Pharmacological Reports
2005, 57, 685–700
ISSN 1734-1140

Review

The serotonergic system and its role in cocaine addiction

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Abstract:
Cocaine is an alkaloid with psychostimulant action and high addictive potential. It possesses high affinity for the transporters of dopamine, serotonin (5-HT) and noradrenaline, and blocks reuptake of the above-mentioned monoamines. The present review summarized the contribution of 5-HT neurotransmitter system to rewarding and aversive properties of cocaine, to cocaine withdrawal and its long-term abuse. The present state of knowledge of 5-HT neurotransmission justifies the opinion that pharmacological manipulation in the 5-HT system may efficiently counteract the effects of cocaine withdrawal and prevent reinstatement of its abuse.

Key words:
cocaine, serotonin (5-HT), serotonin system, serotonin ligands, addiction, reward, relapse, withdrawal

Abbreviations: 5-HT – serotonin, L-5-HTP – L-5-hydroxytryptophan, DA – dopamine, DAT – dopamine transporter, NE – noradrenaline, NET – noradrenaline transporter, SERT – serotonin transporter, SSRI – selective serotonin reuptake inhibitor

Introduction

Cocaine is an alkaloid with psychostimulant action, which possesses high addictive potential. It occurs in leaves of coca (*Erythroxylon coca*) native to tropical forests of South America, mostly Peru and Bolivia. Its leaves have been chewed for their stimulant properties by mountaineers from the Andes since long ago. Coca was brought to Europe in the 16th century but cocaine did not become a very popular stimulant, easily available on the European market before the turn of 19th century. Due to the widespread cocaine use, its detrimental effects got to be conspicuous and its highly addictive potential incited particular concern [81]. Addiction produced by cocaine is a serious medical and social problem of increasing significance also in Poland in the last years [69, 95]. For these reasons, many research laboratories worldwide are engaged in the search for efficient treatment of cocaine addiction, and intensive studies are carried out aimed to explain neurobiological bases of its development [39, 59, 114].

Dopamine (DA) neurotransmission and indirect activation of DA receptors have been established as a central mediator of the cocaine responses [114],

however, serotonin (5-HT) also fulfills an important role in functional cocaine effects [29–31, 100, 110].

Serotonergic (5-HT) neurotransmission in the central nervous system

Serotonin (5-hydroxytryptamine, 5-HT) belongs to evolutionarily the oldest biogenic amines playing the role of neurotransmitter in the central nervous system. It was isolated from mammalian organism in 1946 and from the brain 7 years later. 5-HT is formed in serotonergic neuronal cell bodies from L-tryptophan transformed to L-5-hydroxytryptophan (L-5-HTP) by enzymatic reaction catalyzed by tryptophan hydroxylase. Then, the enzyme aromatic L-amino acid decarboxylase converts L-5-HTP to 5-HT. The neurotransmitter is taken up from neuronal cytoplasm to synaptic vesicles by vesicular monoamine transporter and stored therein. 5-HT is released from the synaptic vesicles to synaptic space by Ca^{2+}-dependent process, while its reuptake from synaptic space to 5-HT neurons is carried out by membrane 5-HT transporter occurring in axons, bodies and/or dendrites of 5-HT neurons. 5-HT is catabolized by mitochondrial type A monoamine oxidase. First, 5-HT is oxidized to aldehyde and then to 5-hydroxyindoleacetic acid (Fig. 1). 5-HT content in the central nervous system constitutes only 1–2% of the whole pool of this monoamine

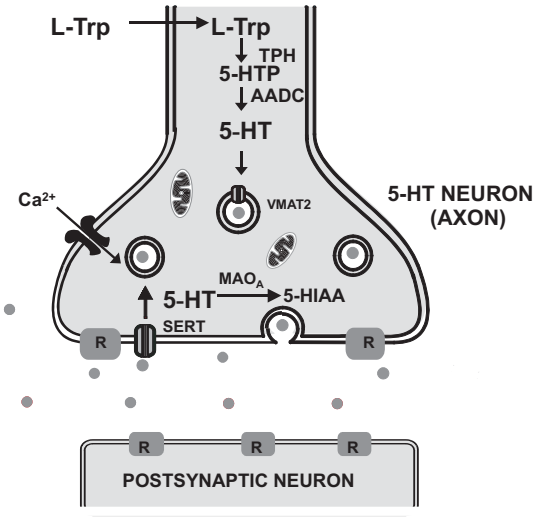

Fig.1. Synthesis and metabolism of 5-HT. Abbreviations: 5-HIAA – 5-hydroxyindoleacetic acid, 5-HT – serotonin, 5-HTP – 5-hydroxytryptophan, AADC – L-aromatic amino acid decarboxylase, L-Trp – L-tryptophan, MAO_A – monoamine oxidase (type A), R – receptor, SERT – 5-HT transporter, TPH – tryptophan hydroxylase, VMAT2 – vesicular monoamine transporter (type 2)

