Partial Dopamine D2/Serotonin 5-HT1A Receptor Agonists as New Therapeutic Agents

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Abstract: The therapeutic efficacy of current antipsychotic or antidepressant agents still present important drawbacks such as delayed onset of action and a high percentage of non-responders. Despite significant advancements in the development of new drugs with more acceptable side-effect profiles, patients with schizophrenia or major depression experience substantial disability and burden of disease. The present review discusses the usefulness of partial dopamine D2/serotonin 5-HT1A receptors agonists in the treatment of schizophrenia, major depression and bipolar disorder as well as in Parkinson’s disease. Partial agonists can behave as modulators since their intrinsic activity or efficacy of a partial agonist depends on the target receptor population and the local concentrations of the natural neurotransmitter. Thus, these drugs may restore adequate neurotransmission while inducing less side effects. In schizophrenia, partial DA D2/5-HT1A receptor agonists (like aripiprazole or bifeprunox), by stabilizing DA system via a preferential reduction of phasic DA release, reduce side effects i.e. extrapyramidal symptoms and improve cognition by acting on 5-HT1A receptors. Aripiprazole appears also as a promising agent for the treatment of depression since it potentiates the effect of SSRIs in resistant treatment depression. Concerning bipolar disorders aripiprazole may have only a benefit effect in the treatment of manic episodes. Conversely, treatment of Parkinson’s disease with partial DA D2/5-HT1A receptor agonists remains still experimental. However several studies suggest that these drugs decrease usually observed side effects (dyskinesia, psychotic-like symptoms) in Parkinson’s disease treatment. Hence, these relatively recent researches provide an exciting future in the discovery of novel stabilizators agents for the management of the latter diseases.

Keywords: Partial agonists, dopamine, serotonin, psychiatric disorders.

INTRODUCTION

Current treatments of neuropsychiatric diseases like schizophrenia and major depression are problematic and unsatisfactory and novel approaches in treating these diseases are desirable. Alterations in monoamine neurotransmission, particularly dopamine (DA) and serotonin (5-hydroxytryptamine, or 5-HT), have been implicated in these diseases. Partial dopamine 2 (D2)/5-HT1A receptor agonists behave as neuronal modulators or stabilizators and seem to restore adequate neurotransmission without inducing severe side effects. In schizophrenia and affective disorders, aripiprazole is the only commercially representative of this pharmacological class. This review will focus on the recent findings of these new drugs, presently under clinical and pre-clinical investigations, in relation to treatment of schizophrenia, major depression, bipolar disorders and Parkinson’s disease.

Regulation of brain DA and 5-HT transmission

DA System

Five subtypes of DA receptors have been described. According to their pharmacological characteristics and their association with G-coupled proteins and adenylyl cyclase, they are grouped in two main family subtypes: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3 and D4). Four DA pathways have been characterized: the mesolimbic, the mesocortical, the nigrostriatal and the tubero-infundibular pathways.

The mesolimbic dopaminergic pathway contains A10 dopaminergic neurons located within the ventral tegmental area (VTA); their associated efferent targets in the ventral striatum including nucleus accumbens (NAcc) and limbic structures (e.g. amygdala and hippocampus). The mesolimbic dopaminergic pathway is involved in emotional and motivational processing [1]. Dysregulation of DA may is currently associated to drug abuse [2]. Moreover, paranoia and psychosis induced by long-term stimulant abuse are similar to schizophrenia symptoms. In schizophrenia, the hyperactivation of the mesolimbic dopaminergic pathway seems to lead to positive symptoms like hallucinations [3].

The mesocortical dopaminergic pathway consists of the A10 dopaminergic neurons and their associated efferent targets in the prefrontal cortex. Contrary to the mesolimbic pathway, the mesocortical pathway is hypoactive in schizophrenia which can be responsible for cognitive and negative symptoms [4].

