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The serotonergic system in Parkinson's disease

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ABSTRACT

Although the cardinal manifestations of Parkinson's disease (PD) are attributed to a decline in dopamine levels in the striatum, a breadth of non-motor features and treatment-related complications in which the serotonergic system plays a pivotal role are increasingly recognised. Serotonin (5-HT)-mediated neurotransmission is altered in PD and the roles of the different 5-HT receptor subtypes in disease manifestations have been investigated. The aims of this article are to summarise and discuss all published preclinical and clinical studies that have investigated the serotonergic system in PD and related animal models, in order to recapitulate the state of the current knowledge and to identify areas that need further research and understanding.

Contents

Abbreviations: [^{3}H], tritiated; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; 5-HTP, 5-hydroxytryptophan; 5-MDOT (5-MeO-DMT), 5-methoxy-N,N-dimethyltryptamine; 5,7-DHT, 5,7-dihydroxytryptamine; 6-OHDA, 6-hydroxydopamine; AADC, aromatic L-amino acid decarboxylase; AIMs, abnormal involuntary movements; BA, Brodmann area; BBC, British Broadcasting Corporation; bid, twice daily; CSF, cerebrospinal fluid; DOI, (±)-2,5-dimethoxy-4-iodoamphetamine; DOPA, dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid; DRN, dorsal raphe nucleus; dyn, dynorphin; EC_{50}, half-maximal effective concentration; enk, enkephalin; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; GP, globus pallidus; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; id, in die (once daily); -ir, immunoreactive; ISH, *in situ* hybridisation; i.v., intravenous; K_d, dissociation constant; KO, knockout; L-, levo; LDAEP, loudness dependence of auditory evoked potentials; LDL, low-density lipoprotein; L-DOPA, L-3,4-dihydroxyphenylalanine (levodopa); mCPP, 1-(*m*-chlorophenyl)piperazine; MDMA, 3,4-methylenedioxymethamphetamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRN, median raphe nucleus; mRNA, messenger ribonucleic acid; MTP, 1-methyl-1,2,3,6-tetrahydropyridine; NHP, non-human primate; nM, nanomole; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; $pERK_{1/2}$, phosphorylated extracellular signal-related kinase isoforms 1 and 2; PET, positron-emission tomography; PK, pharmacokinetic; PPD, preprodynorphin; PPE, preproenkephalin; PPT, preprotachykinin; R-, rectus (right); RBD, REM-sleep behaviour disorder; REM sleep, rapid-eye-movement sleep; SERT, serotonin transporter; SLC6A4, solute carrier family 6, member 4; SN, substantia nigra; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; SP, substance P; SPECT, single-photon emission computed tomography; STN, subthalamic nucleus; TPH, tryptophan hydroxylase; UPDRS, Unified Parkinson's Disease Rating Scale; VH, visual hallucinations; VMAT, vesicular monoaminergic transporter; VTA, ventral tegmental area.

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1. Introduction

Parkinson's disease (PD) was described in 1817 by the British physician James Parkinson (2002). The cardinal motor manifestations of PD, rigidity, tremor, bradykinesia, are secondary to a deficiency of dopamine in the striatum (Marsden, 1982). Dopamine replacement therapy with L-3,4-dihydroxyphenylalanine (L-DOPA) remains the mainstay of PD treatment (Barbeau, 1962, 1969; Cotzias, 1969; Cotzias et al., 1969a,b, 1967; Fahn, 2008; Hornykiewicz, 2002), as it alleviates motor symptoms, but its long-term administration is marred by motor complications such as dyskinesia and wearing-OFF (Bezard et al., 2001; Cenci, 2007; Cenci and Lindgren, 2007; Fabbrini et al., 2007; Fox and Lang, 2008; Jenner, 2008; Obeso et al., 2000). In addition, a range of non-motor symptoms such as depression (Lim et al., 2009; Shiba et al., 2000), impulse-control disorders (Black and Friedman, 2006; Pontone et al., 2006; Voon et al., 2006) and psychotic features (Diederich et al., 2005; Fenelon et al., 2000) are increasingly recognised in PD and contribute significantly to the disability of the patients as the disease progresses (Hely et al., 2005). In a follow-up report of the Sydney Multicenter Study of Parkinson's disease, 15 years after the diagnosis of PD, 95% of patients experienced dyskinesia, whereas 50% experienced hallucinations and depression. According to the results of this study, these non-motor symptoms were more disabling than the motor complications (Hely et al., 2005). Accordingly, an epidemiological study found that PD psychosis requiring antipsychotic therapy is frequently associated with death, nursing home placement, as well as development and progression of dementia (Factor et al., 2003). As will be seen in this review article, the serotonergic system, which undergoes degeneration in PD, is involved in the pathogenesis of these aforementioned symptoms and modulating serotonin (5-HT)-mediated neurotransmission has been the focus of many preclinical and clinical studies which aimed at alleviating both motor and non-motor symptoms of PD.

The aims of this review article are to summarise and discuss all published preclinical and clinical studies that investigated the serotonergic system in PD. We tried to be as exhaustive as possible. Thus, 5-HT, its metabolite 5-hydroxyindoleacetic acid (5-HIAA), its synthesising enzyme tryptophan hydroxylase (TPH), the 5-HT transporter (SERT), as well as the 14 subtypes of 5-HT receptors are discussed. For each of these, we provide a brief description of their physiology and anatomical distribution, a description of the changes occurring in PD and animal models of PD, as well as an overview of the preclinical studies and clinical trials that targeted each in an attempt to alleviate either parkinsonism, dyskinesia and/or non-motor complications.

Table 1
Keywords used for literature search.

3,4-Methylenedioxymethamphetamine, 5-HT, 5-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_2, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D}, 5-HT_{3E}, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, 5-HTP, 5-hydroxytryptamine, 5-hydroxytryptophan, 5-MDOT, 5-MeO-DMT, 6-OHDA, 6-OHDA-lesioned mouse, 6-OHDA-lesioned rat, 8-OH-DPAT, ACP-103, affinity, AIMs, anxiety, aripiprazole, atypical antipsychotic, autoradiography, basal ganglia, binding, BMY-14,802, bradykinesia, brain, buspirone, cardiac fibrosis, cardiac valvular fibrosis, catalepsy, catecholamine, caudate, cisapride, clozapine, common marmoset, cortex, CP-94,253, cyproheptadine, depression, DOI, dopamine, dopamine dysregulation syndrome, dyskinesia, EC_{50}, Ecstasy, fibrosis, flesinoxan, flibanserin, GABA, gambling, gamma-aminobutyric acid, globus pallidus, glutamate, haloperidol, hallucinations, IC_{50}, immunohistochemistry, *in situ* hybridisation, JL-18, K_d, ketanserin, Ki, L-3,4-dihydroxyphenylalanine, L-DOPA, levodopa, M100,907, macaque, marmoset, mCPP, MDL100,907, MDMA, melperone, mesulergine, methysergide, mianserin, mirtazapine, monkey, mood disorder, mosapride, mouse, MPTP, MPTP-lesioned macaque, MPTP-lesioned marmoset, MPTP-lesioned monkey, MPTP-lesioned mouse, MPTP-lesioned primate, mRNA, *N*-desmethylclozapine, non-human primate, noradrenaline, olanzapine, ondansetron, ON-time, oxidopamine, parachlorophenylalanine, pardoprunox, parkinsonian, parkinsonism, Parkinson's disease, PET, piclozotan, pimavanserin, polymorphism, post mortem, potency, primate, psychosis, putamen, quetiapine, R-(+)-8-OH-DPAT, rat, receptor, receptor binding, reserpine, rigidity, risperidone, ritanserin, rodent, rotation, rotational behaviour, RS-102,221, sarizotan, SB-200,646A, SB-206,553, SB-224,289-A, SB-228,357, serotonin, serotonin receptor, serotonin transporter, SERT, shortened motor response, SKF-99,101-H, SPECT, substantia nigra, subthalamic nucleus, tacrine, tandospirone, tegaserod, thalamus, tremor, valvular fibrosis, visual hallucinations, volinanserin, wearing-OFF, and ziprasidone.

2. Methods

Literature was searched through PubMed (http://www.ncbi.nlm.nih.gov/PubMed/) and cross-referencing. Genetic information was gathered from the Online Mendelian Inheritance in Man (OMIM, http://www.ncbi.nlm.nih.gov/omim) website and cross-referencing. Extended search was performed using Google (http://www.google.ca). An update on the on-going clinical trials was found on the National Institute of Health (http://clinicaltrials.gov/), Parkinson Pipeline Project (http://www.pdpipeline.org/), PD trials (http://www.pdtrials.org/), PD Online Research (http://www.pdonlineresearch.org/) and Michael J Fox Foundation (http://www.michaeljfox.org/) websites. In addition, abstracts from the American Academy of Neurology, American Neurological Association, Movement Disorders Society, Society for Neuroscience and World Parkinson Congress from the 2007–2011 annual meetings (included, when applicable) were thoroughly reviewed. Keywords used for the literature search are displayed in Table 1.

Several of the compounds used as dopamine agonists, such as lisuride and rotigotine, exhibit high affinity for the 5-HT receptors (Egan et al., 1998; Marona-Lewicka et al., 2002; Newman-Tancredi et al., 2002a,b; Nishio et al., 1996; Scheller et al., 2009). However, because these agents are not used primarily as 5-HT-modulating drugs in PD, they are not discussed in this article. For similar reasons, the dopamine antagonist metoclopramide, which exhibits moderate/high affinity for 5-HT_3 and 5-HT_4 receptors (Hoyer, 1990; Rizzi et al., 1997), is not included in this review article. Monoamine re-uptake inhibitors, whether selective for SERT or exhibiting affinity for SERT and the noradrenaline and/or dopamine transporters, are not addressed in this review, as they will be covered separately (Huot et al., in preparation). Except for a few studies, the haloperidol-induced catalepsy and reserpine-treated rat models of PD are not discussed, because the two conditions differ markedly from idiopathic PD, the former being a transient and postsynaptic form of parkinsonism, the latter being a transient form of parkinsonism, both conditions without on-going neurodegeneration. For similar reasons, the effects of 5-HT-modulating compounds on drug-induced parkinsonism, except for cases relating to a deterioration of a pre-existing idiopathic PD after introduction of drug therapy, are not discussed.

These excluded topics being mentioned, the current review article includes all of the post mortem and pharmacological studies relating to the 5-HT system performed in human subjects suffering from idiopathic PD. All studies relating to the 5-HT system performed in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned mouse and non-human primate (NHP) and the 6-hydroxydopamine (6-OHDA)-lesioned mouse and rat are also reviewed.

Unless specified otherwise, the term L-DOPA refers to the combination of L-DOPA and an aromatic L-amino acid decarboxylase (AADC, DOPA decarboxylase) inhibitor such as benserazide or carbidopa. Unless specified otherwise, the term striatum refers to the definition provided in the 9th edition of the classic Carpenter's Human Neuroanatomy textbook (Parent, 1996) and encompasses each of the caudate nucleus, putamen and ventral striatum, the latter structure including the nucleus accumbens and the deep portions of the olfactory tubercle.

3. Serotonin

5-HT was first identified by Vittorio Erspamer in the 1930s, when he demonstrated that extracts from enterochromaffin cells induced intestinal contractions. As 5-HT was initially isolated from the enterochromaffin cells of the intestine, it was named enteramine (Erspamer and Vialli, 1937). Pioneering work was done during the next two decades: 5-HT was crystallised and isolated outside of the gastro-intestinal tract, notably in the blood and its actions on organs such as the heart were characterised (Erspamer, 1946, 1948; Erspamer and Boretti, 1951; Erspamer and Ghiretti, 1951; Erspamer and Ottolenghi, 1951; Erspamer and Vialli, 1951; Rapport, 1949; Rapport et al., 1948a,b). The term "serotonin" was coined to describe 5-HT in 1948, when referring to the "serum vasoconstrictor" (Rapport et al., 1948c). Enteramine and 5-HT were recognised as a single entity in 1952 (Erspamer and Asero, 1952). The presence of 5-HT in the brain was demonstrated in 1953 (Twarog and Page, 1953) and in 1954, a relation between 5-HT and psychiatric disorders was suggested (Woolley and Shaw, 1954). Since then, the knowledge of 5-HT has greatly evolved and it is now known that 5-HT mediates several key functions in the body, such as regulation of gastro-intestinal motility, respiration, pain, vasoconstriction and platelet aggregation (Berger et al., 2009).

5-HT neurons in the brain were first mapped by Dahlstroem and Fuxe (1964). In the brain, serotonergic cell bodies are located in the raphe nuclei of the brainstem (areas B_1–B_9, including the nucleus raphe centralis superioralis, dorsalis, magnus, obscurus and pontis) in the rat (Dahlstroem and Fuxe, 1964; Hillarp et al., 1966; Parent et al., 1981; Saavedra, 1977), cat (Poitras and Parent, 1978) and NHP (Jacobowitz and MacLean, 1978; Schofield and Dixson, 1982; Schofield and Everitt, 1981; Sladek et al., 1982). A minority of serotonergic neurons are also found outside of the raphe complex (Poitras and Parent, 1978; Sladek et al., 1982). Raphe nuclei provide 5-HT innervation to the entire brain, including the substantia nigra (SN) (Dray et al., 1976; Fibiger and Miller, 1977; Imai et al., 1986; Lavoie and Parent, 1990), striatum (Imai et al., 1986; Lavoie and Parent, 1990; Miller et al., 1975; Pasik and Pasik, 1982; Steinbusch et al., 1980; van der Kooy and Hattori, 1980), globus pallidus (GP) (Charara and Parent, 1994; Lavoie and Parent, 1990), subthalamic nucleus (STN) (Lavoie and Parent, 1990; Mori et al., 1985), thalamus (Moore et al., 1978) and cortex (Bobillier et al., 1976; Seguela et al., 1989), the core structures of the cortico-basal ganglia-thalamo-cortical loop (Parent and Hazrati, 1995a,b), the physiology of which is disrupted in PD (DeLong, 1990; DeLong and Wichmann, 2007; Parent et al., 2000). The classic model of the basal ganglia circuitry is depicted in Fig. 1.

In the normal human brain, the highest 5-HT levels – assessed by liquid chromatography – are encountered in the brainstem, followed by the hypothalamus and the striatum. Within the cerebral cortex, 5-HT levels are highest in the orbitofrontal and cingulate areas (Bertler, 1961; Mackay et al., 1978). In the normal human, the majority of 5-HT innervation of the basal ganglia comes from the dorsal and, to a lesser extent, the medial raphe nuclei (Parent et al., 2011; Wallman et al., 2011).

Several functions have been attributed to 5-HT in the brain, such as cognition, emotion, motor behaviour and regulation of the circadian rhythm (Benarroch, 2009; Berger et al., 2009; Gerson and Baldessarini, 1980). However, inasmuch as these functions are mediated by the interaction of 5-HT with its receptors, they will be discussed in the corresponding 5-HT receptor sections (*vide infra*).

TPH, the rate-limiting enzyme in 5-HT synthesis, exists in two isoforms, TPH_1 and TPH_2. TPH_1 is expressed in the gastro-intestinal

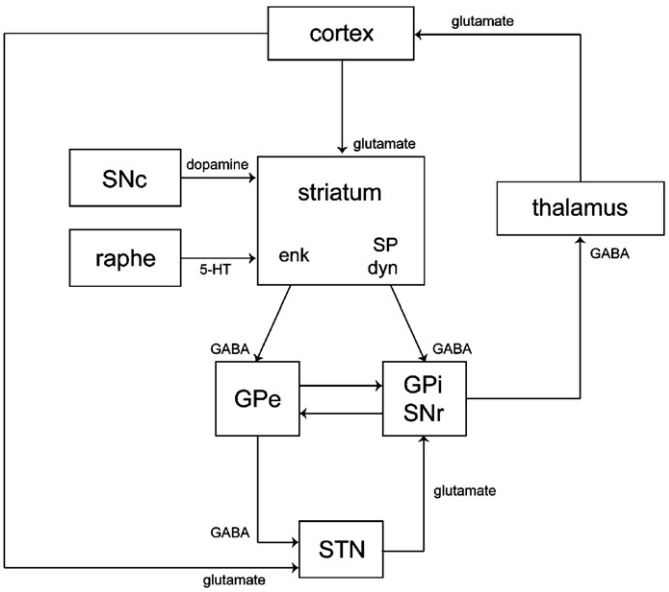

Fig. 1. According to the classic model of the basal ganglia, the cortex sends excitatory glutamatergic inputs to the striatum. These inputs are modulated by nigrostriatal dopaminergic projections which exert an inhibitory effect, via D_2 receptors, on enk-containing striatofugal neurons of the indirect pathway and an excitatory effect, via D_1 receptors, on SP/dyn-containing striatofugal neurons of the direct pathway. In the direct pathway, striatofugal neurons send inhibitory GABAergic projections to the output structures of the basal ganglia, the GPi and SNr, which emit GABAergic fibres towards the ventral tier (ventrolateral and ventral anterior nuclei) of the thalamus. In the indirect pathway, striatofugal GABAergic axons contact the GPe, which sends GABAergic fibres towards the STN. The STN then emits glutamatergic axons towards the output structures of the basal ganglia. Glutamatergic thalamocortical fibres complete the loop. Reciprocal GABAergic fibres connect the GPe and the GPi/SNr complex. The direct and indirect pathways exert opposite effects on movement and an imbalance in their activity is believed to lead to hypokinetic (*i.e.* parkinsonism) or hyperkinetic (*i.e.* dyskinesia) movement disorders. Although not traditionally part of the classical model of the basal ganglia, cortico-STN projections, sometimes referred to as the "hyperdirect pathway", have been added to the illustration (DeLong, 1990; DeLong and Wichmann, 2007; Koprich et al., 2009; Parent, 1990; Parent and Hazrati, 1995a,b; Parent et al., 2000). Likewise, because of their importance in the present review article, serotonergic raphestriatal projections have also been included in the figure.
5-HT: 5-hydroxytryptamine (serotonin); dyn: dynorphin; enk: enkephalin; GABA: gamma-aminobutyric acid; GPe: globus pallidus pars externa; GPi: globus pallidus pars interna; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; SP: substance P; STN: subthalamic nucleus.

tract, pineal gland, spleen and thymus, whereas TPH_2 is expressed selectively in the brain (Sakowski et al., 2006; Walther and Bader, 2003; Walther et al., 2003).

3.1. Serotonin, 5-HIAA, and tryptophan hydroxylase in Parkinson's disease

3.1.1. Serotonin, 5-HIAA and tryptophan hydroxylase in idiopathic Parkinson's disease

As mentioned in Section 1, the serotonergic system is affected in PD. Several studies have demonstrated neuronal loss and dystrophic neurites in the 5-HT-producing raphe nuclei in PD (Gai et al., 1995; Gibb, 1989; Halliday et al., 1990a,b; Paulus and Jellinger, 1991) and Lewy bodies are present within serotonergic raphe neurons (Halliday et al., 1990b; Mann and Yates, 1983; Ohama and Ikuta, 1976). According to the Braak staging of PD, raphe nuclei become affected in Stage 2 and the raphe complex is entirely involved in Stage 3 (Braak et al., 2003, 2004). Neurons from the median raphe nucleus (MRN), which innervate the thalamus (Lavoie and Parent, 1991), and from the pontine reticular formation, are more severely affected than neurons from the nucleus raphe dorsalis (dorsal raphe nucleus, DRN) (Halliday et al., 1990a). The bulbar raphe nuclei – nuclei raphe magnus, obscurus and pallidus – also undergo degeneration, with the loss of pigment-laden neurons and PD-related cytoskeletal pathology (Braak et al., 2000). The neuronal loss in the DRN has been reported to be more severe in depressed than non-depressed PD patients, but there are no differences between demented and non-demented, psychotic and non-psychotic, or akineto-rigid and tremulous PD patients (Frisina et al., 2007, 2009; Paulus and Jellinger, 1991). Thus, to date, there appears to be few correlations between 5-HT cell loss and PD co-morbidities. However, these studies have been limited and further detailed clinicopathological studies are warranted.

The degenerative changes affecting raphe serotonergic neurons lead to a secondary reduction in 5-HT levels. A study using the loudness dependence of auditory evoked potentials (LDAEP), which is considered a reliable marker of central 5-HT function (Hegerl et al., 2001), found evidence of decreased 5-HT function in untreated PD patients; this decrease was reversed 12 weeks after the initiation of L-DOPA therapy (Beucke et al., 2010). In a study presented as an abstract and using encephalofluctuography to measure cerebral neurotransmitter levels, 5-HT levels were not different between PD patients and controls (Wang et al., 2008), thus raising questions about the validity of encephalofluctuography to measure brain 5-HT levels in PD.

As illustrated in Fig. 2, 5-HT levels appear lower in certain brain areas in PD, including the caudate nucleus, putamen, GP, SN, hypothalamus and thalamus (Bernheimer et al., 1961, 1963; Fahn et al., 1971; Kish et al., 2008; Raisman et al., 1986; Scatton et al., 1983; Shannak et al., 1994; Wilson et al., 1996). In these areas, the percentage of 5-HT loss can be as high as 85% in some PD patients (Fahn et al., 1971). The caudate nucleus appears to be more denervated than the putamen (Kish et al., 2008; Wilson et al., 1996); interestingly, this pattern of 5-HT denervation is the opposite of dopamine denervation in PD, where the loss is more severe in the putamen than the caudate nucleus (Fahn et al., 1971). Striatal 5-HT levels do not appear to correlate with the presence of dyskinesia (Kish et al., 2008). In PD, 5-HT levels are also reduced in the frontal cortex (Brodmann area 9, BA_9), the cingulate cortex (BA_{24}), the hippocampus (BA_{34}) and the entorhinal cortex (BA_{28}) (Fig. 3). In these cortical areas, the decrease varies between 40 and 60% (D'Amato et al., 1987; Scatton et al., 1983). 5-HT levels also appear reduced, by 15–20%, in the cerebrospinal fluid (CSF) of PD patients and CSF 5-HT levels correlate negatively with bradykinesia, rigidity and freezing of gait (Tohgi et al., 1993a,b). 5-HT levels in the CSF appear further reduced after L-DOPA therapy, by >50%, when compared to untreated PD patients (Tohgi et al., 1993a). Tryptophan levels are unchanged in the CSF of PD patients, regardless of L-DOPA treatment (Tohgi et al., 1993a).

In spite of lower 5-HT levels in several brain areas in PD, 5-HT could participate in the neurodegenerative processes in PD. Thus, *in vitro*, 5-HT binds to and stabilises alpha (α)-synuclein aggregates of heterogeneous composition, leading to their accumulation (Falsone et al., 2011). In a similar way, TPH could also be involved in the underlying disease process in PD. Indeed, a study which recreated the oxidative environment of PD in cell cultures demonstrated that TPH_2 misfolds and aggregates under oxidative stress, leading the authors to suggest that TPH_2 might, under such circumstances, represent an endogenous neurotoxic protein to 5-HT neurons (Kuhn et al., 2010). Additional studies are needed to characterise further these phenomena, in particular to establish which receptors mediate these interactions and whether they occur or not *in vivo*, as they may have important therapeutic implications.

Levels of the 5-HT metabolite 5-HIAA have also been measured in several brain areas and in the CSF of PD patients. 5-HIAA levels are unaltered in the neocortex (D'Amato et al., 1987; Scatton et al.,

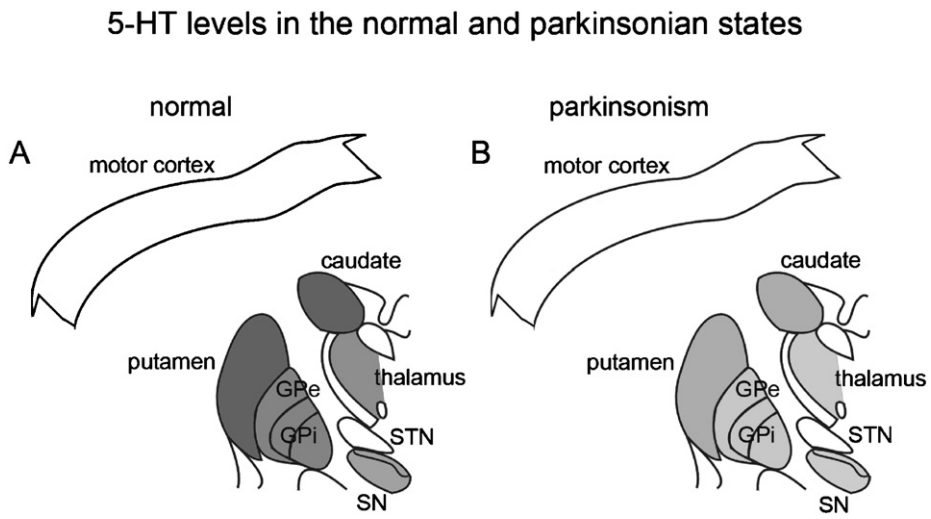

Fig. 2. Serotonergic raphe nuclei undergo degeneration in idiopathic PD, leading to a decrease in 5-HT levels in the basal ganglia. As illustrated, 5-HT levels are decreased (paler shades of grey) in the caudate nucleus, putamen, GP, SN and thalamus of PD patients (B) when compared to normal individuals (A). Although not depicted in this illustration, 5-HT levels are also decreased in the hypothalamus.
These illustrations are not representative of normal anatomy. Thus, although depicted in the figure, the SN and STN are more posterior in the reality.
GPe: globus pallidus pars externa; GPi: globus pallidus pars interna; SN: substantia nigra; STN: subthalamic nucleus.
Basal ganglia illustrations are adapted from Paxinos et al. (2008).

