiol Aging **24**(2): 197-211.

Bracco, F., A. Battaglia, C. Chouza, E. Dupont, O. Gershanik, J. F. Marti Masso and J. L. Montastruc (2004). "The long-acting dopamine receptor agonist cabergoline in early Parkinson's disease: final results of a 5-year, double-blind, levodopa-controlled study." CNS Drugs **18**(11): 733-46.

Bras, J., C. Paisan-Ruiz, R. Guerreiro, M. H. Ribeiro, A. Morgadinho, C. Januario, E. Sidransky, C. Oliveira and A. Singleton (2007). "Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Portugal." Neurobiol Aging.

Breit, S., L. Lessmann, D. Unterbrink, R. C. Popa, T. Gasser and J. B. Schulz (2006). "Lesion of the pedunculopontine nucleus reverses hyperactivity of the subthalamic nucleus and substantia nigra pars reticulata in a 6-hydroxydopamine rat model." Eur J Neurosci **24**(8): 2275-82.

Brodin, E., N. Lindefors and U. Ungerstedt (1983). "Potassium evoked in vivo release of substance P in rat caudate nucleus measured using a new technique of brain dialysis

and an improved substance P-radioimmunoassay." Acta Physiol Scand Suppl **515**: 17-20.

Brotchie, J. M. (2005). "Nondopaminergic mechanisms in levodopa-induced dyskinesia." Mov Disord **20**(8): 919-31.

Buck, K. and B. Ferger (2008). "Intrastriatal inhibition of aromatic amino acid decarboxylase prevents l-DOPA-induced dyskinesia: a bilateral reverse in vivo microdialysis study in 6-hydroxydopamine lesioned rats." Neurobiol Dis **29**(2): 210-20.

Bunzow, J. R., H. H. Van Tol, D. K. Grandy, P. Albert, J. Salon, M. Christie, C. A. Machida, K. A. Neve and O. Civelli (1988). "Cloning and expression of a rat D2 dopamine receptor cDNA." Nature **336**(6201): 783-7.

Bustos, G., J. Abarca, J. Campusano, V. Bustos, V. Noriega and E. Aliaga (2004). "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 **47**(1-3): 126-44.

Calabresi, P., R. Maj, A. Pisani, N. B. Mercuri and G. Bernardi (1992). "Long-term synaptic depression in the striatum: physiological and pharmacological characterization." J Neurosci **12**(11): 4224-33.

Calabresi, P., B. Picconi, A. Tozzi and M. Di Filippo (2007). "Dopamine-mediated regulation of corticostriatal synaptic plasticity." Trends Neurosci **30**(5): 211-9.

Calabresi, P., A. Saiardi, A. Pisani, J. H. Baik, D. Centonze, N. B. Mercuri, G. Bernardi and E. Borrelli (1997). "Abnormal synaptic plasticity in the striatum of mice lacking dopamine D2 receptors." J Neurosci **17**(12): 4536-44.

Calne, D. B., P. F. Teychenne, L. E. Claveria, R. Eastman, J. K. Greenacre and A. Petrie (1974). "Bromocriptine in Parkinsonism." Br Med J **4**(5942): 442-4.

Campusano, J. M., J. Abarca, M. I. Forray, K. Gysling and G. Bustos (2002). "Modulation of dendritic release of dopamine by metabotropic glutamate receptors in rat substantia nigra." Biochem Pharmacol **63**(7): 1343-52.

Carlson, J. D., R. D. Pearlstein, J. Buchholz, R. P. Iacono and G. Maeda (1999). "Regional metabolic changes in the pedunculopontine nucleus of unilateral 6-hydroxydopamine Parkinson's model rats." Brain Res **828**(1-2): 12-9.

Carlsson, A. (1959). "The occurrence, distribution and physiological role of catecholamines in the nervous system." Pharmacol Rev **11**(2, Part 2): 490-3.

Carlsson, A., B. Falck and N. A. Hillarp (1962). "Cellular localization of brain monoamines." Acta Physiol Scand Suppl **56**(196): 1-28.

Carlsson, A. and N. A. Hillarp (1956). "Release of adenosine triphosphate along with adrenaline and noradrenaline following stimulation of the adrenal medulla." Acta Physiol Scand **37**(2-3): 235-9.

Carlsson, A. and M. Lindqvist (1963). "Effect of Chlorpromazine or Haloperidol on Formation of 3methoxytyramine and Normetanephrine in Mouse Brain." Acta Pharmacol Toxicol (Copenh) **20**: 140-4.

Carlsson, A., M. Lindqvist and T. Magnusson (1957). "3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists." Nature **180**(4596): 1200.

Carlsson, A. and B. Waldeck (1958). "A fluorimetric method for the determination of dopamine (3-hydroxytyramine)." Acta Physiol Scand **44**(3-4): 293-8.

Carlsson, A. and B. Waldeck (1964). "A Method for the Fluorimetric Determination of 3-Methoxytyramine in Tissues and the Occurrence of This Amine in Brain." Scand J Clin Lab Invest **16**: 133-8.

Carlsson, T., M. Carta, C. Winkler, A. Bjorklund and D. Kirik (2007). "Serotonin neuron transplants exacerbate L-DOPA-induced dyskinesias in a rat model of Parkinson's disease." J Neurosci **27**(30): 8011-22.

Carlsson, T., C. Winkler, C. Burger, N. Muzyczka, R. J. Mandel, A. Cenci, A. Bjorklund and D. Kirik (2005). "Reversal of dyskinesias in an animal model of Parkinson's disease by continuous L-DOPA delivery using rAAV vectors." Brain **128**(Pt 3): 559-69.

Carlsson, T., C. Winkler, M. Lundblad, M. A. Cenci, A. Bjorklund and D. Kirik (2006). "Graft placement and uneven pattern of reinnervation in the striatum is important for development of graft-induced dyskinesia." Neurobiol Dis **21**(3): 657-68.

Carpenter, M. B., K. Nakano and R. Kim (1976). "Nigrothalamic projections in the monkey demonstrated by autoradiographic technics." J Comp Neurol **165**(4): 401-15.

Carta, M., T. Carlsson, D. Kirik and A. Bjorklund (2007). "Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats." Brain **130**(Pt 7): 1819-33.

Carta, M., H. S. Lindgren, M. Lundblad, R. Stancampiano, F. Fadda and M. A. Cenci (2006). "Role of striatal L-DOPA in the production of dyskinesia in 6-hydroxydopamine lesioned rats." J Neurochem **96**(6): 1718-27.

Cenci, M. A. (2007). "L-DOPA-induced dyskinesia: cellular mechanisms and approaches to treatment." Parkinsonism Relat Disord **13 Suppl 3**: S263-7.

Cenci, M. A., C. S. Lee and A. Bjorklund (1998). "L-DOPA-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic acid decarboxylase mRNA." Eur J Neurosci **10**(8): 2694-706.

Cenci, M. A. and H. S. Lindgren (2007). "Advances in understanding L-DOPA-induced dyskinesia." Curr Opin Neurobiol **17**(6): 665-71.

Cenci, M. A. and M. Lundblad (2006). "Post- versus presynaptic plasticity in L-DOPA-induced dyskinesia." J Neurochem **99**(2): 381-92.

Cenci, M. A. and M. Lundblad (2007). "Ratings of L-DOPA-induced dyskinesia in the unilateral 6-OHDA lesion model of Parkinson's disease in rats and mice." Curr Protoc Neurosci **Chapter 9**: Unit 9 25.

Cenci, M. A., I. Q. Whishaw and T. Schallert (2002). "Animal models of neurological deficits: how relevant is the rat?" Nat Rev Neurosci **3**(7): 574-9.

Chase, T. N. (1998). "Levodopa therapy: consequences of the nonphysiologic replacement of dopamine." Neurology **50**(5 Suppl 5): S17-25.

Chase, T. N. and J. D. Oh (2000). "Striatal mechanisms and pathogenesis of parkinsonian signs and motor complications." Ann Neurol **47**(4 Suppl 1): S122-9; discussion S129-30.

Chaudhuri, K. R., D. G. Healy and A. H. Schapira (2006). "Non-motor symptoms of Parkinson's disease: diagnosis and management." Lancet Neurol **5**(3): 235-45.

Chen, B. T. and M. E. Rice (2001). "Novel Ca2+ dependence and time course of somatodendritic dopamine release: substantia nigra versus striatum." J Neurosci **21**(19): 7841-7.

Choi, W. S., C. A. Machida and O. K. Ronnekleiv (1995). "Distribution of dopamine D1, D2, and D5 receptor mRNAs in the monkey brain: ribonuclease protection assay analysis." Brain Res Mol Brain Res **31**(1-2): 86-94.

Clarke, P. B., D. W. Hommer, A. Pert and L. R. Skirboll (1987). "Innervation of substantia nigra neurons by cholinergic afferents from pedunculopontine nucleus in the rat: neuroanatomical and electrophysiological evidence." Neuroscience **23**(3): 1011-9.

Cobb, W. S. and E. D. Abercrombie (2002). "Distinct roles for nigral GABA and glutamate receptors in the regulation of dendritic dopamine release under normal conditions and in response to systemic haloperidol." J Neurosci **22**(4): 1407-13.

Cobb, W. S. and E. D. Abercrombie (2003). "Differential regulation of somatodendritic and nerve terminal dopamine release by serotonergic innervation of substantia nigra." J Neurochem **84**(3): 576-84.

Cooper, J. R., F. E. Bloom and R. H. Roth (1996). "The biochemical basis of neuropharmacology, 7th ed. New York: Oxford University Press." 231-251.

Corrodi, H., N. A. Hillarp and G. Jonsson (1964). "Fluorescence Methods for the Histochemical Demonstration of Monoamines. 3. Sodium Borohydride Reduction of the Fluorescent Compounds as a Specificity Test." J Histochem Cytochem **12**: 582-6.

Cotzias, G. C., M. H. Van Woert and L. M. Schiffer (1967). "Aromatic amino acids and modification of parkinsonism." N Engl J Med **276**(7): 374-9.

Cowan, R. L., C. J. Wilson, P. C. Emson and C. W. Heizmann (1990). "Parvalbumin-containing GABAergic interneurons in the rat neostriatum." J Comp Neurol **302**(2): 197-205.

Cragg, S. J., C. R. Hawkey and S. A. Greenfield (1997). "Comparison of serotonin and dopamine release in substantia nigra and ventral tegmental area: region and species differences." J Neurochem **69**(6): 2378-86.

Cragg, S. J., C. Nicholson, J. Kume-Kick, L. Tao and M. E. Rice (2001). "Dopamine-mediated volume transmission in midbrain is regulated by distinct extracellular geometry and uptake." J Neurophysiol **85**(4): 1761-71.