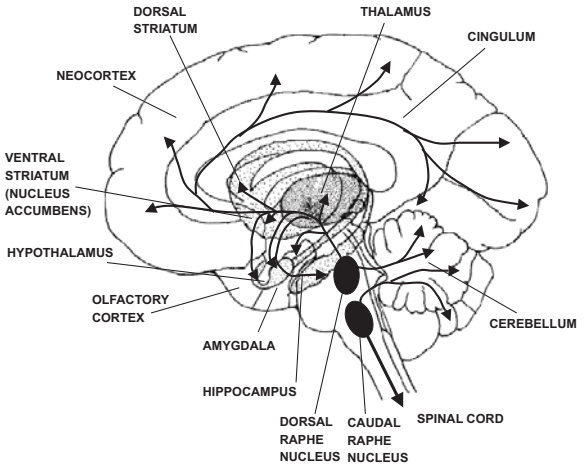

Fig. 2. 5-HT pathways

in the organism. It does not cross blood-brain barrier, so it has to be synthesized locally in the brain. The main assemblages of 5-HT-synthesizing neurons are located in the brainstem. In the brain, 5-HT cells form 9 groups, so-called raphe nuclei, whose relatively small number of neurons by numerous descending and ascending projections innervate almost all brain areas (Fig. 2). For this reason, 5-HT fulfills a significant role in the regulation of many vital functions of the organism (sleep, circadian rhythm, emotional, feeding, cognitive and reproductive behaviors, thermoregulation, nociceptive transmission, motor, endocrine, cardiovascular and respiratory functions, and intestinal peristalsis), and in etiology of the related pathological states (depression, mania, anxiety, schizophrenia, autism, migraine and hypertension) [5, 45].

5-HT acts *via* its receptors. Based on structural (amino acid sequence), biochemical (postreceptor mechanisms of signal transduction) and pharmacological differences, 5-HT receptors were classified into 7 classes and 16 different subtypes (Tab. 1). A majority of these receptors belong to the metabotropic receptor family (transmitting signals through G proteins), except for 5-HT_3 (5-HT_{3A}, 5-HT_{3B} and 5-HT_{3C}) receptors included into the ionotropic receptor family. 5-HT_1 (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}) receptors inhibit adenylate cyclase, 5-HT_2 (5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}) receptors stimulate phospholipase C, 5-HT_4, 5-HT_6 and 5-HT_7 receptors stimulate adenylate cyclase, while mechanism of signal transduction *via* 5-HT_5 (5-HT_{5A} and 5-HT_{5B}) has not been satisfactorily defined so far [5, 6, 9, 21, 35, 45, 63, 64, 70, 76, 91, 104, 113].

Tab. 1. Structure, distribution, functional effects and pharmacology of 5-HT receptors [5, 6, 9, 21, 35, 45, 63, 64, 70, 76, 91, 104, 113]

5-HT$_1$ RECEPTOR FAMILY		
5-HT$_{1A}$ Receptor	Gene/chromosomal localization in humans	5q11.1-13
	Protein structure	421-422 amino acids
	Distribution in the CNS anatomical neuronal	 hippocampus, cingulate and entorhinal cortices, lateral septum, mesencephalic raphe nuclei autoreceptors (soma and dendrities of 5-HT neurons) heteroreceptors (in GLU, ACh, GABA and DA neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 $G_{i/o}$/inhibition of adenylate cyclase activity and cAMP formation, opening of K^+ channels neuronal hyperpolarization facilitation of ACh and NE release; drop in 5-HT and GLU release facilitation of CRH, ACTH and cortisol secretion; drop in growth hormone secretion emotional behavior (anxiolysis), motor behavior (flat body posture, forepaw treading, fail flick, lower lip retraction, locomotor activation), discriminative stimulus, sexual behavior, hyperphagia, hypothermia, pain perception
	Ligands: agonists partial agonists antagonists	 8-OH-DPAT, 8-OH-PIPAT, BP 554, S 14506 BMY 7378, buspirone, gepirone, ipsapirone, MDL 73005EF, NAN-190, SDZ 216525, WAY 100135 NAD 299, p-MPPI, WAY 100635
5-HT$_{1B}$ Receptor	Gene/chromosomal localization in humans	6q13
	Protein structure	386-390 amino acids
	Distribution in the CNS anatomical neuronal	 substantia nigra, ventral tegmental area, globus pallidus, striatum, hypothalamus, hippocampus, frontal cortex autoreceptors (terminals of 5-HT neurons) heteroreceptors (in GABA, ACh, DA and GLU neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 $G_{i/o}$/inhibition of adenylate cyclase activity and cAMP formation inhibition of evoked synaptic potentials facilitation of DA release; drop in 5-HT, GLU, GABA and NE release; modulation of ACh release facilitation of prolactin, ACTH, cortisol and renin secretion emotional behavior (antiaggressive properties), motor behavior (locomotor hyperactivation; rotation, myoclonic jerks), discriminative stimulus, sexual behavior, hypophagia, pain perception, hypothermia
	Ligands: agonists antagonists	 CGS 12066B, CP 94253, CP 93129, donitriptan, GR 46611, RU 24969, rizatriptan, RU 24969, SKF 99101H GR 55562, GR 127935, NAS-181, SB 216641, SB 224289
5-HT$_{1D}$ Receptor	Gene/chromosomal localization in humans	1p34.3-36.3
	Protein structure	374-377 amino acids
	Distribution in the CNS anatomical neuronal	 substantia nigra, globus pallidus, striatum, olfactory cortex, hippocampus, periaqueductal grey, dorsal raphe nucleus autoreceptors (soma, dendrities and terminals of 5-HT neurons) heteroreceptors (in GABA, GLU and ACh neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 $G_{i/o}$/inhibition of adenylate cyclase activity and cAMP formation inhibition of evoked synaptic potentials drop in 5-HT, GLU, GABA and ACh release drop in ACTH, cortisol and prolactin secretion pain perception
	Ligands: agonists antagonists	 GR 46611, L 694247, PNU 109291, PNU 142633 BRL 15572

