

Chapter 2

Serotonin in the Nervous System of Vertebrates

2.1 Synthesis and Metabolism of Serotonin

Serotonin is synthesized in a two-step reaction, from tryptophan to 5-hydroxytryptophan (5-HTP) and then to 5-hydroxytryptamine (serotonin, 5-HT). The latter step is catalyzed by aromatic amino acid decarboxylase (AADC; EC 4.1.1.28), while the first step is catalyzed by tryptophan hydroxylase (TPH; EC 1.14.16.4), the rate-limiting enzyme in serotonin synthesis [1] (Fig. 2.1). TPH is present in the brain mostly in its second isoform, TPH2 [2, 3]. The enzyme uses Fe^{2+} as a cofactor, and oxygen and tetrahydrobiopterin (BH4) as co-substrates. In vitro evidence suggests that the autoregulation of the firing rate of serotonergic neurons depends on sustained tryptophan hydroxylase activity [4]. Consistently with that hypothesis, depolarization or increases in extracellular calcium increases the affinity of TPH for tryptophan and tetrahydrobiopterin [5, 6].

BH4 concentrations in the central nervous system are not at saturation level for TPH [7], and therefore TPH exerts only a fraction of its maximum velocity ($V_{\max}$). Microinjections of BH4 in the brain increase TPH activity [7, 8]. BH4 at physiological levels also enhances the inactivation of TPH by nitric oxide via attack on free protein thiol groups [9], another mechanism which could regulate serotonin synthesis.

The strict requirement for Fe^{2+} and the inhibition of TPH by Fe^{3+} means that cellular metabolism of iron is also critical for serotonin synthesis [10, 11]. This inhibition is dependent on the oxidation of H_2O_2 to O_2 and Fe^{2+} to Fe^{3+} , with the subsequent formation of reactive oxygen species [10]. Therefore, TPH activity is strictly dependent on the redox state of the cell.

In addition to the regulation of TPH activity by its co-factors and co-substrates, another important mechanism of regulation is phosphorylation. Phosphorylation by protein kinase A (PKA; EC 2.7.11.11) increases the $V_{\max}$ of TPH without changing its K_m [12]; similar results were obtained regarding phosphorylation by Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII; EC 2.7.11.17) [13, 14].

Tryptophan hydroxylase is also activated by stress hormones. Psychological or physical stressors, as well as corticosteroid administration, increase TPH activity