Crocker, A. D. (1997). "The regulation of motor control: an evaluation of the role of dopamine receptors in the substantia nigra." Rev Neurosci **8**(1): 55-76.

Dahlström, A. and K. Fuxe (1964a). "Evidence for the Existence of Monoamine-Containing Neurons in the Central Nervous System. I. Demonstration of Monoamines in the Cell Bodies of Brain Stem Neurons." Acta Physiol Scand Suppl: SUPPL 232:1-55.

Dahlström, A. and K. Fuxe (1964b). "A Method for the Demonstration of Adrenergic Nerve Fibres in Peripheral Nerves." Z Zellforsch Mikrosk Anat **62**: 602-7.

Dahlström, A. and K. Fuxe (1965). "Evidence for the Existence of Monoamine Neurons in the Central Nervous System. Ii. Experimentally Induced Changes in the Intraneuronal Amine Levels of Bulbospinal Neuron Systems." Acta Physiol Scand Suppl: SUPPL 247:1-36.

Dal Toso, R., B. Sommer, M. Ewert, A. Herb, D. B. Pritchett, A. Bach, B. D. Shivers and P. H. Seeburg (1989). "The dopamine D2 receptor: two molecular forms generated by alternative splicing." Embo J **8**(13): 4025-34.

Davila, V., Z. Yan, L. C. Craciun, D. Logothetis and D. Sulzer (2003). "D3 dopamine autoreceptors do not activate G-protein-gated inwardly rectifying potassium channel currents in substantia nigra dopamine neurons." J Neurosci **23**(13): 5693-7.

de Kock, C. P., N. Burnashev, J. C. Lodder, H. D. Mansvelder and A. B. Brussaard (2004). "NMDA receptors induce somatodendritic secretion in hypothalamic neurones of lactating female rats." J Physiol **561**(Pt 1): 53-64.

de Kock, C. P., L. N. Cornelisse, N. Burnashev, J. C. Lodder, A. J. Timmerman, J. J. Couey, H. D. Mansvelder and A. B. Brussaard (2006). "NMDA receptors trigger neurosecretion of 5-HT within dorsal raphe nucleus of the rat in the absence of action potential firing." J Physiol **577**(Pt 3): 891-905.

de la Fuente-Fernandez, R., V. Sossi, Z. Huang, S. Furtado, J. Q. Lu, D. B. Calne, T. J. Ruth and A. J. Stoessl (2004). "Levodopa-induced changes in synaptic dopamine levels

increase with progression of Parkinson's disease: implications for dyskinesias." Brain **127**(Pt 12): 2747-54.

Dearry, A., J. A. Gingrich, P. Falardeau, R. T. Fremeau, Jr., M. D. Bates and M. G. Caron (1990). "Molecular cloning and expression of the gene for a human D1 dopamine receptor." Nature **347**(6288): 72-6.

Dekundy, A., M. Lundblad, W. Danysz and M. A. Cenci (2007). "Modulation of L-DOPA-induced abnormal involuntary movements by clinically tested compounds: further validation of the rat dyskinesia model." Behav Brain Res **179**(1): 76-89.

DeLong, M. R. (1990). "Primate models of movement disorders of basal ganglia origin." Trends Neurosci **13**(7): 281-5.

Deng, Y. P., W. L. Lei and A. Reiner (2006). "Differential perikaryal localization in rats of D1 and D2 dopamine receptors on striatal projection neuron types identified by retrograde labeling." J Chem Neuroanat **32**(2-4): 101-16.

Deniau, J. M. and G. Chevalier (1992). "The lamellar organization of the rat substantia nigra pars reticulata: distribution of projection neurons." Neuroscience **46**(2): 361-77.

Di Chiara, G., M. Morelli and S. Consolo (1994). "Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions." Trends Neurosci **17**(6): 228-33.

Di Chiara, G., M. L. Porceddu, P. F. Spano and G. L. Gessa (1977). "Haloperidol increases and apomorphine decreases striatal dopamine metabolism after destruction of striatal dopamine-sensitive adenylate cyclase by kainic acid." Brain Res **130**(2): 374-82.

Double, K. L. and A. D. Crocker (1995). "Dopamine receptors in the substantia nigra are involved in the regulation of muscle tone." Proc Natl Acad Sci U S A **92**(5): 1669-73.

Dray, A., T. J. Gonye, N. R. Oakley and T. Tanner (1976). "Evidence for the existence of a raphe projection to the substantia nigra in rat." Brain Res **113**(1): 45-57.

Ehringer, H. and O. Hornykiewicz (1960). "[Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system.]." Klin Wochenschr **38**: 1236-9.

Eidelberg, E., J. G. Walden and L. H. Nguyen (1981). "Locomotor control in macaque monkeys." Brain **104**(Pt 4): 647-63.

el Mansari, M. and P. Blier (1996). "Functional characterization of 5-HT1D autoreceptors on the modulation of 5-HT release in guinea-pig mesencephalic raphe, hippocampus and frontal cortex." Br J Pharmacol **118**(3): 681-9.

Elbaz, A. and F. Moisan (2008). "Update in the epidemiology of Parkinson's disease." Curr Opin Neurol **21**(4): 454-60.

Elbaz, A. and C. Tranchant (2007). "Epidemiologic studies of environmental exposures in Parkinson's disease." J Neurol Sci **262**(1-2): 37-44.

Elverfors, A., J. Jonason, G. Jonason, G. Leonsson and H. Nissbrandt (1992). "Determination of release of endogenous dopamine from superfused substantia nigra slices." J Neurosci Methods **45**(3): 209-15.

Elverfors, A., E. Pileblad, S. Lagerkvist, F. Bergquist, J. Jonason and H. Nissbrandt (1997). "3-Methoxytyramine formation following monoamine oxidase inhibition is a poor index of dendritic dopamine release in the substantia nigra." J Neurochem **69**(4): 1684-92.

Engberg, G., A. Elverfors, J. Jonason and H. Nissbrandt (1997). "Inhibition of dopamine re-uptake: significance for nigral dopamine neuron activity." Synapse **25**(2): 215-26.

Engel, J. A., C. Fahlke, P. Hulthe, E. Hard, K. Johannessen, B. Snape and L. Svensson (1988). "Biochemical and behavioral evidence for an interaction between ethanol and calcium channel antagonists." J Neural Transm **74**(3): 181-93.

Engelmann, M., K. Ebner, R. Landgraf, F. Holsboer and C. T. Wotjak (1999). "Emotional stress triggers intrahypothalamic but not peripheral release of oxytocin in male rats." J Neuroendocrinol **11**(11): 867-72.

Eränkö, O. (1954). "Histological sampling, chromatographic separation, and determination of adrenaline and noradrenaline in the adrenal medulla." Ann Med Exp Biol Fenn **32**(4): 392-401.

Eränkö, O. (1955a). "Fluorescing islets, adrenaline and noradrenaline in the adrenal medulla of some common laboratory animals." Ann Med Exp Biol Fenn **33**(3): 278-90.

Eränkö, O. (1955b). "Histochemistry of noradrenaline in the adrenal medulla of rats and mice." Endocrinology **57**(3): 363-8.

Fahn, S. and D. Sulzer (2004). "Neurodegeneration and neuroprotection in Parkinson disease." NeuroRx **1**(1): 139-54.

Falck, B., N. A. Hillarp, G. Thieme and A. Torp (1962). "Fluorescence of catechol amines and related compounds condensed with formaldehyde." Brain Res Bull **9**(1-6): xi-xv.

Filloux, F. M., J. K. Wamsley and T. M. Dawson (1987a). "Dopamine D-2 auto- and postsynaptic receptors in the nigrostriatal system of the rat brain: localization by quantitative autoradiography with [3H]sulpiride." Eur J Pharmacol **138**(1): 61-8.

Filloux, F. M., J. K. Wamsley and T. M. Dawson (1987b). "Presynaptic and postsynaptic D1 dopamine receptors in the nigrostriatal system of the rat brain: a quantitative autoradiographic study using the selective D1 antagonist [3H]SCH 23390." Brain Res **408**(1-2): 205-9.

Finger, S. (1994). "Origins of neuroscience." New York: Oxford University Press, Inc. 462 p.

Fiorentini, C., M. C. Rizzetti, C. Busi, S. Bontempi, G. Collo, P. Spano and C. Missale (2006). "Loss of synaptic D1 dopamine/N-methyl-D-aspartate glutamate receptor complexes in L-DOPA-induced dyskinesia in the rat." Mol Pharmacol **69**(3): 805-12.

Fleming, S. M., P. O. Fernagut and M. F. Chesselet (2005). "Genetic mouse models of parkinsonism: strengths and limitations." NeuroRx **2**(3): 495-503.

Fonnum, F., Z. Gottesfeld and I. Grofova (1978). "Distribution of glutamate decarboxylase, choline acetyl-transferase and aromatic amino acid decarboxylase in the basal ganglia of normal and operated rats. Evidence for striatopallidal, striatoentopeduncular and striatonigral GABAergic fibres." Brain Res **143**(1): 125-38.

Fonnum, F., I. Grofova, E. Rinvik, J. Storm-Mathisen and F. Walberg (1974). "Origin and distribution of glutamate decarboxylase in substantia nigra of the cat." Brain Res **71**(1): 77-92.

Fonnum, F., J. Storm-Mathisen and I. Divac (1981). "Biochemical evidence for glutamate as neurotransmitter in corticostriatal and corticothalamic fibres in rat brain." Neuroscience **6**(5): 863-73.

Forster, G. L. and C. D. Blaha (2003). "Pedunculopontine tegmental stimulation evokes striatal dopamine efflux by activation of acetylcholine and glutamate receptors in the midbrain and pons of the rat." Eur J Neurosci **17**(4): 751-62.

Freed, C. R., P. E. Greene, R. E. Breeze, W. Y. Tsai, W. DuMouchel, R. Kao, S. Dillon, H. Winfield, S. Culver, J. Q. Trojanowski, D. Eidelberg and S. Fahn (2001). "Transplantation of embryonic dopamine neurons for severe Parkinson's disease." N Engl J Med **344**(10): 710-9.

Fuxe, K. (1965a). "Evidence for the Existence of Monoamine Neurons in the Central Nervous System. 3. the Monoamine Nerve Terminal." Z Zellforsch Mikrosk Anat **65**: 573-96.

Fuxe, K. (1965b). "Evidence for the Existence of Monoamine Neurons in the Central Nervous System. Iv. Distribution of Monoamine Nerve Terminals in the Central Nervous System." Acta Physiol Scand Suppl: SUPPL 247:37+.

Fuxe, K., L. F. Agnati, M. Zoli, B. Bjelke and I. Zini (1989). "Some aspects of the communicational and computational organization of the brain." Acta Physiol Scand **135**(3): 203-16.