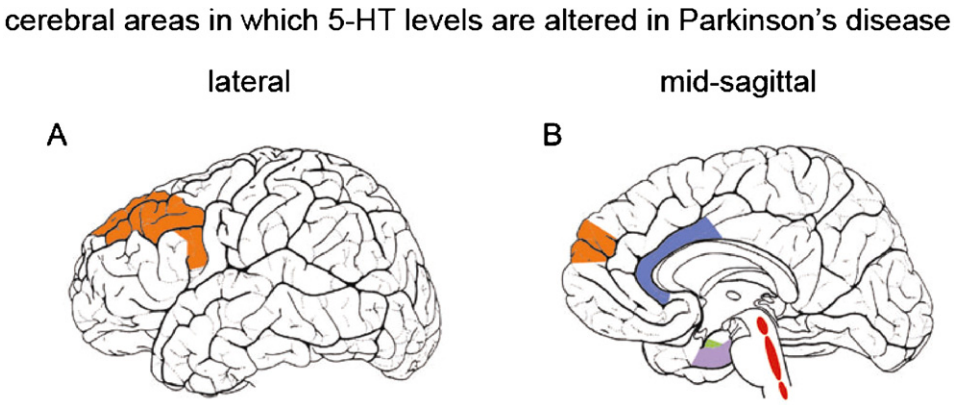

Fig. 3. Serotonergic neurons of the raphe complex (depicted in B, red) undergo degeneration in idiopathic PD, leading to 5-HT deficits in several cortical areas such as Brodmann area (BA) 9 (part of the frontal cortex, depicted in A and B, orange), BA_{24} (the anterior cingulate cortex, depicted in B, blue), BA_{28} (the entorhinal cortex, depicted in B, purple) and BA_{34} (the hippocampal formation, depicted in B, green).
Although not illustrated in this figure, 5-HT levels are significantly reduced in the inferior temporal cortex, the premotor and motor cortex and the primary sensory area of the parkinsonian non-human primate.
Brain illustrations are adapted from Mai et al. (2004).

1983), but are reduced (by 35–40%) in the hippocampus, caudate nucleus and putamen (Raisman et al., 1986; Scatton et al., 1983; Wilson et al., 1996). In the CSF, 5-HIAA levels are reduced in PD when compared to controls (Chase, 1970b,c; Davidson et al., 1977; Gershanik et al., 1978; Gottfries et al., 1969; Granerus et al., 1974; Guldberg et al., 1967; Johansson and Roos, 1967; Mayeux et al., 1984; Olsson and Roos, 1968; Rinne and Sonninen, 1972; Tohgi et al., 1993a,b). The effects of L-DOPA therapy on CSF 5-HIAA levels are unclear, since three studies demonstrated an increase in CSF 5-HIAA levels following L-DOPA intake (Chase, 1970b,c; Godwin-Austen et al., 1971), one found a further reduction (Gershanik et al., 1978) and two found no change (Davidson et al., 1977; Tohgi et al., 1993a). CSF 5-HIAA levels do not correlate with the severity of parkinsonism (Papeschi et al., 1972), age of patients or disease duration (Granerus et al., 1974; Johansson and Roos, 1967). There is possibly a correlation between depressive symptoms and lower CSF 5-HIAA levels (Mayeux et al., 1984), but this is controversial (Granerus et al., 1974). Patients who respond well to L-DOPA tend to have higher CSF 5-HIAA levels than those who respond poorly (Davidson et al., 1977). The administration of probenecid, a drug which reduces the outflow of 5-HIAA from the brain and CSF to the blood (Brodie et al., 1966; Guldberg et al., 1966), does not significantly alter CSF 5-HIAA levels in PD patients (Olsson and Roos, 1968; Vanderheyden et al., 1981). A study measuring urinary 5-HT and 5-HIAA excretion levels found no difference between PD patients and control subjects (Resnick et al., 1962).

The activity of TPH is decreased in the SN of PD patients, but not in other brain areas, including the striatum, GP, thalamus and raphe nuclei (Sawada et al., 1985), which seems at odds with the decrease in 5-HT levels reported in all of these cerebral regions and with the degeneration of the raphe complex in PD.

3.1.2. Serotonin, 5-HIAA and tryptophan hydroxylase in rodent models of Parkinson's disease

As in idiopathic PD, 5-HT levels are generally reduced in rodent models of PD. In the MPTP-lesioned mouse, 5-HT levels are

diminished in the somatosensory and medial prefrontal cortices (Ansah et al., 2007, 2009; Nayyar et al., 2009) and TPH levels are reduced in the frontal cortex (Nayyar et al., 2008). In the vesicular monoaminergic transporter (VMAT) type 2-deficient mouse model of PD, 5-HT levels are decreased and 5-HT turnover (ratio 5-HIAA/5-HT) is increased in the striatum, cortex and hippocampus (Taylor et al., 2009). In the $VMAT_2$-deficient mouse, there is degeneration of the DRN with accumulation of α-synuclein (Alter et al., 2010). In spite of this reduction in 5-HT levels in the striatum of MPTP-lesioned mice, a 5-HT hyperinnervation seems to occur and this 5-HT-immunoreactive (-ir) fibres sprouting negatively correlates with behavioural recovery from the lesion (Rozas et al., 1998). 5-HT hyperinnervation also occurs in the striatum of the pituitary homeobox 3 (Pitx3)-deficient mouse, in which SNc neurons progressively degenerate during development (Smits et al., 2008).

In the adult 6-OHDA-lesioned rat, there is controversy regarding striatal 5-HT and 5-HIAA levels, some studies suggesting they are decreased, with an increase in 5-HT turnover (Brannan et al., 1990; Karstaedt et al., 1994), other studies suggesting that both 5-HT and 5-HIAA levels are unaltered by the lesion (Breese et al., 1984; Erinoff and Snodgrass, 1986; Eskow Jaunarajs et al., 2010b; Gil et al., 2010; Iwamoto et al., 1976; Navailles et al., 2010a). However, other studies have demonstrated sprouting of 5-HT-ir fibres and increased 5-HT levels in the striatum of adult (Commins et al., 1989; Maeda et al., 2003; Zhou et al., 1991) and increased 5-HT levels in the striatum and cortex of young (Breese et al., 1984; Descarries et al., 1992; Dewar et al., 1990; Erinoff and Snodgrass, 1986; Luthman et al., 1987; Snyder et al., 1986; Stachowiak et al., 1984; Towle et al., 1989) 6-OHDA-lesioned rats. To add to the confusion, another study suggested a reduction in 5-HT-ir fibres in the striatum of adult 6-OHDA-lesioned rats (Takeuchi et al., 1991). 5-HT and 5-HIAA levels appear unchanged in the frontal and prefrontal cortices and hippocampus of the 6-OHDA-lesioned rat (Erinoff and Snodgrass, 1986; Eskow Jaunarajs et al., 2010b; Navailles et al., 2010a). Thus, unlike in idiopathic PD, there seems to be a lot of variability in striatal 5-HT levels in the 6-OHDA-lesioned rat. Part of this variability might come from the experimental paradigms used to produce the lesion, for instance the age at which the toxin is injected, the injection site of the toxin, as well as the rat strain used. However, regardless of the cause of the variability, the 6-OHDA-lesioned rat may not be the best model to study changes affecting the 5-HT system in PD.

In one study performed in the 6-OHDA-lesioned rat, L-DOPA administration led to increased striatal 5-HIAA levels (Brannan et al., 1990), whereas another study found a reduction in striatal 5-HIAA levels 60 min following the last L-DOPA dose (Eskow Jaunarajs et al., 2010b). Striatal 5-HIAA levels are higher in dyskinetic than in non-dyskinetic L-DOPA-treated hemiparkinsonian rats (Andersson et al., 2007; Lindgren et al., 2008). One hour after L-DOPA administration, 5-HT levels are diminished, but 5-HIAA levels are increased, in the amygdala of 6-OHDA-lesioned rats, when compared to vehicle-treated rats (Eskow Jaunarajs et al., 2010b).

In the 6-OHDA-lesioned rat, acute L-DOPA administration decreases TPH levels in the DRN, striatum, hippocampus, prefrontal cortex and amygdala; the authors proposed that the downregulation of TPH by L-DOPA constitutes a risk factor for depression in PD (Bishop et al., 2008, 2009b). Similarly, in the bilaterally 6-OHDA-lesioned rat, chronic treatment with L-DOPA leads to a reduction in TPH_2 levels in the DRN (Eskow Jaunarajs et al., 2010a). The findings of these studies are interesting and suggest that L-DOPA itself may cause depression in PD by reducing TPH and, subsequently, 5-HT levels.

The effect of 6-OHDA lesion of the SN pars compacta (SNc) in the rat on the firing rate of neurons from the DRN and the MRN has been investigated in a few studies. Following SNc lesion, DRN and MRN firing rates increase and more neurons fire in bursts, as opposed to the more regular pattern encountered in non-lesioned rats (Chu et al., 2004; Kaya et al., 2008; Wang et al., 2009; Zhang et al., 2007a). Metabolic activity of DRN neurons is also increased after 6-OHDA lesion (Kaya et al., 2008).

A study performed in the rat investigated the effect of injecting simultaneously 6-OHDA and 5-HT in the SNc. In comparison to rats injected with 6-OHDA alone, 6-OHDA/5-HT-injected rats performed better in the rotarod test. Furthermore, combined injection of 6-OHDA and 5-HT reversed the increase in both total and *N*-methyl-D-aspartate (NMDA) glutamate receptors encountered in the cerebellum of 6-OHDA-alone rats (Nandhu et al., 2011). The relevance of these findings to idiopathic PD has yet to be established.

3.1.3. Serotonin, 5-HIAA and tryptophan hydroxylase in non-human primate models of Parkinson's disease

As in the 6-OHDA-lesioned rat, 5-HT levels appear quite variable in NHP models of PD. In the MPTP-lesioned common marmoset (*Callithrix jacchus*) rendered parkinsonian by chronic MPTP injections (given over 5–10 months), both 5-HT and 5-HIAA levels are significantly reduced in the striatum, as well as in the frontal and cingulate cortices (Perez-Otano et al., 1991). Similarly, in the 1-methyl-1,2,3,6-tetrahydropyridine (MTP)-lesioned common marmoset, there is also a reduction in striatal 5-HT and 5-HIAA levels following MTP administration (6 mg/kg over a 9-day period), but the 5-HT turnover is unchanged (van Vliet et al., 2006). Perhaps paradoxically, or perhaps indicative of compensatory changes, in the MPTP-lesioned common marmoset, following a more widely used MPTP regimen (2 mg/kg s.c. for 5 consecutive days), there is an increase in TPH levels in the striatum, accompanied by an increase in 5-HT axonal varicosities; treatment with L-DOPA increases 5-HT varicosities in the GP and further increases axonal varicosity counts in the striatum, in which they also become enlarged (Zeng et al., 2008, 2010). Varicosity enlargement following chronic L-DOPA treatment and emergence of dyskinesia suggests an increased metabolic activity, implying that TPH-ir varicosities might represent a site at which L-DOPA is converted into dopamine within the raphestriatal system (see next section). Similarly, there is an increase in the number of 5-HT-ir fibres in the striatum of the hemi-MPTP-lesioned capuchin (*Cebus*) monkey (Gaspar et al., 1993). In the MPTP-lesioned rhesus macaque (*Macaca mulatta*), chronic MPTP administration (given over 21 weeks) leads to reduction in 5-HT immunoreactivity in BA 9, 11, 24, 25 and 46, *i.e.* cognitive and limbic cortical areas (Masilamoni et al., 2011).

In the MPTP-lesioned rhesus macaque, 5-HT levels are reduced in the inferior temporal, premotor and motor cortices, as well as in the primary sensory area, but not in the striatum, GP, SN or STN (Pifl et al., 1991). In the MPTP-lesioned cynomolgus macaque (*Macaca fascicularis*), one study found unaltered 5-HT levels in the striatum, whether the animals were exposed or not to L-DOPA (Huot et al., 2010h), whereas another study found decreased 5-HT levels in the striatum of L-DOPA-treated and L-DOPA-naïve parkinsonian animals (Riahi et al., 2011). In the green monkey (*Chlorocebus sabaeus*), radiofrequency lesion of the medial SN – an early NHP model of PD, in which there is contralateral bradykinesia and postural tremor – leads to a reduction of 5-HT levels in the caudate nucleus (Goldstein et al., 1969a).

Striatal 5-HT levels appear to correlate with the degree of behavioural recovery following MPTP lesion. Indeed, in a study performed in the MPTP-lesioned vervet monkey (*Chlorocebus pygerythrus*), MPTP doses of 1.3–2.5 mg/kg i.m. led to a behavioural recovery in some animals. The vervet monkeys that recovered exhibited higher striatal 5-HT levels after than prior to the lesion, and post lesion 5-HT levels correlated positively with behavioural

recovery (Boulet et al., 2008). These findings suggest that elevating striatal 5-HT levels could act as a compensatory mechanism promoting behavioural recovery following MPTP lesion. In agreement with a role for 5-HT in behavioural recovery in the parkinsonian state, an experiment performed in the 6-OHDA-lesioned rat showed a significant improvement following intrastriatal tyrosine hydroxylase gene delivery (Bjorklund et al., 2010); however, following lesion of the 5-HT system with the neurotoxin 5,7-dihydroxytrypamine (5,7-DHT), the improvement in the cylinder test performance, a correlate of anti-parkinsonian efficacy, was no longer present (Bjorklund et al., 2010).

3.2. The serotonergic raphestriatal system and L-DOPA-induced dyskinesia

Serotonergic raphestriatal neurons have been suggested to play a pivotal role in PD and L-DOPA-induced dyskinesia. The dopaminergic and 5-HT systems are functionally connected and 5-HT, via its numerous receptors, modulates dopaminergic transmission and dopamine levels in the striatum (Alex and Pehek, 2007; Lucas et al., 2000). The functional integration of the two systems is further emphasised by the fact that, in the rat, lesions of the raphe nuclei result not only in decreases in striatal 5-HT and 5-HIAA levels, but also in increases in striatal levels of the dopamine metabolites homovanillic acid and dihydroxyphenylacetic acid (DOPAC) (Nicolaou et al., 1979).

Serotonergic raphestriatal fibres contain the enzyme AADC (Arai et al., 1996) and can therefore metabolise exogenous L-DOPA into dopamine (Arai et al., 1994, 1995; Gershanik et al., 1978; Maeda et al., 2005; Tanaka et al., 1999; Tison et al., 1991) and release it in an impulse-dependent manner (Miller and Abercrombie, 1999). Following dopamine release, 5-HT terminals also participate in its re-uptake (Berger, 1978; Berger and Glowinski, 1978). Dopamine released in the striatum by 5-HT terminals is thought to act as a "false neurotransmitter" and to be involved in the emergence and the maintenance of L-DOPA-induced dyskinesia (Carta et al., 2007, 2008a,b; Nevalainen et al., 2011). Accordingly, dual lesions of the medial forebrain bundle and the rostral raphe nucleus prevent the emergence of abnormal involuntary movements (AIMs), a correlate of dyskinesia, in the rat (Eskow et al., 2009).

In accordance with a role of 5-HT neurons in the pathogenesis of L-DOPA-induced dyskinesia, intrastriatal grafts of serotonergic neurons to 6-OHDA-lesioned rats exacerbate AIMs severity (Carlsson et al., 2007; Sahin et al., 2010). Moreover, in 6-OHDA-lesioned rats that were grafted mixed dopaminergic and serotonergic neurons, removal of grafted dopaminergic cells by the second 6-OHDA lesion procedure exacerbates dyskinesia severity (Carlsson et al., 2009); a ratio of dopamine to 5-HT neurons of 1:10 within the graft appears sufficient to significantly alleviate AIMs when compared to non-transplanted animals (Garcia et al., 2011), suggesting that minimal physiological dopaminergic transmission is enough to balance the effect of dopamine released by serotonergic neurons. Excessive serotonergic innervation of the striatum could also play a role in the pathophysiology of OFF-period dystonia, as suggested in a series of PD patients with foetal mesencephalic striatal grafts (Politis et al., 2010b, 2011b).

The release of dopamine by raphestriatal serotonergic terminals is accompanied by a decrease in 5-HT release (Maeda et al., 2009, 2010) and, in the 6-OHDA-lesioned rat, chronic L-DOPA treatment is associated with a decrease in 5-HT neuronal function (Navailles et al., 2011). This could be explained by the inhibition of TPH by L-DOPA (Hashiguti et al., 1993; Kuhn and Arthur, 1999). Accordingly, two studies performed in the L-DOPA-treated 6-OHDA-lesioned rat found a negative correlation between striatal dopamine and 5-HT levels (Gil et al., 2010) and a negative correlation between striatal 5-HT levels and AIMs severity (Gil et al., 2011).

In the 6-OHDA-lesioned rat, the serotonergic system appears to release dopamine in areas beyond the striatum such as the prefrontal cortex, the SN pars reticulata (SNr) and the hippocampus, a phenomenon that can be antagonised by the SERT blocker citalopram or by the neurotoxin 5,7-DHT (Navailles et al., 2010b). Accordingly, and in relation with the argument developed in the previous paragraph, L-DOPA administration to the 6-OHDA-lesioned rat leads to a reduction in 5-HT release in the prefrontal cortex and hippocampus (Navailles et al., 2010a).

3.3. 5-HT precursors and agonists as potential therapeutic agents against parkinsonism

Application of the 5-HT precursor 5-hydroxytryptophan (5-HTP) to striatal slides from normal and 6-OHDA-lesioned rats results in an increase in [^{3}H]-dopamine release (Ng et al., 1972). This important discovery and the findings of low 5-HT levels in the basal ganglia in idiopathic PD have led to pharmacological trials with 5-HT precursors in PD and animal models of PD. In the green monkey, administration of 5-HTP following radiofrequency lesion of the SN leads to a reduction in tremor (Goldstein et al., 1969b,c). In contrast, in human, the combination of 5-HTP with a peripheral AADC inhibitor worsens rigidity and bradykinesia, and is ineffective against tremor (Chase, 1970a; Chase et al., 1972). However, L-5-HTP, the L-enantiomer of 5-HTP, alleviates tremor and exerts an antidepressant effect (Sano and Taniguchi, 1972). Parachlorophenylalanine, a 5-HT depletor, does not alter the severity of tremor, rigidity, or bradykinesia (Chase, 1972).

In the 6-OHDA-lesioned rat, the non-selective 5-HT agonist 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT or, rarely, 5-MDOT) (Spencer et al., 1987; Tricklebank et al., 1985; Winter et al., 2000) reduces the number of L-DOPA-induced contraversive rotations (Henry et al., 1998) and, in the MPTP-lesioned macaque, 5-MDOT alleviates dyskinesia, but adversely affects parkinsonism (Gomez-Mancilla and Bedard, 1993).

The results of the preclinical and clinical trials involving 5-HTP and 5-MDOT are summarised in Table 2.

3.4. 5-HT in Parkinson's disease: summary

Numerous studies investigating 5-HT, 5-HIAA and TPH in PD and animal models of PD have been performed. Some important points need be remembered:

- The serotonergic system undergoes degeneration in idiopathic PD, leading to reduced 5-HT levels in several brain areas such as the striatum, GP, SN, several cortical areas, as well as in the CSF. These changes are not well modelled by many widely used animal models.
- Neuronal loss in the DRN seems more severe in depressed than non-depressed PD patients, suggesting a relation between 5-HT and mood disorders in idiopathic PD.
- In the MPTP-lesioned NHP, elevation of striatal 5-HT levels is associated with behavioural recovery.
- Raphestriatal serotonergic neurons, by releasing dopamine synthesised from exogenous L-DOPA, appear to play a critical role in the pathophysiology of L-DOPA-induced dyskinesia.

4. Serotonin transporter

SERT gene (MIM *182138, http://www.ncbi.nlm.nih.gov/omim/182138), also called SLC6A4 (solute carrier family 6, member 4), was cloned in 1991 in the rat (Blakely et al., 1991) and in 1993 in human (Ramamoorthy et al., 1993). The human gene shares 92%

Table 2
5-HTP and 5-MDOT in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	Animal models		Idiopathic PD
	6-OHDA-lesioned rat	MPTP-lesioned NHP	
5-HTP	n/a	n/a	• Deleterious effect on bradykinesia • Deleterious effect on rigidity • No effect on tremor
L-5-HTP	n/a	n/a	• ↓ Tremor • Antidepressant effect
5-MDOT	• ↓ L-DOPA-induced contraversive rotations	• ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA anti-parkinsonian action	n/a
Parachlorophenylalanine	n/a	n/a	• No effect

5-HTP: 5-hydroxytryptophan; 5-MDOT: 5-methoxy-N,N-dimethyltryptamine; 6-OHDA: 6-hydroxydopamine; L-: *levo*; L-DOPA: L-3,4-dihydroxyphenylalanine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; n/a: not available; NHP: non-human primate; PD: Parkinson's disease.

homology with the rat gene, is located on chromosome 17, codes for a 630 amino acid protein, and is expressed on neuronal, platelet, placental and pulmonary membranes. It is a Na^+/Cl^- dependent ionic transporter (Ramamoorthy et al., 1993). SERT is composed of monomers which agglomerate to form oligomers (Kilic and Rudnick, 2000).

In the normal mouse, rat and rhesus macaque brain, autoradiographic binding studies have established that highest SERT levels are encountered in the raphe nuclei, SN, ventral tegmental area (VTA) and thalamus. SERT levels are moderate in the GP, and relatively low in the striatum and neocortex (Ase et al., 2000; Chalon et al., 2003; De Souza and Kuyatt, 1987; Duncan et al., 1992; Gobbi et al., 1990; Hrdina et al., 1990; Kretzschmar et al., 2003; Lin et al., 2004; Strazielle et al., 1996; Zeng et al., 2006). There appears to be species variations, however. Hence, in the pig, a positron emission tomography (PET) study demonstrated that SERT levels in the striatum are comparable to those in the SN and higher than those in the cortex (Kretzschmar et al., 2003).

In the human brain, an autoradiographic binding study has demonstrated that the highest SERT levels are encountered in the DRN (Varnas et al., 2004a). SERT levels in the striatum are higher than those in the neocortex, comparable to those in the GP and SNr, and lower than those in the SNc (Gurevich and Joyce, 1996; Kish et al., 2005; Varnas et al., 2004a).

4.1. Serotonin transporter in Parkinson's disease

As mentioned previously, the serotonergic system undergoes degeneration in PD, leading to alterations in SERT levels. Very few studies assessing SERT levels have been performed in animal models of PD in the L-DOPA-naïve state. Thus, a pilot study, employing only 3 rats, did not find significant changes in SERT binding levels in the striatum of L-DOPA-naïve 6-OHDA-lesioned rats when the denervated striatum was compared to the intact side (Wang et al., 2010). In the L-DOPA-naïve MPTP-lesioned cynomolgus macaque, SERT binding levels are diminished in the putamen and GP (Rylander et al., 2010).

Several single-photon emission computed tomography (SPECT) studies measuring SERT levels in PD have been performed. In early, drug-naïve, PD patients, there is a decrease in thalamic SERT levels when compared to controls and, within PD subjects, thalamic SERT levels are lower in patients with tremor than in non-tremulous patients (Caretti et al., 2007, 2008). However, the fate of thalamic SERT levels in early PD remains uncertain, since a study found no alterations in thalamic SERT levels in early PD patients (Marek et al., 2009). SERT levels in early PD subjects also appear decreased in the temporal cortex and striatum (Marek et al., 2009), but not in the midbrain (Beucke et al., 2011; Marek et al., 2009; Roselli et al., 2010) or DRN (Marek et al., 2008).

Several PET studies have assessed the fate of SERT in PD. A PET study performed in early PD patients did not find any difference in SERT levels between PD subjects and age-matched healthy controls. There was, however, a negative correlation between striatal SERT and DAT levels (Strecker et al., 2011). Other PET studies have found reductions in SERT levels in the striatum (Albin et al., 2008; Brucke et al., 1993; Guttman et al., 2007; Kerenyi et al., 2003; Politis et al., 2010a), as well as in the orbitofrontal cortex, midbrain, cingulate gyrus, amygdala, hippocampus, thalamus and hypothalamus (Albin et al., 2008; Brucke et al., 1993; Guttman et al., 2007; Politis et al., 2010a) of PD patients. In terms of disease progression, the decline in striatal SERT levels seems to precede the decline in midbrain SERT levels (Kim et al., 2003) and SERT levels in the caudal brainstem structures appear to be unaltered after levels have dropped in the midbrain (Albin et al., 2008). In terms of clinical phenomenology, SERT levels in the medial frontal area negatively correlate with the Unified Parkinson's Disease Rating Scale (UPDRS) part I subscore (Haapaniemi et al., 2001), which assesses mentation, behaviour and mood (Fahn et al., 1987; Goetz et al., 2008b), whereas SERT levels are increased in the dorsolateral prefrontal and prefrontal cortices of depressed PD patients (Boileau et al., 2008). SERT levels are also increased in the amygdala, caudal raphe nucleus, hypothalamus and posterior cingulate cortex of depressed PD patients, when compared to non-depressed PD patients (Politis et al., 2010c). Low SERT levels in the thalamus, striatum, amygdala and cingulum are inversely correlated with fatigue in PD (Pavese et al., 2010a,b). There is no correlation between SERT levels in the brain of PD patients and Hoehn and Yahr staging, UPDRS part III subscore or treatment with dopamine agonists (Politis et al., 2010a). A study evaluating the annual decline of SERT function in the raphe nuclei using [^{18}F]-DOPA uptake as a surrogate marker found a 4.7% annual decline in early PD patients over a 3-year period (Pavese et al., 2011). Another PET study has demonstrated abnormal SERT levels in the raphe, striatum, thalamus and hypothalamus, prefrontal cortex, and anterior and posterior cingulate cortex of PD patients with abnormal changes in body mass index over a 12-month period, when compared to healthy controls (Politis et al., 2011a).

Several post mortem studies have also investigated SERT levels in PD brains. An autoradiographic binding study demonstrated decreased SERT levels in the frontal and temporal cortices of PD patients, when compared to controls (D'Amato et al., 1987), although another study failed to find changes in the orbitofrontal and inferotemporal cortices (Chen et al., 1998). Additionally, SERT levels are diminished in the striatum, claustrum, GP pars externa (GPe), SNr, as well as frontal, insular and visual cortices of PD

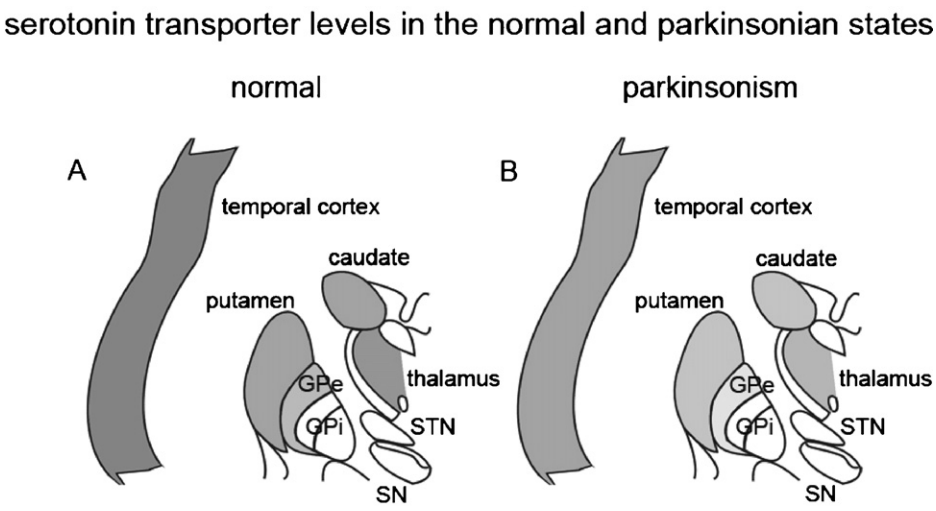

Fig. 4. In PD, serotonin transporter (SERT) levels are reduced in the temporal cortex, caudate nucleus, putamen, GPe and thalamus (B, paler shades of grey) when compared to healthy individuals (A). Although not depicted in this illustration, SERT levels are also diminished in the nucleus accumbens, claustrum and hypothalamus of PD patients. These illustrations are not representative of normal anatomy. Thus, although depicted in the figure, the SN and STN are more posterior in the reality.
GPe: globus pallidus pars externa; GPi: globus pallidus pars interna; SN: substantia nigra; STN: subthalamic nucleus.
Basal ganglia illustrations are adapted from Paxinos et al. (2008).

patients (Chinaglia et al., 1993; Raisman et al., 1986). A study measuring striatal SERT levels by high performance liquid chromatography found a significant reduction in SERT levels in the caudate nucleus, but not in the putamen, of PD patients (Kish et al., 2008). In contrast, an immunohistochemical study using antibodies against SERT discovered a significant increase in SERT optical density in the caudate and putamen as well as a non-significant increase in the number of SERT-ir varicosities in the striatum of PD patients when compared to controls (Bedard et al., 2011).

