

REVIEW

Role of Serotonin in Central Dopamine Dysfunction

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The interaction between serotonin (5-HT) and dopamine (DA)-containing neurons in the brain is a research topic that has raised the interest of many scientists working in the field of neuroscience since the first demonstration of the presence of monoamine-containing neurons in the mid 1960. The bulk of neuroanatomical data available clearly indicate that DA-containing neurons in the brain receive a prominent innervation from serotonin (5-hydroxytryptamine, 5-HT) originating in the raphe nuclei of the brainstem. Compelling electrophysiological and neurochemical data show that 5-HT can exert complex effects on the activity of midbrain DA neurons mediated by its various receptor subtypes. The main control seems to be inhibitory, this effect being more marked in the mesocorticolimbic DA system as compared to the DA nigrostriatal system. In spite of a direct effect of 5-HT by its receptors located on DA cells, 5-HT can modulate their activity indirectly, modifying γ -aminobutyric (GABA)-ergic and glutamatergic input to the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc). Although 5-HT/DA interaction in the brain has been extensively studied, much work remains to be done to clarify this issue. The recent development of subtype-selective ligands for 5-HT receptors will not only allow a detailed understanding of this interaction but also will lead to the development of new treatment strategies, appropriate for those neuropsychiatric disorders in which an alteration of the 5-HT/DA balance is supposed.

Introduction

Dopamine (DA)-containing neurons of the ventral mesencephalon have been designated as A8, A9, and A10 cell groups: these neurons can be collectively designated as the mesotelencephalic DA system [1]. Historically, the mesolimbic DA system was defined as originating in the A10 cells of the ventral tegmental area (VTA) and projecting to structures closely associated with the limbic system. This system was considered to be separated from the nigrostriatal DA system, which originates from the more lateral substantia nigra pars compacta (SNc) (A9 cell group) [1–5] (Figure 1). The mesolimbic and mesocortical DA system appear critically involved in modulation of the functions subserved by cortical and limbic regions, such as motivation, emotional control, and cognition [6]. Substantial evidence indicates that the mesolimbic pathway, particularly the DA cells innervating accumbal areas, is

implicated in the reward value of both natural and drug reinforcers, such as sexual behavior or psychostimulants, respectively [7–9]. The medial prefrontal cortex (mPFC) is generally associated with cognitive functions including working memory, planning and execution of behavior, inhibitory response control, and maintenance of focused attention [6]. In addition, the mesolimbic DA pathway is sensitive to a variety of physical and psychological stressors [10]. Indeed, recent studies have indicated that stress-induced activation of the mesocortical DA neurons may be obligatory for the behavioral expression of such stimuli [11].

The nigrostriatal DA system, which originates from the substantia nigra (A9 cell group), is one of the best studied because of its involvement in the pathogenesis of Parkinson's disease [12]. In mammals, the substantia nigra is a heterogeneous structure that includes two distinct compartments: the SNc and the substantia nigra pars

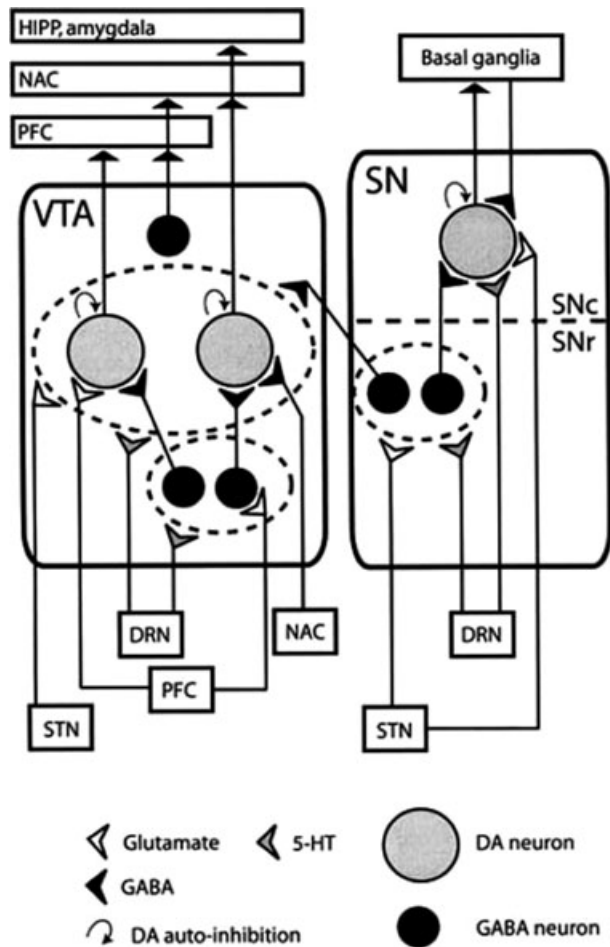


Figure 1 A schematic view of SN and VTA connections. DA neurons receive input from the local GABA-ergic interneurons and input from other brain areas. Both areas receive serotonergic input from the DEN. The dotted line indicates the subdivision of the SN: the SN pars reticulata (SNr) and the SN pars compacta (SNc). Neurons receiving a collective input are grouped (dotted circles). GABA-ergic, glutamatergic and serotonergic inputs are indicated by black, white and gray symbols, respectively. HIPP, hippocampus; NAC, nucleus accumbens; PFC, prefrontal cortex; STN, subthalamic nucleus.

