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New insight into the therapeutic role of the serotonergic system in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a common, late-onset neurodegenerative disorder that shows progressive extrapyramidal motor disorders (e.g., bradykinesia, resting tremors, muscle rigidity and postural instability) and various non-motor symptoms (e.g., cognitive impairment, mood disorders, autonomic dysfunction and sleep disorders). While dopaminergic agents such as L-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine D_2 agonists are widely used for the treatment of PD, there is still high clinical unmet need for novel medications that overcome the limitations of current therapies. Evidence is now accumulating that the serotonergic nervous system is involved in the pathophysiological basis of PD and can provide benefits in the treatment of PD through its diverse functions. Among 5-HT receptor subtypes, 5-HT_{1A}, 5-HT_2, 5-HT_3 and 5-HT_6 receptors play an important role in modulating extrapyramidal motor disorders. In addition, 5-HT_{1A}, 5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_6 receptors are implicated in modulation of cognitive impairment, mood disorders (e.g., depression and anxiety) and/or psychosis, which are frequently observed in patients with PD. Specifically, stimulation of 5-HT_{1A} receptors seems to be effective for multiple PD symptoms including parkinsonism, L-DOPA-induced dyskinesia, cognitive impairment, mood disorders and neurodegeneration of dopamine neurons. Blockade of 5-HT_2 receptors is also likely to improve parkinsonism, depressive mood and cognitive impairment. In addition, it was recently demonstrated that 5-HT_{2A} inverse agonists can alleviate PD psychosis. All these findings emphasize the therapeutic roles of the serotonergic system in PD and stimulate new insight into novel treatments by modulating 5-HT_{1A} and 5-HT_2 receptors.

Contents

Abbreviations: ADL, activities of daily living; COMT, catechol-*O*-methyltransferase; DOI, 2,5-dimethoxy-4-iodoamphetamine; GIRK, G-protein-gated inwardly rectifying potassium; GP, globus pallidus; GPCR, G protein-coupled receptor; GPe, external segment of GP; GPi, internal segment of GP; L-DOPA, L-3,4-dihydroxyphenylalanine; mACh, muscarinic acetylcholine; 6-OH-DA, 6-hydroxydopamine; MAO-B, monoamine oxidase-B; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; PK-A, protein kinase A; PK-C, protein kinase C; QOL, quality of life; TCA, tricyclic antidepressants; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino) tetralin; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; TM, transmembrane; 5-HT, 5-hydroxytryptamine (serotonin); SSRI, selective 5-HT reuptake inhibitor.

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1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a bioactive substance synthesized from tryptophan and is widely distributed in most peripheral tissues and the brain (Jacobs and Azmitia, 1992). 5-HT causes vaso-constriction, facilitates platelet coagulation, works as a chemical mediator in inflammatory processes and regulates functions of the gastrointestinal system in the periphery. Although the 5-HT levels in the brain are negligible (about 2%) as compared to the peripheral levels, it also plays a crucial role in controlling various central nervous system functions including psycho-emotional manifestation, sensori-motor integration, cognitive function, and regulation of endocrine and autonomic systems (Barnes and Sharp, 1999; Baumgarten and Grozdanovic, 1995; Jacobs and Azmitia, 1992; Roth, 1994).

5-HT neurons are located in the raphe nuclei of the brain stem (e.g., pons and medulla oblongata) and project to various brain regions including the cerebral cortex, limbic structures (e.g., hippocampus and amygdala), basal ganglia (e.g., striatum), diencephalon (e.g., thalamus and hypothalamus) and spinal cord (Jacobs and Azmitia, 1992; Törk, 1990). The serotonergic neurotransmission is mediated by 5-HT receptors that are generally classified into 7 families (5-HT$_1$ to 5-HT$_7$) according to the signal cascades, encompassing at least 14 subtypes (5-HT$_{1A, 1B, 1D, 1E, 1F}$, 5-HT$_{2A, 2B, 2C}$, 5-HT$_3$, 5-HT$_4$, 5-HT$_{5A, 5B}$, 5-HT$_6$ and 5-HT$_7$) (Barnes and Sharp, 1999; Baumgarten and Grozdanovic, 1995; Ohno et al., 2012) (Fig. 1). These 5-HT receptors, except for 5-HT$_3$ receptors, are G protein-coupled receptors (GPCRs) with a 7 transmembrane (TM)-spanning structure. They are distributed in the post-synaptic membranes of neurons or nerve terminals innervated by 5-HT neurons and mediate intracellular signal transduction via coupling to individual G proteins (e.g., $G_{i/o}$, G_s and G_q). On the other hand, 5-HT$_3$ receptors are composed of a hetero-pentamer consisting of 5 subunits, 5-HT3A to 5-HT3E, which forms Na^+ and Ca^{2+}-permeable cation channels

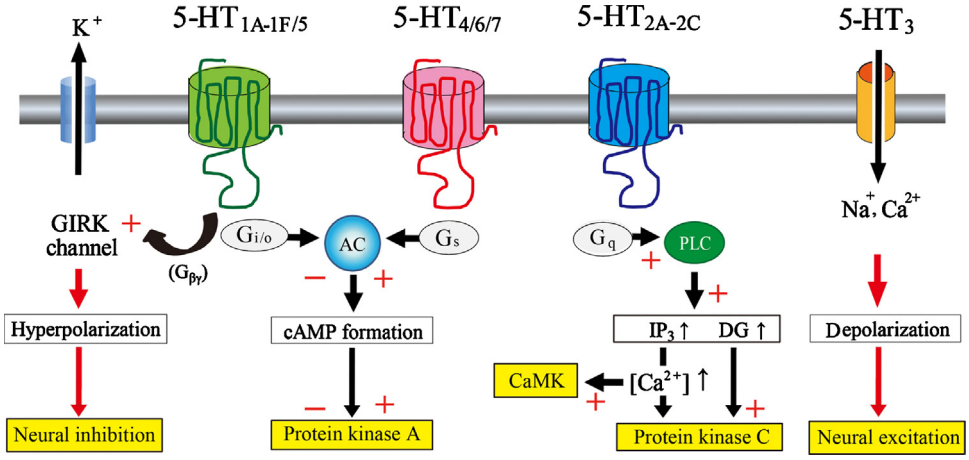

Fig. 1. Signal transduction of 5-HT receptor subtypes. 5-HT receptors are generally classified into 7 families (5-HT$_1$ to 5-HT$_7$) and at least 14 subtypes (5-HT$_{1A, 1B, 1D, 1E, 1F}$, 5-HT$_{2A, 2B, 2C}$, 5-HT$_3$, 5-HT$_4$, 5-HT$_{5A, 5B}$, 5-HT$_6$ and 5-HT$_7$) according to their signal cascades. 5-HT receptors, except for 5-HT$_3$ receptors, are G protein-coupled receptors with a 7 transmembrane-spanning structure, mediating intracellular signal transduction via coupling to individual G proteins (e.g., $G_{i/o}$, G_s and G_q), while 5-HT$_3$ receptors forms Na^+ and Ca^{2+}-permeable cation channels. AC, adenylate cyclase; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; DG, diacylglycerol; GIRK, G-protein-gated inwardly rectifying potassium; IP_3, inositol triphosphate; PLC, phospholipase C.

(Fig. 1) (Thompsons, 2013). In addition to the post-synaptic 5-HT receptors, 5-HT neurons have 2 types of pre-synaptic autoreceptors, 5-HT_{1A} and 5-$HT_{1B/1D}$ receptors. 5-HT_{1A} receptors are located on the cell bodies of 5-HT neurons and negatively control their own firing, while 5-$HT_{1B/1D}$ receptors exist on the nerve terminals of 5-HT neurons and inhibit the release or synthesis of 5-HT as a feedback mechanism (Barnes and Sharp, 1999; Ohno et al., 2012). Furthermore, several studies showed that 5-HT_{2B} receptors also act as a pre-synaptic autoreceptor, regulating 5-HT release (Banas et al., 2011; Doly et al., 2008).

Progress in 5-HT research has led to the development of various therapeutic agents which selectively interact with 5-HT receptors or transporters. These drugs include the selective 5-HT reuptake inhibitors (SSRIs) (e.g., fluoxetine, paroxetine, sertraline and escitalopram), the 5-HT_{1A} agonistic anxiolytics (e.g., buspirone and tandospirone) (Ohno, 2010), the 5-$HT_{1B/1D}$ agonistic antimigraines (e.g., sumatriptan and naratriptan) (Mannix, 2008), the second generation antipsychotics with potent 5-HT_2 blocking actions (e.g., risperidone, olanzapine, quetiapine and lurasidone) (Kapur and Remington, 2001; Meltzer, 1991, 1999; Ohno et al., 1997) and the 5-HT_3 antagonistic antiemetics (e.g., ondansetron and granisetron) (Thompsons, 2013). These serotonergic drugs have being greatly contributed to the current medications for various neurological and neuropsychiatric diseases.

Parkinson's disease (PD) is a common, late-onset neurological disorder with progressive deterioration of extrapyramidal motor functions (Halliday et al., 2014; Henchcliffe and Beal, 2008; Samii et al., 2004). Although the dopaminergic system has long been considered to be the primary cause of PD, several lines of evidence revealed that the serotonergic system also plays important roles in modulating extrapyramidal motor functions (e.g., parkinsonism and L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia) and other non-motor symptoms related to PD (e.g., cognitive impairments and psycho-emotional disorders) (Halliday et al., 2014; Huot and Fox, 2013; McDonald et al., 2003; Meneses, 2013; Miguelez et al., 2014; Ohno, 2011; Ohno et al., 2013; Shimizu and Ohno, 2013). Therefore, a new vision emerges from this evidence that 5-HT receptors are a promising target in the treatment of PD. In this article, we review the functional roles of 5-HT receptors in the pathogenesis and treatment of PD and discuss the therapeutic approaches by modulating 5-HT receptors.

2. Parkinson's disease (PD)

2.1. Clinical symptoms

PD is the second most common neurological disorder in the elderly with a prevalence of about 1% among those older than 60 years (Samii et al., 2004). The general age of onset is the early-to-late 60s while patients with young-onset PD (about 5–10% of total PD patients) show the initial symptoms between 20 and 40 years of age. Patients with PD show progressive extrapyramidal motor disorders, typically hypokinesia (e.g., bradykinesia and impaired walk), resting tremors, muscle rigidity and postural instability (Fig. 2) (Poewe and Mahlknecht, 2009; Samii et al., 2004).