A genetic study performed in an Australian cohort assessing polymorphisms in SERT gene found that, in this population, a 10-copy variable-number tandem repeat element was significantly less common in PD patients than in controls (McCann et al., 2000). A German study found that a polymorphism in SERT promoter was linked to higher Hamilton Depression Rating Scale scores, but found no correlation with the UPDRS part III subscore (Mossner et al., 2001). In a Chinese study, no association was found between depressive symptoms in PD and SERT promoter polymorphisms (Zhang et al., 2009).

The alterations in SERT levels in the thalamus and basal ganglia occurring in PD are illustrated in Fig. 4, whereas the cortical and brainstem areas in which SERT levels are altered in PD are depicted in Fig. 5.

4.2. Serotonin transporter in treatment-related complications

In the 6-OHDA-lesioned rat, SERT levels are increased in the striatum of dyskinetic animals and SERT levels correlate positively with AIMs severity (Rylander et al., 2007, 2008, 2010; Stromberg et al., 2007). In the 6-OHDA-lesioned rat, SERT levels increase in the striatum of rats treated with either low or high dose of L-DOPA for 2–3 weeks, as well as in the cortex of rats treated with high dose of L-DOPA for the same amount of time (Rylander et al., 2010). This increase in striatal SERT levels is not accompanied by increased SERT binding or SERT messenger ribonucleic acid (mRNA) levels in the raphe nucleus, but is rather due to a dose-dependent L-DOPA-induced axonal sprouting (Rylander et al., 2010). L-DOPA treatment also increases the amount of synaptic varicosities making synaptic contacts and amplifies stimulus-dependent dopamine release by

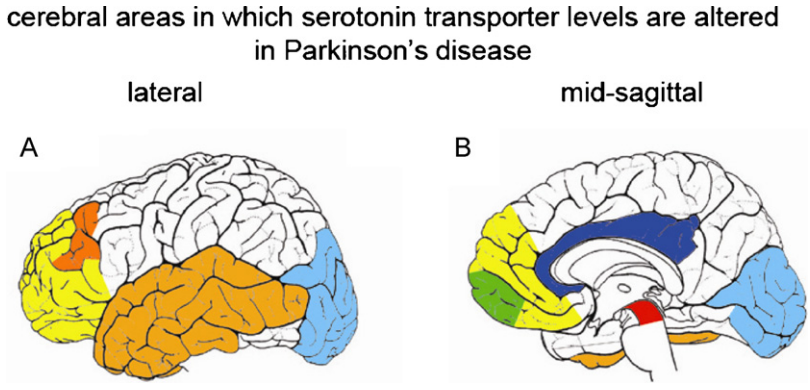

Fig. 5. Serotonin transporter (SERT) levels are reduced in the temporal cortex of PD patients (A and B, dark yellow). There is also a reduction in SERT levels in the orbitofrontal cortex (B, green). SERT levels are diminished in the midbrain of L-3,4-dihydroxyphenylalanine (L-DOPA)-treated PD patients (B, red). Studies have suggested increased SERT levels in the prefrontal (A and B, pale yellow) and dorsolateral prefrontal (A, orange) cortex of depressed PD patients, whereas others have suggested a reduction in SERT levels in the frontal cortex (sum of pale yellow, orange and green areas in A and B). SERT levels are also reduced in the visual (A and B, light blue), cingulate (B, dark blue) and insular cortex, as well as the striatum, amygdala, hippocampus, hypothalamus and thalamus (not illustrated).
Brain illustrations are adapted from Mai et al. (2004).

serotonergic terminals (Rylander et al., 2010). All of these findings are in agreement with a role of striatal serotonergic terminals in the pathogenesis of L-DOPA-induced dyskinesia.

In the MPTP-lesioned cynomolgus macaque, SERT levels remain low for up to 6–8 months following the beginning of L-DOPA therapy if the animals do not develop dyskinesia, but increase to pre-MPTP levels when NHPs become dyskinetic (Rylander et al., 2010), suggesting, as in the 6-OHDA-lesioned rat, a relationship between SERT and dyskinesia.

An autoradiographic binding study performed in PD patients has demonstrated that SERT binding levels are higher in the putamen of dyskinetic L-DOPA-treated subjects than in the putamen of non-dyskinetic L-DOPA-treated patients (Rylander et al., 2010), again suggesting an important role of SERT and serotonergic terminals in the pathophysiology of L-DOPA-induced dyskinesia.

Two SPECT studies have examined SERT levels in L-DOPA-treated PD patients. The first one has discovered decreased SERT levels in the midbrain (Berding et al., 2003), whereas the second one has found a correlation between decreased SERT levels in the dorsal midbrain and abnormal UPDRS part I subscore (Murai et al., 2001). The findings of this last study are in agreement with the post mortem studies cited above which have demonstrated greater degeneration of the DRN and lower 5-HT levels in depressed PD patients and point towards an important role of the 5-HT system in the pathophysiology of non-motor symptoms of PD.

4.3. Serotonin transporter modulators as potential therapeutic agents against parkinsonism and treatment-related complications

Numerous studies with selective and non-selective SERT inhibitors have been performed in PD. They will be reviewed separately (Huot et al., in preparation). A thorough discussion about their efficacy against motor and non-motor symptoms and treatment-related complications of PD is therefore beyond the scope of this article.

4.4. Serotonin transporter in Parkinson's disease: summary

Numerous studies assessing SERT in PD and animal models of PD have been performed. The following points need be remembered:

- SERT levels are reduced in the striatum, GP, midbrain, thalamus and several cortical areas of PD patients.
- Reduction of thalamic SERT levels seems more severe in PD patients with tremor.
- Throughout the progression of the disease, the reduction in SERT levels seems to follow a rostro-caudal pattern in the prosencephalon and brainstem structures.
- Decreased SERT levels in the medial frontal cortex and dorsal midbrain, as well as increased SERT levels in the dorsolateral prefrontal and prefrontal cortices, are associated with depressive symptoms.
- Low thalamic and striatal SERT levels are linked with fatigue in PD.

5. Serotonin receptors

As for 5-HT and SERT, several studies have investigated 5-HT receptors in PD and treatment-related complications. Pioneering studies used non-specific ligands such as [^{3}H]-5-HT as the radioligand and 5-HT as the non-specific displacer to label 5-HT receptors in post mortem tissue (Reisine et al., 1977). The development of new, more specific, radioligands and the advent of new techniques have allowed studying more precisely specific subtypes of 5-HT receptors, although specificity remains an issue with some subtypes, such as the 5-HT$_{1B/1D}$ receptors (*vide infra*).

There are currently 14 subtypes of 5-HT receptors, 13 of which are metabotropic and one ionotropic (Nichols and Nichols, 2008). Several articles have reviewed 5-HT receptor pharmacology and their nomenclature has been updated on several occasions (Barnes and Sharp, 1999; Bradley et al., 1986; Fink and Gothert, 2007; Hoyer et al., 1994, 2002; Humphrey et al., 1993; Nichols and Nichols, 2008).

A thorough review of the physiology and normal function of 5-HT receptors is beyond the scope of this article. Thus, the following sections provide only a brief overview of 5-HT receptors under physiological conditions. The distribution of 5-HT receptors in the normal brain is detailed, in order to facilitate comparison with the changes occurring in PD. The contributions of 5-HT receptors to the motor and non-motor manifestations of PD and treatment-related complications are then discussed in depth.

5.1. 5-HT$_{1A}$ receptors

Human 5-HT$_{1A}$ receptor (MIM *109760, http://www.ncbi.nlm.nih.gov/omim/109760) gene was cloned and sequenced in 1987 (Kobilka et al., 1987). It is an intronless gene coding for a 421 amino acid protein and is located on chromosome 5 (Kobilka et al., 1987). Initially named G-21, the gene was recognised as the 5-HT$_{1A}$ receptor gene in 1988 (Fargin et al., 1988). In the brain, 5-HT$_{1A}$ receptors are located both pre- and postsynaptically, and are coupled to a $G_{i/o}$ protein (Nichols and Nichols, 2008). 5-HT$_{1A}$ monomers form homodimers; the dimerisation process is facilitated by 5-HT$_{1A}$ agonists and impaired by antagonists (Lukasiewicz et al., 2007).

5-HT$_{1A}$ receptors participate in a wide range of behaviours and diseases, such as anxiety (Blier and Ward, 2003; Heisler et al., 1998; Parks et al., 1998; Toth, 2003), cognition (Elliott et al., 2009), depression (Blier and Ward, 2003; Meltzer et al., 2004; Sargent et al., 2000) and schizophrenia (Burnet et al., 1996). 5-HT$_{1A}$ receptor levels decrease in the limbic structures, frontal cortex, and striatum of mice following social isolation (Schiller et al., 2003). 5-HT$_{1A}$ receptors play a role in the regulation of the hypothalamic-pituitary-adrenal axis (Pan and Gilbert, 1992). 5-HT$_{1A}$ receptor agonists exert neuroprotective effects in rodent models of ischaemic (Kamei et al., 2001; Mauler and Horvath, 2005; Prehn et al., 1991) and traumatic brain injuries (Mauler and Horvath, 2005). 5-HT$_{1A}$ receptor activation is neuroprotective against NMDA-mediated excitotoxicity in striatal and mesencephalic cultures (Madhavan et al., 2003). 5-HT$_{1A}$ receptors play a role in psychostimulant addiction (Muller et al., 2007) and mediate some of the effects of hallucinogenic drugs (Pierce and Peroutka, 1989).

In the rat brain, 5-HT$_{1A}$ receptors are most abundant in the DRN and limbic areas. In the DRN, 5-HT$_{1A}$ receptors are somatodendritic and, by acting as auto- or heteroreceptors, they modulate 5-HT-mediated neuronal firing (Riad et al., 2000). 5-HT$_{1A}$ receptors are moderately abundant in the cortex and very low in the basal ganglia (Chalmers and Watson, 1991; Pazos and Palacios, 1985; Pompeiano et al., 1992). In the rat frontal cortex, 5-HT$_{1A}$ receptor mRNA is present in both pyramidal neurons and gamma-aminobutyric acid (GABA)-ergic interneurons (Amargos-Bosch et al., 2004; Santana et al., 2004). In the mouse cortex, 5-HT$_{1A}$ receptor mRNA is present in pyramidal neurons (Amargos-Bosch et al., 2004).

In the NHP brain, highest levels of 5-HT$_{1A}$ receptors are found in the hippocampal formation, followed by the external layers of the motor and premotor cortices. 5-HT$_{1A}$ receptor levels are moderately high in the internal cortical layers, intermediate in the middle cortical layers and the striosomes, and low in the striatal matrix, GP, SN and STN (Frechilla et al., 2001; Huot et al., 2010d,e). A study

Table 3
Effects of 5-HT_{1A} agonists on glutamatergic, serotonergic and dopaminergic transmissions.

Glutamatergic	Serotonergic	Dopaminergic
• ↓ Corticostriatal glutamate release • ↓ Thalamocortical glutamate release • Hyperpolarisation of cortical neurons • ↓ Firing rate of STN neurons	• ↓ Firing rate and baseline activity of DRN neurons • ↓ 5-HT release in the striatum • ↓ Dopamine release in the striatum (dyskinetic state)	• ↑ Dopamine release in the VTA and medial prefrontal cortex

5-HT: serotonin; DRN: dorsal raphe nucleus; STN: subthalamic nucleus; VTA: ventral tegmental area.

using [^{3}H]-5-HT as the radioligand and 5-HT as the non-specific displacer found different results, including high levels in the GP and SNr, but due to the lack of selectivity of [^{3}H]-5-HT and 5-HT to define 5-HT_{1A} receptors, these results are probably not valid (Stuart et al., 1986). In the tree shrew, 5-HT_{1A} mRNA is encountered in cortical pyramidal neurons, but not in cortical GABAergic interneurons (Palchaudhuri and Flugge, 2005). In NHP and human neocortex, the initial axonal segment of pyramidal neurons is highly immunoreactive for 5-HT_{1A} receptors (Cruz et al., 2004; DeFelipe et al., 2001).

In the human brain, 5-HT_{1A} receptor levels are highest in the entorhinal cortex and hippocampus, as well as in the raphe complex. In the frontal cortex, 5-HT_{1A} receptors predominate in the external two layers and are low in the basal ganglia, including the SN (Hall et al., 1997; Hoyer et al., 1986; Pazos et al., 1987a). 5-HT_{1A} mRNA is abundant within the serotonergic neurons of the raphe. In the neocortex, 5-HT_{1A} mRNA is predominantly encountered in the superficial layers (Burnet et al., 1995). 5-HT_{1A} mRNA is low in the striatum (Burnet et al., 1995).

5.1.1. 5-HT_{1A} receptors and modulation of neurotransmitter release along the basal ganglia circuitry

5-HT_{1A} receptors modulate glutamatergic, serotonergic and dopaminergic neurotransmissions along the cortico-basal ganglia-thalamo-cortical loop. Presynaptic 5-HT_{1A} receptors are involved in the regulation of glutamate release (Matsuyama et al., 1996; Tanaka and North, 1993). 5-HT_{1A} agonists reduce glutamate release (Mauler et al., 2001) and can thus modulate corticostriatal and thalamocortical glutamatergic neurotransmissions (Parent and Hazrati, 1995a). Accordingly, administration of sarizotan, a 5-HT_{1A} agonist with additional affinity for the D_3 and D_4 receptors (Table 3), leads to a reduction in striatal glutamate levels in the normal rat (Antonelli et al., 2005). Activation of postsynaptic cortical 5-HT_{1A} receptors induces hyperpolarisation (Araneda and Andrade, 1991) which, according to the classic model of the functional organisation of basal ganglia, will result in a paucity of movement (DeLong, 1990; DeLong and Wichmann, 2007; Parent and Hazrati, 1995a; Parent et al., 2000), perhaps explaining why 5-HT_{1A} receptor agonists might impair L-DOPA anti-parkinsonian action (*vide infra*). Activation of 5-HT_{1A} receptors of STN neurons reduces their firing rate (Stanford et al., 2005). According to the basal ganglia model, a reduction in STN firing will increase movement (DeLong, 1990; DeLong and Wichmann, 2007; Parent et al., 2000), suggesting that 5-HT_{1A} receptors, depending on their anatomical localisation along the cortico-basal ganglia-thalamo-cortical loop, might exert different influences on movement.

With respect to the modulation of serotonergic transmission, 5-HT_{1A} receptor agonists reduce the firing rate and baseline activity of DRN neurons (Sprouse and Aghajanian, 1987, 1988), and systemic or direct application in the DRN of the 5-HT_{1A} agonist 8-OH-DPAT results in a reduction of 5-HT release in the striatum (Kreiss and Lucki, 1994). Systemic administration of the 5-HT_{1A} agonist 8-OH-PIPAT produces similar effects (Knobelman et al., 2000). This effect is likely to be relevant to the dopamine-denervated striatum of PD. Indeed, as mentioned previously, in animal models of PD, raphestriatal 5-HT terminals uptake L-DOPA and metabolise it into dopamine. Accordingly, in the 6-OHDA-lesioned rat, pre-treatment with 8-OH-DPAT before administration of L-DOPA leads to a decrease in striatal dopamine release (Kannari et al., 2001).

5-HT_{1A} receptors also modulate dopamine release from dopaminergic fibres. Thus, the 5-HT_{1A} receptor agonist BAY x 3702 increases dopamine release in the ventral tegmental area and the medial prefrontal cortex (Diaz-Mataix et al., 2005). This mechanism might be relevant for the modulation of dopamine release in early stages of PD, in which the nigrostriatal dopaminergic system is relatively spared. An exhaustive review on the modulation of dopamine release by 5-HT was recently published (Alex and Pehek, 2007).

The effects of 5-HT_{1A} agonists on glutamatergic, serotonergic and dopaminergic transmissions within the basal ganglia are summarised in Table 3.

5.1.2. 5-HT_{1A} receptors in Parkinson's disease

In the adult rat, following neonatal 6-OHDA-lesioning, there is no change in 5-HT_{1A} receptor mRNA (Numan et al., 1995) or protein (Radja et al., 1993) levels in the striatum. In the L-DOPA-naïve MPTP-lesioned macaque, 5-HT_{1A} receptor levels increase in the striosomal compartment of the striatum (Frechilla et al., 2001; Huot et al., 2010d,e). 5-HT_{1A} receptor levels increase in the middle layers, but decrease in the external layers of the motor and premotor cortices of MPTP-lesioned macaques, regardless of their exposure to L-DOPA (Huot et al., 2010d,e). In the MPTP-lesioned macaque, 5-HT_{1A} receptor levels in the matrix of the caudate nucleus increase following chronic L-DOPA therapy (Huot et al., 2010d,e). These changes in 5-HT_{1A} receptor levels in the MPTP-lesioned NHP along the cortico-basal ganglia-thalamo-cortical loop are depicted in Fig. 6. In the ovariectomised, hemi-MPTP-lesioned, L-DOPA-naïve, aged cynomolgus macaque, treatment with 17β-oestradiol leads to reductions in 5-HT_{1A} receptor levels in the anterior cingulate cortex on both the intact and lesioned sides (Sanchez et al., 2011). The authors of that last study claim that their results support a role for oestradiol in 5-HT-mediated neurotransmission in PD, but because the changes occurred simultaneously in the lesioned and non-lesioned sides, a role for oestradiol in 5-HT-mediated transmission in the specific context of PD has yet to be demonstrated.

In the human brain, a PET study has demonstrated decreased 5-HT_{1A} receptor levels in the anterior cingulate cortex, insula and caudate nucleus of PD patients when compared to controls (Ballanger et al., 2011). That PET study also found decreased 5-HT_{1A} receptor levels in the temporal and orbitofrontal cortex and amygdala when depressed PD patients were compared to non-depressed PD subjects (Ballanger et al., 2011). In contrast, a post mortem study found an increase in 5-HT_{1A} receptor levels in the orbitofrontal (BA_{11}) and inferotemporal (BA_{21}) cortex of PD patients, but no clinical details were provided, making it impossible to infer an association with PD symptoms or treatment (Chen et al., 1998). Another post mortem study found higher 5-HT_{1A} receptor levels in the temporal cortex (BA_{36} but not BA_{20}) of depressed PD patients with dementia (Sharp et al., 2008). In a PET study, lower midbrain raphe 5-HT_{1A} receptor levels were

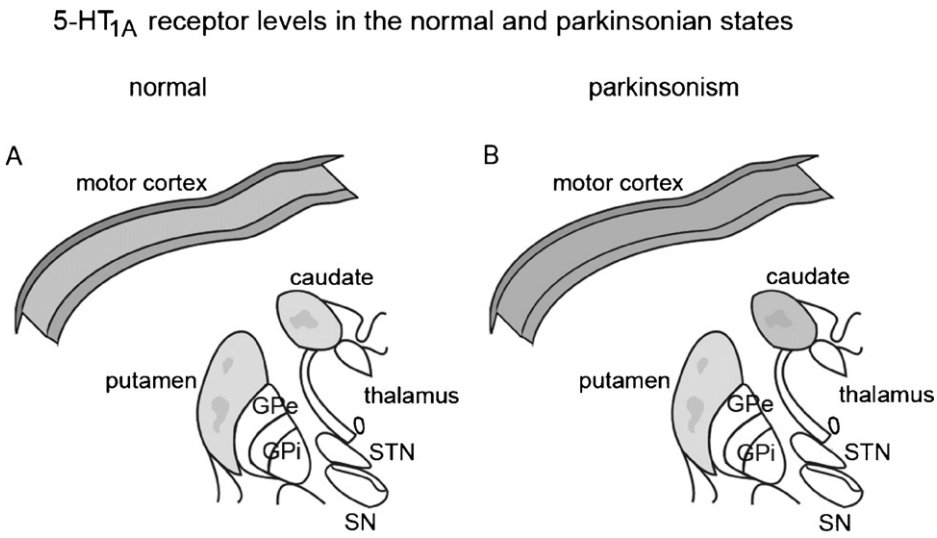

Fig. 6. In the parkinsonian macaque model of PD (B), 5-HT_{1A} receptor levels are upregulated in the middle layers, but downregulated in the external layers of the motor and premotor cortex when compared to the non-parkinsonian macaque (A). 5-HT_{1A} receptor levels are also increased in the striosomes of both the caudate and putamen in the parkinsonian monkey (B), when compared to the non-parkinsonian monkey (A). 5-HT_{1A} receptor levels are unchanged in the internal layers of the cortex and are negligible in the GP, SN and STN. Following chronic L-DOPA therapy, 5-HT_{1A} receptor levels are increased in the matrix compartment of the caudate nucleus (B).
Within the caudate nucleus and putamen, the patchy areas of more intense shading represent the striosomes, whereas the paler surrounding is the extrastriosomal matrix.
Within a specific structure, different shades of grey in A and B indicate an increase (darker grey) or a reduction (paler grey) in 5-HT_{1A} receptor levels.
These illustrations are not representative of normal anatomy. Thus, although depicted in the figure, the SN and STN are more posterior in the reality.
GPe: globus pallidus pars externa; GPi: globus pallidus pars interna; SN: substantia nigra; STN: subthalamic nucleus.
Basal ganglia illustrations are adapted from Paxinos et al. (2008).

encountered in PD patients when compared to healthy controls and, within the PD population, lower midbrain raphe 5-HT_{1A} levels correlated with UPDRS part III tremor composite score (Doder et al., 2003). The brain areas in which these changes in 5-HT_{1A} receptor levels occur are illustrated in Fig. 7.

5.1.3. 5-HT_{1A} receptor modulation as a potential target for parkinsonism and treatment-related complications

Several 5-HT_{1A} receptor agonists have been studied in idiopathic PD and animal models of PD. The pharmacology of these agents is presented in Table 4. As can be seen from this table, none of these compounds is selective for 5-HT_{1A} receptors, which complicates the interpretation of their preclinical/clinical efficacies, or lack thereof. An overview of the results of the preclinical and clinical trials assessing the efficacy of 5-HT_{1A} receptor agonists on parkinsonism and treatment-related motor and non-motor complications is provided in Table 5.

5.1.3.1. Preclinical studies: parkinsonism. 5-HT_{1A} receptor agonists alleviate haloperidol-induced catalepsy in the rat, an effect abolished by the 5-HT_{1A} antagonist WAY-100,635 (Bantick et al., 2001; Ishibashi and Ohno, 2004; Kleven et al., 2005; Lucas et al., 1997; Ohno et al., 2009; Prinssen et al., 2002). In the reserpine-treated rat, the 5-HT_{1A} agonist R-(+)-8-OH-DPAT and the 5-HT_{1A} partial agonist buspirone both increase motor activity (Mignon and Wolf, 2002).

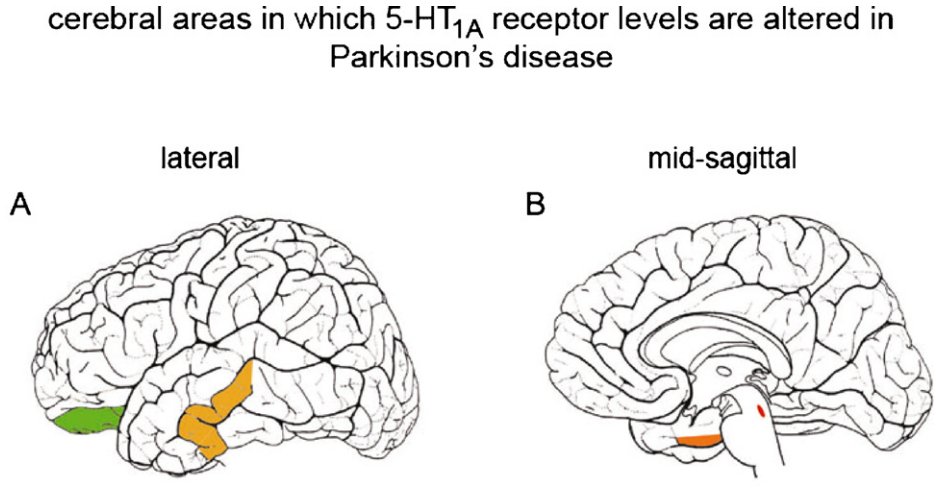

Fig. 7. In the human PD brain, 5-HT_{1A} receptor levels are increased in Brodmann area (BA) 11 (A, green), BA_{21} (A, yellow), BA_{36} (B, orange), as well as in lower midbrain raphe nuclei (B, red).
The changes reported in the premotor and motor cortex in the parkinsonian primate have not been documented in human so far. Thus, the premotor and motor cortical areas are uncoloured in this figure.
Brain illustrations are adapted from Mai et al. (2004).