The nigrostriatal dopaminergic pathway consists of the substantia nigra pars compacta (SNc-A9) and their associated efferent targets in the dorsal striatum. It contains the
majority of brain DA[1]. The SNc-A9 pathway is involved in motor learning and control. Degeneration of this pathway leads to Parkinson’s disease. In addition, blockade of this pathway is associated with movement disorders like extrapyramidal symptoms (EPS) and dyskinesia.

The tubero-infundibular DA pathway consists of DA neurons that project from the periventricular and arcuate nuclei of the hypothalamus to the intermediate lobe of the pituitary. Secretion of prolactine from the lactotroph cells in the pituitary is under the control of DA released by the tubero-infundibular pathway. Consequently, blockade of DA receptors induces hyperprolactinemia [5].

**DA Partial Agonist**

While an agonist mimics the action of a natural neurotransmitter, a partial agonist induces a reduced signaling response compared to the maximum achievable response by a full agonist. The intrinsic activity or efficacy of a partial agonist depends on the sensitivity and responsiveness of the receptors, thus partial agonists can behave as an agonist or antagonist, depending on the target receptor population and the local concentration of the natural neurotransmitter [6]. For example, a partial agonist may act as a DA receptor agonist in the SNc and VTA, where the D2 receptors are somatodendritic autoreceptors and the amount of endogenous DA is relatively low, but as an antagonist at the post-synaptic D2 receptors in the striatum, where the amount of endogenous DA is high [7]. The stimulation of DA autoreceptors suppresses neural firing, whereas the stimulation of terminal receptors inhibits the release of DA [7]. In the VTA, the main receptors involved in mediating local effects of DA are D2 autoreceptors [8]. Nevertheless, it has also been shown that D1 and possibly D3 receptors may play a role in control of DA firing and release [9-11].

In vivo, DA neurons have two types of cellular activity: a tonic activity corresponding to firing and a phasic activity corresponding to bursting. Indeed, they exhibit tonic irregular single spike firing interrupted by bursts of spikes often with decreasing spike amplitude followed by brief silences [12]. It has been also shown that the mean firing rate and the bursting pattern of DA neurons can be modulated independently [13]. A state-dependent shift in discharge pattern might be crucial since burst firing of DA neurons was shown to result in a much larger synaptic DA accumulation than single spike firing [13,14].

**5-HT System**

The 5-HT cell bodies in the brain are located in the brainstem near or on the midline. There is nine 5-HT nuclei in the brainstem [B1-B9, 15] that can be divided in the superior
Partial Dopamine D2/Serotonin 5-HT1A Receptor Agonists

The firing activity consequently decreasing 5-HT release agonist, they hyperpolarize 5-HT neurons, thereby decrease activated by an excess amount of 5-HT, or by an exogenous cell body exert negative feedback on firing activity: when blocking DA receptors and are commonly divided in two generations. The first-generation “typical” antipsychotics reduce DA neurotransmission by blocking DA receptors, predominantly the D2 subtypes. While they reduce positive symptoms, they have the drawback of causing important side effects [29]. For example, they can induce extrapyramidal symptoms (EPS) similar to Parkinsonism syndrome. EPS are directly related to D2 receptor blockade (up to 80% of D2 receptor blockade) of the nigrostriatal pathway [31,32]. Another possible side-effect is hyperprolactinaemia, caused by D2 receptor blockade of the anterior pituitary, which can result in osteoporosis [33,34].

In the 1990’s, the introduction of the second-generation “atypical” antipsychotics such as clozapine was a turning point for treatment of schizophrenia. In contrast to first-generation antipsychotics, they have less side effects on motor function and could potentially decrease both negative and positive symptoms. A main drawback of atypical antipsychotics is that they have important metabolic side effects like weight gain or diabetes [4,27,29]. Second-generation antipsychotics have a higher affinity for 5-HT2A receptors than for D2 receptors and blocks both receptor types. Unlike typical antipsychotics, atypical antipsychotics interact with a large range of other receptors, including cholinergic and serotonergic receptors (e.g. 5-HT1A, 5-HT3, 5-HT6 [4,35,36]). Initially, a balanced occupancy of 5-HT2A and D2-like receptors has been proposed to play a pivotal role in their mechanism of actions [35,37].

