Chapter 19
Serotonin 2B Receptor Interactions with Dopamine Network: Implications for Therapeutics in Schizophrenia

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Abbreviations

5-HT	Serotonin
5-HT_{2B}R	5-HT_{2B} receptor
APD	Antipsychotic drug
CNS	Central nervous system
DA	Dopamine
DRN	Dorsal raphe nucleus
EPS	Extrapyramidal side effects
FC	Frontal cortex
MDMA	3,4-methylendioxymethamphetamine
mPFC	Medial prefrontal cortex
NAc	Nucleus accumbens
NOR	Novel object recognition
PCP	Phencyclidine
VTA	Ventral tegmental area

1 Introduction

The serotonin 2B receptor (5-HT_{2B}R) is the most recent addition to the 5-HT_2R family, which also comprises the 5-HT_{2A}R and the 5-HT_{2C}R subtypes [1]. Formerly called 5-HT_{2F}R, the 5-HT_{2B}R belongs to the seven transmembrane spanning receptor superfamily commonly referred to as G-protein-coupled receptors. It was first cloned and characterized in the rat stomach fundus [2, 3], then in mice [4] and in

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humans [5–7]. It has been shown to be present in various peripheral tissues in both rodents and humans, where it participates in the regulation of several physiological functions such as the gastrointestinal, the vascular, the pulmonary, the cardiac and the immune ones, for review, see [8]. In 1997, a few years after its cloning, the 5-HT_{2B}R was shown to be localized also in the mammalian brain. Immunohistochemistry studies assessing 5-HT_{2B}R protein expression in the rat brain demonstrated its presence in the frontal cortex (FC), the cerebellum, the lateral septum, the dorsal hypothalamus and the medial amygdala [9]. Subsequent investigations showed that 5-HT_{2B}R mRNA is expressed in additional rat brain regions such as the dorsal raphe nucleus (DRN), the locus coeruleus, the cerebellum, the habenula, the hippocampus and the hypothalamic paraventricular nucleus [10]. In humans, 5-HT_{2B}R mRNA was detected in the whole brain, and in particular in the cerebellum, the occipital cortex and the FC [5, 11]. Recent studies in mice have provided information about the cellular localization of 5-HT_{2B}Rs within the central nervous system (CNS), this issue remaining relatively unexplored in rats [8]. Thus, 5-HT_{2B}Rs have been shown to be expressed in primary astrocyte cultures from the neocortex [12], in 5-HT transporter-expressing primary neurons from embryonic raphe nuclei [13], in 5-HT neurons of raphe nuclei [14], in post-natal microglia [15], and in a subpopulation of ventral tegmental area (VTA) DA neurons innervating the nucleus accumbens (NAc) shell subregion [16].

With respect to the peripheral 5-HT_{2B}R, its functional role within the CNS has received much less attention until recently. Indeed, the first studies assessing the role of the central 5-HT_{2B}R on dopamine (DA) ascending pathway activity reported that the 5-HT_{2B}R agonist BW 723C86 and the 5-HT_{2B}R antagonist SB 204741 had no effect on DA neuron firing or on basal DA outflow in the FC, the NAc and the striatum [17, 18]. These negative findings, along with the risk of agonist-induced side effects related to heart-valve pathogenesis [19, 20], probably led to the discontinued use of 5-HT_{2B}R compounds in drug research and development when studying the central 5-HT system, and, in particular, the 5-HT/DA interaction within the CNS. Indeed, it was not until 2008 that the pivotal article by Maroteaux and coworkers showed that the central 5-HT_{2B}R participates in both the neurochemical and behavioral effect of 3,4-methylendioxymethamphetamine (MDMA) in mice [21]. They showed that selective pharmacological blockade with RS 127445 or genetic ablation of the 5-HT_{2B}R reverses MDMA-increased DA outflow in the NAc and 5-HT outflow in the NAc and the VTA, as well as MDMA-induced hyperlocomotion [21]. Subsequently, over the last decade and thanks to the development and availability of potent and high affinity 5-HT_{2B}R antagonists such as LY 266097 and RS 127445 [8, 22, 23], a growing number of studies have confirmed the key role of the central 5-HT_{2B}R in the control of DA and 5-HT neuron activity, and have highlighted its potential as a new pharmacological target for treating several neuropsychiatric disorders such as schizophrenia, depression and drug addiction [8, 14, 16, 24–30].