Fuxe, K. and T. Hökfeldt (1969). "Catecholamines in the hypothalamus and the pituitary gland." Frontiers in Neuroendocrinology (eds. W. Ganong and L. Martini). Oxford University Press, Oxford.: 47-96.

Galeffi, F., L. Bianchi, J. P. Bolam and L. Della Corte (2003). "The effect of 6-hydroxydopamine lesions on the release of amino acids in the direct and indirect pathways of the basal ganglia: a dual microdialysis probe analysis." Eur J Neurosci **18**(4): 856-68.

Garau, L., S. Govoni, E. Stefanini, M. Trabucchi and P. F. Spano (1978). "Dopamine receptors: pharmacological and anatomical evidences indicate that two distinct dopamine receptor populations are present in rat striatum." Life Sci **23**(17-18): 1745-50.

Garcia-Rill, E., C. R. Houser, R. D. Skinner, W. Smith and D. J. Woodward (1987). "Locomotion-inducing sites in the vicinity of the pedunculopontine nucleus." Brain Res Bull **18**(6): 731-8.

Gardoni, F., B. Picconi, V. Ghiglieri, F. Polli, V. Bagetta, G. Bernardi, F. Cattabeni, M. Di Luca and P. Calabresi (2006). "A critical interaction between NR2B and MAGUK in L-DOPA induced dyskinesia." J Neurosci **26**(11): 2914-22.

Geffen, L. B., T. M. Jessell, A. C. Cuello and L. L. Iversen (1976). "Release of dopamine from dendrites in rat substantia nigra." Nature **260**(5548): 258-60.

Gerfen, C. R. (1989). "The neostriatal mosaic: striatal patch-matrix organization is related to cortical lamination." Science **246**(4928): 385-8.

Gerfen, C. R. (1992). "The neostriatal mosaic: multiple levels of compartmental organization." Trends Neurosci **15**(4): 133-9.

Gerfen, C. R., K. A. Keefe and E. B. Gauda (1995). "D1 and D2 dopamine receptor function in the striatum: coactivation of D1- and D2-dopamine receptors on separate populations of neurons results in potentiated immediate early gene response in D1-containing neurons." J Neurosci **15**(12): 8167-76.

Gerfen, C. R., S. Miyachi, R. Paletzki and P. Brown (2002). "D1 dopamine receptor supersensitivity in the dopamine-depleted striatum results from a switch in the regulation of ERK1/2/MAP kinase." J Neurosci **22**(12): 5042-54.

Gillies, A. and D. Willshaw (2004). "Models of the subthalamic nucleus. The importance of intranuclear connectivity." Med Eng Phys **26**(9): 723-32.

Gillies, A. and D. Willshaw (2007). "Neuroinformatics and modeling of the basal ganglia: bridging pharmacology and physiology." Expert Rev Med Devices **4**(5): 663-72.

Giros, B., P. Sokoloff, M. P. Martres, J. F. Riou, L. J. Emorine and J. C. Schwartz (1989). "Alternative splicing directs the expression of two D2 dopamine receptor isoforms." Nature **342**(6252): 923-6.

Glowinski, J. and L. L. Iversen (1966). "Regional studies of catecholamines in the rat brain. I. The disposition of [3H]norepinephrine, [3H]dopamine and [3H]dopa in various regions of the brain." J Neurochem **13**(8): 655-69.

Goetz, C. G., P. Damier, C. Hicking, E. Laska, T. Muller, C. W. Olanow, O. Rascol and H. Russ (2007). "Sarizotan as a treatment for dyskinesias in Parkinson's disease: a double-blind placebo-controlled trial." Mov Disord **22**(2): 179-86.

Golbe, L. I. (1988). "Deprenyl as symptomatic therapy in Parkinson's disease." Clin Neuropharmacol **11**(5): 387-400.

Golbe, L. I., A. N. Lieberman, M. D. Muenter, J. E. Ahlskog, G. Gopinathan, A. N. Neophytides, S. H. Foo and R. C. Duvoisin (1988). "Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease." Clin Neuropharmacol **11**(1): 45-55.

Goldberg, M. S., S. M. Fleming, J. J. Palacino, C. Cepeda, H. A. Lam, A. Bhatnagar, E. G. Meloni, N. Wu, L. C. Ackerson, G. J. Klapstein, M. Gajendiran, B. L. Roth, M. F. Chesselet, N. T. Maidment, M. S. Levine and J. Shen (2003). "Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons." J Biol Chem **278**(44): 43628-35.

Gomez-Gallego, M., E. Fernandez-Villalba, A. Fernandez-Barreiro and M. T. Herrero (2007). "Changes in the neuronal activity in the pedunculopontine nucleus in chronic MPTP-treated primates: an in situ hybridization study of cytochrome oxidase subunit I, choline acetyl transferase and substance P mRNA expression." J Neural Transm **114**(3): 319-26.

Grabb, M. C., V. M. Sciotti, J. M. Gidday, S. A. Cohen and D. G. van Wylen (1998). "Neurochemical and morphological responses to acutely and chronically implanted brain microdialysis probes." J Neurosci Methods **82**(1): 25-34.

Graybiel, A. M. (1984). "Correspondence between the dopamine islands and striosomes of the mammalian striatum." Neuroscience **13**(4): 1157-87.

Graybiel, A. M., T. Aosaki, A. W. Flaherty and M. Kimura (1994). "The basal ganglia and adaptive motor control." Science **265**(5180): 1826-31.

Graybiel, A. M., E. C. Hirsch and Y. A. Agid (1987). "Differences in tyrosine hydroxylase-like immunoreactivity characterize the mesostriatal innervation of striosomes and extrastriosomal matrix at maturity." Proc Natl Acad Sci U S A **84**(1): 303-7.

Greengard, P., A. C. Nairn, J. A. Girault, C. C. Ouimet, G. L. Snyder, G. Fisone, P. B. Allen, A. Fienberg and A. Nishi (1998). "The DARPP-32/protein phosphatase-1 cascade: a model for signal integration." Brain Res Brain Res Rev **26**(2-3): 274-84.

Grenhoff, J., M. Nisell, S. Ferre, G. Aston-Jones and T. H. Svensson (1993). "Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat." J Neural Transm Gen Sect **93**(1): 11-25.

Grenhoff, J., R. A. North and S. W. Johnson (1995). "Alpha 1-adrenergic effects on dopamine neurons recorded intracellularly in the rat midbrain slice." Eur J Neurosci **7**(8): 1707-13.

Grillner, P., A. Bonci, T. H. Svensson, G. Bernardi and N. B. Mercuri (1999). "Presynaptic muscarinic (M3) receptors reduce excitatory transmission in dopamine neurons of the rat mesencephalon." NEUROSCIENCE **91**(2): 557-565.

Grofova, I. (1975). "The identification of striatal and pallidal neurons projecting to substantia nigra. An experimental study by means of retrograde axonal transport of horseradish peroxidase." Brain Res **91**(2): 286-91.

Grofova, I., J. M. Deniau and S. T. Kitai (1982). "Morphology of the substantia nigra pars reticulata projection neurons intracellularly labeled with HRP." J Comp Neurol **208**(4): 352-68.

Groves, P. M. and J. C. Linder (1983). "Dendro-dendritic synapses in substantia nigra: descriptions based on analysis of serial sections." Exp Brain Res **49**(2): 209-17.

Groves, P. M., C. J. Wilson, S. J. Young and G. V. Rebec (1975). "Self-inhibition by dopaminergic neurons." Science **190**(4214): 522-8.

Guerra, M. J., I. Liste and J. L. Labandeira-Garcia (1997). "Effects of lesions of the nigrostriatal pathway and of nigral grafts on striatal serotonergic innervation in adult rats." Neuroreport **8**(16): 3485-8.

Gurney, K., T. J. Prescott and P. Redgrave (2001a). "A computational model of action selection in the basal ganglia. I. A new functional anatomy." Biol Cybern **84**(6): 401-10.

Gurney, K., T. J. Prescott and P. Redgrave (2001b). "A computational model of action selection in the basal ganglia. II. Analysis and simulation of behaviour." Biol Cybern **84**(6): 411-23.

Hajos, M. and S. A. Greenfield (1994). "Synaptic connections between pars compacta and pars reticulata neurones: electrophysiological evidence for functional modules within the substantia nigra." Brain Res **660**(2): 216-24.

Halasz, N., A. Ljungdahl, T. Hokfelt, O. Johansson, M. Goldstein, D. Park and P. Biberfeld (1977). "Transmitter histochemistry of the rat olfactory bulb. I. Immunohistochemical localization of monoamine synthesizing enzymes. Support for intrabulbar, periglomerular dopamine neurons." Brain Res **126**(3): 455-74.

Hammerstad, J. P., J. Carter, J. G. Nutt, G. C. Casten, R. C. Shrotriya, D. R. Alms and D. Temple (1986). "Buspirone in Parkinson's disease." Clin Neuropharmacol **9**(6): 556-60.

Hammond, C., J. M. Deniau, A. Rizk and J. Feger (1978). "Electrophysiological demonstration of an excitatory subthalamonigral pathway in the rat." Brain Res **151**(2): 235-44.

Hattori, T., P. L. McGeer and E. G. McGeer (1979). "Dendro axonic neurotransmission. II. Morphological sites for the synthesis, binding and release of neurotransmitters in dopaminergic dendrites in the substantia nigra and cholinergic dendrites in the neostriatum." Brain Res **170**(1): 71-83.

Hauser, R. A., M. P. McDermott and S. Messing (2006). "Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease." Arch Neurol **63**(12): 1756-60.

Hawkes, C. H., K. Del Tredici and H. Braak (2007). "Parkinson's disease: a dual-hit hypothesis." Neuropathol Appl Neurobiol **33**(6): 599-614.

Hefti, F. and W. Lichtensteiger (1978). "Subcellular distribution of dopamine in substantia nigra of the rat brain: effects of gamma-butyrolactone and destruction of noradrenergic afferents suggest formation of particles from dendrites." J Neurochem **30**(6): 1217-30.

Hemsley, K. M. and A. D. Crocker (2001). "Changes in muscle tone are regulated by D1 and D2 dopamine receptors in the ventral striatum and D1 receptors in the substantia nigra." Neuropsychopharmacology **25**(4): 514-26.

Hikosaka, O. and R. H. Wurtz (1983). "Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus." J Neurophysiol **49**(5): 1285-301.

Holt, D. J., A. M. Graybiel and C. B. Saper (1997). "Neurochemical architecture of the human striatum." J Comp Neurol **384**(1): 1-25.

Inglis, W. L. and P. Winn (1995). "The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation." Prog Neurobiol **47**(1): 1-29.