Partial D2-Like Receptor Agonists in Schizophrenia

Currently, aripiprazole is the only partial D2-like receptor agonist used for schizophrenia treatment. Other agents showing in vivo or in vitro partial D2-like receptor activity represent putative antipsychotics, e.g. bifeprunox [38], SSR181507 [39], sarizotan [40], RGH-188 [41], 3PPP [42], ACR16, OSU6162 [43]. Interestingly, the N-desmethylclozapine, the major metabolites of clozapine, is also a partial D2-like agonist.

There have been several arguments for the use of partial blockade of D2-like receptors rather than a full blockade. First, antipsychotics like haloperidol act as D2-like receptor blockers and at low dose increase the firing activity of DA neurons. However, at high dose they induce an inactivation via a mechanism named “depolarization block” [44,45]. Hence, after chronic treatment, the number of spontaneous active DA neurons is decreased in the VTA, reducing mesolimbic DA transmission [46,47]. In contrast to haloperidol, D2 receptor partial agonists like aripiprazole moderately decrease VTA DA neuronal firing [38,48,49]. Chronic administration of aripiprazole does not affect neuronal firing [48,50]. Rather than the depolarization-block inactivation process, it has been suggested that partial DA receptor agonists induce a stabilization of the DA neurotransmission [6,7,37,51,52]. Aripiprazole and bifeprunox showed a stronger effect on phasic activity (i.e. on bursting) than on tonic activity (i.e. firing) [38] which can be of therapeutic interest [53]. Indeed, the preferential action of partial D2 receptor agonists on bursting activity might stabilize DA system via a preferential reduction of phasic DA release.

Partial DA agonists present high affinity (similar to the natural ligand) for the DA receptors but a relatively low efficacy. Consequently, their effect depends on DA concentra-
tions and thus to the receptor occupancy. In the VTA and SNc, where endogenous DA concentration is relatively low, partial DA agonists largely bind to D2 autoreceptors and suppress the firing activity as agonists. In the striatum, where the level of DA concentration is relatively high, partial D2 agonists suppress neuronal firing presynaptically and inhibit DA release in nerve termination whereas postsynaptically, partial D2 agonists reduce neuronal firing [6,7]. Because partial D2 agonist agents have a weak intrinsic activity, they do not induce full blockade at D2 receptors in the substantia nigra and in the pituitary so they do not induce metabolic and motor side effects [54], which makes them a potential candidate for treating against positive symptoms by reducing DA neurotransmission. In preclinical studies, aripiprazole showed antagonistic activity in animal models of dopaminergic activity (e.g. blockade of apomorphine-induced stereotypy) and agonist activity in an animal model of dopaminergic hypoactivity (blockade of increased DA synthesis in reserpine-treated rats) [55]. Most of typical and classical atypical antipsychotic drugs induce increase in DA release in prefrontal cortex [56,57]. In nucleus accumbens, the typical antipsychotics like haloperidol increased DA release while the atypical antipsychotics clozapine did not [58]. Local application of DA D2 receptor agonist, like quinpirole, inhibits release of DA in prefrontal cortex [59]. However, a decrease of DA in prefrontal cortex induces an increase of DA release in the nucleus accumbens [60]. On the other hand, aripiprazole and bifeprunox seems not modify DA release in prefrontal cortex of rodents [57,61], even if a study from Li et al. [62] suggests that aripiprazole may slightly increase DA release. Interestingly, bifeprunox and only high doses of aripiprazole decrease DA release in rat nucleus accumbens. One may assume that the partial inhibitory effect may restore DA system where it is hypoactive which can be relevant clinically.