Table 4
Pharmacological profile of 5-HT_{1A} receptor ligands studied in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	5-HT_{1A} receptor affinity (nM)	Other binding sites (nM)	References
8-OH-DPAT	0.5–0.6	5-HT_{1B} (710–6607), 5-HT_{1D} (47, IC_{50}), 5-HT_{2A} (>10,000), 5-HT_{2C} (>2427), 5-HT_3 (7079), 5-HT_7 (36–126), α_1 (>2427), α_2 (116), D_2 (86–1746), and D_3 (361)	Colpaert et al. (1992), Domenech et al. (1997), Lejeune et al. (1997), Middlemiss and Fozard (1983), Piercey et al. (1994), and Wood et al. (2000)
R-(+)-8-OH-DPAT	0.47	D_2 (1082) and D_3 (198)	Lejeune et al. (1997)
BMY-14,802 (BMS-181,100)[a]	200	5-HT_{1A} (320), 5-HT_{2A} (1700), α_1 (398), σ (79.4), and D_2 (3981)	Bristow et al. (1991) and Yevich et al. (1992)
Buspirone	9.2–20	5-HT_{1B} (>10,000), 5-HT_{2A} (1300–1737), 5-HT_{2C} (1100–2089), 5-HT_3 (>10,000), α_1 (1000 → 2427), α_2 (>1042–6000), β (8800), and D_2 (13–240)	Colpaert et al. (1992), Glennon et al. (1988), Hamik et al. (1990), and Piercey et al. (1994)
Flesinoxan (DU-29,373)	0.54–1.7	5-HT_{1B} (810), 5-HT_{1D} (160), 5-HT_2 (4500), α_1 (380), κ (5000), D_2 (140), and H_1 (790)	Newman-Tancredi et al. (1998) and Schipper et al. (1991)
Flibanserin (BMIT-17)	1–50	5-HT_{2A} (49–133), 5-HT_7 (990), α_1 (523), D_{2L} (305–785), D_3 (365–479), and D_4 (4–24)	Borsini et al. (2002)
Mirtazapine (Org 3770)	5012	DAT (>10,000), NET (1640–2512), SERT (>7943), 5-HT_{2A} (8.9–69), 5-HT_{2C} (39), 5-HT_3 (7.94), 5-HT_7 (265), α_1 (372–608), α_{2A} (20), α_{2C} (18), D_1 (4167), D_2 (3981), D_3 (5723), H_1 (0.5–1.6), and M (794)	Anttila and Leinonen (2001), de Boer (1996), Fernandez et al. (2005), and Tatsumi et al. (1997)
Pardoprunox	3.16	α_1 (15.8), α_2 (39.8), D_1 (158), D_{2S} (7.94), D_3 (2.51), $D_{4.4}$ (15.8), and M (2512)	Glennon et al. (2006) and McCreary et al. (2007)
Piclozotan (SUN-N4057)	0.47	α_1 (128) and D_2 (84)	Kamei et al. (2006)
Sarizotan (EMD 128130)[a]	0.1–7	5-HT_{1B} (600), 5-HT_{1D} (500), 5-HT_{2A} (587–1560), 5-HT_{2B} (108), 5-HT_{2C} (800–1270), 5-HT_3 (3500 → 10,000), 5-HT_4 (>10,000), 5-HT_{5A} (313), 5-HT_6 (3300), 5-HT_7 (10), α_1 (600), α_2 (7000), σ_1 (590), σ_2 (340), D_1 (6700–9200), D_{2S} (17), D_2 (15), D_3 (7), $D_{4.2}$ (2–3), $D_{4.4}$ (4), and D_5 (634)	Bartoszyk and Kuzhikandathil (2006) and Bartoszyk et al. (2004)
Tandospirone (SM-3997)	27	5-HT_{2A} (1300), 5-HT_{2C} (2600), α_1 (1600), α_2 (1900), and D_2 (1700)	Hamik et al. (1990)

Unless indicated otherwise, values are provided as the dissociation constant (K_d).
5-HT: serotonin; DAT: dopamine transporter; NET: noradrenaline transporter; nM: nanomole; SERT: 5-HT transporter.
[a] Values provided as the half-maximal effective concentration (EC_{50}).

In the rat, both buspirone and 8-OH-DPAT reverse the catalepsy induced by 6-OHDA (Nayebi et al., 2010). In the 6-OHDA-lesioned rat, 8-OH-DPAT also improves the performance at the forepaw adjusting steps test, a correlate of anti-parkinsonian action (Dupre et al., 2008a). In the 6-OHDA-lesioned rat, R-(+)-8-OH-DPAT produces rotations ipsiversive to the lesioned side (Mignon and Wolf, 2007), whereas both racemic 8-OH-DPAT and tandospirone induce rotations contraversive to the lesioned side (Ishibashi and Ohno, 2004; Matsubara et al., 2006). This effect of tandospirone is blocked by WAY-100,635 and is not affected by the D_1 receptor antagonist SCH-23390 (Matsubara et al., 2006). Tandospirone also increases the number of apomorphine-induced contraversive rotations (Matsubara et al., 2006). 8-OH-DPAT decreases amphetamine-induced rotations following ventral mesencephalon transplantation in the striatum of 6-OHDA-lesioned rats (Lane et al., 2009). 5-HT_{1A} (WAY-100,635) and 5-$HT_{1A/1B}$ (pindolol) receptor antagonists do not affect the number of ipsiversive rotations produced by the monoamine re-uptake inhibitor BTS 74,398 (Lane et al., 2005).

In the 6-OHDA-lesioned rat, the full 5-HT_{1A} agonist and partial D_2/D_3 dopamine agonist pardoprunox (Betry et al., 2011; Glennon et al., 2006) elicits contraversive rotations when administered as monotherapy (Jones et al., 2010; McCreary et al., 2010). When administered as monotherapy to the MPTP-lesioned common marmoset, pardoprunox alleviates parkinsonism (Jones et al., 2010). In the L-DOPA-naïve parkinsonian common marmoset, *de novo* therapy with pardoprunox for 28 days elicits significantly less severe dyskinesia than *de novo* therapy with either ropinirole or L-DOPA (Johnston et al., 2010a; McCreary et al., 2010).

5.1.3.2. Preclinical studies: treatment-related complications. 5-HT_{1A} receptor agonists have been extensively studied for their potential to alleviate L-DOPA-induced motor complications. In the 6-OHDA-lesioned rat, 8-OH-DPAT reduces L-DOPA-induced AIMs severity (Carta et al., 2007). 8-OH-DPAT also prolongs L-DOPA anti-parkinsonian action and, in some studies, decreases peak dose rotations (Ba et al., 2007). In combination with the NMDA antagonist MK-801, 8-OH-DPAT increases the number of L-DOPA-induced contraversive rotations while reducing AIMs severity (Dupre et al., 2008c; Eskow et al., 2008). Local application of 8-OH-DPAT in the primary motor cortex (Ostock et al., 2009, 2011), striatum (Bishop et al., 2007, 2009a) or DRN (Eskow et al., 2007a, 2009) leads to a reduction in L-DOPA-induced AIMs severity. Systemic administration or local application of 8-OH-DPAT in the striatum alleviate AIMs induced by the D_1 agonist SKF-81,297 (Dupre et al., 2007a, 2008a,b, 2011) while increasing SKF-81,297-elicited rotational behaviour (Dupre et al., 2008b). 8-OH-DPAT also alleviates AIMs induced by the D_2 agonist quinpirole (Dupre et al., 2007a,b). The combination of 8-OH-DPAT and the 5-HT_{1B} agonist CP-94,253 decreases AIMs severity, by reducing peak dose striatal dopamine levels following L-DOPA administration (Lindgren et al., 2010). 5-HT_{1A} and 5-HT_{1B} receptor agonists also effectively alleviate apomorphine-induced AIMs, but higher doses are required than for relieving L-DOPA-induced AIMs (Carta et al., 2009).

In the 6-OHDA-lesioned rat, 8-OH-DPAT administration reverses L-DOPA-induced increases in striatal c-Fos immunoreactivity, preprodynorphin (PPD) mRNA (Bishop et al., 2007, 2009a; Ostock et al., 2010) and phosphorylated extracellular signal-related kinase isoforms 1 and 2 ($pERK_{1/2}$) (Button et al., 2009). 8-OH-DPAT administration also reverses L-DOPA-induced increase in c-Fos immunoreactivity in the motor cortex (Ostock et al., 2010). However, when 6-OHDA-lesioned rats are primed with SKF-81,297, 8-OH-DPAT/vehicle administration leads to increased levels of PPD, glutamic acid decarboxylase (GAD) 65/67, NR_{2A} and NR_{2B} mRNA in the intact and lesioned striata, whereas 8-OH-DPAT/SKF-81,297 administration reverses SKF-81,297-induced alterations in NR_{2B} mRNA (Dupre et al., 2010).

Table 5
5-HT_{1A} agonists in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	Animal models		Idiopathic PD
	6-OHDA-lesioned rat	MPTP-lesioned NHP	
8-OH-DPAT	• Anti-parkinsonian action as monotherapy • Induces contraversive rotations as monotherapy • ↓ L-DOPA-induced AIMs • ↓ SKF-81,297-induced AIMs • ↓ Quinpirole-induced AIMs • Extends duration of L-DOPA anti-parkinsonian action • ↓ Peak dose striatal dopamine levels in combination with CP-94,253 • Reverses L-DOPA-induced molecular changes in the striatum • *De novo* administration with L-DOPA prevents development of contraversive rotations • *De novo* administration with CP-94,253 and L-DOPA prevents development of AIMs	n/a	n/a
R-(+)-8-OH-DPAT	• Induces ipsiversive rotations as monotherapy	• ↓ L-DOPA-induced chorea, but not dystonia • ↓ Pramipexole-induced chorea • ↓ L-DOPA anti-parkinsonian action	n/a
BMY-14,802 (BMS-181,100)	• ↓ L-DOPA-induced AIMs	n/a	n/a
Buspirone	• Anti-parkinsonian action as monotherapy • *De novo* administration with L-DOPA prevents development of AIMs • ↓ L-DOPA-induced AIMs • ↓ L-DOPA anti-parkinsonian action at high dose • ↓ L-DOPA-induced contraversive rotations	n/a	• ↓ L-DOPA-induced dyskinesia in 4 studies; no effect on dyskinesia in one study • ↓ L-DOPA anti-parkinsonian action • Anxiolytic effect in one study
Flesinoxan (DU-29,373)	• ↓ L-DOPA-induced AIMs	n/a	n/a
Flibanserin (BMIT-17)	• ↓ L-DOPA-induced contraversive rotations	n/a	n/a
Mirtazapine (Org 3770)	n/a	n/a	• ↓ L-DOPA-induced dyskinesia • ↓ Parkinsonian tremor • Could trigger RBD or psychotic features
Pardoprunox	• Induces contraversive rotations as monotherapy	• Anti-parkinsonian action as monotherapy • *De novo* administration as monotherapy elicits less dyskinesia than L-DOPA • ↓ L-DOPA-induced dyskinesia • ↑ L-DOPA anti-parkinsonian action	• ↓ OFF-time duration in one study, but ineffective in another • Anti-parkinsonian action as monotherapy
Piclozotan (SUN-N4057)	• ↓ L-DOPA-induced AIMs	n/a	• ↑ ON-time without dyskinesia duration • ↓ OFF-time duration
Sarizotan (EMD 128130)	• ↓ L-DOPA-induced AIMs • ↓ Wearing-OFF • No effect on L-DOPA-induced contraversive rotations	• ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA anti-parkinsonian action at high dose	• ↓ L-DOPA-induced dyskinesia in two Phase II studies, but ineffective in a 3rd one • No anti-dyskinetic efficacy when compared to placebo in two Phase III studies • ↓ L-DOPA anti-parkinsonian action at high dose
Tandospirone (SM-3997)	• Induces contraversive rotations as monotherapy • ↑ Apomorphine-induced contraversive rotations	n/a	• ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA anti-parkinsonian action

6-OHDA: 6-hydroxydopamine; AIMs: abnormal involuntary movements; L-: *levo*; L-DOPA: L-3,4-dihydroxyphenylalanine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; n/a: not available; NHP: non-human primate; PD: Parkinson's disease; RBD: REM-sleep behaviour disorder; REM: rapid-eye movements.

De novo co-administration of 8-OH-DPAT with L-DOPA to 6-OHDA-lesioned rats prevents the development of contraversive rotational behaviour, as well as L-DOPA-induced increases in striatal dynorphin and GAD mRNA levels (Tomiyama et al., 2005). *De novo* co-administration of 8-OH-DPAT and CP-94,253 with L-DOPA to 6-OHDA-lesioned rats also prevents the development of AIMs and attenuates the up-regulation of striatal FosB (Munoz et al., 2008), a marker of chronic L-DOPA treatment and dyskinesia (Andersson et al., 1999; Cenci et al., 1999).

In the 6-OHDA-lesioned rat, *de novo* administration of buspirone with L-DOPA delays the emergence of AIMs (Eskow et al., 2007b). Combining buspirone with L-DOPA in dyskinetic rats decreases AIMs severity, but impairs rotarod performance at high dose (Dekundy et al., 2007; Paquette et al., 2009b). However, doses of buspirone up to 10 mg/kg do not impair L-DOPA anti-parkinsonian efficacy when assessed by the sensorimotor test (Paquette et al., 2010). Buspirone reduces the number of L-DOPA-induced contraversive rotations (Gerlach et al., 2011b). Buspirone also alleviates AIMs severity in the 6-OHDA-lesioned mouse (Lundblad et al., 2005).

The 5-HT_{1A} full agonist flesinoxan (Paquette et al., 2009b, 2010; Schoeffter and Hoyer, 1988) and the 5-HT_{1A} partial agonist piclozotan (Kamei et al., 2006; Tani et al., 2009, 2010) also reduce L-DOPA-induced AIMs severity in the 6-OHDA-lesioned rat. Either systemic administration (Bartoszyk et al., 2006b) or local application (Marin et al., 2008, 2009) of sarizotan in the STN of 6-OHDA-lesioned rats effectively alleviates L-DOPA-induced AIMs. In a study that did not evaluate AIMs, sarizotan had no effects on rotational behaviour, but attenuated the shortening of L-DOPA response occurring after chronic treatment (equivalent to the wearing-OFF phenomenon) (Bibbiani et al., 2001).

In the 6-OHDA-lesioned rat, the non-selective 5-HT_{1A} agonist and 5-HT_{2A} antagonist flibanserin significantly reduces the number of contralateral rotations elicited by L-DOPA (Gerlach et al., 2009, 2011b). The sigma-1 (σ_1) receptor antagonist BMY-14,802, which is also a 5-HT_{1A} and alpha-1 (α_1) adrenergic receptor agonist (Table 4), decreases AIMs severity in the L-DOPA-treated 6-OHDA-lesioned rat, an effect abolished by WAY-100,635 (Paquette et al., 2007, 2008, 2009a, 2010).

In the 6-OHDA-lesioned rat, WAY-100,635 abolishes the anti-dyskinetic effects of the serotonin re-uptake inhibitors/releasers 3,4-methylenedioxymethamphetamine (MDMA) and fenfluramine, suggesting that a 5-HT_{1A}-mediated mechanism is involved in their anti-dyskinetic action (Bishop et al., 2006), although this mechanism has been challenged recently (Huot et al., 2011b).

In the MPTP-lesioned common marmoset, R-(+)-OH-DPAT dose-dependently reduces the severity of L-DOPA-induced chorea, but not dystonia, and decreases the anti-parkinsonian benefit of L-DOPA (Iravani et al., 2006). R-(+)-OH-DPAT also reduces chorea induced by the dopamine agonist pramipexole (Iravani et al., 2006).

In the MPTP-lesioned common marmoset, pardoprunox enhances L-DOPA anti-parkinsonian action and alleviates L-DOPA-induced dyskinesia (Jackson et al., 2008; Stockwell et al., 2008; Tayarani-Binazir et al., 2010).

In the MPTP-lesioned cynomolgus macaque, sarizotan (<2.0 mg/kg) effectively diminishes L-DOPA-induced dyskinesia severity without compromising L-DOPA anti-parkinsonian efficacy (Bartoszyk et al., 2006a; Bibbiani et al., 2001; Gregoire et al., 2009). However, higher doses of sarizotan impair L-DOPA anti-parkinsonian benefit (Gregoire et al., 2009). A pharmacokinetic (PK) study performed in the cynomolgus macaque demonstrated that L-DOPA treatment does not alter sarizotan plasma levels (Gregoire et al., 2009), whereas a PK study performed in human demonstrated that sarizotan administration does not modulate L-DOPA plasma levels (Krosser et al., 2007).

Thus, 5-HT_{1A} receptor agonists seem to exert an anti-dyskinetic activity when combined to L-DOPA. Two mechanisms have been proposed to explain their anti-dyskinetic actions. The first one refers to the aforementioned modulation of raphestriatal dopamine release. The second one is related to the modulation of corticostriatal glutamate release. Thus, in the 6-OHDA-lesioned rat, administration of 8-OH-DPAT leads to a reduction in striatal glutamate levels (Mignon and Wolf, 2005). In the 6-OHDA-lesioned rat, 8-OH-DPAT-mediated reduction of L-DOPA-induced striatal glutamatergic efflux correlates with a reduction in AIMs severity (Dupre et al., 2009, 2011). There might be a third mechanism by which 5-HT_{1A} agonists alleviate dyskinesia (Huot and Brotchie, 2011). Indeed, 8-OH-DPAT alleviates SKF-81,297-induced AIMs via a mechanism that does not involve modulation of corticostriatal glutamate release (Dupre et al., 2011). Since SKF-81,297 is a D_1 agonist, its mechanism of action involves direct activation of striatal dopaminergic receptors and is not mediated by raphestriatal dopamine release. The mechanism by which 5-HT_{1A} agonists alleviate dyskinesia induced by dopamine agonists remains unclear, but might involve activation of postsynaptic 5-HT_{1A} receptor, as it was recently suggested (Munoz et al., 2009).

5.1.3.3. Clinical studies. Five trials with buspirone in human PD patients have been published. In each of these studies, the number of subjects enrolled was small (≤16) and only one was a randomised, double-blind, placebo-controlled trial (Bonifati et al., 1994). The doses employed were highly variable from one trial to another (4–100 mg p.o. id). Buspirone was ineffective against dyskinesia and worsened parkinsonism in two patients in one study (Hammerstad et al., 1986). Another study found anxiolytic and anti-dyskinetic effects of high dose buspirone, with concomitant worsening of parkinsonism (Ludwig et al., 1986). In two other studies, buspirone exerted an anti-dyskinetic effect (Bonifati et al., 1994; Kleedorfer et al., 1991) but at the expense of decreasing L-DOPA anti-parkinsonian efficacy (Kleedorfer et al., 1991). In two patients with intrastriatal foetal mesencephalic cell grafts, buspirone decreased the severity of OFF-period dystonia (Politis et al., 2010b).

The non-selective 5-HT_{1A} receptor agonist mirtazapine alleviated L-DOPA-induced dyskinesia in a small study (Meco et al., 2003) and a case report (Pact and Giduz, 1999). Mirtazapine also seems effective against parkinsonian tremor (Alarcon and Estrada, 1999; Gordon et al., 2002; Pact and Giduz, 1999). However, the administration of mirtazapine in PD has been associated with the emergence of REM-sleep behaviour disorder (RBD) with hallucinations and confusion (Onofrj et al., 2003). One case report mentions the development of psychotic features following the addition of mirtazapine to L-DOPA, which disappeared following the cessation of mirtazapine and the introduction of clozapine (Normann et al., 1997).

In Phase II studies, sarizotan (2 and 5 mg p.o. bid) effectively reduced L-DOPA-induced dyskinesia severity in idiopathic PD patients (Bara-Jimenez et al., 2005; Olanow et al., 2004). However, the anti-dyskinetic efficacy of sarizotan could not be reproduced in another Phase II study and higher doses (10 mg p.o. id) increased OFF-time duration (Goetz et al., 2006, 2007). In two Phase III studies (PADDY-1 and PADDY-2), sarizotan significantly alleviated dyskinesia when compared to baseline, but the improvement did not differ to the placebo groups (Goetz et al., 2008a; Muller et al., 2006; Rascol et al., 2006).

The anti-dyskinetic efficacy of tandospirone was evaluated in 10 dyskinetic PD patients. Dyskinesia were alleviated in 5 patients, but L-DOPA anti-parkinsonian efficacy was reduced in 4 (Kannari et al., 2002).

Two abstracts state that piclozotan, in combination with L-DOPA, increases duration of ON-time without dyskinesia and

decreases duration of OFF-time (Hauser et al., 2009b; Sage et al., 2009).

In a safety and efficacy study performed in advanced PD patients, pardoprunox did not significantly enhance L-DOPA anti-parkinsonian action, despite a trend towards a reduction in OFF-time duration (Hauser et al., 2009a). However, in another study, pardoprunox significantly reduced OFF-time duration in L-DOPA-treated advanced PD subjects (Bronzova et al., 2010a). In a trial performed in early PD patients, pardoprunox as monotherapy significantly improved motor disability (Bronzova et al., 2008a,b, 2010b). In a Phase II study conducted in early PD patients, pardoprunox and pramipexole were both more effective than placebo as monotherapy and no difference was encountered between the two active treatment arms (Sampaio et al., 2010). In general, pardoprunox seems well tolerated in the PD population (Hauser et al., 2008). A Phase III study comparing pardoprunox to pramipexole and placebo as monotherapy in early PD was recently completed (http://www.clinicaltrials.gov/, NCT00335166), whereas a pilot Phase II study comparing the addition of pardoprunox to the addition of pramipexole to L-DOPA in advanced PD was recently terminated, due to strategic considerations (http://www.clinicaltrials.gov/, NCT00903838).

5.1.4. 5-HT$_{1A}$ receptors in Parkinson's disease: summary

Numerous studies investigating 5-HT$_{1A}$ receptors in PD and animal models of PD have been performed. The following points need be remembered:

- In the MPTP-lesioned macaque, 5-HT$_{1A}$ receptor levels are altered in both the L-DOPA-naïve and L-DOPA-chronic states, suggesting they are involved in the pathophysiology of both the parkinsonian and dyskinetic states.
- In idiopathic PD, 5-HT$_{1A}$ receptor levels increase in the frontal and temporal cortices.
- High 5-HT$_{1A}$ receptor levels in the temporal cortex are associated with depression in PD dementia, whereas lower midbrain raphe 5-HT$_{1A}$ receptor levels correlate with tremor.
- 5-HT$_{1A}$ receptor agonists reverse haloperidol-induced catalepsy in the rat.
- 5-HT$_{1A}$ receptor agonists increase activity in the reserpine-treated rat.
- 5-HT$_{1A}$ receptor agonists have alleviated L-DOPA-induced dyskinesia in several preclinical and clinical studies, but have had no effect on dyskinesia severity in others.
- 5-HT$_{1A}$ receptor agonists may hinder L-DOPA anti-parkinsonian action.

Despite extensive investigation in numerous preclinical and clinical trials, the efficacy of 5-HT$_{1A}$ receptor agonists as anti-dyskinetic agents is inconsistent across studies. Moreover, the anti-cataleptic efficacy of 5-HT$_{1A}$ agonists and their effect on motor activity in the reserpine-treated rat suggest that they can exert an anti-parkinsonian effect, yet they have impaired L-DOPA anti-parkinsonian action in numerous studies.

These apparently contradictory effects of 5-HT$_{1A}$ agonists could be related to their complex pharmacology. Indeed, compounds such as buspirone and tandospirone are partial 5-HT$_{1A}$ agonists (Blier and Ward, 2003; Hamik et al., 1990). Moreover, as presented in Table 4, most of the purportedly selective 5-HT$_{1A}$ receptor agonists are not selective and display affinity for several other neurotransmitter receptors, such as D$_2$-like receptors, which could play a role in both the anti-dyskinetic efficacy and the deleterious effect on parkinsonism encountered in some of the studies cited in the previous sections. This D$_2$-like effect is likely to be important in the mechanism of action of some of the allegedly selective 5-HT$_{1A}$ receptor agonists. Accordingly, when sarizotan and the D$_3$ receptor agonist PD-128,907 are co-administered with L-DOPA to 6-OHDA-lesioned rats, the beneficial effects of sarizotan on contraversive rotations and AIMs are lost (Gerlach et al., 2011a). In addition, a PET study demonstrated that sarizotan 20–50 mg p.o. id leads to equivalent D$_2$ and 5-HT$_{1A}$ receptor occupancies (26–39% vs. 20–29%, respectively) (Rabiner et al., 2002). Furthermore, in order to demonstrate that selective 5-HT$_{1A}$ receptor activation is the mechanism by which the non-selective 5-HT$_{1A}$ receptor agonists reduce dyskinesia, some of the trials cited above have combined the 5-HT$_{1A}$ receptor antagonist WAY-100,635 to 5-HT$_{1A}$ agonists, in order to reverse the anti-dyskinetic efficacy of the agonist compounds. However, WAY-100,635 is also a potent D$_4$ receptor agonist (Chemel et al., 2006; Marona-Lewicka and Nichols, 2009) and this agonist effect on D$_4$ receptors might well contribute to the loss of the anti-dyskinetic effect upon its administration, as suggested by preliminary work performed in the MPTP-lesioned macaque (Huot et al., 2010b). Another possible explanation for the variable effect of 5-HT$_{1A}$ agonists on parkinsonism could be related to their preferential anatomical site of action, if any. Thus, as seen previously, 5-HT$_{1A}$ receptor levels are decreased in the external cortical layers but increased in the middle cortical layers in the MPTP-lesioned macaque (Huot et al., 2010e). Stimulating 5-HT$_{1A}$ receptors along the corticostriatal pathway exerts an anti-dyskinetic effect, as discussed above, by a reduction of glutamate release. Stimulation of thalamocortical 5-HT$_{1A}$ receptors would also decrease glutamate release, resulting in less cortical excitation; while less cortical excitation would result in an anti-dyskinetic action, it might also impair L-DOPA anti-parkinsonian efficacy (Huot et al., 2011a). In order to use 5-HT$_{1A}$ agonists to alleviate L-DOPA-induced dyskinesia without reducing L-DOPA anti-parkinsonian efficacy, it may be necessary to antagonise selectively 5-HT$_{1A}$ receptors along the corticostriatal pathway, therefore highlighting the need for compounds displaying anatomical selectivity in addition to pharmacological selectivity. Compounds with such anatomical selectivity are currently being developed (Newman-Tancredi, 2011).