The present chapter provides an overview of the role of the 5-HT_{2B}R in the control of ascending DA pathway activity, covering neurochemical, electrophysiological and behavioral data mainly obtained from in vivo studies in the rat. After discussing

the role of 5-HT_{2B}Rs in controlling the release of DA in the medial prefrontal cortex (mPFC), the NAc and the striatum, we describe recent neurochemical and molecular findings providing the anatomo-functional basis underlying the effects of 5-HT_{2B}R antagonists on the activity of the mesocorticolimbic DA system. Finally, we present some behavioral data adding functional evidence for the therapeutic potential of 5-HT_{2B}R antagonists in the treatment of schizophrenia.

2 The Central 5-HT_{2B}R and DA Ascending Pathways

2.1 Regulation of DA Neuron Activity: In Vivo Neurochemical and Electrophysiological Data

Compelling in vivo biochemical and electrophysiological data demonstrate that, unlike 5-HT_{2B}R agonists [8, 17, 18, 24], 5-HT_{2B}R antagonists modulate DA ascending pathway activity in a differential manner. Thus, both the 5-HT_{2B}R antagonists RS 127445 and LY 266097 increase and decrease DA outflow in the mPFC and the shell subregion of the NAc, respectively, but do not modify DA outflow in the striatum or in the core subregion of the NAc [24–26]. In line with these results, electrophysiological findings have shown that selective blockade of 5-HT_{2B}Rs has no effect at the level of the substantia nigra pars compacta but decreases the firing rate of DA neurons in the VTA, presumably those projecting to the shell subregion of the NAc [26]. Based on these findings which provide additional support for the insensitivity of the nigrostriatal DA pathway to 5-HT_{2B}R modulation, it is tempting to hypothesize that 5-HT_{2B}R antagonism reduces accumbal DA outflow via an inhibitory modulation of mesoaccumbal DA neuronal firing. Nevertheless, as discussed elsewhere [26], in keeping with the cellular heterogeneity of the VTA [31–34], further studies are needed to identify DA neurons projecting to the NAc or to the mPFC. Altogether, these findings demonstrate that 5-HT_{2B}Rs independently control the activity of the three ascending DA pathways by specifically providing tonic excitatory and inhibitory controls on NAc and mPFC DA outflow, respectively, and no effect in the striatum (Fig. 19.1).

This conclusion contrasts with that offered by the first studies assessing the effect of this receptor on DA neuron activity and reporting that 5-HT_{2B}R blockade has no effect on DA ascending pathway activity [17, 18]. As discussed elsewhere [8], the use of high doses of non-selective 5-HT_{2B} compounds as well as some methodological drawbacks could be responsible for the discrepancies observed.

During recent years, much attention has been devoted to identifying the mechanisms and the anatomo-functional basis underlying the modulatory control exerted by 5-HT_{2B}Rs on the mesocorticolimbic DA system. Interestingly, it has been demonstrated that the opposite effect of 5-HT_{2B}R antagonists on mPFC and NAc shell DA outflow involves a functional interplay between 5-HT_{2B}Rs and 5-HT_{1A}Rs located in the DRN and in the mPFC, respectively (Fig. 19.2). By increasing cortical 5-HT

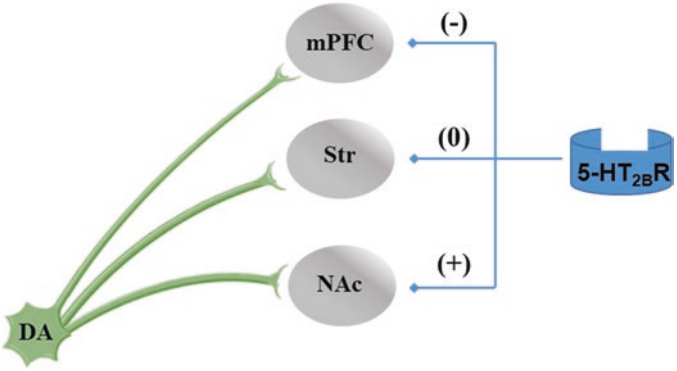

Fig. 19.1 Differential control exerted by central serotonin 2B receptors (5-HT_{2B}Rs) on the activity of ascending dopamine (DA) pathways. They exert a tonic inhibitory control on DA outflow in the medial prefrontal cortex (mPFC), a tonic excitatory control on DA outflow in the nucleus accumbens (NAc), but have no effect at the level of the striatum (Str), for details see [26]