**5-HT1A Receptor Agonists in Schizophrenia**

Presynaptic 5-HT1A receptors are somatodendritic autoreceptors on serotonergic neurons of raphe nuclei. Stimulation by extracellular 5-HT or by a 5-HT1A receptor agonist, suppresses the firing of 5-HT neurons. Postsynaptic 5-HT1A receptors are localised on pyramidal as well as GABAergic interneurons in the hippocampus, frontal and entorhinal cortex, amygdala which have been described as key areas involved in physiopathology of schizophrenia [63]. Postmortem and PET studies have shown that 5-HT1A receptors binding is increased in the frontal cortex of schizophrenic patients ([64-66]; for a review see [67]). Nevertheless, a more recent imaging study using PET failed to demonstrate differences in binding of 5-HT1A receptors in schizophrenic patients compared to healthy subjects [68].

Several compounds including clozapine, ziprasidone and quetiapine have a partial agonistic effect on 5-HT1A receptors [69]. Recent drugs developed as potential antipsychotics, such as bifeprunox, aripiprazole [38], SSR181507, F15063 [39], present a more potent 5-HT1A receptor agonistic effect. Preclinical and clinical studies have evaluated the effect of 5-HT1A agonists on schizophrenia symptoms. For example, the 5-HT1A receptor agonist 8-OH-DPAT increased the effect of the D2-like antagonist raclopride in the conditioned avoidance response (a test used to evaluate an antipsychotic-like effect). The same effect has been observed with haloperidol [70]. Similarly, clinical studies have shown a beneficial effect on psychotic syndromes by simultaneous administration of haloperidol (a typical antipsychotic) and buspirone (a partial 5-HT1A receptor agonist) [71,72].

Historically, the 5-HT2A receptor has been a major target for the development of antipsychotics. It has been shown that antagonism at 5-HT2A receptor coupled to weaker antagonism of DA D2 receptors increases the release of DA in the prefrontal cortex (PFC) [73,74] which may contribute to improved cognition in schizophrenic patients [75]. Importantly, 5-HT1A receptors seem to modulate DA transmission in the PFC in a way similar to 5-HT2A receptor antagonists [67,76-79]. For example, the 5-HT1A agonist 8-OHDPAT increases DA release in this brain area [79-81]. Also, the atypical antipsychotics clozapine and olanzapine (acting as a 5-HT1A receptor agonist and a 5-HT2A antagonist) increase DA release [57,79,82], whereas haloperidol does not [57,83]. Interestingly, administration of the selective 5-HT1A receptor antagonist WAY-100635 reverses the effect of risperidone and olanzapine which do have not a direct action on 5-HT1A receptors [57,82]; [81,84,85]. This effect is blocked by local injection of 5-HT1A antagonist in the mPFC and by a cortical hemi-transection [86], suggesting a mediating role for presynaptic receptors. This suggests that direct or indirect 5-HT1A receptor stimulation may increase DA release in prefrontal cortex.

It has been reported that cognitive impairments are associated with a decrease of DA release in PFC. Clinical studies have reported a beneficial therapeutic effect of the simultaneously administration of a typical or atypical antipsychotic and a 5-HT1A agonist (like tandospirone or buspirone) on cognitive deficits, including verbal learning and memory (see for review [63]). Contrary to this finding, is a study that reported the impaired cognition in healthy volunteers following 5-HT1A agonist administration [87]. In sum, it seems that 5-HT1A receptor stimulation may ameliorate cognitive deficits in schizophrenia (see for review [63,67,88]).

Schizophrenia is often associated with idem affective disorders [89,90]. 5-HT1A agonists induce anxiolytic and antidepressive effects in clinical studies, which makes them potentially interesting for treatment of major depression [91]. In this regard, compounds such as aripiprazole present anxiolytic effects in preclinical tests of anxiety [38,92,93].

