Chapter 16
Drugs of Abuse Affecting 5-HT_{2B} Receptors

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Abbreviations

MDA	3,4-methylenedioxyamphetamine
MDMA	3,4-methylenedioxymethamphetamine
CYP	Cytochrome P450
LSD	Lysergic acid diethylamide
NPS	New psychoactive substances
SERT	Serotonin transporter

1 Introduction

A variety of drugs of abuse affect monoaminergic neurotransmission including the serotonergic system. On the one hand, serotonergic stimulants target the plasmalemmal serotonin transporter (SERT), either as blockers such as cocaine or as substrates such as 3,4-methylenedioxymethamphetamine (MDMA) [1–5]; on the other hand, serotonergic psychedelics mediate their mind-altering effects mainly through activation of serotonergic 5-hydroxytryptamine (5-HT) 2A receptors [6–11]. Moreover, several stimulant-type substances interact with serotonergic receptors [2, 12–16] and some psychedelics inhibit transporter-mediated serotonin reuptake [17] in addition to their main action at the 5-HT_{2A} receptor. Besides stimulants and psychedelics, other drug classes such as synthetic cannabinoids and opioids have been shown to interact with serotonin transporers and receptors [18–20] in addition to their main effects at cannabinoid and opioid receptors, respectively. The 5-HT_{2B} receptor is one potential interaction site for serotonergic drugs of abuse. However, the 5-HT_{2B} receptor is not a primary target for serotonergic drugs as its main expression is in peripheral organs such as liver, kidneys, stomach, and gut, and there is

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only limited expression in the brain [21–25]. Nevertheless, it has been associated with pathways that modulate drug abuse and reinforcing effects of stimulants [26–28]. Furthermore, 5-HT_{2B} receptor interactions with drugs of abuse are of interest as receptor activation has been associated with cardiac valvulopathy, resulting in the market removal of several 5-HT_{2B} agonist prescription drugs, including the appetite suppressant fenfluramine [29–32]. The major metabolite of fenfluramine, norfenfluramine (3-trifluoromethylamphetamine), displays higher affinity and efficacy at the 5-HT_{2B} receptor in comparison to the parent compound [32, 33], indicating that it is mainly responsible for fenfluramine-induced cardiac valvulopathy. Even though fenfluramine has structural similarity to amphetamine, it does not share the potent stimulant effects and abuse is therefore rare [34, 35]. However, the chemical structures of fenfluramine and norfenfluramine suggest that drug-induced cardiac valvulopathy is a potentially severe complication to consider for any amphetamine-type drugs of abuse that stimulate serotonin 5-HT_{2B} receptors [36]. This chapter should give a basic overview over the involvement of 5-HT_{2B} receptors in recreational drug action and associated adverse effects such as cardiac valvulopathy. Different stimulant and psychedelic drugs for which activity at the 5-HT_{2B} receptors has been tested will be discussed.

2 Drugs Stimulating 5-HT_{2B} Receptors

Interference with monoaminergic signaling is the main mechanism of action for stimulants and psychedelics [1, 4, 37]. In addition, interactions with monoaminergic targets have been shown for other drug classes, such as opioids [17] or dissociative anesthetics [38, 39]. Compared to other monoaminergic targets such as 5-HT_{2A} or dopamine receptors, relatively little research has focused on the interactions of drugs of abuse with 5-HT_{2B} receptors. Nevertheless, 5-HT_{2B} receptor interactions have been assessed for various stimulant and psychedelic drugs of abuse, including many new psychoactive substances (NPS) [3, 14, 16, 17, 40–45], which are shown in Tables 16.1 and 16.2, respectively.

2.1 5-HT_{2B} Receptor-Mediated Effects of Stimulants

Despite its limited expression in the brain, the 5-HT_{2B} receptor has been shown to contribute to the mechanism of action of stimulants. For instance, it has been demonstrated that selective 5-HT_{2B} receptor antagonism and 5-HT_{2B} receptor knockout reversed MDMA-induced hyperactivity in mice [28]. Furthermore, it has been demonstrated that inhibition and knockout of the 5-HT_{2B} receptors abolished MDMA-induced efflux of serotonin in the nucleus accumbens and ventral tegmental area [28]. The authors of that study hypothesized that presynaptic 5-HT_{2B} receptors modulate MDMA-induced 5-HT release in serotoninergic raphe neurons. In