5.2. 5-HT$_{1B/1D}$ receptors

Human 5-HT$_{1B}$ receptor (MIM *182131, http://www.ncbi.nlm.nih.gov/omim/182131) gene was cloned and sequenced in 1992 (Hamblin et al., 1992b; Jin et al., 1992; Mochizuki et al., 1992). This intronless gene is located on chromosome 6q13 and codes for a 390 amino acid protein. Human 5-HT$_{1D}$ receptor gene (MIM *182133, http://www.ncbi.nlm.nih.gov/omim/182133) was cloned and sequenced in 1991 (Hamblin and Metcalf, 1991). It is an intronless gene which codes for a 377 amino acid protein (Hamblin and Metcalf, 1991; Weinshank et al., 1992). The gene is located on chromosome 1p36.3-p34.3 (Jin et al., 1992; Libert et al., 1991). Human 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors shares 59% amino acid homology (Hamblin et al., 1992b) and both receptors are coupled to G$_i$ proteins (Hamblin et al., 1992b). 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors form homodimers when expressed alone, but heterodimers when co-expressed (Xie et al., 1999). Human and rat 5-HT$_{1B}$ receptors have different pharmacological profiles, despite sharing 93% amino acid homology and 96% amino acid homology in the transmembrane regions (Adham et al., 1992). Previously, human 5-HT$_{1B}$ receptors were referred to as 5-HT$_{1D\beta}$ receptors, whereas human 5-HT$_{1D}$ receptors were referred to as 5-HT$_{1D\alpha}$ receptors (Hartig et al., 1996). It was suggested to precede human 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors by "h" (h5-HT$_{1B}$ and h5-HT$_{1D}$) and to precede rat receptors by "r" (r5-HT$_{1B}$ and r5-HT$_{1D}$) to highlight the differences between the receptors in the two species (Hartig et al., 1996).

5-HT$_{1B}$ receptors mediate several behaviours. They are involved in addiction (Brunner and Hen, 1997; Przegalinski et al., 2007), aggression (Olivier and van Oorschot, 2005; Ramboz et al., 1996;

Saudou et al., 1994), alcoholism (Crabbe et al., 1996), impulsivity (Brunner and Hen, 1997), learning and memory (Ahlander-Luttgen et al., 2003; Buhot et al., 2003), anxiety and hyperactivity (Brunner et al., 1999; Rempel et al., 1993), and migraine (Sari, 2004). 5-HT_{1B} receptors also modulate the release of neurotransmitters such as 5-HT (Knobelman et al., 2000; Martin et al., 1992; Rutz et al., 2006), acetylcholine (Rutz et al., 2006), dopamine (Benloucif et al., 1993; Sarhan et al., 1999, 2000), GABA (Stanford and Lacey, 1996) and glutamate (Rhoades et al., 1994; Tanaka and North, 1993).

In the rat brain, high levels of 5-HT_{1B} receptors are encountered in the basal ganglia, especially in the GP, SN and STN. Moderate to low levels are found in the amygdala, hippocampus, striatum, DRN and motor cortex (Bruinvels et al., 1993). A similar distribution of 5-HT_{1B} receptor mRNA is found in the rat brain, except in the SN, in which mRNA is virtually undetectable (Bruinvels et al., 1994a). Within the GP and SN, 5-HT_{1B} receptors are localised on the membrane of pre-terminal axons, suggesting they are involved in mediating neurotransmitter release (Riad et al., 2000). In the mouse brain, 5-HT_{1B} mRNA is absent from the GP and SN, despite high binding levels (Boschert et al., 1994).

In the human brain, 5-HT_{1B} receptors predominate in the GP and SN, followed by the periaqueductal central grey region, external cortical layers and striatum (Varnas et al., 2004a). However, that last study employed [^{3}H]-GR 125,743 as the radioligand, a compound that binds non-selectively to 5-$HT_{1B/1D}$ receptors (Domenech et al., 1997; Xie et al., 1999). Similar results were obtained with [^{3}H]-sumatriptan (Pascual et al., 1996), which also binds non-selectively to 5-$HT_{1B/1D}$ receptors (Peroutka and McCarthy, 1989). Another study focussing on the human brainstem encountered high 5-HT_{1B} receptor levels within the periaqueductal central grey region (Castro et al., 1997).

An *in situ* hybridisation (ISH) study found that 5-$HT_{1D\alpha}$ (*i.e.* 5-HT_{1D}) receptor mRNA is very scarce in the rat brain, with moderately abundant levels in the striatum (Bruinvels et al., 1994a). Several autoradiographic receptor binding studies assessing the distribution of 5-HT_{1D} receptors were performed in the rat and human brains (Barone et al., 1994; Bruinvels et al., 1993, 1994b; del Olmo et al., 1996; Herrick-Davis and Titeler, 1988; Miller and Teitler, 1992; Pascual et al., 1996; Waeber et al., 1988a). However, because non-selective radioligands were used or 5-$HT_{1D\beta}$ (*i.e.* 5-HT_{1B}) receptors were being measured, these results will not be discussed further.

5.2.1. 5-$HT_{1B/1D}$ receptors in Parkinson's disease

There does not appear to be any consistent changes in 5-HT_{1B} receptor levels in PD and the lack of commercially available selective ligand complicates their assessment. In the rat brain, following neonatal destruction of nigrostriatal dopaminergic neurons, 5-HT_{1B} receptor levels (assessed with [^{125}I]-cyanopindolol, a non-selective 5-$HT_{1A/1B}$ radioligand (Hamblin et al., 1992a; Hamel et al., 1989)) are increased in the striatum, GP and SN (Radja et al., 1993). In the adult 6-OHDA-lesioned rat, 5-HT_{1B} receptors and their adaptor protein p11 (S100A10) are upregulated in striatonigral neurons following L-DOPA treatment, but not following 6-OHDA lesion without dopaminergic therapy (Svenningsson et al., 2008; Zhang et al., 2008).

An autoradiographic study using [^{3}H]-GR 125,743 found increased 5-$HT_{1B/1D}$ levels in the SNr and putamen of MPTP-lesioned macaques when compared to normal macaques; treatment with L-DOPA elevated 5-$HT_{1B/1D}$ receptor levels in the caudate nucleus, the nucleus accumbens and the GPe (Riahi et al., 2010). In contrast, an autoradiographic binding study using [^{3}H]-sumatriptan as the radioligand found no change in 5-$HT_{1B/1D}$ receptor levels in the putamen, GPe, GP pars interna (GPi) or SN of PD patients in comparison to controls (Castro et al., 1998).

To our knowledge, no study has reported 5-HT_{1D} receptor levels in PD. A study using non-selective ligands, *i.e.* [^{3}H]-5-HT in the presence of 8-OH-DPAT and mesulergine, claimed that 5-HT_{1D} (but more likely 5-$HT_{1D\beta}$, *i.e.* 5-HT_{1B}) receptor levels remain unchanged in various brain areas in PD (Waeber and Palacios, 1989).

5.2.2. 5-$HT_{1B/1D}$ receptor modulation as a potential target for parkinsonism and treatment-related complications

5-$HT_{1B/1D}$ receptor modulators have been studied mostly for their anti-dyskinetic effects. To our knowledge, only one study evaluated their anti-parkinsonian actions. In the common marmoset, following chronic haloperidol treatment, the 5-$HT_{1B/1D}$ receptor agonist SKF-99,101-H reduced motor activity counts and increased parkinsonian disability when administered as monotherapy, whereas the 5-HT_{1B} receptor antagonist SB-224,289-A had no effect. Both drugs had no effect when given as monotherapy to the MPTP-lesioned common marmoset (Jackson et al., 2004). In the L-DOPA-treated MPTP-lesioned common marmoset primed to exhibit dyskinesia, SKF-99,101-H alleviated dyskinesia, but reduced motor activity counts and impaired L-DOPA anti-parkinsonian benefit (Jackson et al., 2004).

In the dyskinetic 6-OHDA-lesioned rat, low/moderate doses of the 5-HT_{1B} receptor agonist CP-94,253 had no effects on AIMs severity when administered in combination with L-DOPA, but acted synergistically with 8-OH-DPAT to reduce AIMs elicited by either L-DOPA or apomorphine (Munoz et al., 2009). At higher doses, CP-94,253 as monotherapy effectively alleviated L-DOPA- and apomorphine-induced AIMs, an effect blocked by the 5-HT_{1B} antagonist SB-224,289 (Carta et al., 2007). That last study also demonstrated a synergy between CP-94,253 and 8-OH-DPAT against L-DOPA-induced AIMs, but not against apomorphine-induced AIMs (Carta et al., 2007). In another study, CP-94,253 significantly alleviated AIMs induced by either L-DOPA or SKF-81,297, in addition to improve the performance of the rats during the forepaw adjusting test (Jaunarajs et al., 2009). CP-94,253 also decreased the number of L-DOPA-induced contraversive rotations and AIMs severity in the 6-OHDA-lesioned mouse, an effect no longer present in the p11-KO mouse (Zhang et al., 2008).

The pharmacological profile of the drugs discussed in this section is provided in Table 6, whereas their effects in the preclinical trials cited in the previous paragraphs are summarised in Table 7. To our knowledge, no clinical trials have been performed with 5-$HT_{1B/1D}$ receptor agonists in idiopathic PD.

5.2.3. 5-$HT_{1B/1D}$ receptors in Parkinson's disease: summary

In comparison to 5-HT_{1A} receptors, few studies investigating 5-$HT_{1B/1D}$ receptors in PD and animal models of PD have been

Table 6
Pharmacological profile of 5-$HT_{1B/1D}$ receptor ligands studied in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	5-$HT_{1B/1D}$ receptor affinity (nM)	Other binding sites (nM)	References
CP-94,253	4.4 (5-HT_{1B}) and 49 (5-HT_{1D})	5-HT_{1A} (89), 5-HT_{2A} (1600), and 5-HT_{2C} (860)	Kenneth Koe et al. (1992)
SB-224,289-A	6.91 (5-HT_{1B}) and 537 (5-HT_{1D})	5-HT_{2A} (1202), 5-HT_{2C} (631), and 5-HT_4 (2042)	Selkirk et al. (1998)
SKF-99,101-H	1.99 (5-HT_{1B}) and 1.91 (5-HT_{1D})	5-HT_{1A} (37.2), 5-HT_{1E} (275), 5-HT_{2A} (1622), 5-HT_{2C} (417), D_2 (4074), and D_3 (5248)	Hagan et al. (1995)

Unless indicated otherwise, values are provided as the dissociation constant (K_d).
5-HT: serotonin; nM: nanomole.

Table 7
5-$HT_{1B/1D}$ modulators in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	Animal models		Idiopathic PD
	6-OHDA-lesioned rat	MPTP-lesioned NHP	
CP-94,253	• ↓ L-DOPA-induced AIMs • ↓ Apomorphine-induced AIMs • ↓ SKF-81,297-induced AIMs • Synergistic effect on L-DOPA-induced AIMs when combined with 8-OH-DPAT	n/a	n/a
SB-224,289-A	n/a	• No effect as monotherapy in the MPTP-lesioned common marmoset	n/a
SKF-99,101-H	n/a	• No effect as monotherapy in the MPTP-lesioned common marmoset • ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA anti-parkinsonian action	n/a

6-OHDA: 6-hydroxydopamine; AIMs: abnormal involuntary movements; L-: *levo*; L-DOPA: L-3,4-dihydroxyphenylalanine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; n/a: not available; NHP: non-human primate; PD: Parkinson's disease.

published. Furthermore, the autoradiographic binding studies assessing the fate of 5-$HT_{1B/1D}$ receptors in PD and related animal models have used non-selective radioligands, thereby limiting their conclusions. Based on the currently available literature, the following conclusions can be made:

- 5-HT_{1B} receptor levels are upregulated in striatonigral neurons of the L-DOPA-treated 6-OHDA-lesioned rat.
- 5-$HT_{1B/1D}$ agonists reduce L-DOPA-induced AIMs in the 6-OHDA-lesioned rat and L-DOPA-induced dyskinesia in the MPTP-lesioned NHP.
- 5-$HT_{1B/1D}$ agonists synergise with 8-OH-DPAT to reduce L-DOPA-induced AIMs.
- 5-$HT_{1B/1D}$ agonists may hinder L-DOPA anti-parkinsonian action.
- To date, no clinical trials have been performed with 5-$HT_{1B/1D}$ agonists in idiopathic PD.

5.3. 5-HT_{1E} and 5-HT_{1F} receptors

To date, no study examining 5-HT_{1E} and 5-HT_{1F} receptors in PD, whether anatomical or behavioural, has been reported. In fact, very little is known about the function of these receptors, even under physiological conditions, due to lack of selective ligands (Barnes and Sharp, 1999).

5.4. 5-HT_{2A} receptors

Human 5-HT_{2A} gene (MIM *182135, http://www.ncbi.nlm.nih.gov/omim/182135) maps to chromosome 13q14–q21 (Hsieh et al., 1990; Sparkes et al., 1991). It is formed by 3 exons separated by 2 introns and codes for a 471 amino acid protein (Chen et al., 1992). Human and rat 5-HT_{2A} receptors share 91.3% homology, but 99.4% homology in their 7 transmembrane domains (Sparkes et al., 1991). 5-HT_{2A} receptor is a $G_{\alpha q}$ protein-coupled receptor and its activation leads to the production of inositol triphosphate/diacylglycerol, arachidonic acid and 2-arachidonylglycerol (Urban et al., 2007). 5-HT_{2A} receptor activation induces Fos expression (Gresch et al., 2002; Mackowiak et al., 1999). 5-HT_{2A} receptor desensitisation can occur with (Ivins and Molinoff, 1991) or without (Roth et al., 1995a) down-regulation. Two serine residues appear to play a critical role in 5-HT_{2A} receptor desensitisation (Gray et al., 2003). 5-HT_{2A} receptors modulate the release of glutamate in the cortex and striatum (Aghajanian and Marek, 1999b; Ferguson et al., 2010a), and dopamine in the striatum and SN (Lucas and Spampinato, 2000; Olijslagers et al., 2004; Parsons and Justice, 1993).

5-HT_{2A} receptors are involved in a variety of behaviours and diseases, such as anxiety (Weisstaub et al., 2006), cognition (Elliott et al., 2009), movement (Dave et al., 2004), schizophrenia (Burnet et al., 1996), attention deficit and hyperactivity disorder (Quist et al., 2000), aggression and suicide (Oquendo et al., 2006; Rosel et al., 2004), and social isolation (Schiller et al., 2003). 5-HT_{2A} receptors mediate some of the effects of hallucinogenic drugs (Aghajanian and Marek, 1999a; Glennon et al., 1983; Krebs-Thomson et al., 1998; Pierce and Peroutka, 1989; Sadzot et al., 1989; Sanders-Bush et al., 1988; Scruggs et al., 2000), play a role in drug addiction (Bubar and Cunningham, 2006) and are involved in the mechanism of action of antipsychotic drugs (Jakab and Goldman-Rakic, 1998). Indeed, as presented in Table 8, all of the atypical antipsychotics discussed in this section exhibit high affinity for 5-HT_{2A} receptors.

In the rat brain, 5-HT_{2A} mRNA is most abundant in the frontal cortex, especially in layer V. Intermediate levels are encountered in the striatum and SNc. 5-HT_{2A} mRNA seems absent from the GP, SNr and STN (Mengod et al., 1990b; Pompeiano et al., 1994). In the rat, autoradiographic binding studies have demonstrated that 5-HT_{2A} receptors are most abundant in the claustrum and middle cortical layers, with moderate levels in the striatum and GP, and low levels in the SN (Leysen et al., 1982; Pazos et al., 1985). Within the middle cortical layers, 5-HT_{2A} receptors are predominantly localised on postsynaptic dendrites of pyramidal neurons, few are localised on presynaptic axons and varicosities, and they are very scarce on glial processes or parvalbumin-positive interneurons (Hamada et al., 1998; Jansson et al., 2001; Miner et al., 2003; Willins et al., 1997). Electron microscopy has demonstrated that 5-HT_{2A} receptors are present on asymmetric type-I synapses (Hamada et al., 1998). Within neurons, the majority of 5-HT_{2A} receptors are cytoplasmic rather than membrane-bound (Cornea-Hebert et al., 1999). In the rat prefrontal cortex, the majority of pyramidal neurons and some interneurons expressing 5-HT_{2A} receptors also express 5-HT_{1A} receptors (Amargos-Bosch et al., 2004; Santana et al., 2004).

In the normal macaque (both cynomolgus and rhesus) brain, 5-HT_{2A} receptors are mostly expressed in the neocortical layers I and III–IV. 5-HT_{2A} receptor levels are much lower in the basal ganglia, including the striatum, GP and SN (Huot et al., 2010h; Lopez-Gimenez et al., 2001b). No 5-HT_{2A} receptor mRNA is present in the striatum, GP or SN (Lopez-Gimenez et al., 2001b).

Autoradiographic receptor binding studies performed in the human brain have demonstrated that the highest 5-HT_{2A} receptor levels are encountered in the middle layers of the cortex; intermediate levels are found in the striatum, low/intermediate

Table 8
Pharmacological profile of 5-HT_{2A} receptor ligands studied in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	5-HT_{2A} receptor affinity (nM)	Other binding sites (nM)	References
Aripiprazole	3.4	SERT (98), 5-HT_{1A} (1.7), 5-HT_{2C} (15), 5-HT_6 (161), 5-HT_7 (14.5), D_1 (410), D_{2S} (0.59), D_{2L} (0.52), D_2 (4.7), D_3 (9.1), and D_4 (260)	Jordan et al. (2002), Lawler et al. (1999), and Stark et al. (2007)
Clozapine	0.5–16	5-HT_{1D} (130), 5-HT_{2C} (1.3–63), 5-HT_3 (52–90), 5-HT_6 (7.9), 5-HT_7 (20), α_1 (9.2), α_2 (62), D_1 (115), D_2 (45–230), D_3 (180–1575), D_4 (9–53), M_1 (3.1), M_2 (48), M_3 (20.1), M_4 (11), M_5 (11.2), and NMDA (589)	Ashby and Wang (1996), Bolden et al. (1991), Bymaster et al. (2001), Herrick-Davis et al. (2000), Lidsky et al. (1993), Liegeois et al. (1995), Richelson and Souder (2000), Selent et al. (2008), Van Tol et al. (1991), and Vanover et al. (2006)
Cyproheptadine	6.5	5-HT_{1A} (700), 5-HT_{2C} (12.6), 5-HT_6 (135), 5-HT_7 (47.9), α_1 (100), α_2 (760), and H_1 (2.7)	Hoyer et al. (1994) and Leysen et al. (1981)
DOI	0.7	5-HT_{2B} (20) and 5-HT_{2C} (2.4)	Nelson et al. (1999)
Fluperlapine	7.9	5-HT_{2C} (19.9), 5-HT_6 (15.8), 5-HT_7 (5.01), D_2 (316), D_4 (130)	Roth et al. (1994) and Roth et al. (1995b)
JL-18	94	D_1 (398), D_2 (530), D_4 (21), and M (48)	Liegeois et al. (1995)
Ketanserin	1.25	VMAT (6–45), 5-HT_{1B} (707), 5-HT_{1D} (138), 5-HT_{2B} (750), 5-HT_{2C} (48), α_1 (30.2), D_2 (200), and H_1 (10)	Boess and Martin (1994), Leysen et al. (1981), Leysen et al. (1982), McKenna and Peroutka (1989), and Zgombick et al. (1997)
MDMA	5100	5-HT_{2B} (500), α_1 (18,400), α_2 (3600), β (19,200), D_1 (148,000), D_2 (95,000), M_1 (5800), M_2 (15,100), H_1 (5700), MAO-A (44,000), MAO-B (370,000), DAT (1572–15,800), and NET (462 (K_d)–27,700 (EC_{50})), SERT (238 (K_d)–15,900 (EC_{50}))	Battaglia et al. (1988), Han and Gu (2006), Huot et al. (2010f), Leonardi and Azmitia (1994), Rothman et al. (2001), Setola et al. (2003), and Verrico et al. (2007)
Melperone	280	α_1 (30.5*), α_2 (960*), D_2 (88), and D_4 (410)	Christensson (1989) and Seeman et al. (1997)
Methysergide	1.07–15	5-HT_{1A} (398), 5-HT_{1B} (200), 5-HT_{1D} (100),5-HT_{2B} (9.1), 5-HT_{2C} (1.26), 5-HT_6 (371), 5-HT_7 (12.6) α_1 (2300), and α_2 (2600)	Bonhaus et al. (1997), Hoyer et al. (1994), Leysen et al. (1981), and Rothman et al. (2000)
Mianserin	0.4	DAT (9400), NET (22*–410*), SERT (1100*–4000), 5-HT_{2C} (4.4), 5-HT_3 (7.1), 5-HT_7 (56), α_1 (54.9), α_{2A} (4.8), α_{2C} (3.8), α_2 (57.5), D_1 (1420), D_2 (2197), D_3 (2841), H_1 (1.0), and M (3981)	de Boer et al. (1988), Fernandez et al. (2005), Hyttel (1982, 1994), Kooyman et al. (1994), Lee et al. (1982), Richelson and Pfenning (1984) and Tatsumi et al. (1997)
N-Desmethylclozapine	7.9	5-HT_{2C} (19.9), 5-HT_6 (126), 5-HT_7 (50.1), α_1 (50.1), D_2 (63.1), D_3 (158), D_4 (63.1), and H_1 (5.0)	Lameh et al. (2007)
Olanzapine	1.48	5-HT_{1A} (610), 5-HT_{1D} (150), 5-HT_{2B} (6.3), 5-HT_{2C} (4.1), 5-HT_3 (57), 5-HT_6 (7.9), 5-HT_7 (79), α_1 (44), α_2 (280), D_2 (20), D_3 (20), D_4 (20), H_1 (0.087), M_1 (2.5), M_2 (18), M_3 (13), M_4 (10), and M_5 (6)	Bymaster and Falcone (2000), Bymaster et al. (2001), Richelson and Souder (2000), and Selent et al. (2008)
Pimavanserin (ACP-103)	0.40–0.50	5-HT_{2C} (1.58–16)	Li et al. (2005) and Vanover et al. (2006)
Quetiapine	31	5-HT_{1A} (300), 5-HT_{1D} (560), 5-HT_{2C} (3500) 5-HT_3 (170), 5-HT_6 (2241), α_1 (8.1), α_2 (80), σ_1 (220), D_1 (455), D_2 (770), H_1 (19), M_1 (120), M_2 (630), M_3 (1320), and M_4 (660)	Bymaster et al. (1996), Bymaster et al. (2001), Hirsch et al. (1996), Richelson and Souder (2000), and Schotte et al. (1996)
Risperidone	0.15–0.16	5-HT_{1A} (190–253), 5-HT_{1D} (3.9), 5-HT_{2C} (32), 5-HT_6 (2586), 5-HT_7 (5), α_1 (0.81–2.7), α_2 (7.54), σ_1 (950), D_1 (534), D_2 (3.13), D_3 (9.5), D_4 (8.5), and H_1 (2.23–5.2)	Bymaster et al. (1996), Bymaster et al. (2001), Hemedah et al. (1999), Leysen et al. (1988), Richelson and Souder (2000), Roth et al. (1994), Schotte et al. (1996), and Seeger et al. (1995)
Ritanserin	0.08–0.9	5-HT_{1A} (1370), 5-HT_{2C} (0.44), 5-HT_7 (25–1995), α_1 (35), α_2 (60), D_1 (718), D_2 (22–30), and H_1 (11.8–24)	Hemedah et al. (1999), Leysen et al. (1985, 1988), Maertens de Noordhout and Delwaide (1986), and Vanover et al. (2006)
R-MDMA	3310	D_2 (25,400), DAT (19,300 (EC_{50}) → 50,000 (K_d)), NET (>20,000 (EC_{50}) → 50,000 (K_d)), and SERT (4740 (EC_{50})–24,500 (K_d))	Huot et al. (2010f), Lyon et al. (1986), and Verrico et al. (2007), Huot et al. (2011b)
Volinanserin (M100,907, MDL100,907)	0.030–0.85	5-HT_{2C} (3.80–136), α_1 (128), σ (87), D_1 (5300), D_2 (2250), D_3 (6700), and D_4 (540)	Kehne et al. (1996), Li et al. (2005), and Vanover et al. (2006)
Ziprasidone	0.12	NET (50), SERT (51), 5-HT_{1A} (1.9), 5-HT_{1D} (2.4), 5-HT_{2C} (0.9), 5-HT_6 (30), α_1 (2.6), α_2 (154), σ_1 (110), D_1 (525), D_2 (2.6), D_3 (7.2), D_4 (32), H_1 (4.6), and M (2440)	Bymaster et al. (2001), Richelson and Souder (2000), Schotte et al. (1996), and Seeger et al. (1995)

Unless indicated otherwise, values are provided as the dissociation constant (K_d).
*: values are provided as the half-maximal effective concentration (EC_{50}). 5-HT: serotonin; DAT: dopamine transporter; DOI: (±)-2,5-dimethoxy-4-iodoamphetamine; MDMA: 3,4-methylenedioxymethamphetamine; NET: noradrenaline transporter; nM: nanomole; R-: *rectus*; SERT: 5-HT transporter; VMAT: vesicular monoaminergic transporter.

levels are found in the GP and SN, and low levels are present in the zona incerta, which encompasses the STN (Hall et al., 2000; Hoyer et al., 1986; Huot et al., 2010a; Pazos et al., 1987b; Varnas et al., 2004a). These results are somewhat variable depending on the radioligand used. A PET study performed in healthy human subjects revealed similar results (Wong et al., 1987). Within the cortex, 5-HT_{2A} receptor mRNA is expressed in both pyramidal cells and interneurons (Burnet et al., 1995).

5.4.1. 5-HT_{2A} receptors in Parkinson's disease

Several studies, mostly post mortem, have assessed the fate of 5-HT_{2A} receptors in animal models of PD and idiopathic PD. In the

neonatal 6-OHDA-lesioned rat, 5-HT_{2A} receptor mRNA increases in the striatum, especially in the lateral sectors; this increase is abolished by the administration of apomorphine or SKF-38,393 (Laprade et al., 1996). In the normal rat striatum, 5-HT_{2A} mRNA is present in neurons whether they express preproenkephalin (PPE) or not, whereas it seems restricted to PPE-expressing neurons in the dopamine-denervated striatum lesioned during the neonatal period (Laprade et al., 1996). In the adult rat, following neonatal destruction of the nigrostriatal system, striatal 5-HT_{2A} receptor levels are increased by up to 60% (Radja et al., 1993).

In the adult rat, 6-OHDA lesion of the nigrostriatal pathway leads to an increase in 5-HT_{2A} receptor mRNA levels in the striatum (Numan et al., 1995; Zhang et al., 2007b), but not in the STN (Zhang et al., 2007b). The striatal increase is abolished by L-DOPA treatment (Zhang et al., 2007b). At odds with these results, a study performed in the L-DOPA-naïve 6-OHDA-lesioned rat reported reduced 5-HT_{2A} receptor levels in the striatum, as well as in the cingulate, insular, prefrontal and primary somatosensory cortices (Li et al., 2010).