"Tremors" are the first symptom and are seen in about 70% of PD patients. Tremors in PD usually occur at rest and show a low frequency of 3–5 Hz. "Muscle rigidity" manifests as an increased

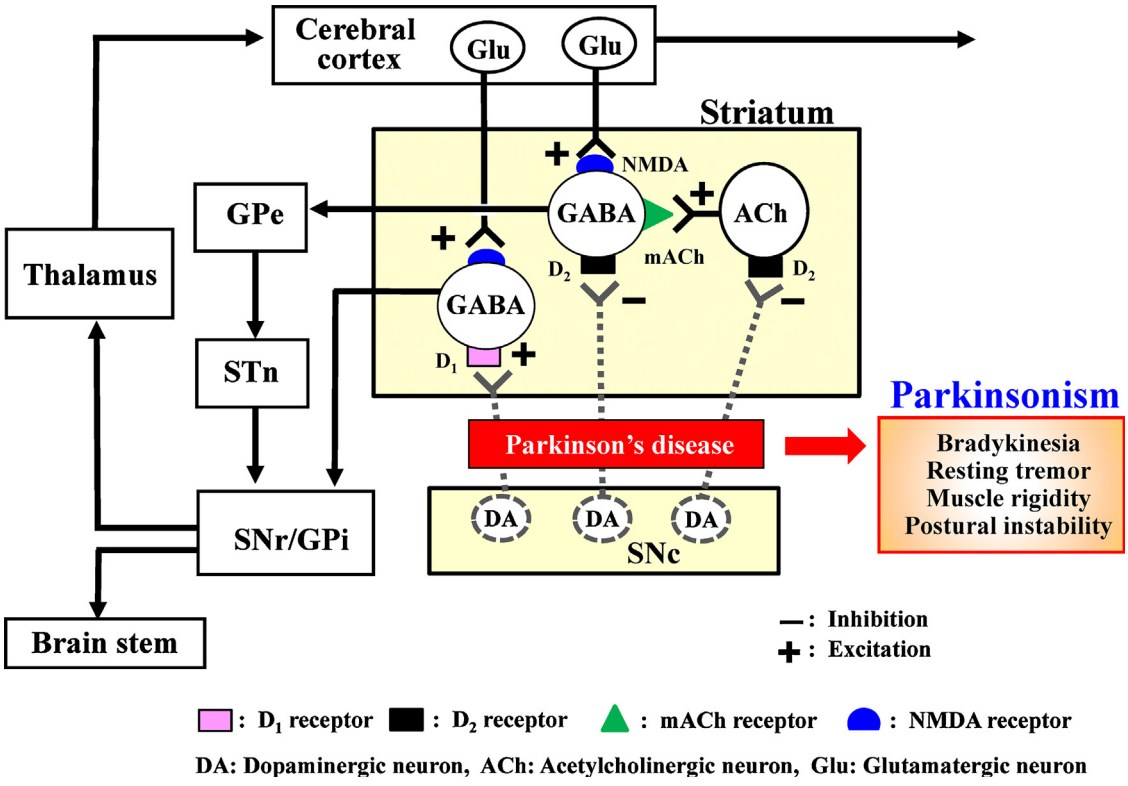

Fig. 2. Neural network relating to pathogenesis of Parkinson's disease. Extrapyramidal motor functions are mainly regulated by the basal ganglia including the striatum, globus pallidus (GP), subthalamic nucleus (STn) and substantia nigra (SN), which forms the basal ganglia-thalamus-cerebral cortex neural network. Medium spiny neurons containing GABA receive excitatory inputs from the cerebral cortex and cholinergic interneurons in the striatum. Medium spiny neurons which directly project to the substantia nigra pars reticulata (SNr) and internal segment of GP (GPi) (direct pathway) express excitatory D_1 receptors and those which indirectly project to the SNr and GPi via the external segment of GP (GPe) and STn (indirect pathway) express inhibitory D_2 receptors. Activities of medium spiny neurons and cholinergic interneurons are tonically regulated by dopaminergic neurons derived from the substantia nigra pars compacta (SNc). However, in patients with Parkinson's disease, the nigro-striatal dopaminergic neurons are degenerated, which activates the striatal medium spiny neurons and cholinergic interneurons and induces various extrapyramidal motor disorders (parkinsonism).

resistance noted during passive joint movement. Rigidity appears without tremors, but is usually more pronounced in the more tremulous limb. Tremors and rigidity are worsened by mental tasks, tension and anxiety. "Bradykinesia" is the most disabling symptom in patients with early PD. It disrupts or slows fine motor tasks such as handwriting, setting buttons and arm swings during walking, and markedly impairs the patients' activities of daily living (ADL). "Postural instability" refers to poor postural balance which leads to an increased risk of falls. It can be assessed by pulling the patient backward to check for balance recovery. "Freezing gait" is usually seen in late stage PD and is characterized by difficulty in initiating gait and avoiding or stopping at an obstacle. Other PD symptoms include salivation, difficulties of speech, dressing and getting up from a chair and leg agility.

Besides the motor symptoms, patients with PD show various non-motor symptoms such as mood disorders (e.g., depression and anxiety), cognitive impairment (e.g., deficits in learning and memory), sleep disturbances (e.g., daytime somnolence, sleep attacks and night-time awakings) and autonomic dysfunctions (e.g., orthostatic hypotension, constipation and urinary symptoms) (Gallagher and Schrag, 2012; Halliday et al., 2014; Huot and Fox, 2013; McDonald et al., 2003; Meireles and Massano, 2012; Poewe and Mahlknecht, 2009; Samii et al., 2004; Shimizu and Ohno, 2013). Among these symptoms, depression and anxiety are very common and are usually comorbid, affecting about 50% of the patients with PD (Gallagher and Schrag, 2012; McDonald et al., 2003; Ohno, 2002; Richard et al., 1996). It is suggested that depression and anxiety are not merely psychological reactions of the patients to the illness, but are closely linked to the neurobiological basis of PD such as neurodegeneration or dysfunctions of the dopaminergic, serotonergic and/or noradrenergic systems. In addition, cognitive impairment develops in about 40% of patients and most patients (more than 80%) manifest dementia at the end-stage of PD (Meireles and Massano, 2012). Cognitive impairment is also often comorbid with other non-motor symptoms (especially depression) in patients with PD, interacting with each other (McDonald et al., 2003). For example, depression worsens cognitive impairment and, at the same time, cognitive impairment is associated with an increased risk of developing depression. Furthermore, depression impairs motor skill and worsens parkinsonian motor symptoms. Therefore, besides the treatment of core motor symptoms (parkinsonism), the control of non-motor symptoms is a key issue for improving the quality of life (QOL) and ADL of the PD patients.

2.2. Pathophysiological basis

Extrapyramidal motor functions are mainly regulated by the basal ganglia including the striatum (i.e., caudate-putamen) and the globus pallidus (GP), which forms the basal ganglia-thalamus-cerebral cortex neural circuit (Miguelez et al., 2014; Ohno et al., 2013; Shimizu and Ohno, 2013; Somola, 2013) (Fig. 2). The majority (about 95%) of striatal neurons are GABAergic medium spiny neurons, which receive excitatory inputs from the cortico-striatal glutamatergic neurons and from cholinergic interneurons within the striatum. In addition, activities of striatal medium spiny neurons and cholinergic interneurons are tonically regulated by dopaminergic neurons derived from the substantia nigra pars compacta (SNc). Medium spiny neurons, which directly project to the substantia nigra pars reticulata (SNr) and internal segment of GP (GPi) (direct pathway), express excitatory D_1 receptors while those indirectly projecting to the SNr and GPi via the external segment of GP (GPe) and subthalamic nucleus (indirect pathway) express inhibitory D_2 receptors (Somola, 2013) (Fig. 2).

In the early stage of PD, dopaminergic neurons degenerate in the ventrolateral part of the SNc, which thereafter extend to other parts of the SNc as the disease progress (Greffard et al., 2006; Milber et al., 2012). The specific loss of the nigro-striatal dopaminergic neurons causes a disinhibition of medium spiny neurons and cholinergic interneurons and increases their firing activities (Fig. 2). Thus, in the pathophysiological condition of PD, the activity of nigro-striatal dopaminergic neurotransmission is largely diminished and that of striatal cholinergic interneurons is elevated. Although the exact mechanisms underlying the degeneration of dopamine neurons are still uncertain, abnormal protein disposition forming Lewy bodies and/or neurites (possibly associated with mutations of the gene encoding α-Synuclein or Parkin), accumulation of endogenous or exogenous toxic compounds (e.g., *N*-methyl (R) salsolinol and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), respectively) and/or the mitochondrial dysfunctions are thought to activate neurotoxic cascades and cause the specific loss of dopaminergic neurons (Henchcliffe and Beal, 2008; Samii et al., 2004).

Besides the loss of nigro-striatal dopaminergic neurons, degeneration and dysfunction of other neurotransmitter systems such as noradrenaline, serotonin and acetylcholine neurons are also reported in PD. There are three main regions containing acetylcholine neurons in the brain; (1) striatal interneruons, (2) Ch4 cholinergic neurons in the nucleus basalis and (3) Ch5 cholinergic neurons in the pedunclopontine nucleus (Halliday et al., 2014). Although acetylcholine interneurons in the striatum are not affected in PD, other Ch4 and Ch5 cholinergic neurons degenerate in PD (Bohnen and Albin, 2011; Yarnall et al., 2011). Noradrenaline neurons in the locus coeruleus projecting to the entire forebrain regions severely degenerate in the late phase of PD (Del Tredici and Braak, 2013; Gaspar and Gray, 1984; Pifl et al., 2012; Zweig et al., 1993). Damage of noradrenaline neurons is temporally associated with a loss of acetylcholinergic neurons in the nucleus basalis, which is considered to be related to cognitive impairment and mood disorders in PD (Gaspar and Gray, 1984; Zweig et al., 1993). Furthermore, 5-HT content and the density of 5-HT transporters (a marker for 5-HT nerve terminals) in the forebrain regions (e.g., striatum and neocortex) are also reduced in the advanced stage of PD (Halliday et al., 1990; Kerenyi et al., 2003; Kish et al., 2008; Politis et al., 2010). Meanwhile, post-synaptic 5-HT_{1A} and 5-HT_{2A} receptors are up-regulated in response to the functional deficit of 5-HT neurons (Chen et al., 1998; Strecker et al., 2011). Interestingly, the level of striatal 5-HT transporter increased in the early stage of PD, which temporally correlated with a reduction in striatal dopamine transporters, implying an initial compensatory mechanism of the serotonergic system in PD (Strecker et al., 2011). Several studies suggest that the compensatory mechanism of the serotonergic system in PD is related to the development of dyskinesia associated with the L-DOPA treatment (Carta and Bezard, 2011; Carta and Tronci, 2014; Politis et al., 2014; Styte and Vissel, 2014). Since serotonergic system is implicated in the control of psycho-emotional and cognitive functions (Barnes and Sharp, 1999; Baumgarten and Grozdanovic, 1995; Jacobs and Azmitia, 1992; Roth, 1994), degeneration of serotonin neurons in late stage of PD seems to be important in generation of non-motor symptoms, such as mood disorders (e.g., depression and anxiety) and cognitive impairments, in patients with PD.

2.3. Current therapy and clinical unmet needs

2.3.1. Treatment of motor symptoms

Patients with PD are responsive to various dopaminergic agents (Fig. 3). The dopamine precursor L-DOPA (levodopa) is the most effective antiparkinsonian agent and remains as the mainstay for PD treatment, allowing the dopamine replacement therapy. L-DOPA is effective for most PD motor symptoms including tremors

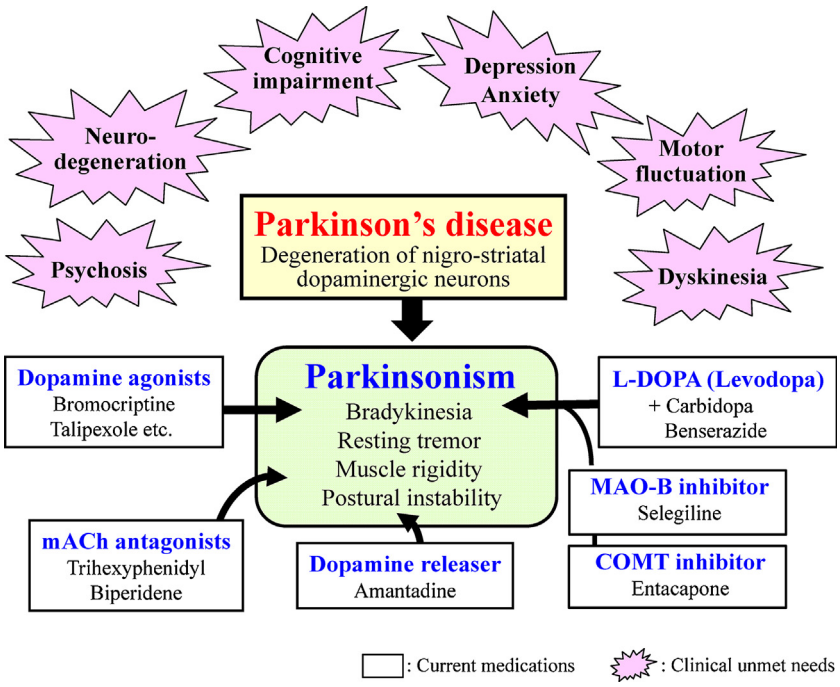

Fig. 3. Current medications for Parkinson's disease and clinical unmet needs. Various dopaminergic agents including L-DOPA and dopamine agonists are widely used to the treatment of Parkinson's disease. Although these agents are generally effective for most symptoms of Parkinson's disease, there are residual unmet needs, including a lack of effectual medications for neurodegeneration, cognitive impairments, mood disorders (e.g., depression and anxiety), dyskinesia or psychosis associated with chronic dopaminergic medications and motor fluctuation (e.g., wearing-off and on-off phenomena) in L-DOPA efficacy. mACh, muscarinic acetylcholine; MAO-B, monoamine oxidase-B; COMT, catechol-*O*-methyltransferase.