Izurieta-Sanchez, P., S. Sarre, G. Ebinger and Y. Michotte (2000). "Muscarinic antagonists in substantia nigra influence the decarboxylation of L-dopa in striatum." Eur J Pharmacol **399**(2-3): 151-60.

Jenkinson, N., D. Nandi, R. Oram, J. F. Stein and T. Z. Aziz (2006). "Pedunculopontine nucleus electric stimulation alleviates akinesia independently of dopaminergic mechanisms." Neuroreport **17**(6): 639-41.

Johannessen, J. N., J. D. Adams, H. M. Schuller, J. P. Bacon and S. P. Markey (1986). "1-Methyl-4-phenylpyridine (MPP+) induces oxidative stress in the rodent." Life Sci **38**(8): 743-9.

Johansson, P. A., M. Andersson, K. E. Andersson and M. A. Cenci (2001). "Alterations in cortical and basal ganglia levels of opioid receptor binding in a rat model of l-DOPA-induced dyskinesia." Neurobiol Dis **8**(2): 220-39.

Johnson, R. D. and J. B. Justice (1983). "Model studies for brain dialysis." Brain Res Bull **10**(4): 567-71.

Kant, G. J. and J. L. Meyerhoff (1978). "Release of endogenous norepinephrine and dopamine from rat brain regions in vitro." Life Sci **23**(21): 2111-7.

Katzenschlager, R., J. Head, A. Schrag, Y. Ben-Shlomo, A. Evans and A. J. Lees (2008). "Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD." Neurology **71**(7): 474-80.

Kawaguchi, Y. (1993). "Physiological, morphological, and histochemical characterization of three classes of interneurons in rat neostriatum." J Neurosci **13**(11): 4908-23.

Kawaguchi, Y., C. J. Wilson, S. J. Augood and P. C. Emson (1995). "Striatal interneurones: chemical, physiological and morphological characterization." Trends Neurosci **18**(12): 527-35.

Kebabian, J. W. and D. B. Calne (1979). "Multiple receptors for dopamine." Nature **277**(5692): 93-6.

Kemp, J. M. and T. P. Powell (1971a). "The site of termination of afferent fibres in the caudate nucleus." Philos Trans R Soc Lond B Biol Sci **262**(845): 413-27.

Kemp, J. M. and T. P. Powell (1971b). "The structure of the caudate nucleus of the cat: light and electron microscopy." Philos Trans R Soc Lond B Biol Sci **262**(845): 383-401.

Khan, Z. U., A. Gutierrez, R. Martin, A. Penafiel, A. Rivera and A. de la Calle (2000). "Dopamine D5 receptors of rat and human brain." Neuroscience **100**(4): 689-99.

Kim, J. S., I. J. Bak, R. Hassler and Y. Okada (1971). "Role of -aminobutyric acid (GABA) in the extrapyramidal motor system. 2. Some evidence for the existence of a type of GABA-rich strio-nigral neurons." Exp Brain Res **14**(1): 95-104.

Kirik, D., B. Georgievska, C. Burger, C. Winkler, N. Muzyczka, R. J. Mandel and A. Bjorklund (2002). "Reversal of motor impairments in parkinsonian rats by continuous intrastriatal delivery of L-dopa using rAAV-mediated gene transfer." Proc Natl Acad Sci U S A **99**(7): 4708-13.

Kirik, D., C. Rosenblad and A. Bjorklund (1998). "Characterization of behavioral and neurodegenerative changes following partial lesions of the nigrostriatal dopamine system induced by intrastriatal 6-hydroxydopamine in the rat." Exp Neurol **152**(2): 259-77.

Kirik, D., C. Rosenblad, A. Bjorklund and R. J. Mandel (2000). "Long-term rAAV-mediated gene transfer of GDNF in the rat Parkinson's model: intrastriatal but not intranigral transduction promotes functional regeneration in the lesioned nigrostriatal system." J Neurosci **20**(12): 4686-700.

Kirouac, G. J., S. Li and G. Mabrouk (2004). "GABAergic projection from the ventral tegmental area and substantia nigra to the periaqueductal gray region and the dorsal raphe nucleus." J Comp Neurol **469**(2): 170-84.

Kish, S. J., J. Tong, O. Hornykiewicz, A. Rajput, L. J. Chang, M. Guttman and Y. Furukawa (2008). "Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease." Brain **131**(Pt 1): 120-31.

Kita, H. and S. T. Kitai (1988). "Glutamate decarboxylase immunoreactive neurons in rat neostriatum: their morphological types and populations." Brain Res **447**(2): 346-52.

Kita, H. and S. T. Kitai (1991). "Intracellular study of rat globus pallidus neurons: membrane properties and responses to neostriatal, subthalamic and nigral stimulation." Brain Res **564**(2): 296-305.

Kita, H. and S. T. Kitai (1994). "The morphology of globus pallidus projection neurons in the rat: an intracellular staining study." Brain Res **636**(2): 308-19.

Koeltzow, T. E., M. Xu, D. C. Cooper, X. T. Hu, S. Tonegawa, M. E. Wolf and F. J. White (1998). "Alterations in dopamine release but not dopamine autoreceptor function in dopamine D3 receptor mutant mice." J Neurosci **18**(6): 2231-8.

Kojima, J., Y. Yamaji, M. Matsumura, A. Nambu, M. Inase, H. Tokuno, M. Takada and H. Imai (1997). "Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey." NEUROSCIENCE LETTERS **226**(2): 111-114.

Koller, W. C., R. Pahwa, K. E. Lyons and A. Albanese (1999). "Surgical treatment of Parkinson's disease." J Neurol Sci **167**(1): 1-10.

Konradi, C., J. E. Westin, M. Carta, M. E. Eaton, K. Kuter, A. Dekundy, M. Lundblad and M. A. Cenci (2004). "Transcriptome analysis in a rat model of L-DOPA-induced dyskinesia." Neurobiol Dis **17**(2): 219-36.

Koob, G. F. (1992). "Drugs of abuse: anatomy, pharmacology and function of reward pathways." Trends Pharmacol Sci **13**(5): 177-84.

Koos, T. and J. M. Tepper (2002). "Dual cholinergic control of fast-spiking interneurons in the neostriatum." J Neurosci **22**(2): 529-35.

Krack, P., P. Pollak, P. Limousin, D. Hoffmann, J. Xie, A. Benazzouz and A. L. Benabid (1998). "Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease." Brain **121 (Pt 3)**: 451-7.

Kreitzer, A. C. and R. C. Malenka (2005). "Dopamine modulation of state-dependent endocannabinoid release and long-term depression in the striatum." J Neurosci **25**(45): 10537-45.

Kreitzer, A. C. and R. C. Malenka (2008). "Striatal plasticity and basal ganglia circuit function." Neuron **60**(4): 543-54.

Krout, K. E., R. E. Belzer and A. D. Loewy (2002). "Brainstem projections to midline and intralaminar thalamic nuclei of the rat." J Comp Neurol **448**(1): 53-101.

Krout, K. E. and A. D. Loewy (2000a). "Parabrachial nucleus projections to midline and intralaminar thalamic nuclei of the rat." J Comp Neurol **428**(3): 475-94.

Krout, K. E. and A. D. Loewy (2000b). "Periaqueductal gray matter projections to midline and intralaminar thalamic nuclei of the rat." J Comp Neurol **424**(1): 111-41.

Krout, K. E., A. D. Loewy, G. W. Westby and P. Redgrave (2001). "Superior colliculus projections to midline and intralaminar thalamic nuclei of the rat." J Comp Neurol **431**(2): 198-216.

Krueger, B. K., J. Forn, J. R. Walters, R. H. Roth and P. Greengard (1976). "Stimulation by dopamine of adenosine cyclic 3',5'-monophosphate formation in rat caudate nucleus: effect of lesions of the nigro-neostriatal pathway." Mol Pharmacol **12**(4): 639-48.

Kuo, S.-H., C. Kenney and J. Jankovic (2008). "Bilateral pedunculopontine nuclei strokes presenting as freezing of gait." Movement Disorders: Official Journal of the Movement Disorder Society **23**(4): 616-9.

L'Hirondel, M., A. Cheramy, G. Godeheu, F. Artaud, A. Saiardi, E. Borrelli and J. Glowinski (1998). "Lack of autoreceptor-mediated inhibitory control of dopamine release in striatal synaptosomes of D2 receptor-deficient mice." Brain Res **792**(2): 253-62.

Lagerkvist, S. (1991). "Sample splitting provides a fast and selective method for determining brain dialysate dopamine and its metabolites. In: Rollema H, Westerink B, Drijfhout W. J., editors. Monitoring Molecules in Neuroscience. Groningen." 136-138.

Lane, E. and S. Dunnett (2008). "Animal models of Parkinson's disease and L-dopa induced dyskinesia: how close are we to the clinic?" Psychopharmacology (Berl) **199**(3): 303-12.

Langston, J. W., M. Quik, G. Petzinger, M. Jakowec and D. A. Di Monte (2000). "Investigating levodopa-induced dyskinesias in the parkinsonian primate." Ann Neurol **47**(4 Suppl 1): S79-89.

Lategan, A. J., M. R. Marien and F. C. Colpaert (1990). "Effects of locus coeruleus lesions on the release of endogenous dopamine in the rat nucleus accumbens and caudate nucleus as determined by intracerebral microdialysis." Brain Res **523**(1): 134-8.

Lategan, A. J., M. R. Marien and F. C. Colpaert (1992). "Suppression of nigrostriatal and mesolimbic dopamine release in vivo following noradrenaline depletion by DSP-4: a microdialysis study." Life Sci **50**(14): 995-9.

Lavoie, B. and A. Parent (1994a). "Pedunculopontine nucleus in the squirrel monkey: cholinergic and glutamatergic projections to the substantia nigra." J Comp Neurol **344**(2): 232-41.

Lavoie, B. and A. Parent (1994b). "Pedunculopontine nucleus in the squirrel monkey: distribution of cholinergic and monoaminergic neurons in the mesopontine tegmentum with evidence for the presence of glutamate in cholinergic neurons." J Comp Neurol **344**(2): 190-209.

Le Moine, C. and B. Bloch (1995). "D1 and D2 dopamine receptor gene expression in the rat striatum: sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum." J Comp Neurol **355**(3): 418-26.

Le Moine, C., E. Normand, A. F. Guitteny, B. Fouque, R. Teoule and B. Bloch (1990). "Dopamine receptor gene expression by enkephalin neurons in rat forebrain." Proc Natl Acad Sci U S A **87**(1): 230-4.

Lee, J., W. M. Zhu, D. Stanic, D. I. Finkelstein, M. H. Horne, J. Henderson, A. J. Lawrence, L. O'Connor, D. Tomas, J. Drago and M. K. Horne (2008). "Sprouting of dopamine terminals and altered dopamine release and uptake in Parkinsonian dyskinaesia." Brain **131**(Pt 6): 1574-87.