Table 16.1 5-HT$_{2B}$ receptor interactions of stimulant drugs of abuse

Drugs	5-HT$_{2B}$ receptor activity			Reference
	K_i [μM]	EC_{50} [μM]	E_{max} [%]	
Aminoindanes				
5-Iodo-2-aminoindane	0.07			Iversen et al. [43]
MDAI	>5			Iversen et al. [43]
MMAI		>10		Luethi et al. [16]
N-methyl-2-AI		>20		Luethi et al. [16]
Benzofurans				
5-APB		0.28 ± 0.12	61 ± 17	Rickli et al. [14]
	0.014	0.015 ± 0.001	92 ± 1	Iversen et al. [43]
5-APDB		1.2 ± 0.6	50 ± 21	Rickli et al. [14]
6-APB		0.14 ± 0.06	70 ± 9	Rickli et al. [14]
	0.004	0.0041 ± 0.003	93 ± 1	Iversen et al. [43]
6-APDB		0.12 ± 0.03	66 ± 17	Rickli et al. [14]
5-MAPDB		>20		Rickli et al. [14]
4-APB		1.0 ± 0.5	38 ± 16	Rickli et al. [14]
7-APB		0.28 ± 0.52	52 ± 17	Rickli et al. [14]
5-EAPB		>20		Rickli et al. [14]
Cathinones				
α–PVP		>20		Rickli et al. [15]
β-Keto-MDA		>20		Rickli et al. [15]
1-Naphyrone	0.4			Iversen et al. [43]
2,3-DMMC		>10		Luethi et al. [16]
2,4-DMMC		>10		Luethi et al. [16]
3-MMC		>10		Luethi et al. [16]
3,4-DMMC		>20		Luethi et al. [16]
BMDP	1.7			Iversen et al. [43]
4–Bromomethcathinone		>20		Rickli et al. [15]
4–Ethylmethcathinone		>20		Rickli et al. [15]
4–Fluoromethcathinone		>20		Rickli et al. [15]
4–Methylmethcathinone		>20		Rickli et al. [15]
Benzedrone	>5			Iversen et al. [43]
MDPPP		>20		Rickli et al. [15]
MDPBP		>20		Rickli et al. [15]
MDPV		>20		Rickli et al. [15]
Mephedrone		>10		Luethi et al. [16]
	0.74			Iversen et al. [43]
Methcathinone		>20		Rickli et al. [15]
Methylethcathinone	>5			Iversen et al. [43]
Methylone		>10		Luethi et al. [5]
Naphyrone	>5			Iversen et al. [43]
		>20		Rickli et al. [15]
Pyrovalerone		>20		Rickli et al. [15]

(continued)

Table 16.1 (continued)

Drugs	5-HT_{2B} receptor activity			Reference
	K_i [μM]	EC_{50} [μM]	E_{max} [%]	
Phenethylamines				
4-Fluoroephedrine		>20		Rickli et al. [15]
4–Fluoroamphetamine		11.4 ± 4.6	49 ± 15	Rickli et al. [15]
4–Fluoromethamphetamine		>20		Rickli et al. [15]
4-Methylamphetamine		0.86 ± 0.38	54 ± 8	Luethi et al. [16]
D-Amphetamine		9.4	8 ± 2	Rickli et al. [15]
D-Methamphetamine		>20		Rickli et al. [15]
Ephedrine		>20		Rickli et al. [15]
MDA		0.85 ± 0.11	52 ± 12	Rickli et al. [14]
MDMA		>20		Rickli et al. [14]
Piperidines				
4-Fluoromethylphenidate		>10		Luethi et al. [3]
4-Methylmethylphenidate		>10		Luethi et al. [3]
Ethylnaphthidate		>10		Luethi et al. [3]
Ethylphenidate		>20		Luethi et al. [3]
Methylphenidate		>10		Luethi et al. [3]
Propylphenidate		>10		Luethi et al. [3]
Other				
4,4′-DMAR		>10		Maier et al. [44]
5-IT		1.5 ± 0.6	36 ± 5	Luethi et al. [16]
Cocaine		>10		Luethi et al. [3]
Dimethylamylamine	>5			Iversen et al. [43]
Methiopropamine	3.9			Iversen et al. [43]
Methylmorphenate		>10		Luethi et al. [3]
Modafinil		>10		Luethi et al. [3]

addition, inhibition and knockout of the 5-HT_{2B} receptor led to an absence of dopamine efflux in the nucleus accumbens, which may have been the result of a lack of activation of postsynaptic serotonin receptors [28]. In a follow-up study, MDMA was shown to induce locomotor sensitization and conditioned place preference in wildtype but not in 5-HT_{2B} receptor knockout or 5-HT_{2B} receptor antagonized mice, underscoring the possible role of 5-HT_{2B} receptors in the reinforcing effects of serotonergic stimulants [27]. However, an increased dose of MDMA induced behavioral effects in all mouse models, potentially due to direct and therefore 5-HT_{2B} receptor independent interaction of MDMA with the dopamine transporter [27]. This assumption is supported by in vitro studies showing serotonin transporter inhibition at low and dopamine transporter inhibition by MDMA at high concentrations [5, 12].