and is usually given in combination with L-aromatic amino acid decarboxylase inhibitors (e.g., carbidopa and benserazide), which prevent the conversion to dopamine in peripheral tissues and facilitate the central action of L-DOPA. Another frequent choice for PD is dopamine agonists that directly stimulate D_2 (and D_3) receptors to alleviate parkinsonism (Fig. 3). These agents are chemically classified into two groups, ergot derivatives (e.g., bromocriptine and pergolide) and non-ergots (e.g., ropinirole and talipexole). Although the efficacy of these agonists is generally similar, ergot derivatives are less selective to dopamine D_2 receptors than non-ergots. In addition, they induce rare but serious side effects such as retroperitoneal, pulmonary and cardiac-valve fibrosis associated with chronic treatments with ergot agonists (Samii et al., 2004; Somola, 2013). The dopamine D_2 agonists are less effective than L-DOPA, but the D_2 agonist monotherapy can sufficiently control the symptoms of early PD. Thereby, treatments generally begin with dopamine agonists for early PD in younger or healthier PD patients while L-DOPA is preferably used as an initial drug for older and frailer patients. Most patients started on dopamine agonist therapy will need the addition of L-DOPA usually in 5 years (Rascol et al., 2000). Amantadine, which enhances dopamine release and weakly blocks *N*-methyl-D-aspartate (NMDA) receptors, exerts mild antiparkinsonian effects and is sometimes used for initial therapy (Fig. 3). Anticholinergic agents such as trihexyphenidyl and beperiden, which block muscarinic acetylcholine (mACh) receptors, are particularly effective for tremors and can be used in young PD patients. However, the usefulness of mACh antagonists is limited (especially in older patients) because they cause various adverse reactions (e.g., intestinal constipation, urinary retention, tachycardia and delusion) and worsen non-motor symptoms (e.g., cognitive impairment) in PD.

Side effects of dopaminergic agents (i.e., L-DOPA, dopamine D_2 agonists, amantadine) include nausea, orthostatic hypotension, psychosis (e.g., hallucinations and delusion), somnolence and sudden sleep attacks (Ohno, 2011; Samii et al., 2004; Somola, 2013). Nausea is a very common side effect especially during the initial treatment and is treatable with peripheral dopamine D_2 antagonists (e.g., domperidone and metoclopramide) which block D_2 receptors at the chemoreceptor-trigger zone of the medulla oblongata. Antiparkinsonian agents often cause orthostatic hypotension by activating D_1 receptors located on the blood vessels. Psychosis is rare in naive PD patients, but often induced by the treatment with dopaminergic agents (i.e., drug-induced psychosis in PD). In this regard, dopamine D_2 agonists are more potent than L-DOPA to cause psychosis. Drug-induced psychosis (e.g., hallucinations, delusion and excitement) in PD is a serious side effect that hampers the continuation of treatment (Goldman and Holden, 2014). Although low doses of second generation (atypical) antipsychotics (e.g., quetiapine) are sometimes given, novel treatments or drugs for PD psychosis are still a major unmet clinical need (Fig. 3).

Long term treatment with L-DOPA often induces dyskinesia that is complex involuntary movement disorders involving dystonic, choreic and athetotic movements in the limbs, hands, trunk and lingual–facial–buccal muscular systems (Fabbrini et al., 2007; Ohno, 2011; Samii et al., 2004; Somola, 2013) (Fig. 3). Although variability exists, the frequency of L-DOPA-induced dyskinesia is reported at 30–80% (Fabbrini et al., 2007). The development of dyskinesia is associated with several factors such as (1) an earlier onset of PD, (2) longer duration of the disease, (3) longer duration of L-DOPA therapy, (4) total L-DOPA exposure and (5) female gender. Although the precise mechanisms are still unknown, supersensitivity of dopamine receptors associated with the disease progress and/or with repeated stimulation of dopamine receptors by PD medications are thought to be important in the pathogenesis of dyskinesia (Cheshire and Williams, 2012; Fabbrini et al., 2007). L-DOPA-induced dyskinesia can be attenuated by reducing the

dose of L-DOPA, but this usually worsens parkinsonian motor symptoms and hampers continued treatment.

L-DOPA also causes motor fluctuations (e.g., wearing-off, delayed-on, on-off phenomena of L-DOPA efficacy) during the chronic treatment (Ohno, 2011; Samii et al., 2004; Somola, 2013) (Fig. 3). About 25–50% of patients treated with low doses of L-DOPA develop motor fluctuations after 5 years (Hely et al., 1994; Koller et al., 1999). Thus, patients feel that the effects of L-DOPA wear off and movements of patients become slower and more tremulous. On-off phenomena stand for sudden switches of L-DOPA effects between mobility (on) and immobility (off). Since the short half-life of L-DOPA is thought to be the primary cause of these motor fluctuations, a frequent treatment schedule by dividing the dosage of L-DOPA is sometimes employed for their management. In addition, inhibitors of catechol-*O*-methyltransferase (COMT) and monoamine oxidase-B (MAO-B) are often used as an adjunctive drug (Ohno, 2011; Samii et al., 2004; Somola, 2013). A peripheral COMT inhibitor entacapone inhibits conversion of L-DOPA into 3-*O*-metyldopa by COMT and increases the blood level of L-DOPA. A MAO-B inhibitor selegiline inhibits the oxidative degradation of dopamine by MAO-B in the brain and enhances L-DOPA efficacy. However, even with these attempts, the antiparkinsonian action of L-DOPA gradually became fragile with the duration of treatment period and the patients need to consider surgical options (e.g., brain ablation and deep-brain stimulation).

2.3.2. Treatment of non-motor symptoms

Non-motor symptoms of PD such as cognitive impairments, mood disorders, sleep disturbances and L-DOPA-induced psychosis significantly disrupt the patients' QOL and ADL (Fig. 3). However, ideal medications or treatments for non-motor PD symptoms have not yet been established. Depression in PD is common and is usually treated with selective 5-HT reuptake inhibitors (SSRIs) and other antidepressants (e.g., tricyclic antidepressants (TCAs)). However, antidepressants that enhance serotonergic activity by inhibiting 5-HT transporters are known to have the potential to worsen extrapyramidal motor disorders (Huot and Fox, 2013; McDonald et al., 2003; Ohno et al., 2011; Tatara et al., 2012; Shimizu and Ohno, 2013). Indeed, nearly the half of the investigators who gave SSRIs to the PD patients was concerned that they might worsen motor functions (McDonald et al., 2003). In addition, SSRIs cause insomnia, agitation, nausea and sexual dysfunction. Thus, the benefits of SSRIs for the treatment of depression in PD are still limited.

There are no established medications or treatments for cognitive impairment in PD (PD dementia). Although some reports showed that the anti-Alzheimer agent donepezil (a cholinesterase inhibitor) was effective for PD-associated cognitive impairment and psychosis (Aarsland et al., 2002; Bergman and Lerner, 2002; Goldman and Holden, 2014), the cholinesterase inhibitors have the potential to induce or worsen extrapyramidal disorders by increasing cholinergic activity in the striatum (Shimizu et al., 2015). It should also be noted that anticholinergic medications for PD (e.g., trihexyphenidyl and beperiden) accelerate cognitive impairment (Ehrt et al., 2010).

Finally, antiparkinsonian agents (e.g., L-DOPA and dopamine agonists) that stimulate dopaminergic activity have a propensity to elicit psychosis (e.g., hallucinations, delusion and excitement) as described previously (Goldman and Holden, 2014; Samii et al., 2004). To reduce the drug-induced psychosis in PD (PD psychosis), discontinuation or reducing the dose of dopaminergic stimulants is necessary, which hampers the continued medications and accelerates the surgical treatment. The PD psychosis is treatable with low doses of second generation antipsychotics (e.g., quetiapine, aripiprazole and risperidone) (Goldman and Holden, 2014), which interact with several 5-HT receptors (Meltzer, 1991, 1999); however, clinicians still must be very careful about the worsening of parkinsonism due to the D_2 blocking activity of these agents.

2.3.3. Clinical unmet needs

Dopaminergic medications (i.e., L-DOPA, dopamine agonists, amantadine, entacapone and selegiline) are generally effective for most PD symptoms; however, there are still high clinical unmet needs in the treatment of PD (Fig. 3), as described previously. The biggest need is a disease-modifying medication or treatment against dopaminergic neurodegeneration, which can prevent degeneration of dopaminergic neurons or enhance regeneration of damaged neurons. Moreover, besides these causal treatments, there also are high clinical needs to improve the current therapy, such as new drugs with novel mechanisms of action for (1) parkinsonism, (2) L-DOPA-induced dyskinesia, (3) cognitive impairment (PD dementia), (4) mood disorders (e.g., depression and anxiety) and (5) PD psychosis (Fig. 3).

Since L-DOPA therapy is the most effective and final treatment for PD so far, more efficacious substitutes for L-DOPA or new drugs which can prolong the period of L-DOPA treatment are required. For this purpose, medications that can reduce side effects associated with L-DOPA treatment (e.g., L-DOPA-induced psychosis and dyskinesia) are desirable. In addition, since most antiparkinsonian agents available to date act through stimulating the dopaminergic nervous system, new medicines that have a novel mechanism of actions distinct from the dopaminergic system may be ideal (non-dopaminergic agents). From these points of view, therapeutic approaches that modulate 5-HT receptor functions seem to be most promising since the serotonergic nervous system is deeply involved in control of both motor (parkinsonism, L-DOPA dyskinesia) and non-motor (cognitive impairment, mood disorders, psychosis) symptoms in PD.

3. Roles of 5-HT receptors in the treatment of PD

3.1. 5-HT_{1A} receptors

3.1.1. Characteristics

5-HT_{1A} receptors are $G_{i/o}$ protein-coupled receptors with a seven TM-spanning structure (Barnes and Sharp, 1999; Pucadyil et al., 2005; Raymond et al., 1999; Ohno, 2011) (Fig. 1). A binding pocket for 5-HT exists in the extracellular region of TM domains, where the amine moiety of 5-HT binds to Asp82 of TM2 and Asp116 of TM3 by an ionic bond and its hydroxyl group binds to Ser199 in TM5 by a hydrogen bond (Pucadyil et al., 2005). Stimulation of $5HT_{1A}$ receptors inhibits adenylate cyclase and reduces cAMP formation via coupling to G_i α, which consequently causes an inhibition of protein kinase A (PK-A) activity. In addition, stimulation of 5-HT_{1A} receptors activates G-protein-gated inwardly rectifying potassium (GIRK) channels by allowing $G\beta\gamma$ subunits to interact with the regulatory sites of GIRK channels. Activation of GIRK channels by 5-HT_{1A} receptor stimulation facilitates K^+ efflux, hyperpolarizes membrane potential and inhibits neural activity (Fig. 1). 8-Hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), RU 24969, flesinoxan, alnespirone, osemozotan (MKC-242) and befiradol are selective and full 5-HT_{1A} agonists. Buspirone, tandospirone, ipsapirone, gepirone and piclozotan (SUN N4057) act as a $5HT_{1A}$ partial agonist with intrinsic activities of about 50–80%. Eltoprazone and pardopurunox (SLV308) are dual agonists of 5-HT_{1A}/5-HT_{1B} and 5-HT_{1A}/D_2 receptors, respectively. WAY-100135 and WAY-100635 are widely used as selective 5-HT_{1A} antagonists.