reticulata (SNr). The SNc represent the major source of striatal DA and, as already mentioned, its degeneration causes Parkinson’s disease. On the contrary, the SNr mainly contains γ -aminobutyric (GABA)-ergic neurons which constitute one of the major efferences of the basal ganglia [12]. These DA-ergic systems receive innervation from serotonergic (5-HT) fibers arising from cell bodies of the two main subdivisions of the midbrain 5-HT-ergic nuclei, the dorsal raphe nuclei (DRN) and the medial raphe (MRN) [13–19]. Serotonin-containing cell bodies of the raphe nuclei send projections to dopaminergic cells both in the VTA and the SN, and to their terminal fields in the nucleus accumbens, prefrontal cortex, and striatum [14–19] (Figure 1). Moreover, electron microscopy demonstrates the presence of synaptic contacts of [³H]5-HT labeled terminals with both DA-ergic and non-DA-ergic dendrites in all subnuclei of the VTA, and the SN pars compacta and reticulata [4,16,19] (Figure 1). The diverse physiological effects of serotonin in the brain are mediated by a variety of distinct receptors. These receptors are presently divided into seven classes (5-HT₁–5-HT₇), which are then subdivided into subclasses with a total of at least 14 different receptors, based upon their pharmacological profiles, cDNA-deduced primary sequences and signal transduction mechanisms [20–22] (Figure 2). Several investigators began to study the behavioral, biochemical, and electrophysiological relevance of these neuroanatomical findings. This research was further spurred by the increasing evidences that most psychotropic drugs, including antidepressants, antipsychotics, opioids, anxiolytics, and psychostimulants exerted their pharmacological actions by interfering with 5-HT-ergic and DA-ergic transmission.

Early studies showed that experimental manipulations aimed at decreasing central 5-HT function, such as selective nerve lesions by neurotoxin, inhibition of 5-HT synthesis, or 5-HT receptor blockade tended to potentiate the behavioral and neurochemical effects of drugs enhancing

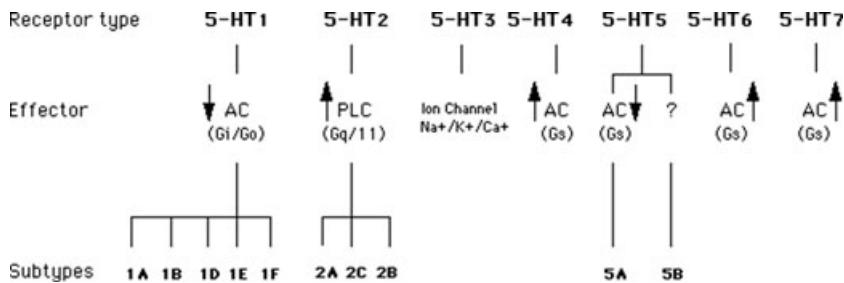


Figure 2 Serotonin receptors.

the dopaminergic transmission such as amphetamine and related compounds, thus leading to the conclusion that central serotonergic systems inhibits DA functions [23]. The interest of our laboratory to investigate 5-HT/DA interaction sprang from these early studies. Our approach was based on *in vivo* electrophysiological and neurochemical techniques. The experimental data gathered over a period of almost 20 years lead to the conclusion that several 5-HT receptor subtypes, including the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT₃, and 5-HT₄ receptors, act to facilitate neuronal DA function and release, while the 5-HT_{2C} receptor mediates an inhibitory effect of 5-HT on the basal electrical activity of dopaminergic neurons and on DA release.

Central serotonergic and dopaminergic systems play an important role in regulating normal and abnormal behaviors [24,25]. Moreover, dysfunctions of 5-HT and DA neurotransmission are involved in the pathophysiology of various neuropsychiatric disorders including schizophrenia, depression, and drug abuse [24–26]. Thus, the development of a number of relatively selective pharmacological agents with agonist or antagonist activity at a specific 5-HT receptor subtype, has allowed investigators to better understand the functional role of these receptors in the control of central DA-ergic function, as serotonin widely contributes to the regulation of a number of behavioral and physiological processes involving both limbic, cortical, and striatal DA pathways [27–30].

Serotonin–Dopamine Interactions in Neuropsychiatric Disorders

Depression

Although dopamine has received little attention in biological research on depression, as compared to other monoamines such as serotonin and noradrenaline, current research on the dopaminergic system is about to change this situation. It is now well-established that disturbances of mesolimbic and nigrostriatal DA function are involved in the pathophysiology of depression [25,26]. Moreover, stress promotes profound and complex alterations involving DA release, metabolism, and receptor densities in the mesolimbic system [31,32]. It seems that exposure to unavoidable/uncontrollable aversive experiences leads to inhibition of DA release in the mesoaccumbens DA system as well as impaired responding to rewarding and aversive stimuli. These alterations could elicit stress-induced expression and exacerbation of some depressive symptoms in humans [32]. Thus, in view of the hypothesis that disinhibition of the mesocorticolimbic DA system underlies the mechanism of action of several antidepressant drugs, the disinhibitory effect of