In contrast, in the MPTP-lesioned macaque, no changes in 5-HT_{2A} receptor levels occur in the cortex and basal ganglia following MPTP lesion. However, chronic L-DOPA treatment leads to an increase in 5-HT_{2A} receptor levels in the striatum, middle layers of the motor cortex and anterior cingulate cortex (Fig. 8) (Huot et al., 2010g,h; Riahi et al., 2011). In the MPTP-lesioned macaque, treatment with L-DOPA and docosohexaenoic acid for one month leads to increased 5-HT_{2A} receptor levels in the nucleus accumbens, putamen, ventromedial caudate nucleus and anterior cingulate cortex when compared to MPTP-lesioned macaques treated with L-DOPA/vehicle (Gregoire et al., 2010). In the ovariectomised, hemi-MPTP-lesioned, L-DOPA-naïve, aged cynomolgus macaque, treatment with 17β-oestradiol leads to increases in 5-HT_{2A} receptor levels in the superior frontal gyrus, caudate and putamen, but not in the anterior cingulate gyrus, on both the intact and lesioned sides (Sanchez et al., 2011). Limitations of this last study were mentioned in the 5-HT_{1A} receptors subsection (*vide supra*).

In idiopathic PD, 5-HT_{2A} receptor levels are decreased in the temporal cortex of patients with (Cheng et al., 1991; Maloteaux et al., 1988) and without (Maloteaux et al., 1988) dementia. The fate of 5-HT_{2A} receptors in the frontal cortex is unclear, as three studies found stable 5-HT_{2A} receptor levels in PD, regardless of disease manifestations (Huot et al., 2010a; Maloteaux et al., 1985, 1988), whereas another one, which did not detail the clinical status of the PD subjects included, found increases in 5-HT_{2A} receptor levels in both BA_{11} and BA_{21} (Chen et al., 1998). In the entorhinal and parietal cortices of demented and non-demented PD patients, 5-HT_{2A} receptor levels do not differ from controls (Perry et al., 1984). 5-HT_{2A} receptor levels increase in the temporal cortex of PD patients with visual hallucinations (VH), when compared to PD patients without VH (Ballanger et al., 2008, 2010; Huot et al., 2009, 2010a). 5-HT_{2A} receptor levels are also elevated in the bilateral inferior occipital gyrus, right fusiform gyrus, bilateral dorsolateral prefrontal cortices, medial orbitofrontal cortex and insula of PD patients with VH (Fig. 9) (Ballanger et al., 2010). 5-HT_{2A} receptor levels also increase in the motor cortex of PD patients, regardless of their cognitive/psychiatric status (Huot et al., 2010a). These changes in 5-HT_{2A} receptor levels in key areas for visual processing and motor control strongly suggest that they mediate L-DOPA-induced VH and motor complications.

5-HT_{2A} receptors could also play a role in pathological gambling and impulsive-compulsive behaviours in PD. Thus, the single nucleotide polymorphism His452Tyr is associated with pathological gambling in PD (Bocquillon et al., 2009), whereas the T102C variant of the allele T102 might predispose to impulsive-compulsive behaviour in PD patients taking low-dose dopaminergic drugs (Lee et al., 2011).

5.4.2. 5-HT_{2A} receptor modulation as a potential target for parkinsonism and treatment-related complications

5-HT_{2A} receptor antagonists have been studied in PD for their potential effects on both motor and non-motor complications of treatment. The majority of the molecules discussed in the next subsections are atypical antipsychotics. Several studies assessing the effects of atypical antipsychotics in idiopathic PD and animal models of PD were performed, because their pharmacological profile makes them less likely to worsen parkinsonism than typical antipsychotics. Indeed, atypical antipsychotics harbour a high

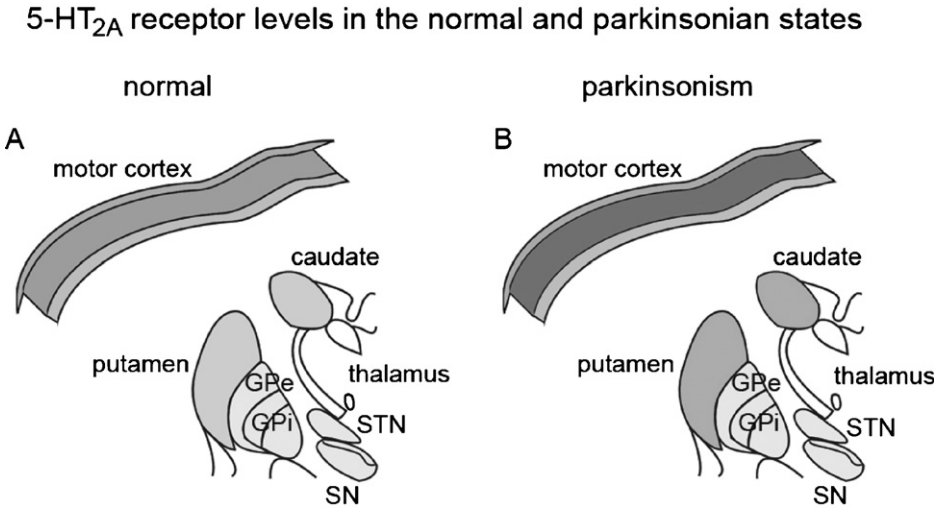

Fig. 8. In the parkinsonian macaque treated chronically with L-3,4-dihydroxyphenylalanine (L-DOPA) (B), 5-HT_{2A} receptor levels increase in the caudate nucleus and putamen, as well as in the middle layers of the motor cortex (darker shades of grey) when compared to non-parkinsonian macaques or to L-DOPA-naïve parkinsonian macaques (A). 5-HT_{2A} receptor levels are very low and unaltered in the GP, SN and STN.
These illustrations are not representative of normal anatomy. Thus, although depicted in the figure, the SN and STN are more posterior in the reality.
GPe: globus pallidus pars externa; GPi: globus pallidus pars interna; SN: substantia nigra; STN: subthalamic nucleus.
Basal ganglia illustrations are adapted from Paxinos et al. (2008).

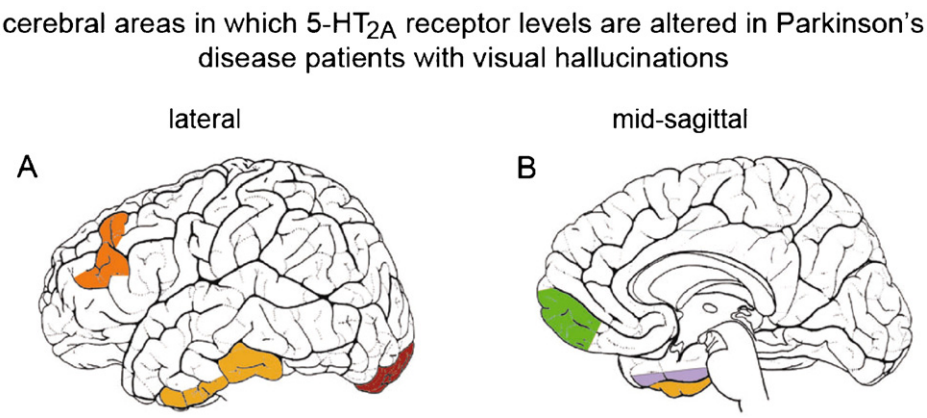

Fig. 9. In PD patients experiencing visual hallucinations, 5-HT_{2A} receptor levels increase in the inferior occipital gyrus (A, red), right fusiform gyrus (B, purple), inferior temporal cortex (A and B, yellow), dorsolateral prefrontal cortex (A, orange), medial orbitofrontal cortex (B, green) and insular cortex (not illustrated). Brain illustrations are adapted from Mai et al. (2004).

5-HT_2/D_2 ratio (Friedman and Factor, 2000), and some of them act as D_2 fast-off antagonists, as they bind only transiently to D_2-like receptors (Kapur and Seeman, 2000; Seeman and Tallerico, 1999). Perhaps surprisingly though, typical antipsychotics remain highly prescribed to PD patients (Wang et al., 2011; Weintraub et al., 2011). Amongst all of the atypical antipsychotics, clozapine is the most extensively studied in idiopathic PD and related animal models, with nearly 100 preclinical and clinical reports/studies published, while quetiapine is the most frequently prescribed one (Weintraub et al., 2011). The pharmacology of the compounds discussed in the next subsections is presented in Table 8, whereas the results of the preclinical and clinical trials performed with 5-HT_{2A} modulators are summarised in Table 9.

5.4.2.1. Preclinical studies: parkinsonism. The non-selective 5-HT_{2A} receptor antagonists ritanserin (Lucas et al., 1997) and clozapine (Ahlqvist et al., 2003), but neither olanzapine nor quetiapine (Ahlqvist et al., 2003), are effective at alleviating SCH-23,390- or raclopride-induced catalepsy in the rat, suggesting that antagonising 5-HT_{2A} receptors could exert an anti-parkinsonian activity. However, neither clozapine nor ritanserin decrease reserpine-induced akinesia in the mouse (Dziewczapolski et al., 1997), somewhat contradicting the results obtained in the cataleptic rat. Moreover, the selective 5-HT_{2A} antagonist volinanserin (M100,907 or MDL100,907) is not effective against haloperidol-induced catalepsy in the rat (Reavill et al., 1999), suggesting that antagonising 5-HT_{2A} receptors may not be the mechanism by which ritanserin and clozapine exert their anti-cataleptic action. However, at odds with this possibility, both ritanserin and volinanserin as monotherapy improve motor deficits in the MPTP-lesioned mouse (Ansah et al., 2011; Ferguson et al., 2008, 2009, 2010b).

Injections of mianserin in the SNr alleviate tacrine-induced jaw movements in the rat (Carlson et al., 2003), a putative model of PD tremor (Salamone et al., 1998). The 5-$HT_{2A/2C}$ inverse agonist pimavanserin (ACP-103) alleviates tacrine-induced tremulous jaw-movements in the rat (Vanover et al., 2008). Clozapine also reduces the vacuous/tremulous jaw movements induced by administration of cholinergic agents to the rat (Chesler and Salamone, 1996; Trevitt et al., 1997).

In the neonatal 6-OHDA-lesioned rat, the non-selective 5-$HT_{2A/2C}$ agonist (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) increases motor activity, an effect which is abolished by the 5-HT_{2A} antagonists ketanserin and volinanserin, but not by the 5-HT_{2C} antagonist RS-102,221 (Bishop et al., 2004), suggesting that selectively stimulating 5-HT_{2A} receptors might increase movement in the parkinsonian state. In the neonatal 6-OHDA-lesioned rat, ketanserin administration does not affect striatal levels of dopamine and DOPAC, and does not increase striatal levels of OH^- (Nowak et al., 2006). In the adult 6-OHDA-lesioned rat, striatal preprotachykinin (PPT) levels are decreased. Treatment with DOI restores normal PPT levels in rostral, central and dorsal–caudal striatal areas (Gresch and Walker, 1999). Treatment with DOI also enhances the locomotor behaviour induced by the D_1 agonist SKF-82,958 (Bishop and Walker, 2003). Motor activity induced by DOI, either alone or in combination with SKF-82,958, is reduced by the administration of ritanserin (Bishop et al., 2003).

MDMA and its R-enantiomer are 5-HT_{2A} partial agonists (Nash et al., 1994). R-MDMA and its racemate counteract haloperidol-induced catalepsy in the rat (Lebsanft et al., 2005a; Schmidt et al., 2002; von Ameln-Mayerhofer et al., 2009). In the 6-OHDA-lesioned rat, MDMA as monotherapy elicits rotations ipsiversive to the lesioned side, whereas R-MDMA does not elicit rotational behaviour (Lebsanft et al., 2005a,b, 2003).

5.4.2.2. Preclinical studies: treatment-related complications. In the neonatal 6-OHDA-lesioned rat, volinanserin significantly reduces SKF-82,958-induced hyperlocomotor activity (Bishop et al., 2005). In the adult 6-OHDA-lesioned rat, volinanserin significantly reduces the number of contraversive rotations induced by SKF-82,958, but does not reduce the number of contraversive rotations elicited by quinpirole or L-DOPA-induced AIMs severity (Taylor et al., 2006). The results of this study raise serious doubts about the anti-dyskinetic efficacy of selective 5-HT_{2A} antagonists, as volinanserin is the most selective 5-HT_{2A} receptor antagonist currently available. However, the doses used by the authors of that study were quite high and at higher doses, volinanserin displays affinity for several receptors, notably 5-HT_{2C} receptors (Table 8). The lack of anti-dyskinetic activity in that study could thus be due to two reasons: either selectively antagonising 5-HT_{2A} receptors does not alleviate dyskinesia or simultaneously antagonising 5-$HT_{2A/2C}$ receptors does not lead to a reduction in AIMs severity in the L-DOPA-treated 6-OHDA-lesioned rat. Unfortunately, no PK analysis was performed in that study and the aforementioned possibility to explain the lack of anti-dyskinetic efficacy of volinanserin in this experimental paradigm remains hypothetical.

When administered to the 6-OHDA-lesioned rat in combination with the monoamine re-uptake inhibitor BTS 74,398, ketanserin does not alter the number of ipsiversive rotations, whereas the mixed 5-HT_2 receptor antagonist and 5-HT_1 agonist methysergide increases their number (Hoyer et al., 1994; Lane et al., 2005). In the MPTP-lesioned macaque, methysergide, in combination with L-DOPA, reduces the severity of dyskinesia, but impairs L-DOPA anti-parkinsonian action (Gomez-Mancilla and Bedard, 1993).

Table 9
5-HT_{2A} antagonists in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	Animal models		Idiopathic PD
	6-OHDA-lesioned rat	MPTP-lesioned NHP	
Aripiprazole	n/a	n/a	• Inconsistent effect on dopaminergic-induced psychiatric complications • Possible deleterious effect on parkinsonism • Possibly ↓ L-DOPA-induced dyskinesia
Clozapine[a]	• ↓ L-DOPA-induced AIMs	• ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA-induced psychosis-like behaviours • No effect on L-DOPA anti-parkinsonian action	• Inconsistent effect on parkinsonism • ↓ L-DOPA-induced dyskinesia • ↓ Apomorphine-induced dyskinesia • ↓ Dopaminergic-induced psychiatric complications • Possibly ↓ tremor
Cyproheptadine	n/a	n/a	• No effect on L-DOPA-induced dyskinesia • No effect on L-DOPA anti-parkinsonian action
DOI	• ↑ Motor activity as monotherapy • Restores normal striatal PPT levels • ↑ SKF-82,958-induced motor activity	n/a	n/a
Fluperlapine	n/a	n/a	• Possibly ↓ dopaminergic psychiatric complications • No effect on parkinsonian disability
JL-18	n/a	• ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA anti-parkinsonian action at high dose	n/a
Ketanserin	• ↓ DOI-induced motor activity • No effect on BTS 74,398-induced ipsiversive rotations	n/a	n/a
Melperone	n/a	n/a	• Possibly ↓ dopaminergic psychiatric complications • No effect on parkinsonism
Methysergide	• ↑ BTS 74,398-induced ipsiversive rotations	• ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA anti-parkinsonian action	• No effect on L-DOPA-induced dyskinesia • No effect on L-DOPA anti-parkinsonian action • Ineffective as monotherapy
MDMA	• Induces ipsiversive rotations as monotherapy • ↓ L-DOPA-induced AIMs • No effect on L-DOPA-induced rotational behaviour	• Transient anti-parkinsonian action as monotherapy • ↓ L-DOPA-induced dyskinesia	• ↓ L-DOPA-induced dyskinesia while extending L-DOPA anti-parkinsonian action (anecdotal case-report)
Mianserin	n/a	n/a	• Possible deleterious effect on parkinsonism • Possibly ↓ dopaminergic psychiatric complications
N-Desmethylclozapine	• ↑ Quinpirole-induced contraversive rotations • No effect as monotherapy	n/a	n/a
Olanzapine	n/a	n/a	• Inconsistent effect on dopaminergic psychiatric complications • Possibly ↓ L-DOPA-induced dyskinesia • Possible anxiolytic effect • Deleterious effect on parkinsonism
Pimavanserin (ACP-103)	• Reverses pre-pulse inhibition deficit following bilateral 6-OHDA lesion • ↓ Amphetamine-induced activity following bilateral 6-OHDA lesion	• ↓ L-DOPA-induced dyskinesia • No effect on L-DOPA anti-parkinsonian action	• Possibly ↓ L-DOPA-induced dyskinesia • Inconsistent effect on dopaminergic psychiatric complications • No effect on L-DOPA anti-parkinsonian action
Quetiapine[a]	• ↓ The shortened motor response following administration of L-DOPA, • ↓ The shortened motor response following administration of SKF-38,392 • ↓ The shortened motor response following administration of quinpirole • No effect on parkinsonism as monotherapy	• ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA-induced psychosis-like behaviours severity • No effect on L-DOPA anti-parkinsonian action • No effect on parkinsonism as monotherapy	• Possibly ↓ dopaminergic-induced psychiatric complications • Possible cognition-enhancing effect • Inconsistent effect on L-DOPA-induced dyskinesia • Inconsistent effect on RBD • Inconsistent effect on parkinsonism

Table 9 (*Continued*)

	Animal models		Idiopathic PD
	6-OHDA-lesioned rat	MPTP-lesioned NHP	
Risperidone	n/a	n/a	• Usually ↓ dopaminergic-induced psychiatric complications • Deleterious effect on parkinsonism
Ritanserin	• ↓ DOI-induced motor activity	n/a	• Possibly ↓ L-DOPA-induced dyskinesia • Possibly ↓ L-DOPA anti-parkinsonian action • Inconsistent effect on tremor • Possible beneficial effect on mood disturbance
R-MDMA	• No effect on rotational behaviour	• ↓ L-DOPA-induced dyskinesia • ↓ L-DOPA-induced psychosis-like behaviours	n/a
Volinanserin (M100,907 or MDL100,907)	• ↓ DOI-induced locomotor activity • ↓ SKF-82,958-induced locomotor activity • ↓ SKF-82,958-induced contraversive rotations • No effect on quinpirole-induced contraversive rotations • No effect on L-DOPA-induced AIMs	n/a	n/a
Ziprasidone	n/a	n/a	• Usually ↓ dopaminergic psychiatric complications • Inconsistent effect on parkinsonism

6-OHDA: 6-hydroxydopamine; AIMs: abnormal involuntary movements; DOI: (±)-2,5-dimethoxy-4-iodoamphetamine; L-: *levo*; L-DOPA: L-3,4-dihydroxyphenylalanine; MDMA: 3,4-methylenedioxymethamphetamine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; n/a: not available; NHP: non-human primate; PD: Parkinson's disease; PPT: preprotachykinin; R-: *rectus*; RBD: REM-sleep behaviour disorder; REM: rapid-eye movements.

[a] The effects of clozapine and quetiapine on several manifestations of PD other than those included in the table are reported in the literature. For an exhaustive list, see text.

In the rat, pimavanserin normalises the deficits in pre-pulse inhibition and attenuates amphetamine-induced hyperactivity following bilateral 6-OHDA lesion, suggesting it exerts an anti-psychotic effect in that animal model (Bonhaus et al., 2009). In the MPTP-lesioned macaque, pimavanserin alleviates L-DOPA-induced dyskinesia without altering L-DOPA anti-parkinsonian benefit (Vanover et al., 2008).

In the L-DOPA-treated 6-OHDA-lesioned rat, clozapine reduces AIMs severity, but does not modify the number of rotations (Lundblad et al., 2002). In the 6-OHDA-lesioned rat, the metabolite of clozapine, *N*-desmethylclozapine, a non-selective 5-$HT_{2A/2C}$ receptor antagonist (Table 8) with partial agonist activity at D_2 and D_3 receptors (Burstein et al., 2005), enhances the number of contraversive rotations elicited by quinpirole, but does not exert any effect as monotherapy (Fox and Brotchie, 1996). In the MPTP-lesioned common marmoset, clozapine reduces the severity of both L-DOPA-induced dyskinesia and psychosis-like behaviours, without altering L-DOPA anti-parkinsonian efficacy (Fox et al., 2010; Visanji et al., 2006). In the MPTP-lesioned macaque, the clozapine analogue and 5-HT_{2A}/D_4 antagonist JL-18 alleviates L-DOPA-induced dyskinesia without altering its anti-parkinsonian action at low dose, but hinders L-DOPA anti-parkinsonian efficacy at high dose (Hadj Tahar et al., 2000), at which it also antagonises D_1 and D_2 receptors (Liegeois et al., 1995).

In the 6-OHDA-lesioned rat treated chronically with L-DOPA, acute challenges of quetiapine abolish the shortened motor response to acute challenges of L-DOPA, SKF-38,392 or quinpirole (Oh et al., 2002). In the MPTP-lesioned primate, quetiapine reduces the severity of both L-DOPA-induced psychosis-like behaviours (Visanji et al., 2006) and dyskinesia (Oh et al., 2002; Visanji et al., 2006), without altering L-DOPA anti-parkinsonian efficacy (Oh et al., 2002; Visanji et al., 2006). Quetiapine as monotherapy has no effect on parkinsonism in the 6-OHDA-lesioned rat or the MPTP-lesioned NHP (Oh et al., 2002).

In the 6-OHDA-lesioned rat, racemic MDMA significantly alleviates L-DOPA-induced AIMs severity, but has no effect on L-DOPA-induced rotations (Bishop et al., 2006). In the MPTP-lesioned common marmoset, MDMA decreases the severity of dyskinesia elicited by either L-DOPA or pramipexole and transiently alleviates parkinsonism as monotherapy (Iravani et al., 2003). In the MPTP-lesioned common marmoset, R-MDMA alleviates L-DOPA-induced dyskinesia and psychosis-like behaviours without impairing L-DOPA anti-parkinsonian efficacy (Huot et al., 2011b,c, 2010f).

5.4.2.3. Clinical studies. In an anecdotal case-report presented by the BBC, MDMA alleviated the severity of L-DOPA-induced dyskinesia and prolonged duration of L-DOPA anti-parkinsonian action (BBC, 2001).

The non-selective 5-$HT_{2A/2C}$ antagonist ritanserin increases nigrostriatal neuronal firing in dopaminergic cells (Ugedo et al., 1989), suggesting it might exert an anti-parkinsonian activity. Accordingly, ritanserin effectively alleviates neuroleptic-induced parkinsonism (Bersani et al., 1990). However, in a few trials performed in idiopathic PD patients, ritanserin was effective against L-DOPA-induced dyskinesia, but impaired L-DOPA anti-parkinsonian action (Maertens de Noordhout and Delwaide, 1986; Meco et al., 1988). Ritanserin could also be effective against tremor (Auff et al., 1987; Hildebrand and Delecluse, 1987) and mood disturbance (Auff et al., 1987) in the PD population. However, in another study, ritanserin was found ineffective against tremor, but improved bradykinesia and gait, when administered as monotherapy or in combination with L-DOPA (Henderson et al., 1992).

Unlike ritanserin, mianserin is ineffective against neuroleptic-induced parkinsonism (Korsgaard and Friis, 1986) and can deteriorate idiopathic PD symptoms (Fujimoto, 2009). A case report study mentioned the presence of VH in a 71-year old PD woman taking L-DOPA, mianserin and lorazepam, but did not discuss the effects of mianserin on VH or motor symptoms (Fenelon et al., 2000). In three other studies, mianserin significantly improved dopaminergic-induced psychiatric complications (Fujimoto et al., 2000, 2008; Ikeguchi and Kuroda, 1995).

The non-selective 5-HT_2 antagonist cyproheptadine does not alleviate L-DOPA-induced dyskinesia and has no effect on motor symptoms (Papavasilliou et al., 1978). Like cyproheptadine, methysergide is not effective against L-DOPA-induced dyskinesia and has no effect on motor symptoms, either as monotherapy or in combination with L-DOPA (Klawans and Ringel, 1973).