5-HT_{1A} receptors are highly expressed in the limbic regions (e.g., hippocampus and amygdala), lateral septum and raphe nuclei (e.g., median raphe nucleus and dorsal raphe nucleus) (Kusserow et al., 2004; Luna-Munguía et al., 2005; Palchaudhuri and Flügge,

2005). They are also distributed at moderate-to-low densities in the cerebral cortex, basal ganglia (e.g., the striatum), thalamus and hypothalamus. 5-HT_{1A} receptors act not only as post-synaptic receptors in various regions of the brain, but also as pre-synaptic autoreceptors in the raphe nuclei (Barnes and Sharp, 1999; Ohno, 2010, 2011). Specifically, 5-HT_{1A} receptors in the raphe nuclei exist on the somata and dendrites of 5-HT neurons, where they negatively regulate the firing of 5-HT neurons (Blier and Ward, 2003). Post-synaptic 5-HT_{1A} receptors are located on post-synaptic membranes of the neurons or nerve terminals (heteroreceptors). They hyperpolarize post-synaptic membranes and inhibit the firing of target neurons in various regions of the brain including the hippocampus, amygdala, lateral septum and striatum (Hadrava et al., 1995; Hirose et al., 1990; Ohno et al., 1995; Tada et al., 1999; Van den Hooff and Galvan, 1992).

3.1.2. Effects on parkinsonism

It is now known that stimulation of 5-HT_{1A} receptors improve extrapyramidal disorders induced by lesioning of dopaminergic neurons (Bezard et al., 2006; Bibbiani et al., 2001; Gerber et al., 1988; Ishibashi and Ohno, 2004; Jones et al., 2010; Matsubara et al., 2006; Nayebi et al., 2010; Oberlander et al., 1987; Shimizu et al., 2010), dopamine depletion (Ahlenius et al., 1993; Ishibashi and Ohno, 2004; Mignon and Wolf, 2002) or blockade of striatal D_2 receptors (Neal-Beliveau et al., 1993; Ohno et al., 2008a,b, 2009; Prinssen et al., 2002; Shimizu et al., 2010, 2013) (Table 1). Namely, 5-HT_{1A} agonists or partial agonists (e.g., 8-OH-DPAT and tandospirone) ameliorated bradykinesia induced by dopaminergic neurotoxins (e.g., MPTP) and akinesia induced by reserpine treatment which depletes central monoamines. Like conventional antiparkinsonian agents, 5-HT_{1A} agonists (e.g., 8-OH-DPAT, RU 24969 and tandospirone) evoked or facilitated contralateral rotation behavior in a 6-hydroxydopamine (6-OH-DA) hemi-lesioned rat parkinsonian model and also improved motor disabilities in a MPTP-treated primate parkinsonian model. In addition, numerous studies have shown that activation of 5-HT_{1A} receptors improves extrapyramidal motor deficits elicited by various dopamine D_2 antagonists (e.g., antipsychotics).

The improvement of extrapyramidal deficits by 5-HT_{1A} agonists is as potent as that by antiparkinsonian agents, L-DOPA, dopamine agonists (e.g., bromocriptine) and mACh antagonists (e.g., trihexyphenidyl), and is completely reversed by 5-HT_{1A} antagonist (e.g., WAY-100135 and WAY-100635) (Ishibashi and Ohno, 2004; Ohno et al., 2008a,b). The antiparkinsonian action of 5-HT_{1A} agonists is further supported by the neurochemical findings that 5-HT_{1A} agonists counteract the striatal Fos protein expression elicited by the D_2 receptor blockade, which was also reversed by the 5-HT_{1A} antagonist (Ohno et al., 2008b, 2009). It should be noted that the ameliorative effect of 5-HT_{1A} agonists on akinesia in reserpine-treated animals was antagonized by the 5-HT_{1A} antagonist WAY-100135, but not by the D_2 antagonist haloperidol (Ahlenius et al., 1993; Ishibashi and Ohno, 2004; Prinssen et al., 2002). This indicates that activation of 5-HT_{1A} receptors alleviate extrapyramidal motor disorders at least partly via non-dopaminergic mechanisms, implying that 5-HT_{1A} agonists can produce anti-parkinsonian actions in an additive fashion with currently available dopaminergic agents.

5-HT_{1A} agonist-induced alleviation of extrapyramidal disorders is resistant to inactivation of pre-synaptic 5-HT_{1A} autoreceptors by the treatment with *p*-chlorophenylalanine (a tryptophan hydroxylase inhibitor), indicating that 5-HT_{1A} agonists exert antiparkinsonian actions at least partly by activating post-synaptic 5-HT_{1A} receptors (Ohno et al., 2008a). In fact, microinjection of 8-OH-DPAT into the striatum significantly alleviated extrapyramidal disorders (Shimizu et al., 2010, 2013). Therefore, it seems likely that the antiparkinsonian action of 5-HT_{1A} agonists is mediated by post-synaptic 5-HT_{1A} receptors in the striatum, probably by inhibiting activities of the striatal medium spiny neurons (Fig. 4). In addition, an injection of 8-OH-DPAT into the cerebral cortex (motor cortex) also alleviated the induction of extrapyramidal disorders (Shimizu et al., 2010, 2013). It is suggested that activation of 5-HT_{1A} receptors in the motor cortex exert antiparkinsonian actions by inhibiting the cortico-striatal glutamatergic neurons, since (1) the activities of striatal medium spiny neurons are positively regulated by glutamatergic neurons derived from the motor cortex (Miguelez et al., 2014; Ohno, 2011; Somola, 2013), (2) local application of 5-HT_{1A} agonist into the cerebral cortex can reduce glutamate release in the striatum (Antonelli et al., 2005) and (3) treatment with NMDA receptor antagonists can attenuate D_2 antagonist-induced Fos expression and extrapyramidal disorders (Chartoff et al., 1999; Hussain et al., 2001; Steece-Collier et al., 2000) (Table 1 and Fig. 4). Furthermore, microdialysis studies have shown that 5-HT_{1A} agonist evokes dopamine release by inhibiting GABAergic interneurons in the prefrontal cortex (Díaz-Mataix et al., 2005; Sakaue et al., 2000). We also observed that 8-OH-DPAT increase striatal dopamine release in a similar fashion (unpublished observation), which can also at least partly account for the antiparkinsonian action of 5-HT_{1A} agonist (Fig. 4).

Table 1
Modulation of Parkinson's disease (PD) symptoms by 5-HT_{1A} receptors.

PD symptoms	Medication	Proposed functional mechanisms	Action site
Parkinsonism	Agonist	Inhibition of striatal neurons (i.e., medium spiny neurons and cholinergic interneurons) (also see Fig. 4)	Striatum (post-synaptic)
		Enhancement of striatal dopamine release by inhibiting striatal GABAergic interneurons (also see Fig. 4)	
		Inhibition of cortico-striatal glutamatergic neurons (also see Fig. 4)	Cerebral cortex (post-synaptic)
Dyskinesia	Agonist	Inhibition of cortico-striatal glutamatergic neurons	Cerebral cortex (post-synaptic)
		Inhibition of 5-HT neuron activity by stimulating 5-HT_{1A} autoreceptors	Raphe nuclei (pre-synaptic)
Cognitive impairment	Partial agonist Antagonist	Enhancement of cholinergic and glutamatergic neuron activities in the basal forebrain (e.g., diagonal band of Broca and medial septum)	Basal forebrain (post-synaptic)
		Enhancement of hippocampal neurons	Hippocampus (post-synaptic)
		Enhancement of hippocampal acetylcholine release	
Mood disorders Depression	Agonist	Desensitization (down-regulation) of 5-HT_{1A} autoreceptors, which leads to tonic activation of 5-HT neurons (also see Fig. 5)	Raphe nuclei (pre-synaptic)
Anxiety	Agonist	Inhibition of neural activities in the limbic regions (e.g., amygdala and hippocampus) and lateral septal nucleus (also see Fig. 5)	Limbic region (post-synaptic)
Neurodegeneration	Agonist	Protection against the damage of dopamine neurons, possibly via interacting astrocytes (remain to be determined)	Astrocytes?

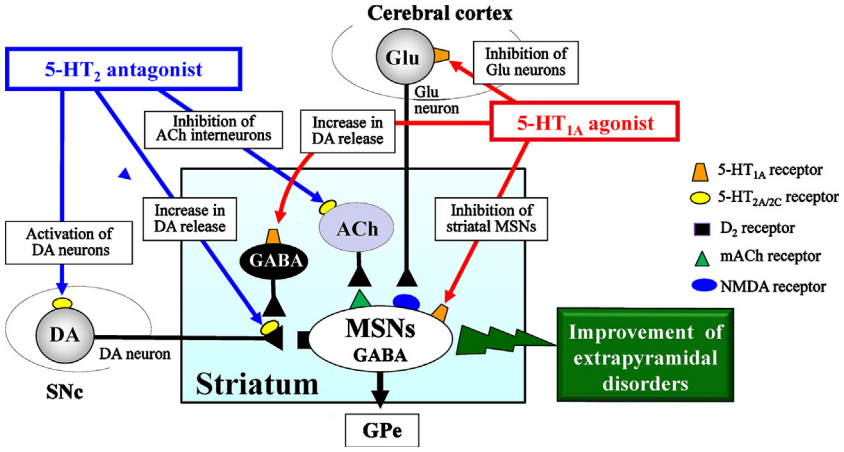

Fig. 4. Action mechanisms of 5-HT_{1A} agonists and 5-HT_2 antagonists in modulating extrapyramidal motor disorders. Stimulation of post-synaptic 5-HT_{1A} receptors ameliorates the extrapyramidal motor disorders (1) by inhibiting (hyperpolarizing) the striatal medial spiny neurons (MSNs), (2) by enhancing the striatal dopamine release (probably via GABAergic interneurons) and (3) by inhibiting the cortico-striatal glutamatergic neurons. Blockade of 5-HT_2 receptors also improves the extrapyramidal disorders (1) by enhancing the activity of nigro-striatal dopaminergic neurons and (2) by enhancing the striatal dopamine release. ACh, acetylcholine; DA, dopamine; Glu, glutamate; GPe, external segment of globus pallidus; mACh, muscarinic acetylcholine; SNc, substantia nigra pars compacta.

3.1.3. Effects on dyskinesia

Previous studies have shown that 5-HT_{1A} receptor agonists inhibit dyskinesia in animal models of PD which were primed (sensitized) to L-DOPA by chronic treatment with L-DOPA (Bishop et al., 2009; Dupre et al., 2008; Tomiyama et al., 2005) (Table 1). Experiments using MPTP-treated primates also showed that 5-HT_{1A} agonists (e.g., 8-OH-DPAT) attenuated L-DOPA dyskinesia (Bezard et al., 2013; Bibbiani et al., 2001; Elliott et al., 1990; Eskow et al., 2007; Grégoire et al., 2009; Iderberg et al., 2015; Muñoz et al., 2008; Ostock et al., 2011). In addition, 5-HT_{1A} agonist (e.g., buspirone, tandospirone, sarizotan and eltoprazine) have been shown to exert antidyskinesic effects in patients with PD (Bara-Jimenez et al., 2005; Bonifati et al., 1994; Kannari et al., 2002; Politis et al., 2014; Svenningsson et al., 2015). Although the exact mechanisms remain to be clarified, the antidyskinetic action of 5-HT_{1A} agonists is mediated at least partly by striatal and cortical 5-HT_{1A} receptors (Table 1), since the microinjection of 5-HT_{1A} agonists (e.g., 8-OH-DPAT) either into the striatum or the motor cortex alleviated L-DOPA-induced dyskinesia (Bishop et al., 2009; Huot et al., 2012; Ostock et al., 2011). In addition, reverse microdialysis application of 5-HT_{1A} agonists into the cerebral cortex (motor areas) inhibited glutamate release in the striatum and reduced the induction of dyskinesia (Antonelli et al., 2005). Therefore, activation of post-synaptic 5-HT_{1A} receptors in the cerebral cortex seems to alleviate L-DOPA-induced dyskinesia by inhibiting the activity of cortico-striatal glutamatergic neurons (Table 1).