Lee, M. S., J. O. Rinne and C. D. Marsden (2000). "The pedunculopontine nucleus: its role in the genesis of movement disorders." Yonsei Med J **41**(2): 167-84.

Levandis, G., E. Bazzini, M. T. Armentero, G. Nappi and F. Blandini (2008). "Systemic administration of an mGluR5 antagonist, but not unilateral subthalamic lesion, counteracts l-DOPA-induced dyskinesias in a rodent model of Parkinson's disease." Neurobiol Dis **29**(1): 161-8.

Levesque, M. and A. Parent (2005). "The striatofugal fiber system in primates: a reevaluation of its organization based on single-axon tracing studies." Proc Natl Acad Sci U S A **102**(33): 11888-93.

LeWitt, P. A. (2006). "Neuroprotection for Parkinson's disease." J Neural Transm Suppl(71): 113-22.

Lewy, F. (1912). "Paralysis agitans. I. Pathologische anatomie." In: Handbuch der neurologie. Lewandowsky M, editor. Berlin: Springer;: 920-933.

Limousin, P. and I. Martinez-Torres (2008). "Deep brain stimulation for Parkinson's disease." Neurotherapeutics **5**(2): 309-19.

Lindgren, H. S., D. Rylander, K. E. Ohlin, M. Lundblad and M. A. Cenci (2007). "The "motor complication syndrome" in rats with 6-OHDA lesions treated chronically with L-DOPA: relation to dose and route of administration." Behav Brain Res **177**(1): 150-9.

Lindgren, N., A. Usiello, M. Goiny, J. Haycock, E. Erbs, P. Greengard, T. Hokfelt, E. Borrelli and G. Fisone (2003). "Distinct roles of dopamine D2L and D2S receptor isoforms in the regulation of protein phosphorylation at presynaptic and postsynaptic sites." Proc Natl Acad Sci U S A **100**(7): 4305-9.

Lindvall, O. and A. Björklund (1974). "The glyoxylic acid fluorescence histochemical method: a detailed account of the methodology for the visualization of central catecholamine neurons." Histochemistry **39**(2): 97-127.

Lindvall, O. and A. Björklund (1978). "Organization of catecholamine neurons in the rat central nervous system." Handbook of psychopharmacology (Iversen L. L, Iversen S. D. and Snyder S. H. eds.). Plenum Press, New York. **Vol. 9** 139-231.

Lindvall, O., A. Björklund and I. Divac (1978). "Organization of catecholamine neurons projecting to the frontal cortex in the rat." Brain Res **142**(1): 1-24.

Logroscino, G. (2005). "The role of early life environmental risk factors in Parkinson disease: what is the evidence?" Environ Health Perspect **113**(9): 1234-8.

Loopuijt, L. D., J. B. Sebens and J. Korf (1987). "A mosaic-like distribution of dopamine receptors in rat neostriatum and its relationship to striosomes." Brain Res **405**(2): 405-8.

Lozano, A. M. and B. J. Snyder (2008). "Deep brain stimulation for parkinsonian gait disorders." JOURNAL OF NEUROLOGY **255**: 30-31.

Ludwig, C. L., D. R. Weinberger, G. Bruno, M. Gillespie, K. Bakker, P. A. LeWitt and T. N. Chase (1986). "Buspirone, Parkinson's disease, and the locus ceruleus." Clin Neuropharmacol **9**(4): 373-8.

Ludwig, M., N. Sabatier, P. M. Bull, R. Landgraf, G. Dayanithi and G. Leng (2002). "Intracellular calcium stores regulate activity-dependent neuropeptide release from dendrites." Nature **418**(6893): 85-9.

Lundblad, M., B. Picconi, H. Lindgren and M. A. Cenci (2004). "A model of L-DOPA-induced dyskinesia in 6-hydroxydopamine lesioned mice: relation to motor and cellular parameters of nigrostriatal function." Neurobiol Dis **16**(1): 110-23.

Lundblad, M., A. Usiello, M. Carta, K. Hakansson, G. Fisone and M. A. Cenci (2005). "Pharmacological validation of a mouse model of l-DOPA-induced dyskinesia." Exp Neurol **194**(1): 66-75.

Maeda, T., K. Nagata, Y. Yoshida and K. Kannari (2005). "Serotonergic hyperinnervation into the dopaminergic denervated striatum compensates for dopamine conversion from exogenously administered l-DOPA." Brain Res **1046**(1-2): 230-3.

Maher, N. E., L. J. Currie, A. M. Lazzarini, J. B. Wilk, C. A. Taylor, M. H. Saint-Hilaire, R. G. Feldman, L. I. Golbe, G. F. Wooten and R. H. Myers (2002a). "Segregation analysis of Parkinson disease revealing evidence for a major causative gene." Am J Med Genet **109**(3): 191-7.

Maher, N. E., L. I. Golbe, A. M. Lazzarini, M. H. Mark, L. J. Currie, G. F. Wooten, M. Saint-Hilaire, J. B. Wilk, J. Volcjak, J. E. Maher, R. G. Feldman, M. Guttman, M. Lew, C. H. Waters, S. Schuman, O. Suchowersky, A. L. Lafontaine, N. Labelle, P. Vieregge, P. P. Pramstaller, C. Klein, J. Hubble, C. Reider, J. Growdon, R. Watts, E. Montgomery, K. Baker, C. Singer, M. Stacy and R. H. Myers (2002b). "Epidemiologic study of 203 sibling pairs with Parkinson's disease: the GenePD study." Neurology **58**(1): 79-84.

Mallet, N., C. Le Moine, S. Charpier and F. Gonon (2005). "Feedforward inhibition of projection neurons by fast-spiking GABA interneurons in the rat striatum in vivo." J Neurosci **25**(15): 3857-69.

Mandel, R. J., K. G. Rendahl, S. K. Spratt, R. O. Snyder, L. K. Cohen and S. E. Leff (1998). "Characterization of intrastriatal recombinant adeno-associated virus-mediated gene transfer of human tyrosine hydroxylase and human GTP-cyclohydrolase I in a rat model of Parkinson's disease." J Neurosci **18**(11): 4271-84.

Martin, L. P. and B. L. Waszczak (1994). "D1 agonist-induced excitation of substantia nigra pars reticulata neurons: mediation by D1 receptors on striatonigral terminals via a pertussis toxin-sensitive coupling pathway." J Neurosci **14**(7): 4494-506.

Martin, L. P. and B. L. Waszczak (1996). "Dopamine D2, receptor-mediated modulation of the GABAergic inhibition of substantia nigra pars reticulata neurons." Brain Res **729**(2): 156-69.

Mazzella, L., M. D. Yahr, L. Marinelli, N. Huang, E. Moshier and A. Di Rocco (2005). "Dyskinesias predict the onset of motor response fluctuations in patients with Parkinson's disease on L-dopa monotherapy." Parkinsonism Relat Disord **11**(3): 151-5.

Mazzone, P., A. Lozano, P. Stanzione, S. Galati, E. Scarnati, A. Peppe and A. Stefani (2005). "Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease." Neuroreport **16**(17): 1877-81.

McGeer, P. L., K. Yasojima and E. G. McGeer (2002). "Association of interleukin-1 beta polymorphisms with idiopathic Parkinson's disease." Neurosci Lett **326**(1): 67-9.

McHaffie, J. G., T. R. Stanford, B. E. Stein, V. Coizet and P. Redgrave (2005). "Subcortical loops through the basal ganglia." Trends Neurosci **28**(8): 401-7.

Meissner, W., P. Ravenscroft, R. Reese, D. Harnack, R. Morgenstern, A. Kupsch, H. Klitgaard, B. Bioulac, C. E. Gross, E. Bezard and T. Boraud (2006). "Increased slow oscillatory activity in substantia nigra pars reticulata triggers abnormal involuntary movements in the 6-OHDA-lesioned rat in the presence of excessive extracellular striatal dopamine." Neurobiol Dis **22**(3): 586-98.

Mela, F., M. Marti, A. Dekundy, W. Danysz, M. Morari and M. A. Cenci (2007). "Antagonism of metabotropic glutamate receptor type 5 attenuates l-DOPA-induced dyskinesia and its molecular and neurochemical correlates in a rat model of Parkinson's disease." J Neurochem **101**(2): 483-97.

Mena-Segovia, J., P. Winn and J. P. Bolam (2008). "Cholinergic modulation of midbrain dopaminergic systems." Brain Research Reviews **58**(2): 265-71.

Michel, F. J., J. M. Robillard and L. E. Trudeau (2004). "Regulation of rat mesencephalic GABAergic neurones through muscarinic receptors." Journal of Physiology-London **556**(2): 429-445.

Miller, A. D. and C. D. Blaha (2005). "Midbrain muscarinic receptor mechanisms underlying regulation of mesoaccumbens and nigrostriatal dopaminergic transmission in the rat." Eur J Neurosci **21**(7): 1837-46.

Miller, D. W. and E. D. Abercrombie (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**(4): 1516-22.

Miller, J. J., T. L. Richardson, H. C. Fibiger and H. McLennan (1975). "Anatomical and electrophysiological identification of a projection from the mesencephalic raphe to the caudate-putamen in the rat." Brain Res **97**(1): 133-6.

Monsma, F. J., Jr., L. C. Mahan, L. D. McVittie, C. R. Gerfen and D. R. Sibley (1990). "Molecular cloning and expression of a D1 dopamine receptor linked to adenylyl cyclase activation." Proc Natl Acad Sci U S A **87**(17): 6723-7.

Monsma, F. J., Jr., L. D. McVittie, C. R. Gerfen, L. C. Mahan and D. R. Sibley (1989). "Multiple D2 dopamine receptors produced by alternative RNA splicing." Nature **342**(6252): 926-9.

Morelli, M., E. Carboni, S. Devoto and G. Di Chiara (1987). "6-Hydroxydopamine lesions reduce specific [3H]sulpiride binding in the rat substantia nigra: direct evidence for the existence of nigral D-2 autoreceptors." Eur J Pharmacol **140**(1): 99-104.

Morgese, M. G., T. Cassano, V. Cuomo and A. Giuffrida (2007). "Anti-dyskinetic effects of cannabinoids in a rat model of Parkinson's disease: role of CB(1) and TRPV1 receptors." Exp Neurol **208**(1): 110-9.

Mrzljak, L., C. Bergson, M. Pappy, R. Huff, R. Levenson and P. S. Goldman-Rakic (1996). "Localization of dopamine D4 receptors in GABAergic neurons of the primate brain." Nature **381**(6579): 245-8.