Table 16.2 5-HT$_{2B}$ receptor interactions of psychedelic drugs of abuse

Drugs	5-HT$_{2B}$ receptor activity			Reference
	K_i [μM]	EC_{50} [μM]	E_{max} [%]	
Benzodifuran				
2C-B-FLY		0.040	56	Rickli et al. [14]
Ergoline				
LSD	0.00057	0.0031	23	Eshleman et al. [42]
		12	71	Rickli et al. [40]
Phenethylamines				
25B-NBOMe		0.01	19	Rickli et al. [40]
25C-NBOMe		0.10	16	Rickli et al. [40]
25D-NBOMe	0.0021	0.032	48	Eshleman et al. [42]
		0.10	22	Rickli et al. [40]
25E-NBOMe	0.0011	0.024	49	Eshleman et al. [42]
		0.06	26	Rickli et al. [40]
25H-NBOMe	0.063	0.46	38	Eshleman et al. [42]
		0.34	11	Rickli et al. [40]
25I-NBOMe	0.0019	0.11	21	Eshleman et al. [42]
		0.13	32	Rickli et al. [40]
25N-NBOMe	0.0087	0.047	58	Eshleman et al. [42]
		0.07	26	Rickli et al. [40]
25P-NBOMe		0.17	23	Rickli et al. [40]
25T2-NBOMe		0.04	31	Rickli et al. [40]
25T4-NBOMe		0.20	27	Rickli et al. [40]
25T7-NBOMe		0.31	14	Rickli et al. [40]
2C-B		0.13	89	Rickli et al. [40]
		0.075	52	Luethi et al. [41]
2C-BI-1		>10		Luethi et al. [45]
2C-BI-2		>10		Luethi et al. [45]
2C-BI-3		>10		Luethi et al. [45]
2C-BI-4		>10		Luethi et al. [45]
2C-BI-5		>10		Luethi et al. [45]
2C-BI-7		>10		Luethi et al. [45]
2C-BI-8		0.22		Luethi et al. [45]
2C-BI-10		>10		Luethi et al. [45]
2C-BI-11		>10		Luethi et al. [45]
2C-BI-12		0.20		Luethi et al. [45]
2C-C		0.28	81	Rickli et al. [40]
2C-D		0.23	77	Rickli et al. [40]
2C-E		0.19	66	Rickli et al. [40]
2C-H		6.2	46	Rickli et al. [40]
2C-I		0.15	70	Rickli et al. [40]
2C-N		0.73	74	Rickli et al. [40]
2C-P		0.13	72	Rickli et al. [40]

(continued)

Table 16.2 (continued)

Drugs	5-HT$_{2B}$ receptor activity			Reference
	K_i [μM]	EC_{50} [μM]	E_{max} [%]	
2C-T-1		0.057	58	Luethi et al. [41]
2C-T-2		0.13	75	Rickli et al. [40]
2C-T-3		0.044	28	Luethi et al. [41]
2C-T-4		0.16	68	Rickli et al. [40]
		0.063	75	Luethi et al. [41]
2C-T-7		0.35	45	Rickli et al. [40]
		0.052	46	Luethi et al. [41]
2C-T-16		0.047	36	Luethi et al. [41]
2C-T-19		0.369	40	Luethi et al. [41]
2C-T-21.5		0.182	40	Luethi et al. [41]
2C-T-22		0.11	35	Luethi et al. [41]
2C-T-25		0.108	32	Luethi et al. [41]
2C-T-27		>10		Luethi et al. [41]
2C-T-28		0.081	34	Luethi et al. [41]
2C-T-30		0.051	61	Luethi et al. [41]
2C-T-31		3.3	44	Luethi et al. [41]
2C-T-33		>10		Luethi et al. [41]
Biscaline		>10		Luethi et al. [45]
DMA	1			Nelson et al. [46]
DOAc	0.31			Nelson et al., [46]
DOB	0.027			Nelson et al. [46]
DOBz	0.035			Nelson et al. [46]
DOC	0.032			Nelson et al. [46]
DOCN	0.77			Nelson et al. [46]
DOF	0.23			Nelson et al. [46]
DOHx	0.03			Nelson et al. [46]
DOI	0.02			Nelson et al. [46]
DOM	0.041	0.15	96	Eshleman et al. [42]
DON	0.17			Nelson et al. [46]
DOPR	0.054			Nelson et al. [46]
DOTB	0.025			Nelson et al. [46]
MEM	0.76			Nelson et al. [46]
Mescaline		>20		Rickli et al. [40]
Mescaline-NBOMe		>20		Rickli et al. [40]
TMA	0.31			Nelson et al. [46]
Tryptamines				
4-OH-DiPT		0.460	55	Rickli et al. [17]
4-OH-MET		>20		Rickli et al. [17]
5-MeO-AMT		0.004	104	Rickli et al. [17]
5-MeO-MiPT		1.5	12	Rickli et al. [17]
DiPT		1.0	103	Rickli et al. [17]