outflow, intra-DRN 5-HT_{2B}R blockade triggers the stimulation of 5-HT_{1A}Rs located on mPFC GABAergic interneurons [35], thereby leading to the activation of pyramidal glutamatergic neurons [36] which drive opposite changes of mPFC and NAc DA outflow through direct or indirect interactions with VTA DA neurons [27, 37]. The involvement of these polysynaptic cortical-subcortical pathways is supported by the finding that the opposite change of mPFC and NAc DA outflow induced by the intra-DRN administration of RS 127445 is suppressed by the intra-mPFC perfusion of the selective 5-HT_{1A}R antagonist WAY 100635 [27]. These results provide the first evidence for a functional role of a specific 5-HT_{2B}R population in the regulatory control of DA neuron activity, and show that the DRN is a key brain region driving the 5-HT_{2B}R-DA system interaction.

Subsequent investigations exploring the mechanisms underlying the facilitatory effect of 5-HT_{2B}R antagonists on DRN 5-HT neurons innervating the mPFC demonstrated that 5-HT_{2B}Rs, in the rat DRN exert a GABA-mediated tonic inhibitory control on 5-HT neurons [38], (Fig. 19.2). This conclusion is supported by several compelling findings. First, it has been shown that intra-DRN perfusion of the GABAAR antagonist bicuculline prevents the increase in DRN and mPFC 5-HT outflow induced by intra-DRN administration of RS 127445 [38]. These results confirm and extend previous observations that peripheral administration of RS 127445 increases the firing rate of DRN 5-HT neurons and 5-HT outflow in the mPFC [27]. Second, the increase in DRN 5-HT outflow induced by the local administration of the selective 5-HT reuptake inhibitor citalopram is potentiated by the intra-DRN administration of RS 127445 only in the absence of bicuculline perfusion into the DRN [38]. Third, in agreement with the above-mentioned in vivo neurochemical findings, in vitro experiments coupling immunohistochemistry to reverse transcription-polymerase chain reaction revealed the presence of 5-HT_{2B}R mRNA on DRN GABAergic interneurons [38].While confirming the DRN as the main site of action of 5-HT_{2B}R antagonists, these results provide the first evidence for the

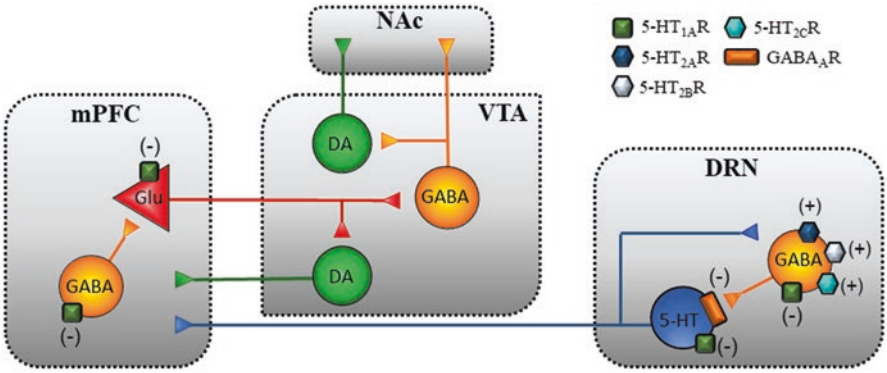

Fig. 19.2 Putative neuronal circuits involved in the opposite effect of serotonin 2B receptor (5-HT_{2B}R) antagonists on dopamine (DA) outflow in the medial prefrontal cortex (mPFC) and the nucleus accumbens (NAc). In the dorsal raphe nucleus (DRN), in addition to the autoinhibitory control exerted by somatodendritic 5-HT_{1A} autoreceptors, 5-HT neurons are regulated by a local negative-feedback circuit involving GABA interneurons. The 5-HT_{2B}R is expressed on these GABA interneurons, together with other post-synaptic 5-HTRs (5-HT_{1A}R, 5-HT_{2A}R and 5-HT_{2C}R), and provides a tonic inhibitory control on 5-HT cells innervating the mPFC *via* $GABA_A$Rs. The 5-HT_{1A}R is expressed in the mPFC by GABA interneurons and pyramidal glutamatergic (Glu) neurons innervating the ventral tegmental area (VTA). In the VTA, Glu afferencies arising from mPFC Glu neurons provide a direct excitatory and GABA-mediated inhibitory control on the mesocortical and mesoaccumbal DA ascending pathways, respectively. Thus, by reducing GABA inhibitory tone, blockade of DRN 5-HT_{2B}Rs leads to increased activity of 5-HT neurons and consequently to increased 5-HT outflow in the DRN and the mPFC. Increased mPFC 5-HT outflow could trigger the stimulation of 5-HT_{1A}Rs expressed by local GABA interneurons. Subsequent disinhibition of mPFC Glu neurons innervating the VTA could respectively stimulate and inhibit the activity of the mesocortical and the mesoaccumbal DA pathways, thereby leading to increased and decreased DA outflow in the mPFC and the NAc, respectively, for details see [26, 27, 38]