SB 206553 and SB 242084 on the mesolimbic DA system might open new possibilities for the employment of 5-HT_{2C} receptor antagonists as antidepressants [33,34]. This hypothesis is consistent with the suggestion that 5-HT_{2C} receptor blockers might exert antidepressant activity [27,29,34–37]. In this respect, it is interesting to note that several antidepressant drugs have been shown to bind with submicromolar affinity to 5-HT_{2C} receptors in the pig brain and to antagonize mCPP-induced penile erections in rats, an effect mediated through the stimulation of central 5-HT_{2C} receptors [37–39]. Based on those findings, Matteo *et al.* [34] have carried out experiments showing that acute administration of amitriptyline and mianserin, two antidepressants with high affinity for 5-HT_{2C} receptors, enhances DA release in the rat nucleus accumbens by blocking these receptor subtypes, in addition to their other pharmacological properties. Interestingly, amitriptyline and mianserin have been tested in the chronic mild stress-induced anhedonia model of depression and were found to be effective in reversing the stress effects [40,41]. The antianhedonic effects of tricyclic antidepressants, mianserin, and fluoxetine were blocked by pretreatment with D₂/D₃ receptor antagonists, thus indicating an involvement of DA in the antidepressant effect of various drugs in this model [40,42]. The ability of antidepressants, such as tricyclics, SSRIs, and mianserin, to affect DA systems, via indirect mechanisms, was also reported by studies of Tanda *et al.* [43,44] suggesting that potentiation of DA release in the rat cortex may play a role in the therapeutic action of antidepressants. The chronic mild stress procedure, which induces a depression-like state in animals, was shown to enhance 5-HT_{2C} receptor-mediated function, as measured *in vivo* by mCPP induced penile erections. In contrast, two different antidepressant treatments (72-h REM sleep deprivation and 10-day administration of moclobemide, a reversible inhibitor of monoamine oxidase type A) resulted in a reduction of this 5-HT_{2C} receptor-mediated function [45]. This was interpreted as an indication that the 5-HT_{2C} receptor may be altered, and presumably may exist in a dysregulated (hypersensitive) state in depressive illness. Thus, adaptive processes resulting from chronic antidepressant treatment (*i.e.*, desensitization and/or downregulation of 5-HT_{2C} receptors) may play an important role in reversing the 5-HT_{2C} receptor system supersensitivity resulting from a depressive state [37,46]. In contrast to most other receptors, 5-HT_{2C} is not classically regulated. Indeed, 5-HT_{2C} receptors appear not only to decrease their responsiveness upon chronic agonist stimulation, but also and paradoxically after chronic treatment with antagonists [47,48]. This mechanism appears to be related to an internalisation process that removes activated cell surface receptors from the plasma

membrane involving a phosphorylation step and possible degradation in lysosomes [47]. As a large number of psychotropic drugs, including atypical antipsychotics, antidepressants, and anxiolytics, can all induce down-regulation of 5-HT_{2C} receptors, it has been suggested that this receptor adaptation plays a role in the therapeutic action of these drugs [47,48]. In this respect, it is interesting to note that chronic treatment with 5-HT₂ agonists or antagonists resulted in a paradoxical down-regulation at the 5-HT_{2A} and 5-HT_{2C} receptors [47–51] and it seems that the down-regulation state occurring after chronic exposure to mianserin in isolated systems as well as in cell cultures, is a direct receptor-mediated mechanism of this drug at these receptors [51]. Therefore, the down-regulating capacity of 5-HT_{2C} agonists and antagonists may play a particularly important role in treating the supersensitivity of 5-HT_{2C} receptors resulting from a depressive state [37,46,48]. The possible involvement of 5-HT_{2C} receptors in the pathogenesis of depressive disorders and in the mode of action of antidepressants is further substantiated by several other observations. For example, acute administration of fluoxetine caused a dose-dependent inhibition of the firing rate of VTA DA neurons [52], and decreased DA release in both the nucleus accumbens and the striatum [53], but it did not affect the activity of DA cells in the SNc [52]. A similar effect, though less pronounced, has been observed with citalopram [52]. Furthermore, mesulergine, an unselective 5-HT_{2C} receptor antagonist, as well as the lesion of 5-HT neurons by the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT), prevented fluoxetine-induced inhibition of VTA DA cells [52]. These results indicate that fluoxetine inhibits the mesolimbic DA pathway by enhancing the extracellular level of 5-HT, which would act through 5-HT_{2C} receptors [52]. This study also demonstrated that fluoxetine-induced inhibition of DA neurons in the VTA was no longer observed after chronic treatment (21 days) with this drug. Interestingly, mCPP inhibited the firing activity of VTA DA neurons in control animals but not in those chronically treated with fluoxetine [52]. The authors suggested that 5-HT_{2C} receptors might be down-regulated after repeated fluoxetine administration. Consistent with this hypothesis is the evidence that chronic treatment with sertraline and citalopram, two selective serotonin reuptake inhibitors (SSRIs), induced tolerance to the hypolocomotor effect of mCPP [54]. This hyposensitivity of 5-HT_{2C} receptors might be a key step for the achievement of an antidepressant effect. Indeed, it is possible to argue that the acute inhibitory effect of fluoxetine on the mesolimbic DA system would mask its clinical efficacy in the early stage of treatment. This masking effect would disappear when the hyposensitivity of 5-HT_{2C} receptors occurs. A series of studies carried out in our lab-

oratory have shown that acute administration of SSRIs such as paroxetine, sertraline, and fluvoxamine causes a slight but significant decrease in the basal firing rate of VTA DA neurons [55]. Therefore, it is conceivable that, similar to fluoxetine, these SSRIs could reduce mesocorticolimbic DA transmission by activating 5-HT_{2C} receptors. Furthermore, employing complementary electrophysiological and neurochemical approaches, and both acute and chronic administration routes, it was found that mirtazapine, nefazodone, and agomelatine, three effective and innovative antidepressants, elicit a robust and pronounced enhancement in the activity of mesocorticolimbic DA pathways. These actions were ascribed to their antagonistic properties at inhibitory, tonically active 5-HT_{2C} receptors, that desensitize after repeated drug administration [56–58].