It has been proposed that 65% of D2 receptors occupancy is necessary for clinical efficacy of treating psychotics, while it must not exceed 80% in order to avoid EPS. Therefore, it is important to develop compounds able to increase this narrow window [31,32]. 5-HT1A receptor agonists can play a role herein [94]. In a preclinical study, administration of the 5-HT1A agonist 8-OH-DPAT reversed the catalepsy induced by D2 receptor antagonists or antipsychotics, by stimulation of the 5-HT1A autoreceptor in the median raphe nuclei [95-97]. In monkeys, 8-OH-DPAT also reduced haloperidol-induced extrapyramidal side effects [98]. A clinical study has demonstrated the same results with the 5-HT1A Receptor agonist buspirone [71]. Interestingly, it has been shown that F15063, SLV313 and bifeprunox, which are potential antipsychotics with a 5-HT1A agonistic activity, induced catalepsy only in presence of the 5-HT1A antagonist WAY-100,635. However, the potential antipsychotic SSR-181507 (a 5-HT1A receptor agonist) did not induce catalepsy after administra-
tion of WAY-100,536, suggesting that alternative antiepileptic mechanisms may exist [99]. Finally, there is strong evidence that that stimulation of 5-HT1A receptors may reduce EPS [97].

Based on these results, we hypothesize that co-administration of a partial 5HT1A receptor agonist and a partial D2-like agonist improves the pharmacological profile of administration of a partial D2-like agonist alone, because co-administration could result in a combined reduced risk of EPS and reduced cognitive disturbances in schizophrenic patients, and potentially improved mood [67,100].

PARTIAL DOPAMINE D2/SEROTONIN 5-HT1A RECEPTOR AGONISTS AND AFFECTIVE DISORDERS

Major Depression

With a lifetime prevalence rate of more than 12% in men and 20% in women, major depression is the most common psychiatric disorder [101,102]. The diagnosis of major depressive disorder requires a distinct change in mood, characterized by sadness or irritability and accompanied by several psychophysiological changes, such as sleep disorders, weight loss or weight gain, decreased interest of pleasure stimuli (e.g. sex, food, social interaction), decreased ability to concentrate, and recurrent thoughts of death and suicide [102]. Although the pathophysiology of depression is poorly understood, the development of different classes of antidepressants during the last four decades was accompanied by the emergence of theories based on deficiencies of central aminergic systems [102]. These theories propose that a deficiency of the cerebral neurotransmission of monoamines would be the underlying cause of depression. Although involvement of catecholamines (noradrenaline and DA) in the effects of antidepressants cannot be excluded, the vast majority of pre-clinical data point toward a central role of 5-HT [103]. This is supported by the success of selective serotonin reuptake inhibitors (SSRIs) as first-line therapy. SSRIs directly act on 5-HT transporter and block its reuptake, leading to enhanced 5-HT neurotransmission [104]. In accordance, depletion of the 5-HT precursor L-tryptophan produces a rapid relapse of depression in patients who have been successfully treated with a SSRI [105].

Therapeutic agents for Major Depression

Even though first generation antidepressant therapy with tricyclic antidepressants and monoamine oxidase inhibitors (IMAO) reduced inhibitors reduced symptoms of depression, their side effects (hypotension, retention urinary, sexual and sleep impairment) and toxicity lead to the search for more tolerable and safe antidepressants. More recent drugs such as SSRIs, selective noradrenaline reuptake inhibitors, noradrenaline and serotonin reuptake inhibitors or atypical antidepressants (such as mirtazapine or agomelatine), have fewer and less severe side effects than these first generation drugs due to their lack of affinity for amines and acetylcholine receptors [106]. In spite of this wide variety of medications available, however, current treatments of depression with pharmacotherapy remains unsatisfactory [107]. Two major problems remain unresolved. First, one-third of the patients does not respond to any treatment and one-third shows only a partial response to any first agent used at an adequate dose for a sufficient time. Second, there is an unde-
endogenous ligand) for the 5-HT 1A receptors, but a relatively low efficacy. As a result, their effect is dependent on the intrinsic concentration of 5-HT and thus to the receptor occupancy. In depressed patients, partial 5-HT receptor agonists are thought to increase the 5-HT neurotransmission in postsynaptic structures (in the cortex and the limbic areas) because of the low 5-HT tone. Indeed, the exogenous partial agonist, such as buspirone or gepirone, would not compete but act in synergy with the endogenous transmitter. Partial agonists can modulate their action (act as agonist or antagonist) according to the state of 5-HT neurotransmission and thus can regulate with perceptiveness this function.