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Tab. 1. Structure, distribution, functional effects and pharmacology of 5-HT receptors [5, 6, 9, 21, 35, 45, 63, 64, 70, 76, 91, 104, 113] – continued from the previous page

5-HT$_{1E}$ Receptor	Gene/chromosomal localization in humans	6q14-15
	Protein structure	365 amino acids
	Distribution in the CNS anatomical neuronal	 frontal and entorhinal cortices, striatum, claustrum, hippocampus, amygdala heteroreceptors (?)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 $G_{i/o}$/inhibition of adenylate cyclase activity and cAMP formation ? ? ? ?
	Ligands: agonists antagonists	 ? ?
5-HT$_{1F}$ Receptor	Gene/chromosomal localization in humans	3p11-14.1
	Protein structure	366 amino acids
	Distribution in the CNS anatomical neuronal	 hippocampus, cingulate and entorhinal cortices, claustrum, caudate nucleus, dorsal raphe nucleus autoreceptors (?)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 $G_{i/o}$/inhibition of adenylate cyclase activity and cAMP formation neuronal hyperpolarization ? ? pain perception
	Ligands: agonists antagonists	 LY 334370, LY 334 864, naratriptan, rizatriptan, sumatriptan, zolmitriptan ?
5-HT$_2$ RECEPTOR FAMILY		
5-HT$_{2A}$ Receptor	Gene/chromosomal localization in humans	13q14-21
	Protein structure	471 amino acids
	Distribution in the CNS anatomical neuronal	 neocortex, entorhinal and pyriform cortices, claustrum, olfactory tubercle, hippocampus, nucleus accumbens, caudate nucleus, ventral tegmental area, hypothalamus heteroreceptors (in DA, GABA, GLU and ACh neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 $G_{q/11}$/enhancement of phospholipase C activity, inositol phosphates and intracellular Ca^{2+} accumulation neuronal depolarization facilitation of DA, GABA and GLU release; drop in NE release facilitation of oxytocin, renin, prolactin, ACTH and cortisol secretion motor behavior (head twitches, wet dog shakes), discriminative stimulus, hyperthermia, pain perception
	Ligands: agonists antagonists	 DOI, DOM ACP 103, AR 116081, cinanserin, ketanserin, M100907, R 96544, SR 46349B

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Tab. 1. Structure, distribution, functional effects and pharmacology of 5-HT receptors [5, 6, 9, 21, 35, 45, 63, 64, 70, 76, 91, 104, 113] – continued from the previous page

5-HT$_{2B}$ Receptor	Gene/chromosomal localization in humans	2q36.3-37.1
	Protein structure	479-504 amino acids
	Distribution in the CNS anatomical neuronal	 cerebellum, septum, hypothalamus, amygdala heteroreceptor (?)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 $G_{q/11}$/enhancement of phospholipase C activity, inositol phosphates and intracellular Ca^{2+} accumulation neuronal depolarization? ? ? motor behavior (grooming), emotional behavior (anxiolysis), hyperphagia, pain perception
	Ligands: agonists antagonists	 BW 723C86 EGIS-7625, LY 23728, LY 266097, LY 287375, RS 127445, SB 200646, SB 204741, SB 215505
5-HT$_{2C}$ Receptor	Gene/chromosomal localization in humans	Xq24
	Protein structure	458-460 amino acids; 14 functional isoforms (editing of mRNA)
	Distribution in the CNS anatomical neuronal	 choroid plexus, olfactory nucleus, pyriform, cingulate and retrospinal cortices, nucleus accumbens, hippocampus, amygdala, striatum, substantia nigra heteroreceptors (in GABA and GLU neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 $G_{q/11}$/enhancement of phospholipase C activity, inositol phosphates and intracellular Ca^{2+} accumulation neuronal depolarization fall in NE and DA release facilitation of prolactin and ACTH secretion motor behavior (hypolocomotion, oral dyskinesis), discriminative stimulus, emotional behavior (anxiogenesis), sexual behavior (penile erection), pain perception, thermoregulation
	Ligands: agonists partial agonists antagonists	 mCPP, MK 212, RO 60-0175, WAY 161503, WAY 163909 IL 639, PNU 22394 RS 102221, SB 242084, SDZ SER-082
5-HT$_3$ RECEPTOR FAMILY		
5-HT$_3$ Receptor	Gene/chromosomal localization in humans	11q23.1-23.2
	Protein structure	487 amino acids (5-HT$_{3A}$); 5 subunits of 5-HT$_3$ receptor: 5-HT$_{3A}$ (4 splice variants), 5-HT$_{3B}$, 5-HT$_{3C}$, 5-HT$_{3D}$, 5-HT$_{3E}$
	Distribution in the CNS anatomical neuronal	 5-HT$_{3A}$: dorsal vagal complex, hippocampus, amygdala, caudate nucleus, cerebral cortex 5-HT$_{3B}$: hippocampus, amygdala, caudate nucleus heteroreceptors (in GABA, ACh and GLU) neurons
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 opening of Na^+, Ca^{2+}, K^+ channels fast neuronal depolarization facilitation of 5-HT, cholecystokinin, DA and GABA release; drop in GLU release; modulation of ACh release facilitation of ACTH and prolactin secretion emotional behavior (anxiogenesis), psychosis, motor behavior (contralateral turning), discriminative stimulus, pain perception, cognition (dysfunction), nausea and vomiting
	Ligands: agonists antagonists	 2-methyl-5-HT, phenylbiguanide, m-chlorophenylbiquanide, SR 57227 bemesetron, dolasetron, granisetron, itasetron, ondansetron, zatosetron, Y 25130