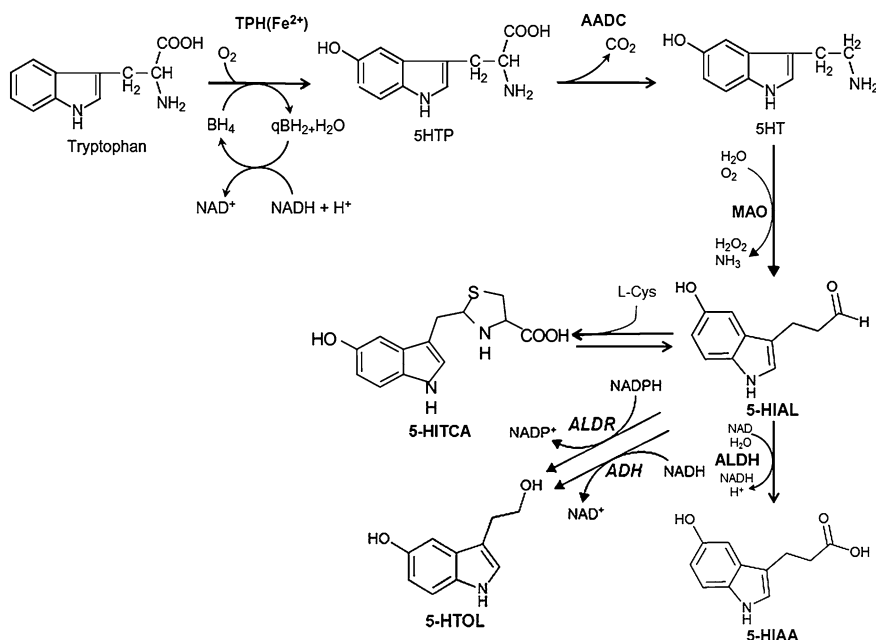


Fig. 2.1 Synthesis and degradation of serotonin. Tryptophan hydroxylase (*TPH*) is the rate-limiting enzyme in the synthesis of serotonin, converting tryptophan into 5-hydroxytryptophan (*5-HTP*). This intermediate step is followed by the conversion of *5-HTP* into serotonin by amino acid decarboxylase (*AADC*). The principal enzyme in serotonin degradation is monoamine oxidase (*MAO*), which catalyzes the oxidative deamination of serotonin into 5-hydroxy-3-indolacetaldehyde (*5-HIAL*). This metabolite can follow three conversion pathways: in the presence of high *L*-cysteine (*L-Cys*) concentrations, *5-HIAL* is transformed into 5-hydroxyindole thiazoladine carboxylic acid (*5-HITCA*). Aldehyde dehydrogenase (*ALDH*) catalyzes the conversion of *5-HIAL* into 5-hydroxyindolacetic acid (*5-HIAA*). Chronic ethanol intake increases activity and/or concentrations of alcohol dehydrogenase (*ADH*) or aldehyde reductase (*ALDR*), which pushes the balance toward the conversion of *5-HIAL* into 5-hydroxytryptophol (*5-HTOL*). Other abbreviations: *BH₂* dihydrobiopterin, *BH₄* tetrahydrobiopterin, *NAD⁺* nicotinamide adenine dinucleotide, *NADH* reduced NAD, *NADP* NAD phosphate, *NADPH* reduced NADP

in the brain [15–17]; in vitro, tryptophan hydroxylase activity is increased in the caudal part of the DRN by application of CRF [17]. This increase in activity is likely caused by alterations in gene expression; neonatal handling decreases, and maternal separation increases the expression of *tpH2* mRNA in caudal and ventrolateral parts of the DRN in rats which are exposed to social defeat as adults [18, 19]. In adult rats, chronic unpredictable stress increases *tpH2* mRNA expression in the caudal part of the DRN, but not in other raphe regions [20].

Tph2 is under the transcriptional control of three important developmental genes, *sim1*, *pet1*, and *lmx1b* [21–23]. In the case of the last two genes, adult deletion downregulates the expression of tryptophan hydroxylase 2 in the DRN [24, 25], suggesting that the environmental regulation of the expression of *tpH2*

might be mediated by direct transcriptional activation by these developmental genes. Indeed, Pet-1 mRNA has been shown to be upregulated by estradiol treatment in ovariectomized rats [26], demonstrating that this gene is susceptible to extrinsic regulation.

Tryptophan hydroxylase inhibition by pharmacological means [through DL-*para*-chlorophenylalanine (DL-pCPA)] has an anticonflict effect [27, 28], increases social interaction [29], and prevents learned helplessness after exposure to unpredictable stress [30]; conversely, panicogenic effects of DL-pCPA were observed in escape paradigms in which lever-press turns off dorsal periaqueductal gray area electrical stimulation [31, 32]. Deletion of *tph2* dramatically decreases brain 5-HT content and produces an anxiogenic effect in the marble burying and open-field tests [33]. Likewise, in BALB/c mice, a strain which is spontaneously more anxious and reactive than the C57BL/6 or 129Sv strains [34, 35], a single-nucleotide polymorphism at *tph2* leads to a decreased catalytic activity of the enzyme and, consequently, decreased serotonin levels in the forebrain [36]. The discrepancy between the behavioral effects of developmental and adult blockade of TPH2 activity suggests that serotonin has an important developmental role in modeling fear and anxiety circuits [37].

After reuptake from the synaptic cleft (see Sect. 2.2, below), serotonin is metabolized by monoamine oxidase (MAO; EC 1.4.3.4) [38], an enzyme that is located in the outer mitochondrial membrane [39]. This enzyme catalyzes the oxidative deamination of serotonin by converting it into 5-hydroxy-3-indolacetaldehyde (5-HIAL), which is further metabolized into 5-hydroxy-3-indolacetic acid (5-HIAA) by aldehyde dehydrogenase type 2 (ALDH2; EC 1.2.1.3) or to 5-hydroxytryptophol (5-HTOL) by aldehyde reductase (ALDR; EC 1.1.1.21) or alcohol dehydrogenase (ADH; EC 1.1.1.1). This latter metabolite is present in the brain at concentrations of only 1–5 % of 5-HIAA levels [40], but can be dramatically increased by ethanol intake [41]. Another minor metabolite is 5-hydroxyindole thiazoladine carboxylic acid (5-HITCA), which is formed from a condensation reaction between L-cysteine and 5-HIAL [42] (Fig. 2.1).