Interestingly, agomelatine, has shown antidepressant efficacy in clinical trials [59–61], and, indeed, it was found to be effective in treating severe depression associated with anxiety symptoms, with a better tolerability and lower adverse effects than other antidepressants such as paroxetine [59]. Recent experimental evidence suggests that 5-HT_{2A} and 5-HT_{2C} receptors can be constitutively active (agonist-independent activity) *in vivo*, and alterations in the constitutive activity of these receptor systems could be involved in the mechanisms underlying anxiety and depression or exploited for therapeutic benefit. Therefore, drugs with inverse agonist properties at these receptors may have more activity *in vivo* to regulate DA neurotransmission than that afforded by simple competitive antagonism [62].

Other serotonin receptors such as 5HT₃ receptors may also contribute to the changes in 5-HT-induced dopamine release [63]. Thus, antidepressant drugs that will block 5-HT_{2C} and activate 5-HT₃ receptors will probably restore serotonin induced DA release in the nucleus accumbens, and normalize depressive-like behavior faster than classical antidepressant drugs [58,63,64]. This suggestion agrees with clinical studies that demonstrated that mirtazapine, which acts on 5-HT_{2C} and 5-HT₃ receptors, and nefazodone, which acts on 5-HT_{2C}, and whose metabolite acts on 5-HT₃ receptors, are characterized by a more rapid onset of behavioral effects of treatment [65]. Further, valproic acid, carbamazepine, and zonisamide, three anticonvulsant mood stabilizers, have been reported to preferentially increase DA release in the mPFC of rats, sharing a common mechanism of action mediated by 5-HT_{1A} receptor activation [66,67]. Thus, both anticonvulsant mood stabilizers and atypical antipsychotic drugs, would be expected to ameliorate or prevent depression, at least in part, via reversal of decreased prefrontal cortical activity by facilitating 5-HT_{1A} activation and its resultant increase in mPFC DA release. A number of

antidepressant agents, such as ipsapirone [68], mirtazapine [69], fluoxetine, and bupropion [70,71], all drugs showing agonistic properties at 5-HT_{1A} receptors, raised extracellular DA in mPFC, and were markedly attenuated by pretreatment with WAY 100635. Also, the combination of atypical antipsychotic drugs in addition to serotonin reuptake inhibitors has recently proven to be beneficial in a number of neuropsychiatric disorders, such as resistant depression, schizophrenia, and obsessive-compulsive disorder, as this method markedly potentiates mPFC DA release elicited by the administration of a single drug alone. Interestingly, acute combination of fluoxetine and olanzapine caused a synergistic and selective effect on the extracellular concentration of dopamine in the medial prefrontal cortex [72,73], and this regional selectivity may account for the mood-stabilizing properties of these drugs. Nevertheless, the combination of long-term fluoxetine with acute olanzapine did not show the synergistic effect on the extracellular of DA observed following acute administration [74] suggesting that the therapeutic benefit of this pharmacological combination may not be associated with changes in the cortical concentration of monoamines, but to postsynaptic blockade of monoaminergic receptors. Thus, activation of 5-HT_{1A} receptors secondary to the combined blockade of 5-HT_{2A/2C} and D_{2/3} receptors seems to be relevant for this action [73–82].

Schizophrenia

Both hypo- and hyperfunction of dopaminergic systems may occur in schizophrenic patients, perhaps even simultaneously, albeit in a region specific manner [83–85]. Thus, whereas a dopaminergic hyperfunction of the mesolimbic system may underlie the development of positive symptoms, a dopaminergic hypofunction of the cortical projections may well be related to the negative symptomatology in schizophrenia. Given the critical role of cortical DA in cognitive functioning [86,87], the hypothesized cortical DA hypofunction may therefore also be implicated in the cognitive disturbances frequently experienced by schizophrenic patients. Hence, it appears likely that both the negative symptoms and cognitive disturbances of schizophrenia may be associated with a hypofunction of the mesocortical DA system.

Currently used antipsychotic drugs are usually divided into two main classes, on the basis of their liability to induce neurological side effects after long-term treatment. Drugs defined as typical antipsychotics (APDs) (e.g., chlorpromazine, haloperidol, trifluoperazine) are known to induce, following repeated administration, various extrapyramidal side effects (EPS) including Parkinson-like syndrome and tardive dyskinesia [88]. On the other hand, chronic treatment with atypical