Table 1 continued on the next page

Tab. 1. Structure, distribution, functional effects and pharmacology of 5-HT receptors [5, 6, 9, 21, 35, 45, 63, 64, 70, 76, 91, 104, 113] – continued from the previous page

5-HT$_4$ RECEPTOR FAMILY		
5-HT$_4$ Receptor	Gene/chromosomal localization in humans	5q31-33
	Protein structure	387-406 amino acids; 9 splice variants (5-HT$_{4A}$, 5-HT$_{4B}$, 5-HT$_{4C}$, 5-HT$_{4D}$, 5-HT$_{4E}$, 5-HT$_{4F}$, 5-HT$_{4G}$, 5-HT$_{4H}$, 5-HT$_{4HB}$)
	Distribution in the CNS anatomical neuronal	 5-HT$_{4A}$: striatum 5-HT$_{4B}$, 5-HT$_{4C}$: hippocampus, cerebral cortex, substantia nigra, ventral tegmental area, striatum 5-HT$_{4D}$: only in the gut heteroreceptor (in ACh, GLU and GABA neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 G_S/enhancement of adenylate cyclase activity and cAMP formation neuronal depolarization (inhibition of slow after-hyperpolarization) facilitation of 5-HT, DA, ACh and GABA release facilitation of ACTH and cortisol secretion emotional behavior (anxiogenesis), cognition (enhancement)
	Ligands: agonists partial agonists antagonists	 BIMU 1, BIMU 8, cisaprid, LS 650155, RS 17017, RS 67506, ML 10302 RS 67333, RS 67506 GR 113808, GR 125487, LY 353433, RS 23597-190, RS 67532, SB 204070, SB 203186
5-HT$_5$ RECEPTOR FAMILY		
5-HT$_{5A}$ Receptor	Gene/chromosomal localization in humans	7q36
	Protein structure	357 amino acids
	Distribution in the CNS anatomical neuronal	 hippocampus, cerebral cortex, thalamus, striatum, hypothalamus, pons, medulla, habenula autoreceptor (?) heteroreceptor (in GABA neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 ? ? ? ? motor behavior (hypoactivation)
	Ligands: agonists antagonists	 ? ?
5-HT$_{5B}$ Receptor	Gene/chromosomal localization in humans	2q11-13
	Protein structure	370-371 amino acids
	Distribution in the CNS anatomical neuronal	 hippocampus, habenula, dorsal raphe nucleus heteroreceptor (?)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 ? ? ? ? ?
	Ligands: agonists antagonists	 ? ?

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Tab. 1. Structure, distribution, functional effects and pharmacology of 5-HT receptors [5, 6, 9, 21, 35, 45, 63, 64, 70, 76, 91, 104, 113] – continued from the previous page

5-HT$_6$ RECEPTOR FAMILY		
5-HT$_6$ Receptor	Gene/chromosomal localization in humans	1p35-36
	Protein structure	438-440 amino acids; 2 splice variants
	Distribution in the CNS anatomical neuronal	 hippocampus, cerebral cortex, nucleus accumbens, caudate nucleus, olfactory tubercle, hypothalamus, ventral tegmental area heteroreceptor (in ACh, GLU and GABA neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 G_S/enhancement of adenylate cyclase activity and cAMP formation neuronal depolarization facilitation of 5-HT, DA and GABA release; fall in ACh release ? motor behavior (yawning, stretching), emotional behavior (anxiogenesis), cognition, food intake
	Ligands: agonists antagonists	 ? RO 04-6790, RO 630563, SB 258585, SB 271046, SB 357134
5-HT$_7$ RECEPTOR FAMILY		
5-HT$_7$ Receptor	Gene/chromosomal localization in humans	10q23.3-24.3
	Protein structure	445-448 amino acids; 4 splice variants: 5-HT$_{7A}$, 5-HT$_{7B}$, 5-HT$_{7C}$, 5-HT$_{7D}$ 5-HT$_{7A,B,C}$: in rats 5-HT$_{7A,B,D}$: in humans
	Distribution in the CNS anatomical neuronal	 hippocampus, thalamus, hypothalamus, suprachiasmatic nucleus, cerebral cortex, amygdala heteroreceptor (in GABA and GLU neurons)
	Function: coupling/signaling electrophysiological neurochemical neuroendocrine behavioral	 G_S/enhancement of adenylate cyclase activity and cAMP formation neuronal depolarization (inhibition of slow after-hyperpolarization) ? facilitation of ACTH and cortisol secretion emotional behavior (anxiogenesis), cognition, hypothermia, regulation of circadian rhythms, seizure activity, pain perception
	Ligands: agonists antagonists	 AS 19 DR 4365, DR 4446, SB 258719, SB 258741, SB 2656104-A, SB 269970-A, SB 691673

? – lack of data. Abbreviations: 5-HT – serotonin; ACh – acetylocholine; ACTH – adrenocorticotropic hormone; CNS – central nervous system; CRH – corticotropin-releasing hormone; DA – dopamine; GABA – γ-aminobutyric acid; GLU – glutamate; NE – noradrenaline