Munoz, A., Q. Li, F. Gardoni, E. Marcello, C. Qin, T. Carlsson, D. Kirik, M. Di Luca, A. Bjorklund, E. Bezard and M. Carta (2008). "Combined 5-HT1A and 5-HT1B receptor agonists for the treatment of L-DOPA-induced dyskinesia." Brain **131**(Pt 12): 3380-94.

Nakanishi, H., H. Kita and S. T. Kitai (1987). "Intracellular study of rat substantia nigra pars reticulata neurons in an in vitro slice preparation: electrical membrane properties and response characteristics to subthalamic stimulation." Brain Res **437**(1): 45-55.

Nandi, D., T. Z. Aziz, N. Giladi, J. Winter and J. F. Stein (2002). "Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus." Brain: A Journal of Neurology **125**(Pt 11): 2418-30.

Nauta, W. J. and W. R. Mehler (1966). "Projections of the lentiform nucleus in the monkey." Brain Res **1**(1): 3-42.

Nedergaard, S., C. Hopkins and S. A. Greenfield (1988). "Do nigro-striatal neurones possess a discrete dendritic modulatory mechanism? Electrophysiological evidence from the actions of amphetamine in brain slices." Exp Brain Res **69**(2): 444-8.

Nestler, E. J. (2001). "Molecular basis of long-term plasticity underlying addiction." Nat Rev Neurosci **2**(2): 119-28.

Nicklas, W. J., I. Vyas and R. E. Heikkila (1985). "Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine." Life Sci **36**(26): 2503-8.

Nieoullon, A., A. Cheramy and J. Glowinski (1977). "Release of dopamine in vivo from cat substantia nigra." Nature **266**(5600): 375-7.

Nirenberg, M. J., J. Chan, Y. Liu, R. H. Edwards and V. M. Pickel (1996). "Ultrastructural localization of the vesicular monoamine transporter-2 in midbrain dopaminergic neurons: potential sites for somatodendritic storage and release of dopamine." J Neurosci **16**(13): 4135-45.

Nissbrandt, H., F. Bergquist, J. Jonason and G. Engberg (2001). "Inhibition of cytochrome P450 2E1 induces an increase in extracellular dopamine in rat substantia nigra: a new metabolic pathway?" Synapse **40**(4): 294-301.

Oertel, W. H. and E. Mugnaini (1984). "Immunocytochemical studies of GABAergic neurons in rat basal ganglia and their relations to other neuronal systems." Neurosci Lett **47**(3): 233-8.

Oertel, W. H., E. Wolters, C. Sampaio, S. Gimenez-Roldan, B. Bergamasco, M. Dujardin, D. G. Grosset, G. Arnold, K. L. Leenders, H. P. Hundemer, A. Lledo, A. Wood, P. Frewer and J. Schwarz (2006). "Pergolide versus levodopa monotherapy in early Parkinson's disease patients: The PELMOPET study." Mov Disord **21**(3): 343-53.

Olanow, C. W., Y. Agid, Y. Mizuno, A. Albanese, U. Bonuccelli, P. Damier, J. De Yebenes, O. Gershanik, M. Guttman, F. Grandas, M. Hallett, O. Hornykiewicz, P. Jenner, R. Katzenschlager, W. J. Langston, P. LeWitt, E. Melamed, M. A. Mena, P. P. Michel, C. Mytilineou, J. A. Obeso, W. Poewe, N. Quinn, R. Raisman-Vozari, A. H. Rajput, O. Rascol, C. Sampaio and F. Stocchi (2004a). "Levodopa in the treatment of Parkinson's disease: current controversies." Mov Disord **19**(9): 997-1005.

Olanow, C. W., M. F. Brin and J. A. Obeso (2000). "The role of deep brain stimulation as a surgical treatment for Parkinson's disease." Neurology **55**(12 Suppl 6): S60-6.

Olanow, C. W., P. Damier, C. G. Goetz, T. Mueller, J. Nutt, O. Rascol, A. Serbanescu, F. Deckers and H. Russ (2004b). "Multicenter, open-label, trial of sarizotan in Parkinson disease patients with levodopa-induced dyskinesias (the SPLENDID Study)." Clin Neuropharmacol **27**(2): 58-62.

Olanow, C. W., C. G. Goetz, J. H. Kordower, A. J. Stoessl, V. Sossi, M. F. Brin, K. M. Shannon, G. M. Nauert, D. P. Perl, J. Godbold and T. B. Freeman (2003). "A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease." Ann Neurol **54**(3): 403-14.

Olson, L., A. Seiger and K. Fuxe (1972). "Heterogeneity of striatal and limbic dopamine innervation: highly fluorescent islands in developing and adult rats." Brain Res **44**(1): 283-8.

Oorschot, D. E. (1996). "Total number of neurons in the neostriatal, pallidal, subthalamic, and substantia nigral nuclei of the rat basal ganglia: a stereological study using the cavalieri and optical disector methods." J Comp Neurol **366**(4): 580-99.

Packard, M. G. and B. J. Knowlton (2002). "Learning and memory functions of the Basal Ganglia." Annu Rev Neurosci **25**: 563-93.

Paden, C., C. J. Wilson and P. M. Groves (1976). "Amphetamine-induced release of dopamine from the substantia nigra in vitro." Life Sci **19**(10): 1499-506.

Pahapill, P. A. and A. M. Lozano (2000). "The pedunculopontine nucleus and Parkinson's disease." Brain **123 (Pt 9)**: 1767-83.

Parent, A. and L. N. Hazrati (1995). "Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop." Brain Res Brain Res Rev **20**(1): 91-127.

Parkinson, J. (1817). "An essay on the shaking palsy." Sherwood, Neely & Jones, London.

Parkinson Study Group (2000). "Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group." Jama **284**(15): 1931-8.

Pavese, N., A. H. Evans, Y. F. Tai, G. Hotton, D. J. Brooks, A. J. Lees and P. Piccini (2006). "Clinical correlates of levodopa-induced dopamine release in Parkinson disease: a PET study." Neurology **67**(9): 1612-7.

Piccini, P., R. A. Weeks and D. J. Brooks (1997). "Alterations in opioid receptor binding in Parkinson's disease patients with levodopa-induced dyskinesias." Ann Neurol **42**(5): 720-6.

Picconi, B., D. Centonze, K. Hakansson, G. Bernardi, P. Greengard, G. Fisone, M. A. Cenci and P. Calabresi (2003). "Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia." Nat Neurosci **6**(5): 501-6.

Pickel, V. M., M. Garzon and E. Mengual (2002). "Electron microscopic immunolabeling of transporters and receptors identifies transmitter-specific functional sites envisioned in Cajal's neuron." Prog Brain Res **136**: 145-55.

Pineyro, G. and P. Blier (1996). "Regulation of 5-hydroxytryptamine release from rat midbrain raphe nuclei by 5-hydroxytryptamine1D receptors: effect of tetrodotoxin, G protein inactivation and long-term antidepressant administration." J Pharmacol Exp Ther **276**(2): 697-707.

Pineyro, G., C. de Montigny and P. Blier (1995). "5-HT1D receptors regulate 5-HT release in the rat raphe nuclei. In vivo voltammetry and in vitro superfusion studies." Neuropsychopharmacology **13**(3): 249-60.

Plaha, P. and S. S. Gill (2005). "Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson's disease." Neuroreport **16**(17): 1883-7.

Porceddu, M. L., O. Giorgi, G. De Montis, S. Mele, L. Cocco, E. Ongini and G. Biggio (1987). "6-Hydroxydopamine-induced degeneration of nigral dopamine neurons: differential effect on nigral and striatal D-1 dopamine receptors." Life Sci **41**(6): 697-706.

Prescott, I. A., J. O. Dostrovsky, E. Moro, M. Hodaie, A. M. Lozano and W. D. Hutchison (2008). "Levodopa enhances synaptic plasticity in the substantia nigra pars reticulata of Parkinson's disease patients." Brain.

Pucak, M. L. and A. A. Grace (1994). "Evidence that systemically administered dopamine antagonists activate dopamine neuron firing primarily by blockade of somatodendritic autoreceptors." J Pharmacol Exp Ther **271**(3): 1181-92.

Rajput, A. H., M. E. Fenton, S. Birdi, R. Macaulay, D. George, B. Rozdilsky, L. C. Ang, A. Senthilselvan and O. Hornykiewicz (2002). "Clinical-pathological study of levodopa complications." Mov Disord **17**(2): 289-96.

Rajput, A. H., M. E. Fenton, T. Di Paolo, H. Sitte, C. Pifl and O. Hornykiewicz (2004). "Human brain dopamine metabolism in levodopa-induced dyskinesia and wearing-off." Parkinsonism Relat Disord **10**(4): 221-6.

Rajput, A. H., W. Martin, M. H. Saint-Hilaire, E. Dorflinger and S. Pedder (1997). "Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial." Neurology **49**(4): 1066-71.

Rascol, O., D. J. Brooks, A. D. Korczyn, P. P. De Deyn, C. E. Clarke and A. E. Lang (2000). "A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group." N Engl J Med **342**(20): 1484-91.

Redgrave, P., L. Marrow and P. Dean (1992). "Topographical organization of the nigrotectal projection in rat: evidence for segregated channels." Neuroscience **50**(3): 571-95.

Redgrave, P., T. J. Prescott and K. Gurney (1999). "The basal ganglia: a vertebrate solution to the selection problem?" Neuroscience **89**(4): 1009-23.

Reubi, J. C., L. L. Iversen and T. M. Jessell (1977). "Dopamine selectively increases 3H-GABA release from slices of rat substantia nigra in vitro." Nature **268**(5621): 652-4.

Rice, M. E. and S. J. Cragg (2008). "Dopamine spillover after quantal release: rethinking dopamine transmission in the nigrostriatal pathway." Brain Res Rev **58**(2): 303-13.

Rice, M. E., C. D. Richards, S. Nedergaard, J. Hounsgaard, C. Nicholson and S. A. Greenfield (1994). "Direct monitoring of dopamine and 5-HT release in substantia nigra and ventral tegmental area in vitro." Exp Brain Res **100**(3): 395-406.

Rinvik, E., I. Grofova and O. P. Ottersen (1976). "Demonstration of nigrotectal and nigroreticular projections in the cat by axonal transport of proteins." Brain Res **112**(2): 388-94.

Rivera, A., I. Alberti, A. B. Martin, J. A. Narvaez, A. de la Calle and R. Moratalla (2002a). "Molecular phenotype of rat striatal neurons expressing the dopamine D5 receptor subtype." Eur J Neurosci **16**(11): 2049-58.

Rivera, A., B. Cuellar, F. J. Giron, D. K. Grandy, A. de la Calle and R. Moratalla (2002b). "Dopamine D4 receptors are heterogeneously distributed in the striosomes/matrix compartments of the striatum." J Neurochem **80**(2): 219-29.