On the other hand, whereas dopaminergic innervation of the striatum are severely damaged by the time of symptom onset in PD, striatal serotonergic nerve terminals are only moderately reduced early in the disease and degenerate at a slower pace (Kish et al., 2008; Politis et al., 2010). In addition, it is known that L-DOPA is taken up into the 5-HT nerve terminals, where it is converted into dopamine and then released to the synaptic cleft (Arai et al., 1995; Carta and Bezard, 2011; Cheshire and Williams, 2012; Maeda et al., 2005; Schmidt and Lovenberg, 1985). Under such situations, because of lack of dopamine autoreceptors in the nerve terminals, serotonergic neurons contribute to excessive dopamine release and cause hyperactivation of dopamine receptors through mishandling of exogenous L-DOPA, which may lead to dyskinesia (Carta and Bezard, 2011; Carta and Tronci, 2014; Politis et al., 2014; Styte and Vissel, 2014). It is thus also possible that 5-HT_{1A} agonist activate 5-HT_{1A} autoreceptors on 5-HT neurons to reduce excessive dopamine release, thereby producing antidyskinetic effects (Table 1) (Carta and Tronci, 2014; Politis et al., 2014; Styte and Vissel, 2014).

3.1.4. Effects on cognitive impairment

Numerous studies have shown that 5-HT_{1A} receptors are implicated in the control of cognitive functions (e.g., learning and memory) (King et al., 2008; Lüttgen et al., 2005; Madjid et al., 2006; Meneses, 2013; Misane and Ogren, 2003; Newman-Tancredi, 2010; Ogren et al., 2008; Ohno et al., 2012; Shimizu and Ohno, 2013). Previous studies demonstrated that a 5-HT_{1A} full agonist 8-OH-DPAT shows biphasic effects, impairment and enhancement of cognitive functions at high and low doses, respectively (King et al., 2008; Lüttgen et al., 2005). This biphasic action was considered to be mediated by activation of post-synaptic 5-HT_{1A} receptors (cognitive inhibition) and pre-synaptic 5-HT_{1A} autoreceptors (cognitive enhancement). Specifically, stimulation of pre-synaptic 5-HT_{1A} autoreceptors seem to enhance the cognitive function by reducing the activity of 5-HT neurons, which consequently inhibits post-synaptic 5-HT_3 and 5-HT_6 receptors negatively regulating the cognitive function (King et al., 2008; Meneses, 2013; Ohno et al., 2012; Shimizu and Ohno, 2013). On the other hand, stimulation of post-synaptic 5-HT_{1A} receptors reduced the cognitive function probably by (1) inhibiting cholinergic and/or glutamatergic neurons in the basal forebrain (e.g., diagonal band of Broca and medial septum), (2) inhibiting the activity of the hippocampal and cortical neurons and (3) inhibiting acetylcholine release within the hippocampus (Ohno et al., 2012; Shimizu and Ohno, 2013). Therefore, 5-HT_{1A} partial agonists or antagonists seem to improve the cognitive impairment by enhancing neural activities in the basal forebrain and hippocampus and by increasing acetylcholine release within the hippocampus (Table 1). Indeed, it is reported that 5-HT_{1A} antagonists (e.g., WAY-100635, WAY-101405, NAD-299 and lecozotan) and partial 5-HT_{1A} agonists (e.g., tandospirone, aripiprazole and lurasidone) improve the cognitive impairments induced by mACh receptor antagonists (e.g., scopolamine) or NMDA receptor antagonists (e.g., MK-801) (Horisawa et al., 2011; Ishiyama et al., 2007; King et al., 2008; Madjid et al., 2006; Misane and Ogren, 2003; Ogren et al., 2008; Newman-Tancredi, 2010). 5-HT_{1A} partial agonists (e.g., tandospirone and buspirone) have also been shown clinically to ameliorate cognitive impairment in patients with schizophrenia (Sumiyoshi et al., 2001, 2007), in which 5-HT_{1A} receptor-induced dopamine release in the cerebral

cortex is implicated (Meltzer and Sumiyoshi, 2008; Sumiyoshi et al., 2001, 2007). On the other hand, it is not conclusive that stimulation of post-synaptic 5-HT$_{1A}$ receptors impair the cognitive function since several studies suggested that 5-HT$_{1A}$ agonists improve cognitive impairments via post-synaptic mechanisms (Depoortère et al., 2010; Lladó-Pelfort et al., 2010; Newman-Tancredi, 2010) and since knockout mice lacking 5-HT$_{1A}$ receptors reportedly showed a deficit of hippocampal-dependent learning (Sarnyai et al., 2000). Further studies are required to delineate the precise mechanisms underlying the control of cognitive functions by 5-HT$_{1A}$ receptors.

3.1.5. Effects on mood disorders

5-HT$_{1A}$ receptors have long been implicated in the pathogenesis and treatment of anxiety and depressive disorder (Baumgarten and Grozdanovic, 1995; Ohno, 2010; Roth, 1994). Numerous studies have shown that 5-HT$_{1A}$ agonists (including partial agonists) produce anxiolytic and antidepressant effects in various animal models (e.g., Vogel's conflict, elevated-plus maze, social interaction, conditioned-fear freezing tests and forced swim test) (Table 1) (Akimova et al., 2009; Feighner and Boyer, 1989; Kataoka et al., 1991; Koek et al., 2001; Matsuda et al., 1995; Ohno, 2010; Schreiber et al., 1994; Shimizu et al., 1992; Stefański et al., 1992; Wieland and Lucki, 1990). Knockout mice lacking 5-HT$_{1A}$ receptors exhibited increased anxiety and depressive symptoms (Klemenhagen et al., 2006; Parks et al., 1998; Ramboz et al., 1998). Conversely, transgenic mice overexpressing 5-HT$_{1A}$ receptors show reduced anxiety behavior. These studies also illustrate that the stimulation of 5-HT$_{1A}$ receptors ameliorates anxiety and depression (Kusserow et al., 2004).

Fig. 5 shows the mechanisms underlying the anxiolytic and antidepressant actions of 5-HT$_{1A}$ agonists. Although 5-HT$_{1A}$ receptors in the raphe nuclei function as pre-synaptic autoreceptors, a line of evidence suggests a crucial role for post-synaptic 5-HT$_{1A}$ receptors in regulating anxiety. First, the microinjection of 5-HT$_{1A}$ agonists directly into a limbic region (e.g., hippocampus) produced significant anxiolytic actions (Kataoka et al., 1991). Second, the lesion of 5-HT neurons possessing pre-synaptic 5-HT$_{1A}$ autoreceptors, did not alter the anxiolytic actions of 5-HT$_{1A}$ agonists (Parks et al., 1998; Shimizu et al., 1992). Finally, a study using a tissue-specific conditional rescue strategy showed that the expression of post-synaptic 5-HT$_{1A}$ receptors in the forebrain (e.g., hippocampus and cerebral cortex) is sufficient to alleviate anxiety in 5-HT$_{1A}$ receptor-knockout mice (Gross et al., 2002). As described previously, 5-HT$_{1A}$ receptors are densely expressed as post-synaptic receptors in the limbic areas (i.e., hippocampus and amygdala) and septum (i.e., lateral septal nucleus), which are linked to the generation and propagation of anxiety, respectively (Ohno, 2010). It is therefore likely that 5-HT$_{1A}$ agonists exert anxiolytic effects by inhibiting the activity of the limbic neurons and lateral septal neurons via the activation of GIRK channels (Table 1 and Fig. 5).

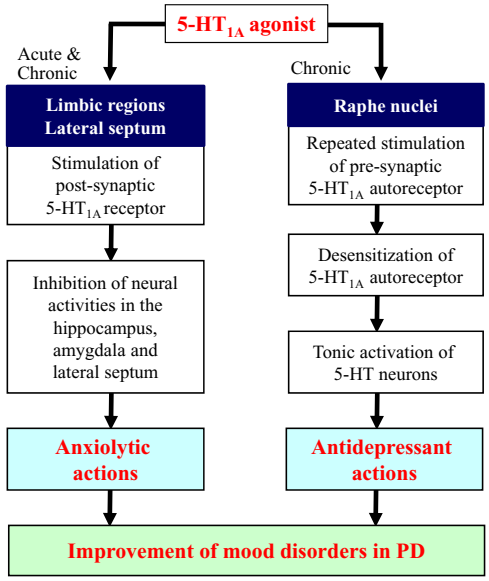

Fig. 5. Action mechanisms 5-HT$_{1A}$ agonists in modulating mood disorders. 5-HT$_{1A}$ receptors are highly expressed in the limbic areas (e.g., hippocampus and amygdala) and lateral septum. Stimulation of post-synaptic 5-HT$_{1A}$ receptors exerts anxiolytic effects by inhibiting the activity of the limbic neurons (i.e., hippocampus and amygdala) and the lateral septal neurons which are involved in generation and propagation of anxiety. In addition, repeated stimulation of pre-synaptic 5-HT$_{1A}$ autoreceptors cause desensitization (down-regulation) of 5-HT$_{1A}$ autoreceptors, which consequently lead to tonic activation of 5-HT neurons and produce antidepressant actions.

On the other hand, 5-HT$_{1A}$ agonists exert the antidepressant activity which usually becomes most prominent following repeated treatments. The antidepressant action of 5-HT$_{1A}$ agonists is now considered to be mediated at least partly by the pre-synaptic mechanism which is similar to that of SSRIs; in that, repeated treatments of animals with 5-HT$_{1A}$ agonists down-regulate and desensitize the pre-synaptic 5-HT$_{1A}$ autoreceptors in the raphe nuclei, relieving 5-HT neurons from 5-HT$_{1A}$ autoreceptor-mediated self-inhibition and resulting in tonic activation of the serotonergic system (Blier and de Montigny, 1987; Godbout et al., 1991; Ohno, 2010; Schechter et al., 1990; Stahl, 1994). Thus, desensitization of pre-synaptic 5-HT$_{1A}$ autoreceptors of raphe neurons projecting to cortico/limbic regions is suggested to be a common mechanism of the antidepressant action among 5-HT$_{1A}$ agonists, SSRIs and other antidepressants (5-HT reuptake inhibitors) (Table 1 and Fig. 5). It should be noted, however, that post-synaptic 5-HT$_{1A}$ receptors mediating anxiolytic, antidepressant and antiparkinsonian actions are known to be unaffected to the repeated treatment with 5-HT$_{1A}$ agonists (Blier and de Montigny, 1987; Chaput et al., 1991; Godbout et al., 1991), allowing sustained therapeutic actions of 5-HT$_{1A}$ agonists during the chronic treatment. In addition, 5-HT$_{1A}$ autoreceptors expressed on raphe-striatal neurons relating to the antidyskinetic action of 5-HT$_{1A}$ agonists also may not be desensitized during the chronic treatment since 5-HT$_{1A}$ agonists show a continued antidyskinetic activity over prolonged administration (Bezard et al., 2013).