(continued)

Table 16.2 (continued)

Drugs	5-HT$_{2B}$ receptor activity			Reference
	K_i [μM]	EC_{50} [μM]	E_{max} [%]	
DMT		3.4	19	Rickli et al. [17]
Psilocin		>20		Rickli et al. [17]

2.2 Stimulant-Induced Cardiac Valvulopathy

5-HT$_{2B}$ receptors are, among others, expressed in cardiovascular tissues [47] and their activation potentially leads to cardiac valvulopathy [29, 48–50]. Therefore, cardiac valvulopathy is a concern to consider for drugs that increase plasma 5-HT levels, directly activate the 5-HT$_{2B}$ receptor, or both. In fact, several prescription drugs have previously been removed from the market due to their potential to induce cardiac valvulopathy in patients [29–32]. However, serotonergic drugs of abuse are typically not associated with a high abuse liability [51–54] and are therefore mostly used sporadically and not on a regular basis. This raises the question of the relevance of 5-HT$_{2B}$-mediated cardiac valvulopathy in recreational drug use. The regular use of the serotonergic drug MDMA has been associated with mild to moderate valvular heart disease, based on a case control study [55]. In this study, 8 of 29 regular MDMA users displayed abnormal echocardiographic results compared with none of the control group. The average use of the MDMA users was very high and described to have consisted of 3.6 MDMA tablets per week with an average duration of drug use of 6.1 years [55]. This underscores the assumption that in particular heavy recreational use of serotonergic stimulants may induce cardiac valvulopathy. Besides these clinical findings from a case control study, 5-HT$_{2B}$ receptor-mediated proliferation of cardiac valvular interstitial cells induced by MDMA has also been demonstrated in vitro [56].

2.3 Stimulants Acting on 5-HT$_{2B}$ Receptors

Table 16.1 shows an overview of 5-HT$_{2B}$ receptor binding and activation potency values for various stimulants, assessed in different studies. Notably, in a study by Rickli and colleagues, MDMA did not activate the 5-HT$_{2B}$ receptor in the functional assay at investigated concentrations (EC_{50} > 20 μM); however, 3,4-methylenedioxyamphetamine (MDA), the main psychoactive *N*-demethylated phase I metabolite of MDMA, potently activated the receptor at submicromolar concentrations [14]. This suggests that the metabolite MDA rather than MDMA itself may lead to valvulopathy and that there could be a significant metabolic contribution to MDMA-induced effects and adverse effect. MDA formation is mainly mediated by cytochrome P450 (CYP) 2B6, with additional contributions from CYP1A2, CYP2C19, and CYP2D6 [57–60]. Therefore, genetic polymorphisms in the genes coding for these enzymes could potentially influence the 5-HT$_{2B}$ receptor-

mediated adverse effects in MDMA users. Notably, however, the sensitivity of the calcium mobilization assays used to determine the functional 5-HT_{2B} receptor activity and the inter-correlation of data obtained with different assays is not clearly understood. For example, only poor correlation between 5-HT_{2A} receptor activation and effects for psychedelics has been observed in several studies [61–63], whereas binding affinity at this receptor was a good predictor of the clinical potency of psychedelics [63]. Thus, the available in vitro 5-HT_{2B} receptor functional data may not be a good predictor of cardiac valvulopathy risk in vivo.