Rivera, A., S. Trias, A. Penafiel, J. Angel Narvaez, Z. Diaz-Cabiale, R. Moratalla and A. de la Calle (2003). "Expression of D4 dopamine receptors in striatonigral and striatopallidal neurons in the rat striatum." Brain Res **989**(1): 35-41.

Robertson, G. S., G. Damsma and H. C. Fibiger (1991). "Characterization of dopamine release in the substantia nigra by in vivo microdialysis in freely moving rats." J Neurosci **11**(7): 2209-16.

Rocca, W. A., S. K. McDonnell, K. J. Strain, J. H. Bower, J. E. Ahlskog, A. Elbaz, D. J. Schaid and D. M. Maraganore (2004). "Familial aggregation of Parkinson's disease: The Mayo Clinic family study." Ann Neurol **56**(4): 495-502.

Rosales, M. G., D. Martinez-Fong, R. Morales, A. Nuñez, G. Flores, J. L. Góngora-Alfaro, B. Flóran and J. Aceves (1997). "Reciprocal interaction between glutamate and dopamine in the pars reticulata of the rat substantia nigra: a microdialysis study." Neuroscience **80**(3): 803-10.

Rosengren, E. (1960). "On the role of monoamine oxidase for the inactivation of dopamine in brain." Acta Physiol Scand **49**: 370-5.

Ross, R. A. and D. J. Reis (1974). "Effects of lesions of locus coeruleus on regional distribution of dopamine-beta-hydroxylase activity in rat brain." Brain Res **73**(1): 161-6.

Roufogalis, B. D., M. Thornton and D. N. Wade (1976). "Specificity of the dopamine sensitive adenylate cyclase for antipsychotic antagonists." Life Sci **19**(6): 927-34.

Rozas, G., M. J. Guerra and J. L. Labandeira-Garcia (1997). "An automated rotarod method for quantitative drug-free evaluation of overall motor deficits in rat models of parkinsonism." Brain Res Brain Res Protoc **2**(1): 75-84.

Rozas, G. and J. L. Labandeira Garcia (1997). "Drug-free evaluation of rat models of parkinsonism and nigral grafts using a new automated rotarod test." Brain Res **749**(2): 188-99.

Rutledge, C. O. and J. Jonason (1967). "Metabolic pathways of dopamine and norepinephrine in rabbit brain in vitro." J Pharmacol Exp Ther **157**(3): 493-502.

Sabatier, N., C. Caquineau, G. Dayanithi, P. Bull, A. J. Douglas, X. M. Guan, M. Jiang, L. Van der Ploeg and G. Leng (2003). "Alpha-melanocyte-stimulating hormone stimulates oxytocin release from the dendrites of hypothalamic neurons while inhibiting oxytocin release from their terminals in the neurohypophysis." J Neurosci **23**(32): 10351-8.

Saner, A. and H. Thoenen (1971). "Model experiments on the molecular mechanism of action of 6-hydroxydopamine." Mol Pharmacol **7**(2): 147-54.

Sano, I., T. Gamo, Y. Kakimoto, K. Taniguchi, M. Takesada and K. Nishinuma (1959). "Distribution of catechol compounds in human brain." Biochim Biophys Acta **32**: 586-7.

Santiago, M. and B. H. Westerink (1990). "Characterization of the in vivo release of dopamine as recorded by different types of intracerebral microdialysis probes." Naunyn Schmiedebergs Arch Pharmacol **342**(4): 407-14.

Santiago, M. and B. H. Westerink (1991a). "Characterization and pharmacological responsiveness of dopamine release recorded by microdialysis in the substantia nigra of conscious rats." J Neurochem **57**(3): 738-47.

Santiago, M. and B. H. Westerink (1991b). "The regulation of dopamine release from nigrostriatal neurons in conscious rats: the role of somatodendritic autoreceptors." Eur J Pharmacol **204**(1): 79-85.

Santini, E., E. Valjent, A. Usiello, M. Carta, A. Borgkvist, J. A. Girault, D. Herve, P. Greengard and G. Fisone (2007). "Critical involvement of cAMP/DARPP-32 and extracellular signal-regulated protein kinase signaling in L-DOPA-induced dyskinesia." J Neurosci **27**(26): 6995-7005.

Sarre, S., H. Yuan, N. Jonkers, A. Van Hemelrijck, G. Ebinger and Y. Michotte (2004). "In vivo characterization of somatodendritic dopamine release in the substantia nigra of 6-hydroxydopamine-lesioned rats." J Neurochem **90**(1): 29-39.

Sato, C., A. Morgan, A. E. Lang, S. Salehi-Rad, T. Kawarai, Y. Meng, P. N. Ray, L. A. Farrer, P. St George-Hyslop and E. Rogaeva (2005). "Analysis of the glucocerebrosidase gene in Parkinson's disease." Mov Disord **20**(3): 367-70.

Savasta, M., A. Dubois and B. Scatton (1986). "Autoradiographic localization of D1 dopamine receptors in the rat brain with [3H]SCH 23390." Brain Res **375**(2): 291-301.

Scarnati, E., A. Proia, E. Campana and C. Pacitti (1986). "A microiontophoretic study on the nature of the putative synaptic neurotransmitter involved in the pedunculopontine-substantia nigra pars compacta excitatory pathway of the rat." Exp Brain Res **62**(3): 470-8.

Schapira, A. H. (2008). "Progress in neuroprotection in Parkinson's disease." Eur J Neurol **15 Suppl 1**: 5-13.

Schulte, T., L. Schols, T. Muller, D. Woitalla, K. Berger and R. Kruger (2002). "Polymorphisms in the interleukin-1 alpha and beta genes and the risk for Parkinson's disease." Neurosci Lett **326**(1): 70-2.

Seeman, P., T. Lee, M. Chau-Wong and K. Wong (1976). "Antipsychotic drug doses and neuroleptic/dopamine receptors." Nature **261**(5562): 717-9.

Selemon, L. D. and P. S. Goldman-Rakic (1985). "Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey." J Neurosci **5**(3): 776-94.

Semba, K. and H. C. Fibiger (1992). "Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study." J Comp Neurol **323**(3): 387-410.

Sesack, S. R., C. Aoki and V. M. Pickel (1994). "Ultrastructural localization of D2 receptor-like immunoreactivity in midbrain dopamine neurons and their striatal targets." J Neurosci **14**(1): 88-106.

Smith, A. D. and J. P. Bolam (1990a). "The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones." Trends Neurosci **13**(7): 259-65.

Smith, Y. and J. P. Bolam (1990b). "The output neurones and the dopaminergic neurones of the substantia nigra receive a GABA-containing input from the globus pallidus in the rat." J Comp Neurol **296**(1): 47-64.

Sokoloff, P., B. Giros, M. P. Martres, M. L. Bouthenet and J. C. Schwartz (1990). "Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics." Nature **347**(6289): 146-51.

Spano, P. F., S. Govoni and M. Trabucchi (1978). "Studies on the pharmacological properties of dopamine receptors in various areas of the central nervous system." Adv Biochem Psychopharmacol **19**: 155-65.

Sprouse, J. S. and G. K. Aghajanian (1986). "(-)-Propranolol blocks the inhibition of serotonergic dorsal raphe cell firing by 5-HT1A selective agonists." Eur J Pharmacol **128**(3): 295-8.

Sprouse, J. S. and G. K. Aghajanian (1987). "Electrophysiological responses of serotoninergic dorsal raphe neurons to 5-HT1A and 5-HT1B agonists." Synapse **1**(1): 3-9.

St-Hilaire, M., E. Landry, D. Levesque and C. Rouillard (2005). "Denervation and repeated L-DOPA induce complex regulatory changes in neurochemical phenotypes of striatal neurons: implication of a dopamine D1-dependent mechanism." Neurobiol Dis **20**(2): 450-60.

Stanford, I. M. and M. G. Lacey (1996). "Differential actions of serotonin, mediated by 5-HT1B and 5-HT2C receptors, on GABA-mediated synaptic input to rat substantia nigra pars reticulata neurons in vitro." J Neurosci **16**(23): 7566-73.

Starkey, S. J. and M. Skingle (1994). "5-HT1D as well as 5-HT1A autoreceptors modulate 5-HT release in the guinea-pig dorsal raphe nucleus." Neuropharmacology **33**(3-4): 393-402.

Starr, M. (1987). "Opposing roles of dopamine D1 and D2 receptors in nigral gamma-[3H]aminobutyric acid release?" J Neurochem **49**(4): 1042-9.

Stefani, A., A. M. Lozano, A. Peppe, P. Stanzione, S. Galati, D. Tropepi, M. Pierantozzi, L. Brusa, E. Scarnati and P. Mazzone (2007). "Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease." Brain **130**(Pt 6): 1596-607.

Stein, J. F. (2009). "Akinesia, motor oscillations and the pedunculopontine nucleus in rats and men." Exp Neurol **215**(1): 1-4.

Sullivan, M. A., H. Chen and H. Morikawa (2008). "Recurrent inhibitory network among striatal cholinergic interneurons." J Neurosci **28**(35): 8682-90.

Sunahara, R. K., H. C. Guan, B. F. O'Dowd, P. Seeman, L. G. Laurier, G. Ng, S. R. George, J. Torchia, H. H. Van Tol and H. B. Niznik (1991). "Cloning of the gene for a human dopamine D5 receptor with higher affinity for dopamine than D1." Nature **350**(6319): 614-9.

Surmeier, D. J., J. Eberwine, C. J. Wilson, Y. Cao, A. Stefani and S. T. Kitai (1992). "Dopamine receptor subtypes colocalize in rat striatonigral neurons." Proc Natl Acad Sci U S A **89**(21): 10178-82.

Surmeier, D. J. and S. T. Kitai (1994). "Dopaminergic regulation of striatal efferent pathways." Curr Opin Neurobiol **4**(6): 915-9.

Surmeier, D. J., W. J. Song and Z. Yan (1996). "Coordinated expression of dopamine receptors in neostriatal medium spiny neurons." J Neurosci **16**(20): 6579-91.

Sveinbjornsdottir, S., A. A. Hicks, T. Jonsson, H. Petursson, G. Gugmundsson, M. L. Frigge, A. Kong, J. R. Gulcher and K. Stefansson (2000). "Familial aggregation of Parkinson's disease in Iceland." N Engl J Med **343**(24): 1765-70.

Szczypka, M. S., R. J. Mandel, B. A. Donahue, R. O. Snyder, S. E. Leff and R. D. Palmiter (1999). "Viral gene delivery selectively restores feeding and prevents lethality of dopamine-deficient mice." Neuron **22**(1): 167-78.

Takada, M., H. Tokuno, Y. Ikai and N. Mizuno (1994). "Direct projections from the entopeduncular nucleus to the lower brainstem in the rat." J Comp Neurol **342**(3): 409-29.