5-HT implication in the rewarding and aversive effects of cocaine

Cocaine changes functions of many systems in the body with the disadvantageous alterations observed the most frequently in the cardiovascular system and in the liver while its main target is the brain. Clinical picture after cocaine use depends mostly on its dose. Cocaine taken occasionally at low doses induces in humans so-called "*rush*", i.e. euphoria, it stimulates the cortex and brainstem, giving a sensation of vigilance and being energized. When higher doses of this drug are taken, symptoms described as "cocaine *high*" are experienced, which include enhancement of euphoric sensation, increase in motor activity, intensification of sensory perception, talkativeness, and suppression of appetite and feeling of thirst. Very high cocaine doses cause memory and cognition disturbances, distorted judgments, paranoidal symptoms, visual and auditory hallucinations and hyperlocomotion [32, 81]. Although the above symptoms are well-correlated with plasma cocaine level, it should be emphasized that not every person reacts similarly,

and inter-individual differences or hypersensitivity modify this relationship. This means that due to inter-individual differences, cocaine taken at the same low dose can induce subjectively positive sensations (connected with euphoria) in one person and negative experiences in another (anxiety, nervousness and personality disorders). Positive subjective effects of cocaine, i.e. its euphorigenic properties, are the most frequent focus of researchers' interest because these effects are experienced as pleasure and are the cause of frequent cocaine abuse which develops into the disease of the brain, i.e. addiction.

Neurochemical mechanism of cocaine action has been established relatively well. Cocaine was shown to have high affinity for DA transporter (DAT; K_i = 277 nM), 5-HT transporter (SERT; K_i = 217 nM) and noradrenaline (NE) transporter (NET; K_i = 144 nM) [60] and to block reuptake of the above-mentioned monoamines (K_i, values of 640, 140 and 1600 nM, respectively) [83]. Therefore, the question arises what is the contribution of these three neurotransmitters to euphorigenic properties of cocaine.

In vivo experiments on animals with the use of a combination of behavioral models and microdialysis demonstrated that cocaine administration by an experimenter to rats concomitantly increased their locomotor activity and elevated DA and 5-HT release in the nucleus accumbens [12]. Similar changes in DA and 5-HT neurotransmission were observed during intravenous cocaine self-administration, which is the model that the best simulates cocaine abuse in humans because cocaine-induced subjective positive reinforcing effect (equivalent to reward) in animals corresponds to euphoric effects in humans [27]. It was revealed that not limited cocaine self-administration (for 12 h) led to persistent elevation of the accumbal DA and 5-HT levels [74]. Extracellular DA and 5-HT levels were also increased in the globus pallidus throughout a 3-h experimental session in rats, with no coexistent changes in γ-aminobutyric acid or glutamate level [96]. Although the above-mentioned results indicate that rewarding cocaine effects are accompanied by simultaneous DA and 5-HT release, they do not answer the question whether both neurotransmitters are indispensable for expression of the cocaine effect. In order to solve this problem, a significance of DA, 5-HT and NE transporters in rewarding cocaine effects was analyzed since, as already mentioned, they are the direct target of cocaine.

Prominent role of the blockade of DAT (and consequently DA neurotransmission) in rewarding cocaine action ("*DAT-is-it*" hypothesis) is corroborated by a relationship between DAT saturation (> 60%) by cocaine and its euphorigenic and stimulant effects

Tab. 2. Basal locomotor activity and behavioral responses to cocaine in single monoamine transporter knock-out mice

Genotype	Basal locomotor activity	Effects of cocaine			
		Locomotor hyperactivation	Locomotor sensitization	Conditioned place preference	Self-administration
DAT					
wild-type	– [36, 98]	+ [36, 67]	+ [67]	+ [98]	+ [87]
heterozygous	– [98]	– [67]	– [67]	+ [98]	
homozygous	↑ [36, 98]	– [36, 67]	– [67]	+ [98]	+ [87]
NET					
wild-type	– [67, 115]	+ [67, 115]	+ [67, 115]	+ [115]	+ [90]
heterozygous					
homozygous	↓ [67, 115]	↑ [115] ↓ [67]	↑ [67] –[115]	↑ [115]	↓ [90]
SERT					
wild-type				+ [98]	
heterozygous				↑ [98]	
homozygous				↑ [98]	

+ effect existent; – lack of effect; ↑ effect increased compared to wild-type; ↓ effect existent, but was reduced compared to wild-type; wild-type (+/+); heterozygous (+/–); homozygous (–/–)

Tab. 3. Cocaine-induced conditioned place preference in double monoamine transporter knock-out mice

Genotype		Cocaine-induced conditioned place preference
DAT	NET	
wild-type	wild-type	+ [41, 107]
homozygous	homozygous	+ [41, 107]
NET	SERT	
wild-type	wild-type	+ [40]
wild-type	homozygous	+ [40]
heterozygous	homozygous	+ [40]
homozygous	wild-type	+ [40]
homozygous	heterozygous	+ [40]
homozygous	homozygous	↑ [40]
DAT	SERT	
wild-type	wild-type	+ [97]
wild-type	heterozygous	+ [97]
wild-type	homozygous	↑ [97]
heterozygous	wild-type	+ [97]
heterozygous	heterozygous	+ [97]
heterozygous	homozygous	↑ [97]
homozygous	wild-type	+ [97]
homozygous	heterozygous	– [97]
homozygous	homozygous	– [97]

+ effect existent; – lack of effect; ↑ effect increased compared to wild-type; wild-type (+/+); heterozygous (+/–); homozygous (–/–)

(so-called "*high*") in humans [108], and by a strong correlation between affinity for DAT and rewarding effect of cocaine and other psychostimulants [61, 84, 99]. On the other hand, a weak or completely absent addictive liability of other than cocaine DAT inhibitors (methylphenidate and mazindol, respectively; [19, 46]) contradicts the importance of DAT blockade to rewarding cocaine effects. Moreover, studies in healthy volunteers showed that > 60% DAT blockade in the striatum by methylphenidate or cocaine not in every person led to manifestation of the "*high*" symptoms [109]. This can suggest that the marked DAT saturation by methylphenidate or cocaine is not sufficient for manifestation of euphoric effects of these substances (i.e. those leading to the compulsion to take the drug). Studies in healthy volunteers and on animals conducted so far refuted the significance of SERT and NET in cocaine rewarding effect because different 5-HT [40, 103, 117, 118] and NE [40, 49] reuptake inhibitors did not exhibit addictive liability and were not self-administered by animals.