As mentioned above, clozapine was extensively studied against a variety of manifestations in PD. Clozapine enhances L-DOPA anti-parkinsonian action (Arevalo and Gershanik, 1993; Bennett et al., 1993, 1994; Factor and Friedman, 1997; Friedman and Lannon, 1989; Gershanik et al., 1992; Morgante et al., 2002; Pinter and Helscher, 1993; Roberts et al., 1989; Rui Silva et al., 1995), reduces drug-induced parkinsonism (Zullino and Rodondi, 2004), apomorphine- (Durif et al., 1996, 1997) and L-DOPA-induced dyskinesia (Bennett et al., 1993, 1994; Durif et al., 1997, 2004; Factor and Brown, 1992; Factor and Friedman, 1997; Friedman and Lannon, 1989; Gomide et al., 2007, 2008; Pierelli et al., 1998; Trosch et al., 1998), OFF-period dystonia (Juncos, 1996), stroke-induced hemiballism (Al-Yacoub et al., 2004; Factor and Friedman, 1997), psychotic manifestations (Auzou et al., 1996; Bear et al., 1989; Bernardi and Del Zompo, 1990; Brewer et al., 1995; Chacko et al., 1995; Chacon, 2004; Connemann and Schonfeldt-Lecuona, 2004; Cudkowicz et al., 1996; Diederich et al., 2000; Diraoui et al., 2004; Factor and Brown, 1992; Factor et al., 1992, 1994, 2001, 1995; Factor and Friedman, 1997; Fernandez et al., 2004a; Fernandez and Durso, 1998; FrenchClozapineParkinsonStudyGroup, 1999; Friedman et al., 1992, 1998; Friedman and Lannon, 1989; Frieling et al., 2007; Gershanik et al., 1992; Goetz et al., 2000; Gomide et al., 2007, 2008; Gonski, 1994; Inzelberg et al., 1998; Jimenez-Jimenez et al., 1997, 1998; Juncos, 1996; Kahn et al., 1991; Klein et al., 2003, 2007; Koller et al., 1994; Lew and Waters, 1992, 1993; Linazasoro et al., 1993, 1992; Menza et al., 1999; Merims et al., 2006, 2005; Micheli et al., 2005; Morgante et al., 2002; Normann et al., 1997; Ostergaard and Dupont, 1988; Ozsancak et al., 1997; ParkinsonStudyGroup, 1999; Pfeiffer et al., 1990; Pinter and Helscher, 1993; Pollak et al., 2004; Prueter et al., 2003; Rabey et al., 2009, 1995; Rich et al., 1995; Roane et al., 1998; Roberts et al., 1989; Rosenthal et al., 1992; Ruggieri et al., 1997; Rui Silva et al., 1995; Sa and Lang, 2001a,b; Scholz and Dichgans, 1985, 1988; Schwingenshuh et al., 2009; Svetel et al., 1997; Thomas and Friedman, 2010; Trosch and Group, 1996; Wagner et al., 1996; Wolk and Douglas, 1992; Wolters et al., 1990, 1989), bipolar disorder (Kim et al., 1994; Thomas et al., 2008), paraphilias (Fernandez and Durso, 1998), tremor (Bonuccelli et al., 1994, 1997; Factor and Friedman, 1997; Fischer et al., 1990; Friedman et al., 1992, 1996, 1997; Friedman and Lannon, 1990a,b; Gonski, 1994; Jansen, 1994; Linazasoro et al., 1993, 1992; Ostergaard and Dupont, 1988; Pakkenberg and Pakkenberg, 1986; ParkinsonStudyGroup, 1999; Simoes et al., 1992; Thomas and Friedman, 2010; Trosch et al., 1998; Trosch and Group, 1996), akathisia (Factor and Friedman, 1997; Linazasoro et al., 1993, 1992; Trosch et al., 1998; Trosch and Group, 1996) and pain (Factor and Friedman, 1997; Juncos, 1996; Trosch and Group, 1996). Clozapine is also reportedly effective against anxiety (Trosch et al., 1998; Trosch and Group, 1996), depression (Trosch et al., 1998; Trosch and Group, 1996), hypersexuality (Ruggieri et al., 1997; Trosch et al., 1998; Trosch and Group, 1996), pathological gambling (Rotondo et al., 2010) and sleep disturbance (Koller et al., 1994; Rosenthal et al., 1992; Trosch et al., 1998; Trosch and Group, 1996). In a case report, successfully treated hallucinations recurred after five years of active clozapine therapy, even though the patient was still under treatment (Greene, 1995). Clozapine was deemed effective against psychotic features in case report studies of schizophrenic patients with concomitant idiopathic PD (Friedman et al., 1987; Orr et al., 2001; Valis et al., 2008) and in case reports of idiopathic PD patients with schizoaffective disorder (Frye et al., 1993; Valis et al., 2008); in all of these case reports, however, the possibility of drug-induced parkinsonism was not clearly excluded. In a single case report, clozapine unmasked idiopathic PD, confirmed by dopamine transporter SPECT, in a schizophrenic woman (Urban et al., 2003). Clozapine was reported useful in cases of dopaminergic psychosis in which risperidone therapy had failed (Rich et al., 1995). Clozapine also improved psychosis and drug-induced parkinsonism in 6 HIV-positive patients (Lera and Zirulnik, 1999). One study investigated the electroencephalogram of PD patients treated with low dose clozapine and found unaltered tracings in the majority of cases; slow waves were the most commonly encountered anomaly (Neufeld et al., 1996). The clozapine-like compound fluperlapine also improves dopaminergic-induced psychotic manifestations in PD, without worsening motor features (Scholz and Dichgans, 1985). A Phase II study assessing the efficacy of clozapine in the treatment of PD psychosis was on-going without recruitment until recently, but its current status is unknown (http://www.clinicaltrials.gov/, NCT00004826).

In all of the aforementioned studies, the doses of clozapine used were much lower than those used to treat schizophrenia. A PK study determined that the plasma levels of clozapine and *N*-desmethylclozapine required to treat adequately PD psychotic symptoms are 40–50 fold lower than those required to treat schizophrenia effectively (Meltzer et al., 1995). At such doses, 5-HT_2 receptor occupancy is greater than either D_1 or D_2 receptor occupancy (Nordstrom et al., 1995).

A minority of publications reported a lack of efficacy of clozapine against either psychotic or motor symptoms in PD. Thus, clozapine did not significantly improve psychotic manifestations in a few reports (Ellis et al., 2000; Meco and Bernardi, 2007; Schindehutte and Trenkwalder, 2007). Likewise, an exacerbation of dyskinesia following a switch from olanzapine to clozapine is reported (Sa and Lang, 2001a,b) and, although rare, reports of deterioration of parkinsonism under clozapine treatment are published (Koller et al., 1994; Pollak et al., 2004; Thomas and Friedman, 2010; Wolters et al., 1989, 1990).

Despite the numerous aforementioned trials in which clozapine demonstrated some efficacy, many clinicians are reluctant to use clozapine as a first-line therapy against tremor, psychosis and dyskinesia, because of the potentially life-threatening side-effects of the drug and the complex and continuous monitoring required. Clozapine is usually well-tolerated by PD patients (Bloomfield et al., 2011) and the adverse effects caused by clozapine in the PD population are the same as those reported in the general population. Thus, leucopoenia (Connemann and Schonfeldt-Lecuona, 2004; Ellis et al., 2000; Gomide et al., 2007; Jansen, 1994; Merims et al., 2006; Onofrj et al., 2000; ParkinsonStudyGroup, 1999; Pollak et al., 2004; Rudolf et al., 1997; Thomas and Friedman, 2010; Trosch and Group, 1996), thrombocytopaenia (Rudolf et al., 1997) and aplastic anaemia (Ziegenbein et al., 2003) are all described in clozapine-treated PD patients. Monitoring for haematologic complications is now done routinely when patients are prescribed clozapine (Novartis, 2010). One case report of serotonin-like syndrome following abrupt discontinuation of clozapine in a PD patient is published (Zesiewicz et al., 2002). Prevalence of diabetes amongst clozapine PD users is not higher than in the general population (Fernandez et al., 2004b). Other clozapine-induced side effects frequently evoked in the studies cited above are drooling, orthostatic hypotension and sedation.

Like clozapine, quetiapine appears effective against dopaminergic psychotic manifestations of PD (Brandstadter and Oertel, 2002; Dewey and O'Suilleabhain, 2000; Evatt et al., 1996; Fernandez et al., 1999, 2000, 2009a,b, 2003; Gimenez-Roldan et al., 2003; Grandas et al., 2008; Hoshiyama et al., 2008; Juncos et al., 1999, 1998; Klein et al., 2007; Lopez del Val and Santos, 2004; Menza et al., 1999; Merims et al., 2006, 2005; Morgante et al.,

2002; Parsa and Bastani, 1998; Prueter et al., 2003; Reddy et al., 2002; Shiah et al., 2006; Sommer, 2001; Targum and Abbott, 2000; Tolleson et al., 2011; Weiner et al., 2000; Yamamoto et al., 2010). Quetiapine might also be effective in the treatment of punding (Fasano et al., 2010). Quetiapine also exerts a beneficial effect on cognition (Juncos et al., 1999; Weiner et al., 2000). However, quetiapine seems less effective than the other atypical antipsychotics against PD psychosis. Indeed, studies have suggested that clozapine is more effective than quetiapine (Klein et al., 2007; Merims et al., 2006) and patients whose psychotic symptoms were unresponsive to quetiapine have been switched successfully to either clozapine (Brandstadter and Oertel, 2002; Dewey and O'Suilleabhain, 2000; Fernandez et al., 1999) or olanzapine (Ito et al., 2005). Accordingly, in other patients, switching from either clozapine or olanzapine to quetiapine resulted in a loss of antipsychotic efficacy (Fernandez et al., 1999). In a few studies, quetiapine (up to 800 mg p.o. id) was not more effective than placebo against psychotic manifestations (Frieling et al., 2007; Kurlan et al., 2007; Ondo et al., 2005; Prohorov et al., 2006; Rabey et al., 2007), or not effective at all (Agarwal et al., 2008; Connemann and Schonfeldt-Lecuona, 2004; Duggal and Singh, 2008; Fernandez et al., 2004c; Micheli et al., 2005; Schindehutte and Trenkwalder, 2007; Wickremaratchi et al., 2006).

Reports also exist in which quetiapine alleviated psychotic manifestations in PD patients who had not responded to clozapine, olanzapine or risperidone (Juncos et al., 1999; Weiner et al., 2000). One study which directly compared the antipsychotic efficacy of clozapine and quetiapine found no difference between the two drugs, but clozapine improved the UPDRS motor subscore, whereas quetiapine did not (Morgante et al., 2002). In PD patients whose psychotic symptoms are treated successfully with either clozapine or quetiapine, discontinuation of the antipsychotic treatment leads to a recurrence of symptoms in 50% of cases (Morgante et al., 2007). Neither clozapine nor quetiapine prevent motor improvement when dopaminergic therapy is initiated in PD patients with concomitant schizophrenia (Friedman, 2011).

The efficacy of quetiapine against L-DOPA-induced dyskinesia is unclear, with two reports showing an improvement (Baron and Dalton, 2003; Gimenez-Roldan et al., 2003) and a third one showing no effect (Katzenschlager et al., 2004). Reports of transient improvement of parkinsonism on quetiapine therapy are published (Juncos et al., 1998, 1999). Increases in the severity of dyskinesia, tremor and anxiety are reported in one PD patient following a switch from clozapine to quetiapine (Fernandez et al., 2000).

Three case-reports highlighting the efficacy of quetiapine against RBD in PD were presented as an abstract (Carvalho et al., 2009). However, the efficacy of quetiapine against RBD is unclear, since quetiapine was ineffective in the treatment of PD-associated RBD in another study (Zangaglia et al., 2006). Regardless of its efficacy, or lack thereof, against RBD, quetiapine does not alter sleep architecture when administered to PD patients, according to a polysomnography study (Fernandez et al., 2009a,b).

Although quetiapine is generally well tolerated in PD, there are a few reports of worsening of motor symptoms with the drug (Baron and Dalton, 2003; Fernandez et al., 2003; Reddy et al., 2002; Shiah et al., 2006) and there is one report of a tardive dyskinesia-like syndrome caused by quetiapine in a PD patient (Sommer, 2001). In another case-report, quetiapine induced akathisia (Prueter et al., 2003), which disappeared following its discontinuation and replacement by clozapine (Prueter et al., 2003). There is one report of dystonia and agitation triggered by quetiapine in a demented PD patient (Leey et al., 2008). In the PD population, both clozapine and quetiapine (Sitburana et al., 2008) therapies tend to cause slight weight loss, which is in contrast to use in psychiatric patients, where weight gain is the norm (Leadbetter et al., 1992). Quetiapine does not affect low-density lipoprotein (LDL) cholesterol, triglyceride or leptin levels in PD patients (Rustembegovic et al., 2006). Quetiapine-induced rhabdomyolysis (Stephani and Trenkwalder, 2010) and hypersexuality (Juncos et al., 1998) have both been reported in the PD population.

Several trials with olanzapine in PD are published. The antipsychotic efficacy of olanzapine in PD is unclear, since it was effective against psychotic manifestations in several reports (Aarsland et al., 1999; Chacon, 2004; Chacon et al., 2002; Friedman, 1998; Gimenez-Roldan et al., 2001; Graham et al., 1998; Gupta et al., 2004a; Ito et al., 2005; Jha and Munro, 2008; Molho and Factor, 1999; Moretti et al., 2003; Onofrj and Thomas, 2001; Sa and Lang, 2001a,b; Weiner et al., 1998; Wickremaratchi et al., 2006; Wolters et al., 1996), but ineffective in several others (Breier et al., 2002; Diraoui et al., 2004; Frieling et al., 2007; Goetz et al., 2000; Jimenez-Jimenez et al., 1998; Lopez-Meza et al., 2005; Marsh et al., 2001; Ondo et al., 2002; Rudolf et al., 1999). Olanzapine also appears to exert an anxiolytic effect (Moretti et al., 2003). Olanzapine effectively alleviated L-DOPA-induced dyskinesia in a few reports (Manson et al., 2000; Sa and Lang, 2001b). However, clinicians are often reluctant to use olanzapine in PD due to its deleterious effects on parkinsonism, even when doses as low as 1.25 mg p.o. id are employed (Agarwal et al., 2008; Breier et al., 2002; Chacon et al., 2002; Friedman, 1998; Friedman et al., 1998; Frieling et al., 2007; Gimenez-Roldan et al., 2001; Goetz et al., 2000; Graham et al., 1998; Ito et al., 2005; Jimenez-Jimenez et al., 1998; Manson et al., 2000; Marsh et al., 2001; Molho and Factor, 1999; Ondo et al., 2002; Onofrj and Thomas, 2001; Prueter et al., 2003; Rudolf et al., 1999; Weiner et al., 1998, 2000; Wickremaratchi et al., 2006). There is one report of pancytopaenia induced by olanzapine in a PD patient (Onofrj and Thomas, 2001). Unlike quetiapine, olanzapine adversely affects LDL cholesterol, triglyceride and leptin levels in PD patients (Rustembegovic et al., 2006).

Risperidone appears effective against psychotic features in PD (Cudkowicz et al., 1996; Ford et al., 1994; Meco et al., 1994a,b, 1997; Workman et al., 1997), but failed to improve them in one study (Ellis et al., 2000). Risperidone may adversely affect parkinsonism (Cudkowicz et al., 1996; Ford et al., 1994; Gupta et al., 2004a; Rich et al., 1995). The use of risperidone, olanzapine or quetiapine by PD patients increases their risk of bone fracture (Dore et al., 2009).

Ziprasidone appears effective against PD psychosis (Connemann and Schonfeldt-Lecuona, 2004; Duggal and Singh, 2008; Gomez-Esteban et al., 2005; Lopez del Val and Santos, 2004; Micheli et al., 2005; Oechsner and Korchounov, 2005; Schindehutte and Trenkwalder, 2007; Shiah et al., 2006). In a small case-series, ziprasidone alleviated depression and bipolar symptoms in PD patients previously treated without success with either olanzapine or risperidone (Berkowitz, 2006). Although generally effective and well tolerated, absence of antipsychotic effect (Mahgoub and Hossain, 2006; Micheli et al., 2005) and worsening of parkinsonism (Gomez-Esteban et al., 2005; Micheli et al., 2005) in ziprasidone-treated PD patients are both reported. There is one case-report in which ziprasidone triggered a neuroleptic-malignant syndrome in a PD patient (Gray, 2004).

Unlike the other antipsychotics, aripiprazole is a 5-HT_{2A} receptor antagonist with partial agonist activity at 5-HT_{1A} (Jordan et al., 2002) and D_2 (Burstein et al., 2005) receptors. Aripiprazole was effective against PD psychosis in a few reports (Friedman et al., 2006; Lopez-Meza et al., 2005; Mahgoub and Hossain, 2006), but ineffective in others (Connemann and Schonfeldt-Lecuona, 2004; Fernandez et al., 2004c; Friedman et al., 2006; Schonfeldt-Lecuona and Connemann, 2004). Aripiprazole may worsen motor function (Fernandez et al., 2004c; Friedman et al., 2006; Meco et al., 2007; Schonfeldt-Lecuona and Connemann, 2004; Wickremaratchi et al., 2006) and cause tardive dyskinesia (Agarwal et al., 2008) in PD patients. Low dose aripiprazole can successfully alleviate L-DOPA-induced dyskinesia (Meco et al., 2007, 2009).

The combination of divalproex and aripiprazole successfully treated a manic episode in a PD woman (Gupta et al., 2004b). Aripiprazole was effective against psychotic symptoms in a schizophrenic woman with superimposed PD, although the diagnosis of idiopathic PD was not convincingly established in the report (Fujino et al., 2010).

In idiopathic PD, pimavanserin effectively alleviates L-DOPA-induced dyskinesia (Roberts, 2006) and psychotic behaviour (Bonhaus et al., 2009; Roberts, 2006), without worsening motor function (Bonhaus et al., 2009; Mills et al., 2008b; Roberts, 2006). However, according to other studies, pimavanserin does not significantly reduce the severity of psychotic behaviour (Friedman et al., 2010; Meltzer et al., 2010; Mills et al., 2008b; Revell et al., 2008), possibly because of a strong placebo response (Friedman et al., 2010). The drug appears to be safe and well tolerated in the PD population (Friedman et al., 2010; Mills et al., 2010, 2008a, 2009a,b). A Phase III study assessing the antipsychotic efficacy of pimavanserin in PD is currently recruiting patients, whereas another one has recently been completed; no results are currently available (http://www.clinicaltrials.gov/, NCT00550238, NCT00658567).

Melperone is a non-selective 5-HT_{2A} antagonist (Ichikawa et al., 2002) which effectively alleviated L-DOPA-induced psychotic features without impairing L-DOPA anti-parkinsonian efficacy in one study (Barbato et al., 1996). A Phase II study assessing the efficacy of melperone against PD psychosis was recently completed and the drug did not alleviate dopaminergic psychosis (http://www.clinicaltrials.gov/, NCT00125138).

In its 2006 practice parameters for the evaluation and treatment of depression, psychosis, and dementia in PD, the American Academy of Neurology states that "clozapine should be considered (level B), quetiapine may be considered (level C), but olanzapine should not be considered (level B)" for the treatment of PD psychosis (Miyasaki et al., 2006).

5.4.3. 5-HT_{2A} receptors in Parkinson's disease: summary

5-HT_{2A} receptors and their modulation have been extensively studied in PD and animal models of PD. Based on the available literature, the following conclusions can be made:

- 5-HT_{2A} receptor levels are increased in the striatum and middle layers of the motor cortex of dyskinetic MPTP-lesioned macaques, as well as in the motor cortex of idiopathic PD patients.
- 5-HT_{2A} receptor levels are increased in the temporal cortex of PD patients experiencing VH.
- 5-HT_{2A} receptors therefore appear linked to both motor and non-motor complications of dopaminergic replacement therapy.

As highlighted in the previous subsections, several preclinical and clinical studies have examined the modulation of 5-HT_{2A} receptors in PD. As for the majority of 5-HT_{1A} receptor agonists discussed in the 5-HT_{1A} receptor subsection (*vide* above), the lack of selectivity of the purportedly selective 5-HT_{2A} antagonists studied in PD precludes strong conclusions based exclusively on pharmacological premises with respect to their efficacy against motor and non-motor symptoms. Thus, as displayed in Table 8, the majority of the 5-HT_{2A} antagonists exhibit, in addition to their high affinity for 5-HT_{2A} receptors, high affinity for other serotonergic, dopaminergic, adrenergic and/or muscarinic receptors. Their interaction with these other receptors is likely to play an important role in their biological effects. Furthermore, the vast majority of the clinical trials performed with 5-HT_{2A} antagonists in PD consist in case-reports or uncontrolled, non-randomised studies encompassing small numbers of patients, often with contradictory results, making it difficult to draw strong conclusions.

Notwithstanding these limitations, non-selective 5-HT_{2A} receptor antagonists have shown some degree of efficacy against L-DOPA-induced dyskinesia, psychotic behaviour, tremor, and depression (*vide* Table 9). However, the lack of efficacy of volinanserin, the most selective 5-HT_{2A} antagonist available, against L-DOPA-induced AIMs in the 6-OHDA-lesioned rat raises doubts on the anti-dyskinetic potential of selective 5-HT_{2A} antagonists/inverse agonists. The risk of worsening parkinsonism varies depending on the compounds used and their extra-5-HT_{2A} receptor affinity, but appears minimal with clozapine, quetiapine, R-MDMA and pimavanserin.

Although no study investigated the mechanisms by which modulating 5-HT_{2A}-mediated neurotransmission alleviates dyskinesia, a possible explanation could be related to 5-HT_{2A}-mediated modulation of corticostriatal glutamate release (Huot et al., 2011a, 2010c). As mentioned above, 5-HT_{2A} receptor levels are increased in the cortex and striatum of MPTP-lesioned macaques treated chronically with L-DOPA, suggesting enhanced 5-HT_{2A}-mediated neurotransmission along the corticostriatal pathway in the dyskinetic state. Increased 5-HT_{2A} receptor-mediated neurotransmission potentiates glutamatergic neurotransmission, by increasing glutamate release (Aghajanian and Marek, 1997) and intensifying NDMA-mediated depolarisation (Neuman and Rahman, 1996; Rahman and Neuman, 1993). In accordance with this potential mechanism, post mortem and pharmacological studies have demonstrated that glutamatergic neurotransmission is altered in the dyskinetic state (Calabresi et al., 2008; Hallett et al., 2005; Johnston et al., 2010b; Mela et al., 2007; Samadi et al., 2008). Moreover, a recent study performed in the L-DOPA-untreated MPTP-lesioned mouse revealed that intrastriatal administration of volinanserin reduces striatal glutamate levels (Ansah et al., 2011; Ferguson et al., 2010a).

Another hypothetical mechanism by which 5-HT_{2A} receptors may be involved in the pathophysiology of L-DOPA-induced dyskinesia relates to the regulation of dopamine release by the surviving nigrostriatal axons (Huot et al., 2011a, 2010h). Indeed, 5-HT_{2A} receptor activation enhances nigrostriatal dopaminergic neurotransmission (Lucas et al., 2000; Lucas and Spampinato, 2000; Pehek et al., 2006; Schmidt et al., 1994); therefore, antagonising 5-HT_{2A} receptors would reduce striatal dopamine levels. Although decreasing striatal dopamine levels would reduce L-DOPA-induced dyskinesia severity, it might also impair L-DOPA anti-parkinsonian efficacy.

5.5. 5-HT_{2B} receptors

To our knowledge, no studies involving 5-HT_{2B} receptors, either anatomical or pharmacological, have been performed in PD. Nevertheless, 5-HT_{2B} receptors are an important consideration in PD therapy, as they are believed to mediate the cardiac fibrosis which occurs during treatment with certain ergot-derived dopamine receptor agonists (Fitzgerald et al., 2000; Roth, 2007; Rothman et al., 2000). Cardiac valvular fibrosis was reported following treatment with the ergot-derived dopamine agonists pergolide (Pritchett et al., 2002; Van Camp et al., 2003, 2004), bromocriptine (Serratrice et al., 2002) and cabergoline (Dhawan et al., 2005). These dopamine agonists all bind with high affinity to 5-HT_{2B} receptors, at which they act as agonists (Millan et al., 2002). Accordingly, valvular regurgitation seems more prevalent in PD patients treated with the dopamine agonists pergolide and cabergoline than in controls (Schade et al., 2007; Zanettini et al., 2007). In contrast, lisuride is a 5-HT_{2B} antagonist and to date, no cases of lisuride-induced valvular disease have been reported (Hofmann et al., 2006). Cumulative dose and long-term treatment could be risk factors leading to the development of cabergoline-induced valvulopathy (Yamamoto et al., 2006). Studies on valvular

heart disease in dopamine agonist-treated PD patients were ongoing until recently, but their current status is unknown (http://www.clinicaltrials.gov/, NCT00196898, NCT00202657). Cases of pleuro-pulmonary (Bleumink et al., 2002) and retroperitoneal (Jimenez-Jimenez et al., 1995; Kunkler et al., 1998) fibrosis in PD patients taking pergolide have also been reported; it therefore seems that ergot-derived dopamine agonists – with a 5-HT_{2B} agonist activity – could potentially induce fibrotic changes on every serosal membrane of the body.

5.6. 5-HT_{2C} receptors

The 5-HT_{2C} gene (MIM *312861, http://www.ncbi.nlm.nih.gov/omim/312861) was cloned in 1988 (Julius et al., 1988). The human 5-HT_{2C} receptor gene is located on chromosome Xq24 (Milatovich et al., 1992). 5-HT_{2C} receptors are $G_{q/11}$ protein-coupled receptors that stimulate phospholipase C-catalysed hydrolysis of phosphatidylinositol bisphosphate (Milatovich et al., 1992). The gene contains 4 exons interrupted by 3 introns (Stam et al., 1994). One short variant of the 5-HT_{2C} receptor gene has been cloned (Canton et al., 1996). 5-HT_{2C} receptor monomers form homodimers (Herrick-Davis et al., 2004, 2006). Several isoforms of the 5-HT_{2C} receptor exist, with different G protein-coupling properties, intracellular signalling (Burns et al., 1997; McGrew et al., 2004; Niswender et al., 1999; Price and Sanders-Bush, 2000; Wang et al., 2000) and drug binding potency (Herrick-Davis et al., 1999). 5-HT_{2C} receptors play a role in learning and stress (Du et al., 2007), drug addiction (Bubar and Cunningham, 2006; Muller and Carey, 2006), weight control (Nilsson, 2006; Reynolds et al., 2006; Tecott et al., 1995), epilepsy (Tecott et al., 1995), hallucinogenic drug effects (Smith et al., 1998), anxiety (Hackler et al., 2006; Harada et al., 2006), suicide (Niswender et al., 1999), depression (Iwamoto et al., 2005) and schizophrenia (Sodhi et al., 2001).

In the rat brain, 5-HT_{2C} receptors are highly expressed in the choroid plexus and limbic areas (Abramowski et al., 1995; Clemett et al., 2000; Mengod et al., 1990a; Pompeiano et al., 1994). Within the basal ganglia, they are highest in the STN and SNc (Abramowski et al., 1995; Clemett et al., 2000; Mengod et al., 1990a; Pompeiano et al., 1994). Moderate levels are found in the striatum and GP (Abramowski et al., 1995; Clemett et al., 2000; Pompeiano et al., 1994), in which very few intrinsic neurons contain 5-HT_{2C} mRNA (Eberle-Wang et al., 1997). Numerous intrinsic neurons containing 5-HT_{2C} mRNA are found in the entopeduncular nucleus and STN (Eberle-Wang et al., 1997).

In the human brain, 5-HT_{2C} mRNA is most abundant within the choroid plexus and limbic areas. High 5-HT_{2C} mRNA levels are also encountered in the striatum and SNc, but not in the GP or SNr. In the cerebral cortex, 5-HT_{2C} mRNA appears confined to layer V (Pasqualetti et al., 1999). Some autoradiographic binding studies have assessed the localisation of 5-HT_{2C} receptors in the human (Pazos et al., 1987a) and non-human (Lopez-Gimenez et al., 2001a) primate. However, they have used [^{3}H]-mesulergine as the radioligand and, as presented in Table 10, mesulergine is a non-specific ligand that binds to 5-$HT_{2A/2C}$ receptors. For this reason, the results of these studies are not detailed here.

5-HT_{2C} receptors modulate neuronal activity and neurotransmission within the basal ganglia. Thus, *in vitro* studies have demonstrated that 5-HT_{2C} receptor blockade reduces STN neuronal firing (Stanford et al., 2005), whereas 5-HT_{2C} receptor activation depolarises SNr neurons (Rick et al., 1995; Stanford and Lacey, 1996). 5-HT_{2C} receptor blockade increases dopamine release along the mesolimbic/mesocortical and, to a lesser extent, nigrostriatal pathways, whereas 5-HT_{2C} receptor activation reduces dopamine release along these dopaminergic tracts (Alex et al., 2005; Di Giovanni et al., 2000; Di Matteo et al., 2001; Gobert et al., 2000; Lucas and Spampinato, 2000; Millan et al., 1998; Olijslagers et al., 2004).