Takakusaki, K., T. Habaguchi, J. Ohtinata-Sugimoto, K. Saitoh and T. Sakamoto (2003). "Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction." Neuroscience **119**(1): 293-308.

Takakusaki, K., J. Oohinata-Sugimoto, K. Saitoh and T. Habaguchi (2004). "Role of basal ganglia-brainstem systems in the control of postural muscle tone and locomotion." Prog Brain Res **143**: 231-7.

Takakusaki, K., N. Tomita and M. Yano (2008). "Substrates for normal gait and pathophysiology of gait disturbances with respect to the basal ganglia dysfunction." J Neurol **255 Suppl 4**: 19-29.

Tanaka, H., K. Kannari, T. Maeda, M. Tomiyama, T. Suda and M. Matsunaga (1999). "Role of serotonergic neurons in L-DOPA-derived extracellular dopamine in the striatum of 6-OHDA-lesioned rats." Neuroreport **10**(3): 631-4.

Tarazi, F. I., A. Campbell, S. K. Yeghiayan and R. J. Baldessarini (1998). "Localization of dopamine receptor subtypes in corpus striatum and nucleus accumbens septi of rat brain: comparison of D1-, D2-, and D4-like receptors." Neuroscience **83**(1): 169-76.

Tepper, J. M. and J. P. Bolam (2004). "Functional diversity and specificity of neostriatal interneurons." Curr Opin Neurobiol **14**(6): 685-92.

Tepper, J. M., T. Koos and C. J. Wilson (2004). "GABAergic microcircuits in the neostriatum." Trends Neurosci **27**(11): 662-9.

Tepper, J. M., L. P. Martin and D. R. Anderson (1995). "GABAA receptor-mediated inhibition of rat substantia nigra dopaminergic neurons by pars reticulata projection neurons." J Neurosci **15**(4): 3092-103.

Tepper, J. M., B. C. Sun, L. P. Martin and I. Creese (1997). "Functional roles of dopamine D2 and D3 autoreceptors on nigrostriatal neurons analyzed by antisense knockdown in vivo." J Neurosci **17**(7): 2519-30.

Terman, D., J. E. Rubin, A. C. Yew and C. J. Wilson (2002). "Activity patterns in a model for the subthalamopallidal network of the basal ganglia." J Neurosci **22**(7): 2963-76.

Ternaux, J. P., F. Hery, S. Bourgoin, J. Adrien, J. Glowinski and M. Hamon (1977). "The topographical distribution of serotoninergic terminals in the neostriatum of the rat and the caudate nucleus of the cat." Brain Res **121**(2): 311-26.

Tillerson, J. L., W. M. Caudle, M. E. Reveron and G. W. Miller (2002). "Detection of behavioral impairments correlated to neurochemical deficits in mice treated with moderate doses of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine." Exp Neurol **178**(1): 80-90.

Timmerman, W. and E. D. Abercrombie (1996). "Amphetamine-induced release of dendritic dopamine in substantia nigra pars reticulata: D1-mediated behavioral and electrophysiological effects." Synapse **23**(4): 280-91.

Timmerman, W. and B. H. Westerink (1995). "Extracellular gamma-aminobutyric acid in the substantia nigra reticulata measured by microdialysis in awake rats: effects of various stimulants." Neurosci Lett **197**(1): 21-4.

Tretiakoff, K. (1919). "Contribution a l'Etude de L'Anatomie pathologique du Locus Niger de Soemmering avec quelques déductions relatives a` la pathogénie des troubles du tonus musculaire et De La Maladie de Parkinson." Doctoral Thesis, Univ. Paris.

Trevitt, J. T., B. B. Carlson, K. Nowend and J. D. Salamone (2001). "Substantia nigra pars reticulata is a highly potent site of action for the behavioral effects of the D1 antagonist SCH 23390 in the rat." Psychopharmacology (Berl) **156**(1): 32-41.

Trevitt, T., B. Carlson, M. Correa, A. Keene, M. Morales and J. D. Salamone (2002). "Interactions between dopamine D1 receptors and gamma-aminobutyric acid mechanisms in substantia nigra pars reticulata of the rat: neurochemical and behavioral studies." Psychopharmacology (Berl) **159**(3): 229-37.

Udenfriend, S. and C. R. Creveling (1959). "Localization of dopamine-beta-oxidase in brain." J Neurochem **4**: 350-2.

Ueki, A. (1983). "The mode of nigro-thalamic transmission investigated with intracellular recording in the cat." Exp Brain Res **49**(1): 116-24.

Ungerstedt, U. (1968). "6-Hydroxy-dopamine induced degeneration of central monoamine neurons." Eur J Pharmacol **5**(1): 107-10.

Ungerstedt, U. (1971a). "Postsynaptic supersensitivity after 6-hydroxy-dopamine induced degeneration of the nigro-striatal dopamine system." Acta Physiol Scand Suppl **367**: 69-93.

Ungerstedt, U. (1971b). "Stereotaxic mapping of the monoamine pathways in the rat brain." Acta Physiol Scand Suppl **367**: 1-48.

Usiello, A., J. H. Baik, F. Rouge-Pont, R. Picetti, A. Dierich, M. LeMeur, P. V. Piazza and E. Borrelli (2000). "Distinct functions of the two isoforms of dopamine D2 receptors." Nature **408**(6809): 199-203.

van der Kooy, D. and T. Hattori (1980). "Dorsal raphe cells with collateral projections to the caudate-putamen and substantia nigra: a fluorescent retrograde double labeling study in the rat." Brain Res **186**(1): 1-7.

Van Tol, H. H., J. R. Bunzow, H. C. Guan, R. K. Sunahara, P. Seeman, H. B. Niznik and O. Civelli (1991). "Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine." Nature **350**(6319): 610-4.

Wang, Y., R. Xu, T. Sasaoka, S. Tonegawa, M. P. Kung and E. B. Sankoorikal (2000). "Dopamine D2 long receptor-deficient mice display alterations in striatum-dependent functions." J Neurosci **20**(22): 8305-14.

Wang, Z., L. Kai, M. Day, J. Ronesi, H. H. Yin, J. Ding, T. Tkatch, D. M. Lovinger and D. J. Surmeier (2006). "Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons." Neuron **50**(3): 443-52.

Westerink, B. H. and W. Timmerman (1999). "Do neurotransmitters sampled by brain microdialysis reflect functional release? Analytica chimica acta 379(3):263-274."

Westin, J. E., H. S. Lindgren, J. Gardi, J. R. Nyengaard, P. Brundin, P. Mohapel and M. A. Cenci (2006). "Endothelial proliferation and increased blood-brain barrier permeability in the basal ganglia in a rat model of 3,4-dihydroxyphenyl-L-alanine-induced dyskinesia." J Neurosci **26**(37): 9448-61.

Westin, J. E., L. Vercammen, E. M. Strome, C. Konradi and M. A. Cenci (2007). "Spatiotemporal pattern of striatal ERK1/2 phosphorylation in a rat model of L-DOPA-induced dyskinesia and the role of dopamine D1 receptors." Biol Psychiatry **62**(7): 800-10.

Wilson, C. J., P. M. Groves and E. Fifkova (1977). "Monoaminergic synapses, including dendro-dendritic synapses in the rat substantia nigra." Exp Brain Res **30**(2-3): 161-74.

Winkler, C., D. Kirik, A. Bjorklund and M. A. Cenci (2002). "L-DOPA-induced dyskinesia in the intrastriatal 6-hydroxydopamine model of parkinson's disease: relation to motor and cellular parameters of nigrostriatal function." Neurobiol Dis **10**(2): 165-86.

Winkler, C., D. Kirik and A. Björklund (2005). "Cell transplantation in Parkinson's disease: how can we make it work?" Trends Neurosci **28**(2): 86-92.

Wise, R. A. and P. P. Rompre (1989). "Brain dopamine and reward." Annu Rev Psychol **40**: 191-225.

Vizi, E. S. (1982). "Non-synaptic intercellular communication: presynaptic inhibition." Acta Biol Acad Sci Hung **33**(2-3): 331-51.

Woolf, N. J. and L. L. Butcher (1986). "Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain." Brain Res Bull **16**(5): 603-37.

Voss, T. and B. Ravina (2008). "Neuroprotection in Parkinson's disease: myth or reality?" Curr Neurol Neurosci Rep **8**(4): 304-9.

Wotjak, C. T., J. Ganster, G. Kohl, F. Holsboer, R. Landgraf and M. Engelmann (1998). "Dissociated central and peripheral release of vasopressin, but not oxytocin, in response to repeated swim stress: new insights into the secretory capacities of peptidergic neurons." Neuroscience **85**(4): 1209-22.

Xiao, D., E. Bastia, Y. H. Xu, C. L. Benn, J. H. Cha, T. S. Peterson, J. F. Chen and M. A. Schwarzschild (2006). "Forebrain adenosine A2A receptors contribute to L-3,4-dihydroxyphenylalanine-induced dyskinesia in hemiparkinsonian mice." J Neurosci **26**(52): 13548-55.

Yin, H. H. and B. J. Knowlton (2006). "The role of the basal ganglia in habit formation." Nat Rev Neurosci **7**(6): 464-76.

Yoshida, M. and W. Precht (1971). "Monosynaptic inhibition of neurons of the substantia nigra by caudato-nigral fibers." Brain Res **32**(1): 225-8.

Yurek, D. M. and S. B. Hipkens (1993). "Intranigral injections of SCH 23390 inhibit amphetamine-induced rotational behavior." Brain Res **623**(1): 56-64.

Yurek, D. M. and S. B. Hipkens (1994). "Intranigral injections of SCH 23390 inhibit SKF 82958-induced rotational behavior." Brain Res **639**(2): 329-32.

Zapata, A., J. M. Witkin and T. S. Shippenberg (2001). "Selective D3 receptor agonist effects of (+)-PD 128907 on dialysate dopamine at low doses." Neuropharmacology **41**(3): 351-9.

Zhang, Q. J., J. Liu, Y. Wang, S. Wang, Z. H. Wu, W. Yan, Y. P. Hui and U. Ali (2008). "The firing activity of presumed cholinergic and non-cholinergic neurons of the pedunculopontine nucleus in 6-hydroxydopamine-lesioned rats: an in vivo electrophysiological study." Brain Res **1243**: 152-60.

Zheng, F. and S. W. Johnson (2003). "Metabotropic glutamate and muscarinic cholinergic receptor-mediated preferential inhibition of N-methyl-D-aspartate component of transmissions in rat ventral tegmental area." Neuroscience **116**(4): 1013-20.

Zhou, F. C., S. Bledsoe and J. Murphy (1991). "Serotonergic sprouting is induced by dopamine-lesion in substantia nigra of adult rat brain." Brain Res **556**(1): 108-16.