The azapirones (gepirone, buspirone, tandospirone and ipsapirone) which act as partial 5-HT 1A receptor agonist [129,138] have shown efficacy in the treatment of anxiety [139] and major depression [140-142]. Buspirone is a commercially agent available but used as a single agent appears to be non-effective [143]. Early clinical trials conducted with an immediate release (IR) formulation of gepirone, buspirone and ipsapirone showed antidepressant efficacy after eight weeks [141,144], but has the disadvantages of poor tolerability (dizziness, nausea, insomnia, headache and asthenia [91]) and a limited efficacy (short half-life and rapid absorption from the gastrointestinal tract). More recently, azapirones have been reformulated as an extended-release (ER) tablet which increases their half life, allowing more gradual and sustained absorption from the gastrointestinal tract while lowering peak plasma gepirone concentration [145]. Wilcox et al. [146] showed that gepirone ER administration had antidepressant efficacy 1 week until 6 weeks of treatment with a daily dose of 70mg but not with 40mg. More recently, several studies also demonstrated the short-term and the long-term effectiveness of gepirone ER administration [140,147,148]. Interestingly, gepirone IR and ER administration seems to be effective to prevent relapse in major depression [148,149]. In conclusion, ER administration improves the tolerability and enhances the effectiveness of azapirones [150].

While these results from clinical trials support the efficacy and the tolerability of ER formulation of gepirone in major depressive disorder, it should be noted that results are less conclusive concerning other azapirones (buspirone and ipsapirone). In addition, azapirones are rapidly metabolized into 1-(2-pyrimidinyl)piperazine (1-PP) which is an alpha-2 adrenoreceptor antagonist, like mirtazapine [134,151] an effective antidepressant drug. However, the antidepressant-like effect of 1-PP is not well established [131,152,153].

**Bipolar Disorder**

Bipolar disorder is a severe chronic illness associated with abnormal structure and function of the central nervous system with high rates of recurrence, disability, social impairment, and suicide that affects about 1-6% of the population. Although the disorder is defined by sequentially occurrence of manic and depressive episodes, the depressive episodes are the more handicapping aspect of the illness. Specifically, the depressive episodes are more numerous, last longer, and are less responsive to treatment than the manic episodes [154].

**Therapeutic Agents for Bipolar Disorder**

The origin of this psychiatric disorder seems to be an excessive cellular excitation. The goals of pharmacological treatments for bipolar disorder are, first, to decrease this hyperexcitability and stabilize mood, and second, to prevent the recurrence of depressive and manic episodes. Traditional mood-stabilizing agents such as lithium and anticonvulsive agents (valproate or lamotrigine) are currently used as first-line medications for the treatment of manic episodes, but there is a lack of treatment for bipolar depressive episodes. These agents yield inadequate responses to about 20-40% of the patients and have severe side effects such as tremors, gastrointestinal disorders, tiredness, somnolence, and cognitive impairment in memory and concentration.

Because of these limitations of current treatments of bipolar disorder, the use of antipsychotics and other psychotropic agents has been investigated [155]. Short-term studies (3-4 weeks) suggest that atypical antipsychotics (olanzapine, risperidone, ziprasidone) have beneficial effects on manic ([156-159] and depressive episodes [160]. However, few studies have been conducted to demonstrate the continued efficacy of these agents as monotherapy for longer-term management of bipolar disorder. For example, a placebo-controlled study showed maintenance of the efficacy of risperidone monotherapy over 12 weeks [161] and aripiprazole seems to have similar effects.