It should be noted that 5-HT$_{1A}$ agonists are superior to conventional anxiolytics benzodiazepines in terms of their safety profile. A typical benzodiazepine diazepam at anxiolytic doses readily caused various side effects including sedation, somnolence, muscle relaxation, impaired motor coordination, cognitive impairments and psychophysical dependence. In contrast, 5-HT$_{1A}$ agonistic anxiolytics lack these benzodiazepines-like side effects (Ohno, 2002, 2010). This is considered to be due to the specific expression of 5-HT$_{1A}$ receptors in the limbic structures (e.g., hippocampus, amydgala and lateral septum) relating to generation and propagation of anxiety whereas benzodiazepine receptors are widely distributed throughout the brain and inhibit neuronal activities (Ohno, 2010). Thus, 5-HT$_{1A}$ agonists seem to be favorable in treating anxiety-depressive symptoms in the elderly like patients with PD or Alzheimer's disease.

3.1.6. Effects on neurodegeneration

A line of studies has shown that activation of 5-HT$_{1A}$ receptors can protect against neurotoxicity in various models including glutamate-induced excitotoxicity, ethanol and other chemically-induced apoptosis, brain ischemic and/or hypoxic damage (Druse et al., 2004; Oosterink et al., 1998; Pazos et al., 2013; Ramos et al., 2004; Suchanek et al., 1998). In addition, Bezard et al. (2006) showed that selective 5-HT$_{1A}$ agonists (e.g., BAY 639044 and

repinotan) can prevent the MPTP-induced loss of dopamine neurons and significantly delay the onset of parkinsonian motor symptoms in mouse and macaque models of PD (Table 1). A recent study also demonstrated that 8-OH-DPAT protected 6-OH-DA-induced damage of dopamine neurons in a mouse model of PD (Miyazaki et al., 2013). All these findings illustrate that activation of 5-HT_{1A} receptors provides benefits in the treatment of PD via neuroprotective actions. Although neuroprotective mechanisms of 5-HT_{1A} agonists remain to be clarified, Miyazaki et al. (2013) demonstrated that activation of 5-HT_{1A} receptor induced proliferation of astrocytes and elevated the level of the antioxidant molecule metallothionein-1/-2 in the striatum, which seems to prevent progressive dopaminergic neurodegeneration (Table 1).

3.1.7. Other effects

Evidence with regard to the role of 5-HT_{1A} receptors in other PD symptoms is limited. Interestingly, it is known that 5-HT_{1A} receptors modulate the incidence of nausea and vomiting. Indeed, a previous study showed that 5-HT_{1A} agonists inhibited D_2 agonist (i.e., apomorphine)-induced emesis in various animal models (e.g., dogs, pigeons, cats and house shrews) (Depoortère et al., 2008). It is therefore likely that 5-HT_{1A} agonists are useful to prevent the dopamine stimulant-induced nausea and/or emesis in the treatment of PD.

3.2. 5-HT_2 receptors

3.2.1. Characteristics

5-HT_2 receptors are a GPCR coupled to G_q protein and their stimulation activates phospholipase C and increases the levels of inositol triphosphate and diacylglycerol, which consequently activate Ca^{2+}/calmodulin- and protein kinase C (PK-C)-cascades (Fig. 1). 5-HT_2 receptors can be classified into three subtypes, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors. 5-HT_{2A} and 5-HT_{2C} receptors are highly expressed in the brain whereas 5-HT_{2B} receptors are mainly distributed in the peripheral tissues (e.g., stomach fundus) (Barnes and Sharp, 1999). 5-HT_{2A} receptors are expressed at high densities in various brain regions including the cerebral cortex (e.g., neocortex, entorhinal cortex and piriform cortex) and limbic structures (e.g., olfactory tubercle, nucleus accumbens and hippocampus). 5-HT_{2C} receptors are also widely expressed in the cortex (e.g., neocortex, cingulate cortex and piriform cortex), limbic structures (e.g., nucleus accumbens, hippocampus and amygdala) and basal ganglia (e.g., striatum and substantia nigra). 2,5-Dimethoxy-4-iodoamphetamine (DOI) is a known 5-HT_2 agonist, but it cannot differentiate 5-$HT_{2A/2B/2C}$ subtypes. Ritanserin and ketanserin are widely used as a specific antagonist for 5-$HT_{2A/2C}$ receptors and volinanserin (MDL-100,907) is a selective 5-HT_{2A} antagonist. Pimavanserin (ACP-103) is a selective inverse agonist for 5-HT_{2A} receptors, which has been recently shown to be effective for psychosis in patients with PD (Meltzer and Roth, 2013).

3.2.2. Effects on parkinsonism

It is well known that blockade of 5-HT_2 receptors ameliorates extrapyramidal motor disorders associated with antipsychotic (D_2 antagonist) treatment (Table 2). This is actually one of the pharmacological bases of drug discovery research for the second generation antipsychotics and contributed to the development of new atypical antipsychotics which preferentially interact with 5-HT_2 receptors (e.g., clozapine, risperidone, perospirone, olanzapine and quetiapine) (Kapur and Remington, 2001; Meltzer, 1991, 1999; Ohno et al., 1997; Reavill et al., 1999). The ameliorative action of 5-HT_2 antagonists (e.g., ritanserin) against extrapyramidal disorders was mostly equipotent to that of mACh antagonists (e.g., trihexyphenidyl) (Ohno et al., 1994). In addition, 5-HT_2 antagonists have been shown to improve motor impairments in animal models of PD and in patients with PD (Ferguson et al., 2010; Henderson et al., 1992) (Table 2). The antiparkinsonian action of 5-HT_2 antagonists was further supported by neurochemical findings that 5-HT_2 antagonists reverse various responses of striatal neurons induced by D_2 receptor antagonism, including increases in acetylcholine release, dopamine turnover ratios (ratios of dopamine level to those of dopamine metabolites) and Fos protein expression in the striatum (Alex and Pehek, 2007; Ishibashi et al., 1996; Ishida et al., 1996).

Since 5-HT neurons tonically inhibit nigro-striatal dopaminergic neurons via 5-HT_2 receptors, blockade of 5-HT_2 receptors can relieve the 5-HT_2 receptor-mediated inhibition and increase neural firing of nigro-striatal dopaminergic neurons (Ugedo et al., 1989) (Table 2 and Fig. 4). In addition, it is known that dopamine release in the striatum is negatively regulated by 5-HT_2 receptors located on the dopaminergic nerve terminals and the antagonism of 5-HT_2 receptors facilitates striatal dopamine release (Dewey et al., 1995; Saller et al., 1990). Thus, 5-HT_2 antagonists exert their antiparkinsonian action by increasing striatal dopamine release via blocking 5-HT_2 receptors on nigral dopaminergic neurons and those on striatal dopaminergic nerve terminals (Kapur and Remington, 2001; Ohno, 2011; Ohno et al., 2013) (Fig. 4). In addition, a previous electrophysiological study showed that 5-HT_{2C} receptors are expressed in and excite the striatal cholinergic interneurons, suggesting that 5-HT_2 antagonists reduced extrapyramidal disorders by reducing the cholinergic activity in the striatum (Bonsi et al., 2007). Furthermore, a recent study suggests that reduction of the striatal glutamate level may also be involved in antiparkinsonian action of 5-HT_{2A} antagonists (Ferguson et al., 2014). Although it is still controversial which 5-HT_2 subtype is involved in the antiparkinsonian action of 5-HT_2 antagonists, both 5-HT_{2A} and 5-HT_{2C} receptors are likely to be involved in modulating extrapyramidal disorders since either antagonist specific for 5-HT_{2A} (Ferguson et al., 2010) or 5-HT_{2C} (Reavill et al., 1999) receptors can reportedly reduce extrapyramidal disorders.

Table 2
Modulation of Parkinson's disease (PD) symptoms by 5-HT_2 receptors.

PD symptoms	Medication	Proposed functional mechanisms	Action site
Parkinsonism	Antagonist	Enhancement of striatal dopamine release (also see Fig. 4) Enhancement of activity of nigral dopamine neurons (also see Fig. 4)	Striatum (post-synaptic) Substantia nigra (post-synaptic)
Cognitive impairment	Antagonist	Enhancement of NMDA receptor-mediated transmission in the cerebral cortex	Cerebral cortex (post-synaptic)
Mood disorders Depression Anxiety	Antagonist	Modulation of cortical neuron activities Desensitization (down-regulation) of 5-HT_2 receptors	Cerebral cortex (post-synaptic)
Psychosis	Inverse agonist	Possibly by modulation of cortical neuron activities (remain to be determined)	Cerebral cortex (post-synaptic)

3.2.3. Effects on cognitive impairment

Although information is still limited, it is suggested that 5-HT_2 receptor play an important role in cognitive functions (Meneses, 2013). Several studies demonstrated 5-HT_2 agonists (e.g., DOI) induce and 5-HT_2 antagonists (e.g., ritanserin and M100907) ameliorate the cognitive deficits in various animal models (Boast et al., 1999; Ceglia et al., 2004; Dougherty and Oristaglio, 2013; Hadamitzky et al., 2009; Snigdha et al., 2010). The ameliorative actions of 5-HT_2 antagonists are supported by the fact that 5-HT_2 receptors inhibit NMDA-mediated glutamatergic neurotransmission in the cerebral cortex (Table 2) (Arvanov et al., 1999). These findings suggest that blockade of 5-HT_2 receptors may provide benefits for the treatment of cognitive impairment in some disease conditions including PD, particularly because the down-regulation of NMDA receptors was reported in a PD model treated with 6-OH-DA (Xu et al., 2012).

3.2.4. Effects on mood disorders

5-HT_2 receptors have long been implicated in pathogenesis of various neuropsychiatric disorders (Baumgarten and Grozdanovic, 1995; Meltzer, 1999). Although 5-HT_2 antagonists per se are not clinically available to date, their efficacies have been confirmed for various diseases including depression, anxiety, schizophrenia, addiction and sleep disorder (Bakish et al., 1993; Bersani et al., 1991; De Leeuw and Westenberg, 2008; Millan, 2005; Sharpley et al., 1994) (Table 2). Particularly, the antidepressant effects of 5-HT_2 antagonists are well established both in animals and patients, and are expected to be beneficial in the treatment of PD.

5-HT_2 receptors are abundantly expressed in the cerebral cortex, which project glutamatergic axons to a number of subcortical regions potentially involved in symptomatology of mood disorders, such as the nucleus accumbens (e.g., anhedonia and addiction), amygdaloid nuclei and hippocampus (e.g., anxiety, tension, fear and depressive mood), hypothalamus (e.g., endocrine and autonomic failures) (Barnes and Sharp, 1999; Ohno et al., 2012; Roth, 1994). Thus, modulation of cortical neuron activities (especially in the frontal cortex) by 5-HT_2 receptors seems to be important in the pathogenesis of mood disorders (Table 2). In the cerebral cortex, 5-HT_2 receptors are highly distributed in apical dendrites of pyramidal neurons, where serotonergic neurons are densely innervated. In addition, 5-HT_2 receptors also exist in GABAergic interneurons that negatively regulate pyramidal neuron activity. Therefore, activation of 5-HT_2 receptors evokes both excitation and inhibition of pyramidal neurons, the latter being mediated through 5-HT_2 receptor-induced excitation of GABAergic interneurons. In addition, 5-HT_2 receptors are responsible for induction of depression and anxiety and the suppression or down-regulation of 5-HT_2 receptors seems to contribute to the alleviation of mood disorders. Particularly, down-regulation of 5-HT_{2A} and/or 5-HT_{2C} receptors following chronic treatment with antidepressants or anxiolytics (including SSRIs) is thought to be a key mechanism for their clinical efficacies (Table 2) (Stahl, 1994).