antipsychotic drugs (e.g., clozapine, risperidone, sertindole, zotepine) is associated with a low incidence of neurological side effects [88]. Moreover, atypical antipsychotic drugs do not increase plasma prolactin levels in humans [88]. The hypothesis that typical antipsychotics produce their clinical effects, as well as EPS, by blocking DA D₂ receptors in the mesolimbic and nigrostriatal systems, respectively [88], is now generally accepted. In contrast, the mechanisms responsible for the clinical effects of atypical antipsychotic drugs are still not clear. Numerous studies have shown that the so-called “atypical antipsychotics” such as clozapine, amperozide, olanzapine, risperidone and others, compared to the typical antipsychotics haloperidol or (-) sulpiride, stimulate the release of DA more potently in the mPFC and mesocorticolimbic innervated areas, than in the striatum [89–96]. This selective action is associated with a lower incidence of EPS, and with a greater ability to improve negative symptoms and cognitive functions in schizophrenia [24,88,97,98]. As a common property of these drugs, that distinguishes them from the typical antipsychotics, is their high affinity for the 5-HT_{2A} receptor, it has been suggested that potent 5-HT_{2A} antagonism, in relation to a weaker DA D₂ receptor antagonism, contributes to their beneficial effects [99]. Thus, pretreatment with the selective 5-HT_{2A} antagonist M100907 before administration of the D₂ antagonists haloperidol, sulpiride or raclopride produced an increase in mPFC DA release, which was not observed by these compounds administered alone [89,95,100,101]. Interestingly, M100907 potentiated low but not high dose haloperidol-induced DA release in the mPFC and inhibited that in the nucleus accumbens [100,101], thus, weak D₂ and potent 5-HT_{2A} receptor blockade may have an important influence on the preferential increase of mPFC DA release by the atypical antipsychotics and on their clinical effectiveness. Further, evidence has been provided that this effect may be mediated by actions of released 5-HT interacting with 5-HT_{1A} receptors. In fact, reversal by WAY100635 of the potentiation of DA release in mPFC induced by selective antagonism at 5-HT_{2A} and D₂ receptors suggested that facilitation of 5-HT_{1A} receptor stimulation is essential to the simultaneous blockade of 5-HT_{2A} and D₂ receptors to increase cortical DA release [89,100].

Interestingly, 8-OH-DPAT, a 5-HT_{1A} agonist, or amperozide and M100907, two 5HT_{2A} receptor antagonists, inhibited the ability of amphetamine to increase DA release in rat nucleus accumbens and striatum [101–103]. Thus attenuation of stimulated DA release in the nucleus accumbens and striatum by 5-HT_{1A} receptor agonism and/or 5-HT_{2A} antagonism, may contribute to reverse neuroleptic-induced catalepsy in rats. In this respect, combining antagonist/partial agonist activity at dopamine

D₂ and agonist activity at serotonin 5-HT_{1A} receptors is one of the approaches that has recently been chosen to develop the new generation of antipsychotics, including bifeprunox, SSR181507 and SLV313, in that 5-HT_{1A} receptor activation greatly reduces or prevents the cataleptogenic potential of these novel antipsychotics [104–106]. Interestingly, 5-HT_{1A} receptor activation and dopamine D₂ receptor antagonism underlie the electrophysiological and neurochemical profile of F15063 as measured by determination of DRN and VTA electrical activity that increased catecholamine levels in the medial prefrontal cortex and decreased 5-HT levels in the hippocampus [107].

As already mentioned, preferential increase of DA release in the mPFC seems to be a common mechanism of action of atypical antipsychotic drugs, an effect which might be relevant for their therapeutic action on negative symptoms of schizophrenia [94]. In this respect, it is important to note that the selective 5-HT_{2C} receptor antagonist SB 242084 markedly increases DA release in the frontal cortex of awake rats [108,109]. Thus, it is possible to argue that blockade of 5-HT_{2C} receptors might contribute to the preferential effect of atypical antipsychotics on DA release in the prefrontal cortex. It is noteworthy to mention recent data showing that atypical antipsychotic drugs (clozapine, sertindole, olanzapine, ziprasidone, risperidone, zotepine, tiospirone, fluperlapine, tenilapine), which produce little or no EPS while improving negative symptoms of schizophrenia, exert substantial inverse agonist activity at 5HT_{2C} receptors [110–112]. Thus, 5-HT_{2C} receptor inverse agonism might underlie the unique clinical properties of atypical antipsychotic drugs [111]. Interestingly, there is preclinical evidence indicating that 5-HT_{2C} receptor blockade is responsible for reducing EPS: 5-HT_{2C} but not 5-HT_{2A} receptor antagonists were capable of inhibiting haloperidol-induced catalepsy in rats [113]. On the other hand, the blockade of DA-ergic neurotransmission in the nucleus accumbens via D₂ receptor antagonism or partial agonism is considered the primary mechanism underlying antipsychotic efficacy for the positive symptoms (i.e., hallucinations, delusions, and thought disorder) of schizophrenia. Thus, an alternative approach to blocking dopamine D₂ receptors may be to reduce the activity of the mesolimbic pathway without affecting that of the nigrostriatal system, thus avoiding potential extrapyramidal side effect liabilities. The selective effects shown by the 5-HT_{2C} receptor agonists on the mesolimbic DA pathway suggest that 5-HT_{2C} receptor agonists should have antipsychotic efficacy without the EPS associated with typical antipsychotics. To this end, recently, the antipsychotic efficacy of the selective 5-HT_{2C} receptor agonist WAY-163909 was preclinically evaluated by *in vivo* microdialysis, electrophysiology, and various animal models of schizophrenia [114], showing

selectivity for the mesolimbic system and an interesting profile similar to that of an atypical antipsychotic, when given acutely or chronically in mice and rats, facilitating cortical DA-ergic neurotransmission and reducing that of the nucleus accumbens, without affecting the nigrostriatal DA activity.