Besides MDA, several benzofuran NPS potently activated the 5-HT_{2B} receptor at submicromolar concentrations [14, 43]. Therefore, as shown for MDMA in vivo [27, 28], 5-HT_{2B} receptor activation may directly contribute to the effects of these novel drugs of abuse. Furthermore, regular and heavy use of benzofuran NPS may potentially result in heart damage; however, benzofurans have so far not been linked to any case of cardiac valvulopathy. Only a few other non-benzofuran stimulants displayed potent agonism at the 5-HT_{2B} receptor, such as 4-methylamphetamine (4-MA) or 5-(2-aminopropyl)indole (5-IT). The amphetamine derivative 4-MA was originally developed as an appetite suppressant but was never marketed [64]. Its recent reappearance on the illicit drug market has almost exclusively been limited to being a contaminant in street amphetamine samples [65]. The mixture of amphetamine and 4-MA has been linked to extreme hyperthermia and several fatalities, likely explained by the high difference in dopaminergic *vs.* serotonergic activity of the two substances [15, 16, 65]. The indole derivative 5-IT is a highly potent stimulant NPS that has been associated with various fatal intoxications in recent years [16, 66–69]. Furthermore, Iversen and colleagues reported submicromolar binding affinities at the 5-HT_{2B} receptor for the NPS 5-iodo-aminoindane, mephedrone, naphyrone, 1-naphyrone, and methylenedioxy-aminotetralin [43]. Mephedrone is not a potent agonist at the receptor [16] and no functional activity has been determined for the other substances. Therefore, it is not certain whether these substances act as agonists at the 5-HT_{2B} receptor.

2.4 5-HT_{2B} Receptor-Mediated Effects of Psychedelics

The subjective effects of psychedelics are primarily mediated by 5-HT_{2A} receptor activation [9–11, 70–72]. In addition, correlation between receptor activation and psychedelic effect potencies have been reported for the 5-HT_{2B} [46] and 5-HT_{2C} receptors [6, 7, 63], which is not surprising given that 5-HT_2 receptors share significant sequence homology [73]. However, there is currently no clear consensus on the importance of the 5-HT_{2B} and 5-HT_{2C} receptors in the mechanism of action of psychedelics.

2.5 *Psychedelics Acting on 5-HT$_{2B}$ Receptors*

5-HT$_{2B}$ receptor interactions for various psychedelics are listed in Table 16.2. For most of the substances, only receptor activation potency but no receptor affinity values have been reported. Most phenethylamine and tryptamine psychedelics activated the 5-HT$_{2B}$ receptor at submicromolar or low micromolar concentrations. As reported for the 5-HT$_{2A}$ receptor, no correlation between 5-HT$_{2B}$ receptor activation and clinical potency of psychedelic was observed in a study comparing receptor activation potencies of a considerable amount of psychedelics with their reported human doses [63]. Eshleman and colleagues reported 5-HT$_2$ receptor affinities as well as functional activity for six phenethylamine psychedelics and lysergic acid diethylamide (LSD) [42]. All compounds displayed highest binding affinity and activation potency for the 5-HT$_{2A}$ receptors; nevertheless, for several substances, high affinity and activation potency (K_i and EC_{50} < 100 nM) was observed at the 5-HT$_{2B}$ receptor [42]. A remarkable difference in receptor activation in two different functional assays has been reported for LSD. Whereas an EC_{50} of 12 μM has been measured with a calcium mobilization assay [40], an EC_{50} of 3 nM has been reported when a stimulation of inositol monophosphate (IP-1) formation assay was used [42]. To gain a clearer picture of the involvement of 5-HT$_{2B}$ receptors in the action of psychedelics, more in vitro and in vivo research is needed.

3 Conclusion

Several stimulant and psychedelic drugs of abuse activate the 5-HT$_{2B}$ receptor at pharmacologically relevant concentrations. Animal studies with MDMA suggest that the 5-HT$_{2B}$ receptor contributes to the effects of serotonergic stimulants, possibly by 5-HT-dependent regulation of dopamine release. Furthermore, stimulants that activate the 5-HT$_{2B}$ receptor may put regular and heavy users at risk of cardiac valvulopathy. The main classes of stimulant drugs of abuse that interact with 5-HT$_{2B}$ receptors are benzofurans and amphetamines with a distinct serotonergic *vs.* dopaminergic activity.

In addition to stimulants, various phenethylamine and tryptamine psychedelics activate the 5-HT$_{2B}$ receptor. However, the role of 5-HT$_{2B}$ receptor activation in the mechanism of action of psychedelic remains unclear. As psychedelics do not lead to dependence and are mostly not used on a regular basis, cardiac valvulopathy is likely not a risk to consider for users.

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