3.2.5. Effects on psychosis

5-HT_2 receptors in the cerebral cortex are implicated in the pathogenesis of schizophrenia and psychosis (Baumgarten and Grozdanovic, 1995; Meltzer, 1999). Activation of 5-HT_2 receptors is known to be responsible for negative symptoms (e.g., anhedonia, apathy, emotional withdrawal) of schizophrenia and also for drug-induced psychotic symptoms (e.g., hallucinations, delusion and excitation) (Table 2) (Duinkerke et al., 1993; Meltzer, 1991; 1999). Indeed, several compounds (e.g., LSD and DOI) that can stimulate 5-HT_2 receptors have hallucinogenic actions. Conversely, suppression of 5-HT_2 receptors may improve psychosis induced by dopaminergic medications in patients with PD (Goldman and Holden, 2014; Huot et al., 2010). Consistent with this notion, it has been recently shown that the 5-HT_{2A} receptor inverse agonist pivamanserin (ACP-103) significantly alleviated PD psychosis without worsening motor functions (Cummings et al., 2014; Meltzer et al., 2010; Meltzer and Roth, 2013). These clinical studies illustrate a novel therapy for PD psychosis, indicating that dopamine stimulants-induced psychosis in PD is treatable by the reverse agonism of 5-HT_{2A} receptors (Table 2).

3.2.6. Other effects

Evidence is not sufficient with regard to the role of 5-HT_2 receptors in modulating other PD symptoms, which include L-DOPA-induced dyskinesia and neurodegeneration of dopaminergic neurons. However, a previous study showed that the 5-HT_{2A} inverse agonist pivamanserin reduced cholinergic tremors in rats and L-DOPA-induced dyskinesia in a MPTP-treated monkey model of PD (Vanover et al., 2008). This may extend the potential utility of 5-HT_{2A} inverse agonists in the treatment of L-DOPA-induced dyskinesia. Further studies are required to elucidate the functions of 5-HT_2 receptors in the treatment of PD.

3.3. Other 5-HT receptors

3.3.1. 5-HT_3 receptors

5-HT_3 receptors are composed of a hetero-pentamer consisting of 5-HT3A to 5-HT3E subunits and act as a cation channel permeable for Na^+ and Ca^{2+} (Barnes and Sharp, 1999; Thompsons, 2013) (Fig. 1). Thus, activation of 5-HT_3 receptors depolarizes post-synaptic membranes and excites the target neurons. 5-HT_3 receptors are also located on the nerve terminals of acetylcholinergic and glutamatergic neurons and regulate the neurotransmitter release. It is well known that 5-HT_3 receptors play a crucial role in regulating emetic responses and that selective 5-HT_3 antagonists effectively suppress nausea and vomiting, especially as elicited by anti-tumor agents (e.g., cisplatin) (Thompsons, 2013). In the central nervous system, 5-HT_3 receptors are implicated in the pathogenesis of anxiety and cognitive disorders (Davies, 2011; Meneses, 2013; Ohno et al., 2012). 2-Methyl-5-HT and chlorophenylbiguanide are known as 5-HT_3 agonists and many 5-HT_3 antagonists (e.g., ondansetron, granisetron, azasetron and tropisetron) are clinically available as anti-emetic drugs.

Previous studies have shown that 5-HT_3 receptor antagonists (e.g., ondansetron and granisetron) attenuated antipsychotic (D_2 antagonist)-induced extrapyramidal disorders (Akhondzadeh et al., 2009; Ohno et al., 2011; Silva et al., 1995; Tatara et al., 2012; Zhang et al., 2006), suggesting their potential utility for the treatment of PD (Table 3). Although the mechanisms for the antiparkinsonian actions of 5-HT_3 antagonists are unknown, we previously showed that a microinjection of ondansetron into the striatum, like its systemic treatment, can inhibit bradykinesia induction (Ohno et al., 2011). This suggests that post-synaptic 5-HT_3 receptors in the striatum are at least partly involved in induction or augmentation of antipsychotic-induced extrapyramidal disorders. Since previous studies showed that 5-HT_3 agonists stimulate glutamate release in various regions of the brain (Ashworth-Preece et al., 1995; Funahashi et al., 2004; Jeggo et al., 2005), 5-HT_3 antagonists may reduce extrapyramidal disorders by inhibiting glutamate release in the striatum (Table 3).

Many studies showed that 5-HT_3 antagonists enhance cognitive functions and alleviate cognitive deficits associated with aging or the drug treatments in various animal models (e.g., Morris water maze test and novel object recognition test) (Table 3) (Arnsten et al., 1997; Barnes et al., 1990; Gil-Bea et al., 2004; Hodges et al., 1996). Interestingly, several clinical studies have shown that 5-HT_3 antagonist ondansetron significantly improved both cognitive impairments and antipsychotic-induced extrapyramidal side effects in patients with schizophrenia (Akhondzadeh et al.,

Table 3
Modulation of Parkinson's disease (PD) symptoms by 5-HT_3, 5-HT_4 and 5-HT_6 receptors.

5-HT receptors	PD symptoms	Medication	Proposed functional mechanisms	Action site
5-HT_3 receptor	Parkinsonism	Antagonist	Possibly by inhibiting striatal glutamate release (remain to be determined)	Striatum (post-synaptic)
	Cognitive impairment	Antagonist	Enhancement of cortical acetylcholine release	Cerebral cortex (post-synaptic)
5-HT_4 receptor	Cognitive impairment	Agonist	Enhancement of acetylcholine release in the cerebral cortex and hippocampus Enhancement of neural activities in the cortical and limbic regions	Cerebral cortex, Hippocampus (post-synaptic)
5-HT_6 receptor	Parkinsonism	Antagonist	Inhibition of striatal cholinergic interneurons	Striatum (post-synaptic)
	Cognitive impairment	Antagonist	Inhibition of GABAergic neurons in the cerebral cortex and limbic regions	Cerebral cortex, Hippocampus (post-synaptic)

2009; Zhang et al., 2006). Although further studies are required to validate the clinical efficacy of 5-HT_3 antagonists in PD, these findings suggest that antagonism of 5-HT_3 receptors may be useful for improving cognitive impairments, as well as extrapyramidal motor deficits, in clinical settings. Amelioration of cognitive impairment by 5-HT_3 antagonists are thought to be mediated by enhanced release of acetylcholine in the cerebral cortex (Table 3) (Giovannini et al., 1998; Gil-Bea et al., 2004). Furthermore, it has been shown that blockade of 5-HT_3 receptors produce anxiolytic and antipsychotic actions in various animal models (Barnes and Sharp, 1999). Thus, 5-HT_3 receptor antagonists may also have potential to ameliorate non-motor symptoms (e.g., mood disorders and psychosis) in PD.

3.3.2. 5-HT_4 receptors

5-HT_4 receptors are G_s protein-coupled receptors and activate adenylate cyclase, cAMP formation and the PK-A cascade (Fig. 1) (Barnes and Sharp, 1999; Ohno et al., 2012). 5-HT_4 receptors are expressed at high density in the hippocampus and basal ganglia (e.g., striatum) while moderate levels of 5-HT_4 receptors are also found in the cerebral cortex, medial septum and amygdala.

Previous studies demonstrated that 5-HT_4 agonists (e.g., RS67333 and RS17017) enhance cognitive functions and 5-HT_4 antagonists (e.g., SDZ20557 and GR125487) cause impairments in learning and memory formation in various animal models (Fontana et al., 1997; Galeotti et al., 1998; Lamirault and Simon, 2001; Mohler et al., 2007) (Table 3). Especially, 5-HT_4 receptors are thought to play an important role in the acquisition and consolidation of memory (King et al., 2008; Lamirault and Simon, 2001). Although the precise mechanisms for the procognitive action of 5-HT_4 agonists are still uncertain, stimulation of 5-HT_4 receptors is known to enhance acetylcholine release in the cerebral cortex and hippocampus (Table 3) (Consolo et al., 1994; King et al., 2008; Siniscalchi et al., 1999). Besides these actions, 5-HT_4 receptors block Ca^{2+}-dependent K^+ currents via activating the PK-A cascade and inhibit afterhyperpolarization of the action potentials (Bickmeyer et al., 2002). These actions excite target neurons in the cerebral cortex and hippocampus, which may be related to the pro-cognitive action of 5-HT_4 agonists (Table 3). Therefore, though further clinical studies are necessary, 5-HT_4 agonists may alleviate cognitive impairment in patients with PD.

We have previously shown that blockade of 5-HT_4 receptors did not reduce or enhance bradykinesia induction (Ohno et al., 2011), suggesting that the role of 5-HT_4 receptors in regulation of extrapyramidal disorders is minimal. The role of 5-HT_4 receptors in modulating other PD symptoms (e.g., L-DOPA-induced dyskinesia, mood disorders and psychosis) is still uncertain.

3.3.3. 5-HT_6 receptors

5-HT_6 receptors are coupled to Gs protein and their stimulation activates the adenylate cyclase–cAMP–PK-A cascade (Barnes and Sharp, 1999; Ohno et al., 2012) (Fig. 1). 5-HT_6 receptors are predominantly expressed in the brain, specifically in the basal ganglia (e.g., striatum and nucleus accumbens), limbic regions (e.g., olfactory tubercles and hippocampus) and cerebral cortex at high density. Immunohistochemical studies also revealed that 5-HT_6 receptors are highly located in GABAergic neurons (Marcos et al., 2006; Ward and Dorsa, 1996; Woolley et al., 2004). 5-HT_6 receptors have been implicated in psycho-emotional disorders (e.g., schizophrenia and depression), eating disorders, cognitive deficits in schizophrenia and Alzheimer's disease (King et al., 2008; Woolley et al., 2004).

Since 5-HT_6 receptors are densely expressed in the striatum, they appear to modulate the extrapyramidal motor function. Although an early study showed that the 5-HT_6 antagonist (i.e., Ro04-6790) had no effect on haloperidol-induced catalepsy (Bourson et al., 1998), we confirmed that the 5-HT_6 antagonist (i.e., SB-258585) significantly alleviated antipsychotic-induced extrapyramidal disorders (e.g., bradykinesia and catalepsy) (Ohno et al., 2011; Shimizu et al., 2015; Tatara et al., 2012) (Table 3). In addition, microinjection of SB-258585 into the striatum, likely to systemic injection, reduced the induction of extrapyramidal side effects (Ohno et al., 2011; Tatara et al., 2012). These findings illustrate the involvement of striatal 5-HT_6 receptors in modulating extrapyramidal disorders, strongly suggesting that the 5-HT_6 receptor blockade provide benefits in treating PD. The antiparkinsonian action of 5-HT_6 antagonists was further supported by an electrophysiological study using single cell PCR techniques (Bonsi et al., 2007), which demonstrated that 5-HT_6 receptors are expressed in the striatal cholinergic interneurons and positively regulate their firing. Since the activation of striatal cholinergic interneurons evokes or facilitates extrapyramidal disorders (Shimizu et al., 2015), 5-HT_6 antagonists are likely to alleviate parkinsonism by inhibiting the activity of cholinergic interneurons in the striatum (Table 3).

Transgenic animals overexpressing 5-HT_6 receptors showed deficits of learning behaviors, which could be reversed by a 5-HT_6 antagonist (Mitchell et al., 2007) (Table 3). Conversely, treatment of animals with antisense mRNA of 5-HT_6 receptors improved the performance in the Morris water maze test (Woolley et al., 2001). In addition, several studies have shown that 5-HT_6 antagonists enhance cognitive functions or reverse amnesia induced by mACh antagonists (King et al., 2004; Lieben et al., 2005; Hirst et al., 2006; Woolley et al., 2003). These pro-cognitive actions of 5-HT_6 antagonists are thought to be brought about by relieving the GABAergic neural inhibition in the cerebral cortex and/or limbic structures (Table 3) since 5-HT_6 receptors are highly expressed in GABAergic neurons (Marcos et al., 2006; Ward and Dorsa, 1996; Woolley et al., 2004) and since stimulation of 5-HT_6 receptors increased GABA release in these brain regions (Schechter et al., 2008). Thus, it seems likely that the blockade of 5-HT_6 receptors provide benefits in improving cognitive impairment in PD.