5.6.1. 5-HT_{2C} receptors in Parkinson's disease

To our knowledge, only two studies have assessed the fate of 5-HT_{2C} receptors in idiopathic PD and animal models of PD. In the 6-OHDA-lesioned rat, 5-HT_{2C} receptor mRNA levels are decreased in the striatum, but not in the STN (Zhang et al., 2007b); L-DOPA treatment has no effect on 5-HT_{2C} mRNA levels in these two structures (Zhang et al., 2007b). In dyskinetic PD patients, 5-HT_{2C} receptor levels are elevated in the SNr, when compared to healthy controls (Fox and Brotchie, 2000a).

5.6.2. 5-HT_{2C} receptor modulation as a potential target against parkinsonism and treatment-related complications

5.6.2.1. Preclinical studies. The pharmacology of the compounds discussed in the current subsection is presented in Table 10.

In the rat, the 5-$HT_{2B/2C}$ receptor antagonist SB-228,357 reduces haloperidol-induced catalepsy, an effect which is not achieved by antagonising selectively 5-HT_{2B} receptors with SB-215,505, suggesting that 5-HT_{2C} receptor antagonists effectively alleviate catalepsy (Reavill et al., 1999).

Administration of the non-selective 5-HT_{2C} receptor agonist 1-(*m*-chlorophenyl)piperazine (mCPP) systemically or local application in the STN of normal rats cause oral AIMs (Eberle-Wang et al., 1996; Mehta et al., 2001). Following 6-OHDA lesion, the intensity of systemically, but not intra-STN, mCPP-induced oral AIMs is increased (De Deurwaerdere and Chesselet, 2000). In the normal rat, mCPP administration elevates Fos levels in the striatum and STN (De Deurwaerdere and Chesselet, 2000). Following 6-OHDA lesion, mCPP administration reduces Fos levels in the medial striatum and increases Fos levels in the entopeduncular nucleus, but does not alter Fos levels in the STN (De Deurwaerdere and Chesselet, 2000).

In the MPTP-lesioned mouse, the selective 5-HT_{2C} receptor antagonist SB-206,553 has no effects on motor deficits (Ferguson et al., 2010b). In the 6-OHDA-lesioned rat, SB-206,553 increases the number of contraversive rotations induced by SKF-82,958, but does not cause any rotations when administered as monotherapy

Table 10
Pharmacological profile of 5-HT_{2C} receptor ligands studied in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	5-HT_{2C} receptor affinity (nM)	Other binding sites (nM)	References
mCPP[a]	81	5-HT_{1A} (1259), 5-HT_{2A} (224), and 5-HT_{2B} (63)	Hoyer et al. (1994) and Porter et al. (1999)
Mesulergine	1.9	5-HT_{2A} (3.8), 5-HT_7 (10), D_1 (2500), and D_2 (8)	Bonhaus et al. (1997), Closse (1983), Hemedah et al. (1999), and Markstein (1983)
RS-102,221	3.5	5-HT_{2A} (141), 5-HT_{2B} (813), α_{2A} (316), and σ_1 (501)	Bonhaus et al. (1997)
SB-200,646A	398	5-HT_{2A} (6310) and 5-HT_{2B} (631)	Bonhaus et al. (1997), Forbes et al. (1993), and Kennett et al. (1994)
SB-206,553	12.6	5-HT_{2A} (1660), 5-HT_{2B} (1.26), and 5-HT_4 (5012)	Forbes et al. (1995) and Kennett et al. (1996)
SB-228,357	0.79	5-HT_{2A} (100), and 5-HT_{2B} (7.9)	Bromidge et al. (2000) and Reavill et al. (1999)

Unless indicated otherwise, values are provided as the dissociation constant (K_d).
[a] Values provided as the half-maximal effective concentration (EC_{50}) mCPP: 1-(*m*-chlorophenyl)piperazine; nM: nanomole.

(Fox and Brotchie, 2000b). Systemic administration of the selective 5-HT_{2C} receptor antagonists SB-200,646A and SB-206,553 to the 6-OHDA-lesioned rat enhances quinpirole anti-parkinsonian action (Fox et al., 1998). Injection of SB-206,553 in the SNr ipsilateral to the 6-OHDA lesion exerts an anti-parkinsonian effect (Fox et al., 1998). In the hemi-parkinsonian rat, the 5-HT_{2C} antagonist mesulergine induces contralateral rotations (Ringwald et al., 1982), an effect that might be mediated via its agonist action at D_2 receptors (*vide infra*).

5.6.2.2. Clinical studies. In idiopathic PD patients, adding mesulergine to L-DOPA improves tremor, rigidity, bradykinesia and the ON–OFF phenomenon (Baas et al., 1985; Biesemeyer et al., 1983; Burton et al., 1985; Dupont et al., 1986; Fox and Brotchie, 1999; Jankovic et al., 1985; Jellinger, 1982; Lieberman et al., 1986; Rascol et al., 1986; Schneider et al., 1985). Two studies found that the addition of either mesulergine or bromocriptine to L-DOPA produces an extra anti-parkinsonian benefit of similar magnitude (Baas et al., 1985; Burton et al., 1985). In combination with L-DOPA, mesulergine improves mood, but may trigger hallucinations (Hoehn, 1984) and exacerbate dyskinesia (Jankovic et al., 1985), although the increase in dyskinesia can be minimised by reducing L-DOPA doses (Hoehn, 1984; Rascol et al., 1986). When administered *de novo* as monotherapy, mesulergine exerts an anti-parkinsonian action (Dupont et al., 1986; Wright et al., 1986) which, although significant, is not as potent as the anti-parkinsonian effect of L-DOPA (Dupont et al., 1986).

It is noteworthy that the effects of mesulergine in PD are unlikely to be entirely due to its actions at 5-HT_{2C} receptors, since mesulergine and its metabolite bind with high affinity to D_2 receptors (Table 10) (Markstein, 1983). Mesulergine exerts a biphasic activity at D_2 receptors, the first phase being antagonistic, the second being agonistic (Enz et al., 1984).

5.6.3. 5-HT_{2C} receptors in Parkinson's disease: summary

Very little is known about 5-HT_{2C} receptors in PD. Indeed, only two post mortem studies assessed the fate of 5-HT_{2C} receptors in idiopathic PD or animal models of PD and these two studies investigated very circumscribed brain structures; therefore, the fate of 5-HT_{2C} receptors in PD remains largely unknown. Additionally, the pharmacological studies performed in PD with 5-HT_{2C} receptor antagonists were done with atypical antipsychotics or mesulergine, none of which are selective for 5-HT_{2C} receptors, thus precluding any conclusions that would be specific to 5-HT_{2C} receptors. However, because they are involved in the modulation of nigrostriatal dopamine release, 5-HT_{2C} receptors represent an attractive, yet largely unexplored, therapeutic target against both parkinsonism and dyskinesia. Table 11 summarises the results of the preclinical and clinical studies performed with 5-HT_{2C} modulators in PD and animal models of PD.

5.7. 5-HT_3 receptors

Human 5-HT_{3A} receptor subunit gene (MIM *182139, http://www.ncbi.nlm.nih.gov/omim/182139) is located on chromosome 11q23.1–q23.2 (Weiss et al., 1995) and was cloned in 1995 (Miyake et al., 1995). The gene contains 7 exons (Bruss et al., 2000) and codes for a 478 amino acid protein with a potential signal peptide of 23 residues (Miyake et al., 1995). Human 5-HT_{3B} receptor subunit gene (MIM *604656, http://www.ncbi.nlm.nih.gov/omim/604654) was identified in 1999 (Davies et al., 1999). It contains 9 exons, is located on chromosome 11q23.1, and codes for a 441 amino acid protein (Davies et al., 1999). Unlike the other 5-HT receptors, 5-HT_3 receptors are ionotropic receptors, *i.e.* ligand-gated ion channels (Derkach et al., 1989; Maricq et al., 1991). 5-HT_{3A} subunits form functional homo-oligomers (Brown et al., 1998), whereas 5-HT_{3B} subunits need to oligomerise with 5-HT_{3A} subunits to be expressed at cell surface (Boyd et al., 2003). 5-$HT_{3A/3B}$ hetero-oligomers exhibit greater ionic conductance than 5-HT_{3A} homo-oligomers (Davies et al., 1999). Genes for subunits 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} have also been described in human (Niesler et al., 2003). 5-HT_3 receptors play a role in anxiety (Bill et al., 1992; Costall et al., 1993; Delagrange et al., 1999), schizophrenia (Thompson et al., 2006), emesis (Thompson and Lummis, 2007), learning and attention (Harrell and Allan, 2003), substance dependence and craving (Dawes et al., 2005; Johnson et al., 2002), pain (Wolf, 2000) and pruritus (Schworer and Ramadori, 1993). 5-HT_3 receptors are involved in the control of dopamine release and dopamine levels in the striatum (Benloucif et al., 1993; Chen et al., 1991; Costall et al., 1987; Parsons and Justice, 1993; Yoshimoto et al., 1992), as well as on striatal slices (Blandina et al., 1989; Zazpe et al., 1994).

In the mouse brain, 5-HT_3 receptors and their mRNA are most abundant in limbic forebrain areas and brainstem nuclei (Tecott et al., 1993; Waeber et al., 1988b), and are low in the basal

Table 11
5-HT_{2C} antagonists in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	Animal models		Idiopathic PD
	6-OHDA rat	MPTP NHP	
mCPP	• Causes oral AIMs when administered as monotherapy • Modulates Fos levels in the striatum and entopeduncular nucleus	n/a	n/a
Mesulergine	• Induces contraversive rotations when administered as monotherapy	n/a	• Anti-parkinsonian action as monotherapy • ↑ L-DOPA anti-parkinsonian action • Possible beneficial effect on mood when combined to L-DOPA • May trigger hallucinations • May ↑ L-DOPA-induced dyskinesia
RS-102,221	• No effect on DOI-induced motor activity	n/a	n/a
SB-200,646A	• ↑ Quinpirole anti-parkinsonian action	n/a	n/a
SB-206,553	• No effect on rotational behaviour when administered as monotherapy systemically • ↑ SKF-82,958-induced contraversive rotations • ↑ Quinpirole anti-parkinsonian action • Anti-parkinsonian action when injected in the SNr ipsilateral to the lesion	n/a	n/a

6-OHDA: 6-hydroxydopamine; AIMs: abnormal involuntary movements; DOI: (±)-2,5-dimethoxy-4-iodoamphetamine; L-: *levo*; L-DOPA: L-3,4-dihydroxyphenylalanine; mCPP: 1-(*m*-chlorophenyl)piperazine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; n/a: not available; NHP: non-human primate; PD: Parkinson's disease; SNr: substantia nigra pars reticulata.

Table 12
Pharmacological profile of the 5-HT_3 receptor ligand studied in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	5-HT_3 receptor affinity (nM)	Other binding sites (nM)	References
Ondansetron	1.6–3.98	5-HT_{1B} (3700), 5-HT_{1D} (20,000), 5-HT_{2C} (5000), 5-HT_4 (1200), α_1 (3400), μ (2900), σ (680), and M_1 (5100)	Bymaster et al. (2001) and van Wijngaarden et al. (1993)

Unless indicated otherwise, values are provided as the dissociation constant (K_d).
nM: nanomole.

ganglia (Waeber et al., 1988b). Similarly, in the rat brain, 5-HT_3 receptors predominate in brainstem nuclei and limbic forebrain areas. Intermediate levels are found in the neocortex, and low levels are encountered in the SN and striatum (Gehlert et al., 1993; Kilpatrick et al., 1987). In the human brain, the highest levels of 5-HT_3 receptors are encountered in the area postrema and nucleus tractus solitarius, whereas 5-HT_3 receptors are very scarce in the neocortex and basal ganglia (Parker et al., 1996; Waeber et al., 1989). In contrast with these two studies, which used [^{3}H]-ICS-205,930 and [^{3}H]-zacopride as the radioligands, another study using [^{3}H]-granisetron as the radioligand found moderate 5-HT_3 receptor levels in the SN and high levels in the striatum (Bufton et al., 1993).

5.7.1. 5-HT_3 receptors in Parkinson's disease

In the 6-OHDA-lesioned rat, 5-HT_3 receptor levels are reduced in synaptosomal preparations of the entorhinal and prefrontal cortices ipsilateral to the lesion (Cicin-Sain and Jenner, 1993). One post mortem study measuring 5-HT_3 receptor levels in putamen synaptosomes from idiopathic PD patients did not find any difference in comparison to control subjects (Steward et al., 1993). To our knowledge, no other study addressing the fate of 5-HT_3 receptors in PD has been published.

In the 6-OHDA-lesioned rat, the firing activity of pyramidal neurons of the medial prefrontal cortex ipsilateral to the lesion is reduced following intravenous administration or local application of the 5-HT_3 agonist SR-57227A (Zhang et al., 2011). The clinical importance of this phenomenon remains to be established.

5.7.2. 5-HT_3 receptor modulation as a potential target against parkinsonism and treatment-related complications

Only two clinical studies have been performed with selective 5-HT_3 receptor ligands in PD. In one study, the 5-HT_3 antagonist ondansetron (*vide* Table 12) significantly reduced the severity of dopaminergic psychosis, without affecting L-DOPA anti-parkinsonian efficacy (Zoldan et al., 1995). In another trial, ondansetron significantly alleviated VH (Zoldan et al., 1993).

5.7.3. 5-HT_3 receptors in Parkinson's disease: summary

5-HT_3 receptors remain poorly studied in PD. The fate of 5-HT_3 receptors in PD and treatment-related complications is largely unknown. If 5-HT_3 receptor antagonists appear effective against L-DOPA-induced psychiatric complications, their effect on L-DOPA-induced dyskinesia has not been assessed. However, inasmuch as 5-HT_3 receptors regulate striatal dopamine release, appropriate modulation of 5-HT_3 receptors could theoretically alleviate L-DOPA-induced dyskinesia or enhance L-DOPA anti-parkinsonian action. Studies are needed to verify those hypotheses as well as to expand the knowledge about 5-HT_3 receptors in PD.

5.8. 5-HT_4 receptors

Human 5-HT_4 receptor gene (MIM *602164, http://www.ncbi.nlm.nih.gov/omim/602164) was cloned in 1997 and is located on chromosome 5q31–q33 (Blondel et al., 1997; Cichon et al., 1998; Claeysen et al., 1997). The gene spans 700 kb, contains 38 exons (Bockaert et al., 2004) and codes for a 387 amino acid protein (Blondel et al., 1997). 5-HT_4 receptors are coupled to a G_s protein and promote cAMP formation (Dumuis et al., 1988). 5-HT_4 receptors form homodimers (Berthouze et al., 2007). 5-HT_4 receptors are involved in learning and memory (Lamirault and Simon, 2001; Lelong et al., 2001; Terry et al., 1998), gastro-intestinal motility (Tazawa et al., 2002), eating control (Jean et al., 2007), modulation of GABAergic signalling (Bianchi et al., 2002; Cai et al., 2002), hippocampal plasticity (Kemp and Manahan-Vaughan, 2005; Mlinar et al., 2006) and modulation of 5-HT neurotransmission in the hippocampus (Ge and Barnes, 1996). 5-HT_4 receptors play a role in pathologies such as seizure susceptibility (Compan et al., 2004), bipolar disorder (Ohtsuki et al., 2002), stress-induced anorexia (Compan et al., 2004) and suicide (Rosel et al., 2004).

5-HT_4 receptors exert a modulatory effect on neuronal firing and neurotransmission within the basal ganglia circuitry. Indeed, in rat slices, 5-HT_4 antagonists block the 5-HT-induced increase in STN neuronal firing rate (Stanford et al., 2005). 5-HT_4 receptors regulate dopamine release in rat striatal slices and *in vivo* in the rat striatum (Benloucif et al., 1993; Bonhomme et al., 1995; Steward et al., 1996) and SN (Thorre et al., 1998). 5-HT_4 receptors regulate morphine-induced dopamine release in the rat striatum, but not in the nucleus accumbens, and they do not modulate amphetamine- or cocaine-induced striatal dopamine release (Porras et al., 2002).

In the rat brain, high 5-HT_4 mRNA levels are encountered in the limbic areas and nucleus accumbens; moderate levels are present in the caudate nucleus and putamen, and low levels are found in the STN (Ullmer et al., 1996; Vilaro et al., 1996). In the human brain, high 5-HT_4 mRNA levels are present in the striatum, and 5-HT_4 mRNA appears absent from the GP and SN (Bonaventure et al., 2000). Autoradiographic binding studies have demonstrated high 5-HT_4 receptor levels in the striatum, GP and SN of the mouse, rat, guinea pig and pig-tail macaque (*Macaca nemestrina*) (Jakeman et al., 1994; Uchiyama-Tsuyuki et al., 1996; Waeber et al., 1994). Similar findings are encountered in the human brain (Bonaventure et al., 2000; Domenech et al., 1994; Marner et al., 2009; Reynolds et al., 1995; Varnas et al., 2003, 2004a). In the human neocortex, the highest 5-HT_4 receptor levels are found in the external cortical layers (Varnas et al., 2003, 2004a). In the striatum, 5-HT_4 receptors are not located on nigrostriatal terminals (Compan et al., 1996; Crespi et al., 1995), but are rather localised on striatal projection neurons (Mengod et al., 1996; Patel et al., 1994, 1995).

5.8.1. 5-HT_4 receptors in Parkinson's disease

Few studies have addressed the fate of 5-HT_4 receptors in PD. In the 6-OHDA-lesioned rat, one study found no change in striatal 5-HT_4 receptor levels (Patel et al., 1995), whereas another one found increases in the caudal – but not rostral – striatum and the GP (Compan et al., 1996). 5-HT_4 receptor levels are unchanged in the putamen and SN of PD patients, when compared to healthy controls (Reynolds et al., 1995; Wong et al., 1995).

5.8.2. 5-HT_4 receptor modulation as a potential target against parkinsonism and treatment-related complications

In PD, compounds with activity at 5-HT_4 receptors have been studied mainly for their prokinetic effect on the gastro-intestinal tract. Thus, the 5-HT_4 agonist mosapride (*vide* Table 13) improves gastro-intestinal motility and constipation in PD patients (Asai et al., 2005; Liu et al., 2005). Mosapride appears to increase

Table 13
Pharmacological profile of 5-HT_4 receptor ligands studied in idiopathic Parkinson's disease and animal models of Parkinson's disease.

	5-HT_4 receptor affinity (nM)	Other binding sites (nM)	References
Cisapride	14.3–117	5-HT_{1A} (1600), 5-HT_{1D} (675), 5-HT_{2A} (3.1), 5-HT_{2B} (1000), 5-HT_3 (61–684), α_1 (79), α_2 (2700), σ (110), D_2 (50), and M_1 (5400)	Mikami et al. (2008), Suzuki et al. (1999), and Yoshikawa et al. (1998)
Mosapride	69.9–347	5-HT_{2A} (1890), 5-HT_{2B} (330), and D_2 (823)	Mikami et al. (2008) and Yoshikawa et al. (1998)
Tegaserod	13.2–19.4	5-HT_{1A} (18.7), 5-HT_{1B} (30), 5-HT_{1D} (19), 5-HT_{2A} (68), 5-HT_{2B} (9.1), 5-HT_7 (302), and D_2 (122)	Mikami et al. (2008)

Unless indicated otherwise, values are provided as the dissociation constant (K_d).
nM: nanomole.

duration of ON-time and to reduce motor fluctuations (Asai et al., 2005). The 5-HT_4 partial agonist tegaserod also seems beneficial against constipation in PD (Morgan and Sethi, 2007), but its efficacy is inconsistent across studies (Sullivan et al., 2006). The 5-HT_4 agonist cisapride improves colonic transit and constipation in PD (Jost and Schimrigk, 1993, 1994, 1997), but its efficacy fades over time (Jost and Schimrigk, 1997). Cisapride increases mean and peak plasma L-DOPA levels, and improves visuo-manual coordination and gait (Neira et al., 1995). In one study, cisapride decreased the latency of onset of action of L-DOPA and alleviated the "no-ON" phenomenon (Djaldetti et al., 1995). Exacerbation of PD tremor by cisapride has been reported (Sempere et al., 1995). In 2002, the Movement Disorders Society concluded that there was insufficient evidence on the efficacy of cisapride against gastro-intestinal dismotility in PD to recommend its use (MovementDisordersSociety, 2002).

5.8.3. 5-HT_4 receptors in Parkinson's disease: summary

5-HT_4 receptors are abundant in the striatum, in which they are localised on striatofugal neurons. They participate in the regulation of dopamine release in the striatum. Despite their abundance within the basal ganglia, 5-HT_4 receptor agonists/antagonists have not been studied against the manifestations of PD or treatment-related complications. No studies with 5-HT_4 modulators have been performed in animal models of PD. In idiopathic PD, studies interested in 5-HT_4 receptor modulation have focussed on the assessment of the prokinetic efficacy of 5-HT_4 receptor agonists on gastro-intestinal motility. These trials have demonstrated that 5-HT_4 agonists improve constipation and colonic transit time in PD patients. Probably because of their favourable effect on gastro-intestinal motility which likely increases L-DOPA absorption, 5-HT_4 receptor agonists increase plasma L-DOPA levels and duration of ON-time, decrease the time required to switch ON, and reduce the severity of motor fluctuations. Should studies with 5-HT_4 modulator in PD be undertaken, it will be important to select compounds more selective than those cited in the current review. Indeed, as presented in Table 13, cisapride harbours high affinity at both 5-HT_{2A} and D_2 receptors, and tegaserod is a potent 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and D_2 ligand. As discussed earlier, interaction with these sites could alter parkinsonism and dyskinesia severity, which would make it difficult to conclude on the role played by the specific targeting of 5-HT_4 receptors in the context of PD.

5.9. 5-HT_5 receptors

To our knowledge, no study investigating 5-HT_5 receptors in PD or PD animal models was performed. 5-HT_5 receptors appear very few in the striatum and GP (Oliver et al., 2000; Pasqualetti et al., 1998; Plassat et al., 1992), but seem relatively abundant in the SN and STN (Oliver et al., 2000).

5.10. 5-HT_6 receptors

Although some of the compounds discussed above exhibit some affinity for 5-HT_6 receptors, it is not their primary mechanism of action, and the role played by their effect at 5-HT_6 receptors in their overall biological action in PD is unclear. High levels of 5-HT_6 receptors are found in the striatum and moderate levels in the SN (Gerard et al., 1997; Kohen et al., 1996; Monsma et al., 1993; Ruat et al., 1993a). To our knowledge, no study has assessed 5-HT_6 receptor levels or 5-HT_6 pharmacological modulation in PD or related animal models. The only study investigating 5-HT_6 receptors in PD found an association between the 5-HT_6 receptor gene polymorphism C267T and PD (Messina et al., 2002).

5.11. 5-HT_7 receptors

Although some of the compounds discussed earlier such as the 5-HT_{1A} receptor agonist 8-OH-DPAT display affinity for the 5-HT_7 receptors, it is not their principal mechanism of action, and it is hard to assess the impact of their interactions with 5-HT_7 receptors on their biological effects in PD. 5-HT_7 receptors appear to be few within the basal ganglia (Bonaventure et al., 2002, 2004; Neumaier et al., 2001; Ruat et al., 1993b; Varnas et al., 2004b). To our knowledge, no study investigated 5-HT_7 receptors in PD or animal models of PD.

6. Concluding remarks

The serotonergic system has been extensively studied in PD and, through complex interactions with its numerous receptor subtypes, 5-HT is involved in both motor and non-motor symptoms and treatment-related complications. The purported involvement of the SERT and the various 5-HT receptors in PD are summarised in Table 14.

As mentioned previously, however, a lot of the putative functions of 5-HT receptors in PD are inferred from pharmacological studies, the majority of which used non-selective ligands. For instance, the anti-dyskinetic and antipsychotic actions of clozapine and other atypical antipsychotics are usually attributed to a 5-HT_{2A} antagonist effect. However, clozapine, the most extensively studied 5-HT-modulating compound in PD, is a non-selective molecule that binds to several 5-HT and extra-5-HT receptors, all of which are likely to contribute, to some extent, to its behavioural effects. In addition, the majority of the clinical studies published with 5-HT-modulating drugs consist in case-reports or small, uncontrolled, unblinded, non-randomised studies, often with contradictory results, all of which further limit the interpretation of the currently available literature. Further studies with more selective molecules and more rigorous design are thus needed to better clarify the biological and behavioural effects of stimulating/antagonising specific 5-HT receptor subtypes in PD.

Despite the impressive number of studies cited in this exhaustive review, the majority of 5-HT receptors have been poorly studied or not studied at all in PD. 5-HT_3 and 5-HT_4 receptors illustrate well this reality. As mentioned above, 5-HT_3 and 5-HT_4 receptors are present in the basal ganglia where they modulate striatal dopamine release. To date, however, the fate of 5-HT_3 and 5-HT_4 receptors in PD remains largely unknown and no trials have specifically examined their potential anti-parkinsonian

Table 14
Involvement of SERT and serotonin receptors in Parkinson's disease and treatment-related complications.

	5-HT transporter/receptors							
	SERT	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_3	5-HT_4
Parkinsonism		↙	↙			↙		
Dyskinesia		↙	↙	↙		↙		
Tremor	↙	↙	↙	↙				
Psychosis				↙			↙	
Depression	↙	↙	↙	↙				
Anxiety		↙	↙	↙				
Constipation								↙
Heart valvulopathy					↙			
Serosal fibrosis					↙			

To date, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_5, 5-HT_6 and 5-HT_7 receptors have not been linked to any manifestation of PD or treatment-related complications.
5-HT: serotonin; PD: Parkinson's disease; SERT: 5-HT transporter.

and/or anti-dyskinetic properties, even though their anatomical localisation and their biological function would suggest their modulation might alleviate both parkinsonism and dyskinesia, thereby leading to promising new therapies. However, until studies specifically address these points, the role of 5-HT_3 and 5-HT_4 receptors in parkinsonism and dyskinesia will remain hypothetical. Equally, at the moment, the fate and possible involvement of 5-HT_{1E}, 5-HT_{1F}, 5-HT_5, 5-HT_6 and 5-HT_7 receptors in PD are unknown. As mentioned above, 5-HT_6 and 5-HT_7 receptors are present in the basal ganglia, suggesting that their modulation might alter parkinsonism and/or dyskinesia severity. Studies that will lead to a better comprehension of the role, or lack thereof, of 5-HT_6 and 5-HT_7 in parkinsonism and treatment-related complications are urgently needed, as they might lead to the development of new therapies.

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