Since there is no substance which would block cocaine binding to different membrane transporters, this mechanism of cocaine action can be eliminated only by genetic manipulations. In homozygous DAT–/– or heterozygous DAT +/– mice, rewarding cocaine effect and conditioned place preference still were not abolished though these animals did not show locomotor effects of cocaine (Tab. 2). Whereas this result does not completely rebut the significance of DA as a critical substrate of rewarding cocaine effect, it indicates that there is another target, other than DAT, through which cocaine produces its rewarding effect.

Assuming that cocaine is so-called "*dirty drug*", i.e. it concomitantly blocks various membrane transporters, researchers generated mice knocked out of two different transporters. Rewarding effect of cocaine in the model of conditioned place preference was eliminated in homozygous DAT–/–SERT–/– and heterozygous DAT–/–SERT+/– mice but not in DAT/NET or NET/SERT homozygotes (Tab. 3). Interestingly, elimination of NET, or SERT, or NET/SERT proteins also did not weaken rewarding cocaine effects, on the contrary, its effects were even augmented (Tab. 2). Results of the above-described experiments indicate that SERT plays an important role in the modulation of expression of rewarding or aversive cocaine effects, while NET blockade can be responsible only for its aversive effects.

Significance of SERT blockade (and, consequently, of the enhancement of 5-HT neurotransmission) in the rewarding effect has been confirmed by results of other experiments on knockout mice demonstrating that fluoxetine (5-HT reuptake inhibitor devoid of rewarding effects in humans and animals, see above)

Tab. 4. The fluoxetine- and the nisoxetine-induced conditioned place preference in single monoamine transporter knock-out mice

Genotype	Conditioned place preference	
	Effects of fluoxetine	Effects of nisoxetine
DAT		
Wild-type	– [40]	– [40]
heterozygous	– [40]	– [40]
homozygous	+ [40]	+ [40]
NET		
wild-type	– [40]	– [40]
heterozygous	– [40]	– [40]
homozygous	+ [40]	– [40]
SERT		
wild-type	– [40]	– [40]
heterozygous	– [40]	– [40]
homozygous	– [40]	– [40]

+ effect existent; – lack of effect; wild-type (+/+); heterozygous (+/–); homozygous (–/–)

caused conditioned place preference in DAT protein knockout mice (Tab. 4). Rewarding effects of fluoxetine are preserved also in NET but not SERT knockout mice. It is worth adding that elimination of DAT (but not NET and SERT) switches on the rewarding effects of nisoxetine (NE reuptake inhibitor) in mice (Tab. 4).

The above genetic manipulations of the mechanism of cocaine reward form the basis for weakening/abolishment of euphorigenic effects of cocaine (inhibition of cocaine binding to the binding sites on DA and 5-HT transporters, i.e. so-called "rewarding transporters") and for enhancement of aversive experiences (anxiety, nervousness) by preservation of cocaine binding to the binding sites on NET (so-called "aversive transporter"). Furthermore, rewarding effects of fluoxetine in homozygous DAT–/– or NET –/– mice indicate that the lack of these elements shifts the balance between rewarding and aversive effects of 5-HT, which can result, among other things, from 5-HT influence on its different receptors (Tab. 5). For instance, stimulation of 5-HT_{1B} receptors augments cocaine self-administration (i.e. 5-HT acting *via* this receptor strengthens cocaine rewarding effects), while activation of 5-HT_{1A} and 5-HT_{2C} receptors suppresses these effects of cocaine (i.e. 5-HT acting *via* these receptors can strengthen aversive effects of cocaine).

Serotonin implication in cocaine withdrawal

Cocaine withdrawal results in development of a set of symptoms (so-called withdrawal syndrome), in which, in terms of clinical picture, two phases can be distinguished [81]. Clinical symptoms of early phase of cocaine withdrawal syndrome (so-called "*crush*", lasting about 4 days after cessation of cocaine abuse) include depression, ahedonia, insomnia, fatigue, hyperphagia and drug craving. In this phase, depression symptoms are the most aggravated, what can indicate a drop or disruption of 5-HT neurotransmission caused by cocaine withdrawal. While in humans only the symptoms are an indirect evidence of 5-HT deficit, in animals, microdialysis studies have actually demonstrated the decreased 5-HT level in the nucleus accumbens during withdrawal from cocaine self-administration [28, 73, 74]. It is worth emphasizing that preclinical studies demonstrated a direct proportion between duration of cocaine self-administration and the drop in 5-HT level in the nucleus accumbens during withdrawal [74]. DA in the nucleus accumbens in cocaine withdrawal was observed to be decreased, but the deficit was smaller in comparison with a drop in 5-HT level [74]. Interestingly, local application of exogenous 5-HT into the nucleus accumbens in the rat reversed DA deficit in this structure induced by cocaine withdrawal [74]. Therefore, 5-HT applied in this way not only reversed functional disorders in 5-HT system but also triggered a quick compensatory adaptive mechanism supporting adequate tonus in the DA system. As indicated by preclinical studies with microdialysis, the DA release in the nucleus accumbens can be raised by peripheral application of selective 5-HT reuptake inhibitors (SSRI), and by peripheral or local application of 5-HT_{1B}, 5-HT_{2A} and 5-HT_{3} receptor agonists or 5-HT_{2C} receptor antagonists [8, 10, 20, 24, 26, 42, 65, 72, 116]. In the context of cocaine addiction, particular role has been ascribed to 5-HT_{1B} receptor agonists, since these compounds are devoid of their own rewarding effects [75]. Thus, these pharmacological substances can have a double benefit, because reversal of 5-HT neurotransmission deficit leads to suppression of the symptoms of depression, insomnia, hyperphagia, aggression and anxiety, whereas a rise in the synaptic DA level alleviates ahedonia and, moreover, normalizes DA reward system (restores attractiveness of natural rewards and control over their acquiring). Augmentation of 5-HT neurotransmission by a substance, which does not have rewarding effect on its own can also weaken formation of an association between cocaine and conditioned stimulus associated with its taking.