location of the 5-HT_{2B}R in a specific cell population in the rat brain, and demonstrate its role in controlling the local negative-feedback loop regulating DRN 5-HT neuron activity via GABA interneurons (see Fig. 19.2), [38–41]. Of note, among the different 5-HTRs located on DRN GABA interneurons (5-HT_{2A}R, 5-HT_{2C}R and 5-HT_{1A}R) and participating in the local control of 5-HT neurons [39–41], the 5-HT_{2B}R is the only one providing a tonic control on 5-HT neurons [38]. From a functional point of view, these findings provide additional information on the mechanisms subsuming the effect of 5-HT_{2B}R antagonists on the mesocorticolimbic DA system, which has been shown to result from their ability to increase the activity of DRN 5-HT neurons projecting to the mPFC [27]. However, these data contrast with recent findings in mice showing that 5-HT_{2B}Rs are located on 5-HT neurons and exert a direct positive control on 5-HT neuron activity [42]. As discussed elsewhere [8, 38], these discrepant findings may result from species related anatomo-functional differences, so additional comparative studies between rats and mice are required to identify possible differences in the brain cellular distribution of the 5-HT_{2B}R.

2.2 5-HT$_{2B}$R Antagonists: Behavioral Data and Therapeutic Potential for the Treatment of Schizophrenia

Altogether, the neurochemical findings discussed above indicate that 5-HT$_{2B}$R antagonists may provide a useful pharmacological tool for treating neuropsychiatric disorders requiring the independent control of ascending DA pathways. In this context, schizophrenia is an emblematic mental illness that could benefit from 5-HT$_{2B}$R antagonist treatment. It is characterized by three main groups of symptoms: positive (i.e. hallucinations, delusions), negative (i.e. social interaction deficits, blunted affect) and cognitive (i.e. working and reference memory deficits, executive function impairments, decreased vigilance) [43–45]. This multimodal symptomatology is classically related to an imbalance in central DA neurotransmission: positive symptoms are thought to result from DA hyperfunction in the NAc, whereas negative and cognitive symptoms might involve DA hypofunction in the FC [45, 46]. The pharmacological treatment of schizophrenia is based on the use of DA-D$_2$ receptor antagonists classified as typical and atypical antipsychotic drugs (APDs) [43]. Although effective in controlling positive symptoms, typical APD such as haloperidol and chlorpromazine are responsible for the occurrence of extrapyramidal side effects (EPS) due to altered striatal DA activity [43, 47]. On the other hand, atypical APDs, of which clozapine is the prototype, display a wider therapeutic spectrum covering positive, negative and cognitive symptoms with a limited propensity to induce EPS [43, 44].

Thus, given their unique DAergic profile of effects, 5-HT$_{2B}$R antagonists should be able to improve all the symptoms of schizophrenia without inducing EPS by restoring normal DA function. This hypothesis has been demonstrated by recent studies in rats assessing their effectiveness in different DA-dependent behavioral models classically used to predict the ability of APDs to alleviate positive [hyperlocomotion induced by the non-competitive N-methyl-D-aspartate receptor antagonist phencyclidine (PCP)] and cognitive [PCP-induced deficit in novel object recognition (NOR) test] symptoms of schizophrenia, as well as their propensity to induce EPS (catalepsy test), [45]. These behavioral tests are known to be related to increased, reduced and altered DA function in the NAc, the mPFC and the striatum, respectively [47–49]. Thus, in line with their differential effects on DA outflow in these brain regions, the 5-HT$_{2B}$R antagonists RS 127445 and LY 266097 have been shown to reduce the hyperlocomotion induced by PCP [26]. This result is consistent with previous findings showing that 5-HT$_{2B}$R blockade reduces amphetamine-induced hyperlocomotion [24], another behavioral model used to investigate the potential of APDs to restore normal accumbal DA function [45]. Furthermore, both 5-HT$_{2B}$R antagonists were able to reverse PCP-induced NOR deficit to a similar extent as clozapine [26]. Finally, unlike haloperidol, neither RS 127445 nor LY 266097 produced a cataleptic state [26].