Agents acting at multi-receptor sites appear to be more promising as antipsychotic drugs, and recent data show that blockade of DA receptors and combined antagonism at 5-HT_{2A} as well as 5-HT_{2C} receptors may be involved in the therapeutic effects of novel antipsychotics [97,98,100,115]. Interestingly, ritanserin, a mixed 5-HT_{2A/2C} receptor antagonist, has been reported to potentiate the D_{2/3} receptor antagonist raclopride-induced DA release in the medial prefrontal cortex and nucleus accumbens, but not in the striatum [116]. Another putative atypical antipsychotic drug SR46349B, that shares both 5-HT_{2A} and 5-HT_{2C} receptor antagonism, increased cortical DA release and potentiated haloperidol induced DA release in both mPFC and nucleus accumbens, suggesting that 5-HT_{2C} receptor antagonism may also contribute to the potentiation of DA release produced by haloperidol [100]. A novel putative atypical antipsychotic ACP-103, inverse agonist at both 5-HT_{2A} and 5-HT_{2C} receptors, increased DA release in the mPFC but not in the nucleus accumbens, and potentiated low dose of haloperidol-induced DA release in the mPFC, while inhibiting that in the nucleus accumbens [117]. Taken together, these data suggest that combined 5-HT_{2A/2C} receptor antagonism may be more advantageous than selective 5-HT_{2A} antagonism alone as an adjunct to D₂ antagonism and 5-HT_{1A} stimulation to improve cognition and negative symptoms in schizophrenia.

Parkinson's Disease

The major pathology in Parkinson's disease is the degeneration of pigmented dopamine-producing neurons, particularly within the SNc, which causes a consequent reduction of dopamine levels in the striatum, and changes in the basal ganglia–thalamo–cortical network activity [118–120]. The neural mechanisms underlying the generation of parkinsonian symptoms are thought to involve reduced activation of primary motor and premotor cortex and supplementary motor areas, secondary to overactivation of the output regions of the basal ganglia, that is, SNr and globus pallidus internus (GPI) [121], largely because of excessive excitatory drive from the subthalamic nucleus (STN), consequent to dopamine loss in the striatum [119,120]. Therapy for Parkinson's disease consists mainly of amelioration of the symptoms with classical dopaminomimetics [122]. This treatment, however, is characterized by declining efficacy and the

occurrence of disabling side-effects [123]. Functional inhibition of GPi or STN, has provided an alternative to lesioning, by deep brain stimulation associated with modest side-effects [124]. As serotonergic projections from the DRN innervate all components of the basal ganglia circuitry [119,120], it is likely that 5-HT plays a role in regulating the basal ganglia's activities, and of particular interest with respect to the development of new treatments for Parkinson's disease are 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} receptors [119,125]. Stimulation of 5-HT_{1A} receptors might be expected to reduce 5-HT release in several brain regions, including the basal ganglia, and reduce the activity of glutamatergic inputs to the striatum, that may have both antiparkinsonian and antidyskinetic actions [119]. Moreover, stimulation of striatal 5-HT_{1B} receptors may modulate levodopa metabolism to dopamine in 5-HT terminals [126]. 5-HT_{1B} receptors in the pallidum and substantia nigra reduce GABA release thus having either antiparkinsonian or antidyskinetic actions [119]. Another interesting application of the data regarding the functional role of 5-HT_{2C} receptors in the basal ganglia is the possible use of 5-HT_{2C} receptor antagonists in the treatment of Parkinson's disease, and 5-HT_{2C} agonists to reduce the problems of levodopa-induced dyskinesia [119,127]. As already mentioned, 5-HT_{2C} receptors are located in the SNr and medial segment of the pallidal complex in the rat and human brain [13,128], and enhanced 5-HT_{2C} receptor-mediated transmission within the output regions of the basal ganglia in Parkinsonism appears to contribute to their overactivity [127]. In addition, 5-HT_{2C}-like receptor binding is increased in a rat model of Parkinsonism [129] and in human Parkinsonian patients [130]. Interestingly, systemic administration of the 5-HT_{2C} receptor antagonist SB 206553 enhanced the anti-Parkinsonian action of the DA D₁ and D₂ agonists in the 6-hydroxydopamine-lesioned rats [131,132], suggesting that the use of a 5-HT_{2C} receptor antagonist in combination with a DA receptor agonist may reduce the reliance upon dopamine replacement therapies and may thus reduce the problems associated with long term use of currently available antiparkinsonian agents [127].

Drugs of Abuse

Substantial evidence indicates that the mesolimbic pathway, particularly the dopaminergic system innervating accumbal areas, is implicated in the reward value of both natural and drug reinforcers, such as sexual behavior or psychostimulants, respectively [7,8,133]. Therefore, blocking or stimulating several 5-HT receptor subtypes, including the 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT₃ subtypes, modulates both the neurochemical and the behavioral effects of addictive drugs. 5-HT₃ antagonism

has been shown to counteract the increase of accumbal DA release induced by various drugs of abuse, such as ethanol, nicotine, morphine, or cocaine [134–139]. Systemically, ICS205-930, ondansetron, and MDL72222 attenuated morphine-induced DA release in the nucleus accumbens [134,135,137,140], nevertheless, intra VTA, but not intra-accumbal, infusion of ICS205-930, was able to counteract the action of morphine [140], suggesting that selective antagonism on VTA 5-HT₃ receptors is able to modulate the morphine's action in the mesolimbic system. Furthermore, intra-accumbal infusion of ondansetron strongly reduced the enhancement of DA release elicited by a high but not a low dose of morphine in the same area [137] so, it was proposed that in addition to increased DA tone, increased 5-HT release is required to trigger the excitatory action of accumbal 5-HT₃ receptors on DA release. Systemic pretreatment with ICS205-930 also attenuated ethanol-induced increase of DA efflux in the nucleus accumbens [134,141]. Furthermore, local infusion of ICS205-930 into the VTA [142] or in the nucleus accumbens [143] prevented ethanol's action in both areas. In addition, the 5-HT₃ agonist mCPBG had additive effect on DA release when infused in the nucleus accumbens concomitantly to the systemic injection of ethanol in rats [143]. Therefore, Yoshimoto *et al.* [144] showed that chronic alcohol intake increases the sensitivity of accumbal 5-HT₃ receptors in rats, thus suggesting their involvement in alcohol dependence.