The dominating symptom of the late phase of cocaine withdrawal, lasting from several weeks to months, is drug craving, motivating a person to get the drug at all costs, though anxiety, ahedonia and memory and concentration deficits are also observed [81]. All the above-listed symptoms result from the deepening DA and 5-HT deficit [28, 74] and neuroadaptive changes in the nervous system in functioning of these neurotransmitters [50, 51]. Drug craving, which is the state of cocaine seeking can be produced in a similar way in humans and animals, and motivational value of cocaine-associated stimuli or cocaine itself is the trigger of seeking behavior [25, 34, 66].

As shown by experiments on animals, restoration of seeking behavior by cocaine administration is connected with enhancement of DA and 5-HT release in subcortical structures (ventral and dorsal striatum) and in the prefrontal cortex [11, 94]. Presentation of reward-associated cues in rats [47, 48, 112] but not in

Tab. 5. 5-HT receptor ligands and rewarding effects of cocaine in preclinical studies

5-HT receptor subtype	Change in receptor function			Effects of cocaine		
				Self-administration	Conditioned place preference	
					Acquisition	Expression
5-HT_{1A}	↓	*Knockout*		↑ [86]		
	↑	Agonist	8-OH-DPAT	↓ [77]		
		Agonist	buspirone		– [2]	– [2]
5-HT_{1B}	↓	*Knockout*		↑ [89]	– [7]	
		Antagonist	GR 127935	– [75]		
	↑	*Receptor Overexpression*			↑ [71]	
		Agonist	CP 94253	↑ [75]	↑ [18]	
		Agonist	RU 24969	↑ [75]		
5-HT_{2A}	↓	Antagonist	cinanserin	– [80		
		Antagonist	M100907	– [33]		
		Antagonist	ketanserin	– [13, 62]		
		Antagonist	olanzapine	↓ [68]		
		Antagonist	ritanserin	– [78]		
		Antagonist	SR 46349B	– [29]		
5-HT_{2C}	↓	*Knockout*		↑ [88]		
		Antagonist	SB 242084	↑ [33] –[13, 29]		
	↑	Agonist	RO 60-0175	↓ [39]		
5-HT_{3}	↓	Antagonist	bemesetron	– [62]	– [17] ↓ [55]	↓ [101] –[55]
		Antagonist	ondansetron	↓ [23]	↓ [23]	
		Antagonist	tropisetron		– [17]	↓ [101]
	↑	*Receptor Overexpression*			↓ [3]	

↑ increase; ↓ reduction; – lack of effect

monkeys [11] is accompanied by a rise in the extracellular DA level in the ventral and dorsal striatum, while 5-HT level in the prefrontal cortex of monkeys declines [11]. The fact that sertraline, an SSRI, also extinguishes place preference is an additional proof of the influence of 5-HT neurotransmission on motivational value of cocaine-associated environmental cues [44]. The implication of 5-HT neurotransmission in drug craving induced by cocaine itself (unconditioned stimulus) or environmental cues (conditioned stimuli) was the best pictured in an extinction/reinstatement procedure in the model of cocaine self-administration (Tab. 6). Results of these preclinical studies indicate that alleviation of drug craving could be achieved in two ways: (1) by counteracting (in the withdrawal phase, *viz*. during 5-HT deficit) the decreases in 5-HT level by application of indirect 5-HT agonists, which suppress conditioned stimulus-induced seeking behavior [1, 14], whereas 5-HT_{1B} and 5-HT_{2C} receptor agonists seem also to efficiently weaken effects of cocaine itself [1, 39], and (2) by diminishing motivational effects of cocaine (5-HT_{1A} and 5-HT_{2A} receptor antagonists; [13, 29, 33, 93]) and cocaine-associated conditioned stimuli (5-HT_{2A} receptor antagonists; [13, 29]). It is worth noting that there is a discrepancy between suppression of seeking behavior as well by lowering of 5-HT neurotransmission (antagonists, chemical lesions, 5-HT synthesis blockade) as by enhancing of 5-HT neurotransmission (agonists). Similar contradictory effects of 5-HT ligands were confirmed by several clinical trials which showed that, on the one hand, lowering of 5-HT level by removal of its precursor, L-tryptophan, from the diet suppressed the conditioned stimulus-precipitated drug craving [92], and on the other hand, application of fluoxetine [79, 111; but not 38], fenfluramine [16], fenfluramine