Table 4
Therapeutic roles of 5-HT receptors in the treatment of Parkinson's disease.

5-HT receptor	Parkinsonism	Dyskinesia	Cognitive impairment	Mood disorders	Psychosis	Neuro-degeneration
5-HT_{1A} receptor (Full or partial agonist)	✓	✓	✓	✓	–	✓
5-HT_2 receptor (Antagonist or inverse agonist)	✓	–	✓	✓	✓	–
5-HT_3 receptor (Antagonist)	✓	–	✓	?	–	–
5-HT_4 receptor (Agonist)	–	–	✓	–	–	–
5-HT_5 receptor (Antagonist)	–	–	–	–	–	–
5-HT_6 receptor (Antagonist)	✓	–	✓	–	–	–
5-HT_7 receptor (Antagonist)	–	–	–	–	–	–

✓, effective; ?, potentially effective; –, not effective.

Based on above evidence, the blockade of 5-HT_6 receptors is expected to be useful for the treatment of extrapyramidal disorders and cognitive impairment in PD although effects of 5-HT_6 antagonists on other PD symptoms (e.g., L-DOPA-induced dyskinesia and psychosis) remain unknown. Several new 5-HT_6 receptor antagonists are now being evaluated such as BGC20-761, Ro-4368554, PRX-07034, SB-742457 (Maher-Edwards et al., 2010, 2011; Mitchell et al., 2006; Mitchell and Neumaier, 2008; Mohler et al., 2012). It should be noted, however, that 5-HT_6 antagonists may cause or worsen depressive mood since 5-HT_6 receptors are reported to be responsible for the antidepressant effects of SSRIs (Svenningsson et al., 2007).

3.3.4. Others

Other 5-HT receptor subtypes (e.g., 5-HT_5 and 5-HT_7 receptors) seem to be insignificant in modulating extrapyramidal motor disorders. In our previous study (Ohno et al., 2011), neither 5-HT_{5A} nor 5-HT_7 receptors antagonist affected serotonergic modulation (i.e., potentiation) of extrapyramidal disorders (i.e., bradykinesia and catalepsy) induced by D_2 receptor blockade. In addition, although several studies have suggested that 5-$HT_{1B/1D}$ and 5-HT_7 receptors are also involved in the control of cognitive functions, information is still very limited.

4. Novel therapeutic approaches by modulating 5-HT_{1A} and 5-HT_2 receptors

Table 4 summarizes the therapeutic roles of 5-HT receptors in the treatment of PD by illustrating the potential efficacy against the core motor symptoms (parkinsonism), L-DOPA-induced dyskinesia, cognitive impairment, mood disorders and PD psychosis. Among 5-HT receptor subtypes, 5-HT_{1A} and 5-HT_2 receptors are expected to provide high benefits in the treatment of PD, exhibiting wide clinical efficacy (Table 4).

Stimulation of 5-HT_{1A} receptors provides benefits as follows: (1) 5-HT_{1A} agonists (including partial agonists) improve extrapyramidal disorders caused by both degeneration of dopaminergic neurons and the blockade of striatal D_2 receptors by drugs. (2) 5-HT_{1A} agonists attenuate dyskinesia associated with chronic L-DOPA treatment. 5-HT_{1A} partial agonists alleviate (3) cognitive impairment and (4) mood disorders (depression and anxiety), which are frequently observed in patients with PD. In addition, (5) 5-HT_{1A} agonists have a potential to prevent the disease progression of PD by protecting against dopaminergic cell damage. Finally, (6) 5-HT_{1A} agonists are likely to be effective for nausea and vomiting associated with conventional anti-parkinsonian agents (Fig. 6). It should be noted that the antiparkinsonian action (e.g., enhancement of locomotor activity) of 5-HT_{1A} agonists in Parkinson's models is mediated at least partly by mechanisms independent from dopaminergic activity (non-dopaminergic mechanisms), suggesting that 5-HT_{1A} agonists produce antiparkinsonian efficacy in an additive fashion even in combined treatment with conventional dopaminergic medications (e.g., L-DOPA and dopamine agonists). Therefore, combined therapy with 5-HT_{1A} agonists and dopaminergic stimulants allow the augmentation therapy for parkinsonism or can reduce the dosage of each drug (e.g., L-DOPA), which may lead to attenuation of the side effects, extension of the L-DOPA treatment period and reduction of the motor fluctuation associated with chronic L-DOPA therapy.

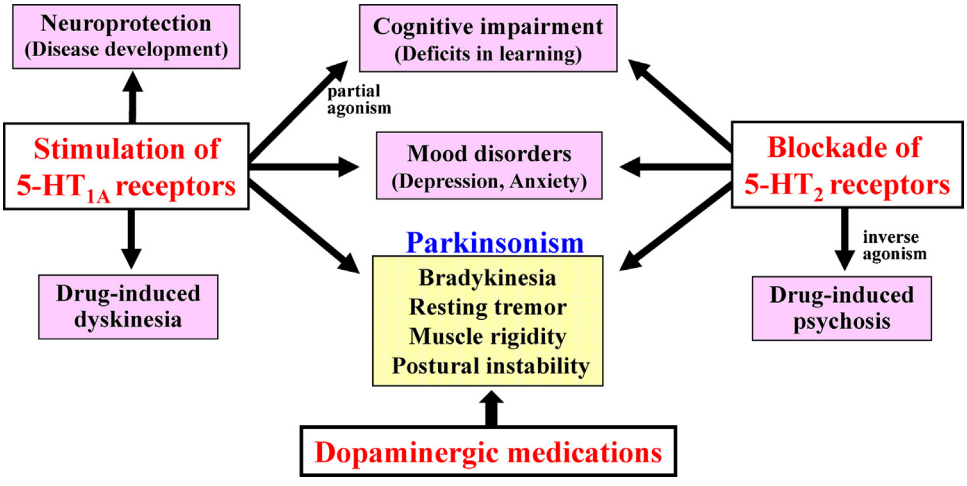

Fig. 6. Novel therapeutic approaches for Parkinson's disease by modulating 5-HT_{1A} and 5-HT_2 receptors. 5-HT_{1A} and 5-HT_2 receptors seem to be a favorable target for the treatment of Parkinson's disease. Stimulation of 5-HT_{1A} receptors may provide benefits in the treatment of Parkinson's disease with improving (1) extrapyramidal parkinsonism, (2) cognitive impairment (e.g., deficits in learning and memory), (3) mood disorders (e.g., depression and anxiety) and (4) reduced the incidence of drug-induced dyskinesia. 5-HT_{1A} agonists may also have a potential to prevent disease development of Parkinson's disease by protecting dopaminergic neurons. Blockade of 5-HT_2 receptor is expected to be effective for (1) parkinsonism, (2) cognitive impairment and also for (3) mood disorders. In addition, 5-HT_{2A} inverse agonists can alleviate psychosis in Parkinson's disease induced by dopaminergic medication.

5-HT_2 receptors are another promising therapeutic target for PD. Particularly, (1) blockade of 5-HT_2 receptor seems to be effective for parkinsonism. In addition, 5-HT_2 antagonists may improve (2) cognitive impairment and also (3) mood disorders (e.g., depression and anxiety) in PD. Finally, it is now documented that (4) the 5-HT_{2A} inverse agonist can alleviate drug-induced psychosis in PD (Fig. 6). Although further studies are required, 5-HT_{2A} inverse agonist may also be effective for dyskinesia since pivamanserin has been shown to reduce L-DOPA-induced dyskinesia in a MPTP-treated monkey PD model (Vanover et al., 2008).

As a novel therapeutic approach, adjunctive application of new or current 5-HT_{1A} agonists (e.g., tandospirone, flesinoxan and osemozotan), 5-HT_2 antagonists (e.g., ritanserin) or 5-HT_{2A} inverse agonists (e.g., pivamanserin) in combination with dopaminergic medications (e.g., L-DOPA and dopamine agonists) may allow an augmentation therapy for the core motor symptoms of PD with extended efficacies to non-motor symptoms (e.g., cognitive impairment and mood disorders) and improved safety profile (e.g., reduced induction of dyskinesia and psychosis) (Fig. 6). Alternatively, new 5-HT ligands which combine a D_2 agonistic action with 5-HT_{1A} agonistic and/or 5-HT_2 antagonistic actions are particularly of interest as a new class of antiparkinsonian agent. In this regards, rotigotine, which is widely used for PD and the restless legs syndrome (Benitez et al., 2014), shows a relatively high affinity to 5-HT_{1A} receptors (Ki = 30 nM, cf. Ki = 13.5 nM for D_2 receptors) and acts as a partial agonist (Scheller et al., 2009). In addition, several new compounds which possess combined D_2 and 5-HT_{1A} agonistic actions were recently reported. For example, pardoprunox acts a high-affinity full agonist for 5-HT_{1A} receptors and also as a partial agonist at dopamine D_2 receptors (Glennon et al., 2006). It induced contralateral rotation behavior in 6-OH-DA-treated dopaminergic hemi-lesioned rats and alleviated hypolocomotion and L-DOPA-induced motor disability in MPTP-treated common marmosets (Jones et al., 2010; Tayarani-Binazir et al., 2010). Randomized double-blind studies showed that pardoprunox significantly improved motor impairment in patients with PD (Bronzova et al., 2010; Hauser et al., 2009). Furthermore, aporphine analogs with a D_2 and 5-HT_{1A} dual agonist profile are also reported to exhibit antiparkinsonian actions and reverse L-DOPA-induced dyskinesia (Zhang et al., 2011). Although further clinical studies are necessary, these agents may be useful in the treatment of PD.

5. Concluding remarks

The deficit in the function of nigrostriatal dopaminergic neurons has long been considered as the primary cause for PD and the most current medications modulate the activity of dopaminergic system. However, it is now evident that neural networks other than the dopaminergic system are also closely linked to the pathogenesis of motor and non-motor symptoms in PD. In this article, we focused on the therapeutic roles of the serotonergic system and reviewed the functions of 5-HT receptors in the pathogenesis and treatment of PD. Previous studies have shown that activation of 5-HT_{1A} receptors exerts various effects that can improve the current PD therapy. These actions include (1) improvement of parkinsonism, (2) L-DOPA dyskinesia and (3) cognitive impairment, (4) antidepressant and anxiolytic actions and (5) neuroprotective actions for dopaminergic neurons. In addition, the 5-HT_2 blocking action seems to improve (1) extrapyramidal PD symptoms, (2) cognitive impairment, (3) mood disorders and (4) PD psychosis. Furthermore, the antagonism of 5-HT_3 and 5-HT_6 receptors or the activation of 5-HT_4 receptors is also expected to provide benefits in the PD treatment (improvement of parkinsonism and cognitive impairment). Although most evidence so far is obtained from basic researches, all these findings emphasize new insight into the novel therapeutic approaches by modulating 5-HT receptor functions. Especially, the ligands modulating 5-HT_{1A} and/or 5-HT_2 receptor functions are considered to have a relatively wide efficacious profile. Therefore, an adjunctive application of 5-HT_{1A} agonists or 5-HT_2 antagonists with dopamine agents (e.g., L-DOPA and dopamine agonists) could be a promising strategy. In addition, new dopamine D_2 agonists which possess combined 5-HT_{1A} agonistic and/or 5-HT_2 antagonistic activities are expected to become the next generation antiparkinsonian agents. These therapeutic approaches modulating the serotonergic activity may overcome the limitations of the current PD treatment in terms of clinical efficacy as well as drug safety. Further clinical researches are needed to warrant the usefulness of serotonergic system in the treatment of PD.

Conflict of interest

The authors declare no conflict of interest of this review.

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