**Partial D2-Like Receptor Agonists in Manic Episodes**

Studies have demonstrated that aripiprazole is effective and well tolerated in the treatment of acute bipolar mania [162,163]. Aripiprazole had superior efficacy to haloperidol in response rates and tolerability in a 12-week acute mania trial in patients with bipolar I disorder in acute manic or mixed episodes [164]. Furthermore, aripiprazole monotherapy was superior to placebo in maintaining efficacy in patients with a recent manic/mixed episode who were stabilized and maintained on a regimen of aripiprazole for 12 weeks [164-166], 26 weeks [167] and 100 weeks [168]. Vieta et al. [169] demonstrated that adjunctive aripiprazole therapy to lithium or valproate showed significant improvements in mania symptoms from one week in bipolar patients with manic or mixed episodes who were partially nonrespon- sive to lithium/valproate monotherapy. The same result has been observed with other atypical antipsychotics. The use of risperidone [170], olanzapine [171] and quetiapine [172] as adjunctive agent enhanced the response to classical treatment. While the beneficial effect of aripiprazole was clear in the treatment of manic episodes, there is no evidence that aripiprazole monotherapy has superior efficacy compared to placebo treatment at the end of the treatment in bipolar depression at the dose use [160]. Furthermore, aripiprazole has important side effects such as akathisia, insomnia, nausea, restless or dry mouth [160].

**PARTIAL DOPAMINE D2/SEROTONIN 5-HT 1A RECEPTOR AGONISTS AND PARKINSON’S DISEASE**

Parkinson’s disease (PD) is a very frequent neurodegenerative disease that results from the loss of dopaminergic cells in the SNc and is mainly characterized by motor defi-
Partial D_{2}-Like Receptor Agonists in PD

D_{2}-like receptors are abundant in motor areas such as the basal ganglia. The highest density of dopaminergic receptors in the VTA and SNc corresponds to the D_{2} subtype, whereas the D_{3} subtype only exhibits a moderate density and the D_{4} subtype appears to be absent in these neuronal structures [9,186]. In contrast, D_{3} and D_{4} receptors are located in limbic and cortical areas and may contribute to the psychiatric disturbances occurring with DA agonists and L-DOPA therapeutics. Hence, the major receptor subtype involved in mediating local effects of DA in the VTA seems to be the D_{2} autoreceptor [8,187] whereas D_{3} and possibly D_{3} receptors may play a less important role in controlling DA neuronal firing and release [9-11]. Accordingly, an in vitro electrophysiological study has shown that DA fails to inhibit dopaminergic neuronal activity from D_{2} receptor-deficient mice [188].

Full DA receptor agonists can induce dyskinesia and psychotic-like symptoms including hallucinations (probably due to the overstimulation of extra-striatal DA receptors) or somnolence [189,190]. It has been suggested that such side-effects could be counteracted by the use of partial D_{2}-like receptor agonists [191]. These compounds might stimulate D_{2} and D_{3} receptors when the dopaminergic tone is low, while counteracting excessive stimulation of the DA D_{2} and D_{3} receptor when the dopaminergic tone is high [191]. It is also possible that partial agonists would modulate dopaminergic transmission in a specific region, resulting in the restoration of dopaminergic transmission which is perturbed in PD patients [191]. The primary motor symptoms of PD could potentially be treated by moderate stimulation of striatal DA receptors, while not maximally stimulating these receptors (which is thought to account for the development of dyskinesia in PD patients [190]). Furthermore, preventing psychosis-like symptoms using partial DA receptor agonists might be possible since they would not maximally stimulate dopaminergic receptors in mesolimbic and mesocortical pathways [178,192].

5-HT_{1A} Receptor Agonists in PD

5-HT_{1A} receptor agonists could reduce the incidence of dyskinesia. The 5-HT_{1A} receptor agonist tandosipirone reduced dyskinesia in L-DOPA-treated PD patients [193]. More recently, preclinical and clinical studies suggest that sarizotan, a 5-HT_{1A} receptor agonist that possesses weak D_{3} and D_{2} receptor agonist activity, could ameliorate dyskinetic symptoms in association with L-DOPA [194,195].