These findings providing additional support for the therapeutic relevance of 5-HT$_{2B}$R antagonists for treating schizophrenia suggest that these compounds could represent a new class of atypical APDs, given their ideal profile of effects expected

to alleviate cognitive and positive symptoms, without eliciting EPS [8, 26]. However, as discussed elsewhere [8, 26], this proposal has to be confirmed, so additional investigations are required to profile the acute or chronic effects of 5-HT_{2B}R antagonists in a palette of other experimental conditions predictive of therapeutic efficacy or side effects [45, 50]. Their involvement in metabolism, body mass and diabetic disorders, commonly referred to as "metabolic syndrome" [43, 45], as well as their ability to alleviate the negative symptoms of schizophrenia deserve dedicated studies.

In addition to the therapeutic potential of 5-HT_{2B}R antagonists per se, 5-HT_{2B}Rs could contribute to the therapeutic benefit of atypical APDs, many of which (clozapine, amisulpride, asenapine, aripiprazole, cariprazine) display antagonist properties at the 5-HT_{2B}R [51–55] and the DA-D_2R, together with partial agonist properties towards the 5-HT_{1A}R [45, 56]. This hypothesis is supported by the ability of 5-HT_{2B}R blockade to potentiate and decrease haloperidol-induced DA outflow in the mPFC and the NAc, respectively [24, 26], together with the functional role of 5-HT_{1A}R stimulation in the 5-HT_{2B}R-mediated control of DA outflow [27].

Importantly, these conclusions pointing to the potential of 5-HT_{2B}R antagonists for treating schizophrenia diverge from those offered by studies in mice showing that genetic ablation of 5-HT_{2B}Rs generate an antipsychotic-sensitive schizophrenic-like phenotype [29]. As discussed elsewhere [8, 26], in keeping with the role of 5-HT_{2B}Rs in brain maturation [15], developmental neural adaptations triggered by the permanent suppression of this receptor as well as species-related anatomo-functional differences may account for these divergences. Nonetheless, although additional investigations are warranted to clarify this issue, these findings support the role of 5-HT_{2B}Rs in the neurobiology and/or improved treatment of schizophrenia.

3 Conclusions and Perspectives

In conclusion, this chapter provides an updated overview of the important advances in the understanding of the physiological role of the central 5-HT_{2B}R in the control of DA ascending pathways and the anatomo-functional basis underlying this interaction. Specifically, the findings reported herein identify the DRN as a major site of action for the 5-HT_{2B}R-dependent control of DA and 5-HT neuron activity. First, the differential control exerted by 5-HT_{2B}R antagonists on the mesocorticolimbic DA system takes place in the DRN and involves complex polysynaptic cortico-subcortical pathways driven by a functional interplay between DRN 5-HT_{2B}Rs and mPFC 5-HT_{1A}Rs [27]. Second, in the DRN, 5-HT_{2B}Rs are located on GABA interneurons and exert a tonic inhibitory control on 5-HT neurons projecting to the mPFC by participating in the control of the local negative-feedback loop regulating 5-HT neuron activity [38].

From a clinical point of view and in keeping with their unique profile of effects on DA network, the data reported here highlight the therapeutic potential of 5-HT_{2B}R antagonists for the treatment of schizophrenia, a major neuropsychiatric disorder

whose optimal treatment requires the independent control of ascending DA pathways [8, 44, 45].

Additional experiments are warranted to obtain a deeper insight into the pathophysiological role of the 5-HT_{2B}R in the mammalian brain, and to verify the extent to which the contrasting findings observed between rats and mice are related to anatomo-physiological differences between species and/or to brain development-related factors. In addition, further investigations in a larger palette of experimental conditions including long-term treatments are mandatory to confirm the therapeutic potential of 5-HT_{2B}R antagonists for treating schizophrenia [8, 45]. In this context, investigations in advanced genetic models such as conditional 5-HT_{2B}R knock-out animals should be pursued. Finally, these data reported in this chapter provide additional knowledge about the regulation of ascending DA pathways by the central 5-HT system, and highlight the legitimacy of 5-HT_{2B}Rs as key modulators of the activity of the central DA network.

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