Tab. 6. 5-HT neurotransmission and reinstatement of cocaine-seeking behavior in rats

Factor which induces cocaine-seeking behavior	Agent which alters cocaine-seeking behavior	Reinstatement of cocaine seeking behavior
Unconditioned stimulus (cocaine)	5-HT_{1A} receptor antagonist (WAY 100635)	↓ [13, 93]
	5-HT_{2A} receptor antagonist (M100907, SR 46349B)	↓ [29, 33]
	5-HT_{1B} receptor agonist (RU 24969)	↓ [1]
	5-HT_{2C} receptor agonist (RO 60-0175)	↓ [39]
	SSRI (fluoxetine)	– [4, 14]
	5-HT releaser (fenfluramine)	– [14]
	5-HT_{2C} receptor antagonist (SB 242084, SDZ SER-082)	– [13, 29, 33]
Conditioned stimulus (cue associated with cocaine self-administration)	SSRI (fluoxetine)	↓ [14]
	5-HT releaser (fenfluramine)	↓ [14]
	5-HT_{1B} receptor agonist (RU 24969)	↓ [1]
	5-HT-depleting agent (p-CPA)	↓ [105]
	5-HT lesion (5,7-DHT)	↓ [106]
	5-HT_{2A} receptor antagonist (SR 46349B, ketanserin)	↓ [13, 29]
	5-HT_{1A} receptor antagonist (WAY 100635)	– [13]
	5-HT_{2C} receptor antagonist (SB 242084, SDZ SER-082)	– [29]

↓ reduction; – lack of effect

+ fentermine [54] or a nonselective 5-HT_{2C} receptor agonist mCPP [15] lessened symptoms of drug craving and diminished cocaine intake. It is worth emphasizing that manipulations of the 5-HT neurotransmission seem particularly beneficial in alleviating drug craving since similar interference with DA system (i.e. DA receptor blockade or elevation of postsynaptic function of DA system with bromocriptine or amantadine, D_2 receptor agonists) does not abate drug craving in cocaine addicts [43, 53, 59].

Serotonin implication in long-term cocaine abuse

Long-term cocaine abuse leads to addiction (i.e. to compulsive drug taking), mood disturbances, paranoia and auditory hallucinations [81]. Several neurological disturbances (cerebral stroke), cardiologic (e.g. arterial hypertension, tachycardia, atherosclerosis, ischemic heart disease) and pulmonary (e.g. respiratory tract infection, fluid lung) complications also appear [81]. One of the hallmarks of cocaine addiction is a tendency to reinstatement, even after a prolonged abstinence period. It was observed that long-term cocaine abuse (as multiple "binges") in humans was accompanied by aggravation of paranoidal psychoses (so-called sensitization). This phenomenon has been used in studies on animals in which multiple and intermittent treatment with cocaine led to gradual augmentation of its locomotor effects and stereotypic behaviors after the withdrawal period [52, 56, 85]. Animal studies revealed that 5-HT_{2A} (SR 46439B and ketanserin [30, 31]) and 5-HT_3 (ondansetron; [54, but not 102]) receptor antagonists and 5-HT_{2C} receptor agonist MK 212 [30] administered before the challenge cocaine dose inhibited cocaine sensitizing effects, while 5-HT_{1B} receptor agonist (CP 94253) enhanced expression of cocaine sensitization [82]. Preclinical studies of cocaine often involve testing of the effects of potential anti-addictive substances during the second and subsequent induced sensitizations [22, 23, 58]. In this model, 5-HT_{2A} (ketanserin) and 5-HT_3 (ondansetron) receptor antagonists applied for several days during the first relapse (but after cocaine administration) or during withdrawal were efficient in preventing the development of behavioral sensitization [22, 23, 57, 58]. Ondansetron proved also efficacious in abolishing the reinstatement of cocaine self-administration in rats [23].

The results of these experiments indicate that pharmacological profile of 5-HT_{2A} and 5-HT_3 receptor antagonists may suggest their potential therapeutic efficacy in suppressing psychotic symptoms of cocaine

and reinstatement of its use. Ondansetron, a 5-HT_3 receptor antagonist and well-established antiemetic used in radio- and chemotherapy, is currently tested in clinical trials as a potential anti-addictive medication [37].

Conclusions

The present state of knowledge of 5-HT neurotransmission justifies the opinion that pharmacological manipulation in the 5-HT system can efficiently counteract the effects of cocaine withdrawal and prevent reinstatement of its abuse. The 5-HT_{1B}, 5-HT_{2A} and 5-HT_3 receptors have been attributed a particular role in this respect but precise explanation of their role and mode of implication in the mechanism of cocaine action requires further intensive studies.

It should be emphasized that massive effort to find efficient pharmacotherapy of consequences of cocaine use has concentrated mostly on DA system ligands. Despite the fact that DA fulfills a vital role in cocaine action, attempts to apply ligands of this system in the treatment of cocaine addiction proved little efficient so far [59]. Besides poor clinical efficacy, compounds of this type have disadvantageous side effect, limiting their use [59]. Hence, although medicinal substances acting on DA system are still searched for (replacement of cocaine, i.e. introduction of a DA reuptake inhibitor with low addictive liability or substances acting directly on DA receptors; [37]), a new approach to the problem of drug abuse involving a pharmacological manipulation of the 5-HT system can constitute an alternative therapy of cocaine addiction.

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Received:
July 5, 2005; in revised form: August 29, 2005.