It has been suggested that the neurodegenerative processes underlying PD result from loss of 5-HT input from the DRN to the striatum [196]. L-DOPA may be converted to DA in remaining serotonergic neurons and the non-physiological release of DA may lead to abnormal DA receptor stimulation in the striatopallidal pathways, in turn resulting in the generation of L-DOPA-induced dyskinesias [196]. Suppressing the activity of 5-HT inputs to the striatum via presynaptic 5-HT_{1A} agonists may reduce L-DOPA-induced dyskinesia. Studies with 5-HT_{1A} agonists have suggested a reduction in L-DOPA-induced dyskinesia but a worse PD disability [197]. Importantly, Carta et al. [196] have shown that dyskinesia induced by chronic L-DOPA treatment in rats with 6-OHDA-induced lesions of the nigrostriatal DA pathway is critically dependent on the integrity and function of the serotonergic system. Removal of the 5-HT afferents or dampening 5-HT neuronal activity by 5-HT_{1A} and 5-HT_{1B} agonist ligands, resulted in a blockade of the L-DOPA-induced dyskinesias, suggesting that dysregulated DA release from 5-HT terminals is the “prime trigger” of dyskinesia in the rat PD model. In animals with complete DA lesions, the spared 5-HT innervation was unable to sustain the therapeutic effect of L-DOPA, suggesting that DA released as a “false transmitter” from 5-HT terminals is detrimental rather than beneficial. The potent synergistic effect of low doses of 5-HT_{1A} and 5-HT_{1B} agonists to suppress dyskinesia, without affecting the anti-parkinsonian effect of L-DOPA in presence of spared DA terminals, suggests that early use of these drugs could counteract the development of dyskinesia in PD patients [196]. Interestingly, 5-HT dysfunction can also be observed in 6-OHDA-lesioned rats. Wang et al. [198] have shown that unilateral lesion of the rat nigrostriatal pathway induces an increase of neuronal firing of 5-HT neurons associated with desensitized 5-HT_{1A} autoreceptors. Moreover, the degeneration of the nigrostriatal pathway leads to a marked reduction of 5-HT_{1A} receptor density in the hippocampal formation, midbrain raphe nuclei and prefrontal cortex of the MPTP-treated monkeys and PD patients [199,200]. Conversely, high frequency stimulation of the subthalamic nucleus, a well admit antiparkinsonian therapy, has been shown to reduce 5-HT neuronal firing [201], further suggesting the involvement of 5-HT system in the pathophysiology of PD. Finally and as mentioned above, one may assume that 5-HT_{1A} agonism may be also beneficial against depression and cognitive impairment frequently observed in PD patients [202,203].

CONCLUSION

In this review, focus has been placed on the putative therapeutic benefit of partial dopamine D_{2} and serotonin 5-HT_{1A} receptors agonists in the treatment of schizophrenia,
major depression, bipolar disorders and Parkinson’s disease. While several studies are in accordance with the marked interest of partial D2/5-HT1A agonists in reducing side effects i.e. extrapyramidal symptoms and cognitive impairments in schizophrenic patients, various researches are still needed to emphasize their beneficial utility in major depression, bipolar disorders and Parkinson’s disease. Treatment with aripiprazole in major depression as monotherapy or as adjuvant with a classical antidepressants seems to improve the antidepressant response whereas, in bipolar disorder, only partial dopamine D2 receptors agonists show advantages in the treatment of manic episodes. Differently, if treatment of Parkinson’s disease with partial D2 and 5-HT1A receptors agonists is still at the experimental phase, increasing studies report a decrease of side effects with these drugs. Hence, these relatively recent researches provide an exciting future in the discovery of novel stabilizers agents for the management of the latter diseases.

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