There are, however, contrasting results in the case of amphetamine or cocaine. Systemic administration of the 5-HT₃ antagonists MDL72222 and zacopride has been shown to attenuate both cocaine- or amphetamine-induced DA release in the nucleus accumbens [138,139,145], while, other studies have shown that systemic 5-HT₃ receptor antagonism had no effect on DA efflux enhanced by these drugs in the same area [137,146,147]. Therefore, the fact that drugs of abuse stimulate DA release through different cellular mechanisms leads to the possibility that their effect on DA function could be modulated by the 5-HT₃ receptor only under specific conditions, in that it requires a concomitant increase in both endogenous DA and 5-HT tones and operates selectively on the depolarization-dependent exocytosis of DA.

Pharmacological studies have shown that the acute administration of 5-HT_{1B} receptor agonists augments cocaine-evoked DA overflow within the nucleus accumbens [148]. The ability of extracellular 5-HT to facilitate mesolimbic DA release through 5-HT_{1B} receptors has implications for psychostimulant abuse. Likewise, studies have shown that systemic or intra-VTA 5-HT_{1B} receptor agonism (CP 93129 and RU 24969, respectively) potentiated cocaine-induced increase in DA efflux in the

nucleus accumbens and decreased GABA release in the VTA [148,149]. Dopaminergic activity from the mesolimbic pathway may then be disinhibited by the stimulation of 5-HT_{1B} receptors on GABA-ergic projection neurons from the nucleus accumbens to the VTA, resulting in a potentiated response to cocaine. There is also evidence that VTA 5-HT_{1B} receptors may be involved, in part, in mediating the activating effects of ethanol on mesolimbic DA neurons, in that activation and blockade of VTA 5-HT_{1B} receptors potentiated and attenuated, respectively, the ethanol-induced increases in extracellular DA concentrations in both the VTA and the ipsilateral nucleus accumbens [150]. Taken together, these studies suggest that 5-HT_{1B} and/or 5-HT₃ receptor antagonism could be beneficial in treating psychostimulant abuse.

5-HT_{2A} and 5-HT_{2C} receptor subtypes have also been implicated in modulating responses to psychostimulants and may play a role in their rewarding effects. The fact that addictive drugs act through different cellular mechanisms leads to the possibility that their effects on DA release could be modulated differentially by each of the 5-HT_{2A} or 5-HT_{2C} receptor subtypes. For example, it has been reported that the increased locomotor activity, as well as the accumbal DA release, elicited by phencyclidine is further enhanced by the blockade of 5-HT_{2C} receptors [109], while antagonism at 5-HT_{2A} receptors had opposite effects [151]. A similar picture emerges when considering the influence of these receptors on 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)-induced effects on DA neuron activity. Thus, the selective 5-HT_{2A} antagonist MDL 100,907 significantly reduced hyperlocomotion and stimulated DA release produced by MDMA while the selective 5-HT_{2C} antagonists SB 242084 and SB 206553 potentiated it [152–155].

It was recently found that SB 206553 administration potentiates both the enhancement of DA release in the nucleus accumbens and striatum, and the increased DA neuron firing rate induced by morphine both in the VTA and the SNc [156]. Consistent with these findings, stimulation of central 5-HT_{2C} receptors has been shown to inhibit morphine-induced increase in DA release in the nucleus accumbens of freely moving rats [157]. A series of studies showed that blockade of 5-HT_{2A} or 5-HT_{2C} receptors had opposite effects on cocaine-induced locomotor activity. Thus, 5-HT_{2A} receptor blockade with M100,907 attenuated cocaine-induced locomotion, whereas 5-HT_{2C} blockade with SB 242084 or SB 206553 enhanced cocaine-induced activity [158–161]. Consistent with these data obtained in rats, 5-HT_{2C} receptor null mutant mice showed enhanced cocaine-induced elevations of DA levels in the nucleus accumbens, and marked increase in locomotor response to cocaine as compared to wild-type mice, suggesting that

selective 5-HT_{2C} receptor agonist treatments may represent a promising novel approach for treating cocaine abuse and dependence [162]. In line with this hypothesis, it was previously found that RO 60-0175 reduced cocaine-reinforced behavior by stimulating 5-HT_{2C} receptors [163]. Moreover, these authors also showed that RO 60-0175 reduced ethanol- and nicotine-induced self-administration and hyperactivity [164,165]. Consistent with this evidence, we showed that the selective activation of 5-HT_{2C} receptors by RO 60-0175 blocks the stimulatory action of nicotine on SNc DA neuronal activity and DA release in the corpus striatum [166,167]. The mesolimbic DA system appeared to be less sensitive to the inhibitory effect of 5-HT_{2C} receptors activation on nicotine-induced stimulation, indeed a higher dose of RO 60-0175 was necessary to prevent the enhancement of VTA DA neuronal firing elicited by acute nicotine. Furthermore, pretreatment with the 5-HT_{2C} agonist did not affect nicotine-induced DA release in the nucleus accumbens [166]. Interestingly, in animals treated repeatedly with nicotine, pretreatment with RO 60-0175 reproduced the same pattern of effects on the enhancement in DA neuronal firing caused by challenge with nicotine, and as a result was effective only at a higher dose in preventing nicotine excitation in the VTA compared to the SNc. Furthermore, the 5-HT_{2C} receptors agonist counteracted nicotine-induced DA release both in the striatum and in the nucleus accumbens in rats chronically treated with this alkaloid, even if this effect was observed only with the highest dose of RO 60-0175 [166,167]. Therefore, we hypothesized that after repeated nicotine exposure an up-regulation of 5-HT_{2C} receptors occurs only in the DA mesolimbic system and the blocking of its hyperfunction by 5-HT_{2C} receptor activation might be a useful approach in reducing nicotine reward, and eventually helping in smoking cessation.

Conclusion

Serotonergic and dopaminergic systems are closely related in the central nervous system, and the involvement of 5-HT receptors in the control of central DA activity is now well established. Recent evidence suggests that dysfunction of dopaminergic and serotonergic neurotransmitter systems contributes to various disorders including depression, schizophrenia, Parkinson's disease and drug abuse. Thus, the use of a complementary dialysis and electrophysiological approach, together with several highly selective ligands, has permitted important insights into the complex pattern of reciprocal interactions via which multiples classes of 5-HT receptors control the activity of central dopaminergic pathways. These data

facilitate interpretation of the influence upon central DA-ergic systems exerted by 5-HT and diverse classes of antidepressant, antipsychotic and psychostimulant agents, and suggest numerous possible receptorial strategies for modulation (potentiation) of their therapeutic actions.

Moreover, the scenario is complicated by some experimental caveats. Most of the agonists and antagonists used in the studies reviewed here are selective but are not specific enough to identify receptors involved, especially when used in relatively high concentrations. Most of the *in vivo* data, obtained by extracellular recordings are from *putative* DA neurons identified by their firing properties. Nevertheless, these classical identification criteria are deceptive. In fact, the presence of a functionally distinct non-dopaminergic (but not GABA-ergic) population of neurons in the VTA with overlapping characteristics has been demonstrated [168], which is likely to have been included in the analysis of DA neurons in the electrophysiological studies that we reviewed. In addition, these studies are carried out in anaesthetized rats. Although DA neurons are autoactive, their impulse activity and response to natural neurochemical inputs are strongly affected by general anaesthesia. Some alterations appear to be specific to the general anaesthetic used, while others probably reflect changes in the activity of afferent inputs, brain metabolism, and neurotransmitter uptake that are typical to any type of general anaesthesia. Most of the data are obtained using chloral hydrate that is known to exert subtle effects on the basal activity and pharmacological responsiveness of midbrain DA neurons [169]. Therefore, taking consideration of the aforementioned, when extracellular unit activity from single DA neurons in anaesthetized rats are performed, it is of paramount importance that they are subsequently labelled with the use of the juxtacellular technique, and neurochemically characterized with immunofluorescence for Tyrosine Hydroxylase. Moreover, the utilization of microiontophoresis or reverse dialysis might be encouraged. In fact, despite their methodological constraints, they remain almost the only way of applying relatively few molecules rapidly into the vicinity of central synapses. The techniques get closer to mimicking synaptically released neurotransmitters than any other, and can show direct or indirect effects. Despite the large body of data available on this subject there still a number of points that need to be elucidated. Thus, it would be important to establish the exact brain site(s) involved in the control of DA neuronal activity by the various 5-HT receptor subtypes. For example, it would be important to determine whether or not the effects of the selective activation of 5-HT subtypes are mediated at the level of the nuclei of origin of the DA-ergic systems (i.e., in the SNc or the VTA); whether or not their effects are direct or indirect (e.g., mediated by GABA-ergic transmis-

sion) and whether or not feed-back pathways originating from projection areas of the nigro-striatal and mesocorticolimbic systems are involved in their overall effect upon DA neuronal function. Lastly, the majority of the effects described herein were acquired upon acute drug administration. This approach is eminently suitable to the characterization of the functional roles of various auto- and heteroreceptor subtypes. However, inasmuch as the majority of the therapeutic agents are often administered chronically, and may trigger adaptive changes, it would be interesting to expand the present observations with studies of long-term drug administration.

The intensive research in medicinal chemistry will help this field of investigation. In fact, more selective ligands for 5-HT receptors are currently produced. In the future, the use of such selective ligands, especially agonists of 5-HT receptors, would certainly be helpful in determining their functional importance and their involvement in the pathogenesis of diseases, not exclusively of the CNS. However, it should be kept in mind that although selective receptor ligands are an important and indispensable research tool, they rarely happen, in practice, to be drugs. This is likely due to a need to act on different neurotransmitter systems to obtain a therapeutic effect since neuropsychiatric disorders are not pure DAergic dysfunction. Many questions need to be answered before we can truly understand how these serotonin receptors regulate DA neuronal activity in the brain. The challenge ahead is to build on this foundation and keep up this engaging adventure: the interaction between serotonin and dopamine systems is far from being completely revealed.

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Conflict of Interest

The authors declare no conflict of interest.

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