The chemical reaction catalyzed by MAO uses flavin adenine dinucleotide (FAD) as a redox cofactor [43]. Covalent attachment of FAD to cysteine residues is critical for enzymatic activity [44]. The first step in the reaction is reduction of FAD to FADH₂, coupled to the conversion of the amine group of serotonin to imine; a second step is the oxidation of FADH₂ with the conversion of oxygen into hydrogen peroxide, followed by the hydrolysis of the imine into the corresponding aldehyde and ammonia [45].

Monoamine oxidase is present in two isoforms in mammals, MAO A and MAO B, with the first having higher affinity for serotonin than MAO B [46]. Both isozymes are found in serotonergic neurons, but in different compartments: while MAO B is found in mitochondria at the soma, MAO A is found in mitochondria at the synaptic terminals [45]. This compartmentalization responds to the physiological requirements of serotonin synthesis and metabolism: 5-HT synthesis is much greater in the cell body than in axon terminals [47, 48]; if MAO A was to be

localized in the soma, metabolism of serotonin would compete with the gradient-based mechanism of 5-HT vesicular uptake [45].

MAO A inhibition increases serotonin concentrations in the synaptic cleft while decreasing the firing rate of serotonergic neurons in the raphe [49, 50]. These effects are thought to underlie the antidepressant efficacy of MAO inhibitors. This class of drugs also has clinical efficacy in the treatment of panic and post-traumatic stress disorders, but not in generalized anxiety disorder (Table 1.1). Consistently, MAO A knockout mice do not show alterations in anxiety-like behavior in the plus-maze [51].

2.2 Transport of Serotonin: SERT and Uptake₂

The extracellular levels of serotonin must be tightly controlled by uptake into astrocytes and presynaptic neurons in order to fulfill the behavioral and physiological functions of serotonin. At least two mechanisms are responsible for this uptake. The most well known and well studied of these mechanisms is transport by a high-affinity, sodium- and chloride-dependent transporter, SERT (5-HTT, SLC6A4) [52, 53]. This protein is highly concentrated in the raphe nuclei and in the prefrontal cortex, as well as in thalamocortical afferents [54–56]. A physical interaction between the serotonin transporter and type 1 nitric oxide synthase (L-arginine, NADPH oxygen oxidoreductase 1; NOS-1; EC 1.14.13.39) has been observed; this interaction decreases SERT membrane trafficking, and in human embryonic kidney HEK293 cells transfected with SERT and NOS-1 serotonin leads to cyclic guanosine monophosphate (cGMP) formation through a transport-dependent mechanism. Increased NO production in SERT/NOS-1-transfected HEK293 cells triggered by a calcium ionophore or by nitric oxide donors does not affect serotonin reuptake, but NOS-1-deficient mice show increased 5-HT uptake [57].

Likewise, the isoform I α of cGMP-dependent protein kinase (PKGI α ; EC 2.7.11.12) colocalizes with SERT in both intracellular and cell surface domains of RN46A cells, an immortalized lineage of rat serotonergic raphe neurons, and is co-immunoprecipitated with SERT when stably transfected in HeLa cells [58]. Different from NOS-1, however, the interaction with PKGI α increases surface expression of SERT [59]. In RN46A cells and in the basophilic leukemia cell line RBL-2H3, the administration of 8-bromo-cGMP, a PKG activator, stimulates SERT surface trafficking [60] and serotonin uptake [61], an effect which is blocked by pretreatment with a membrane-permeant kinase inhibitor [58] and with a p38 mitogen-activated protein kinase (p38 MAPK; EC 2.7.12.2) inhibitor or a protein phosphatase 2A (PP2A; EC 3.1.3.16) inhibitor [62]. Likewise, treatment with a p38 MAPK inhibitor decreases the interaction between SERT and the PP2A catalytic subunit [63], suggesting that PP2A is downstream of p38, which is downstream to PKG. SERT activation by PKG is also blocked by mutation of a threonine residue near the cytoplasmic end of the fifth transmembrane helix [64], suggesting that the PKG-dependent, p38-independent phosphorylation of this

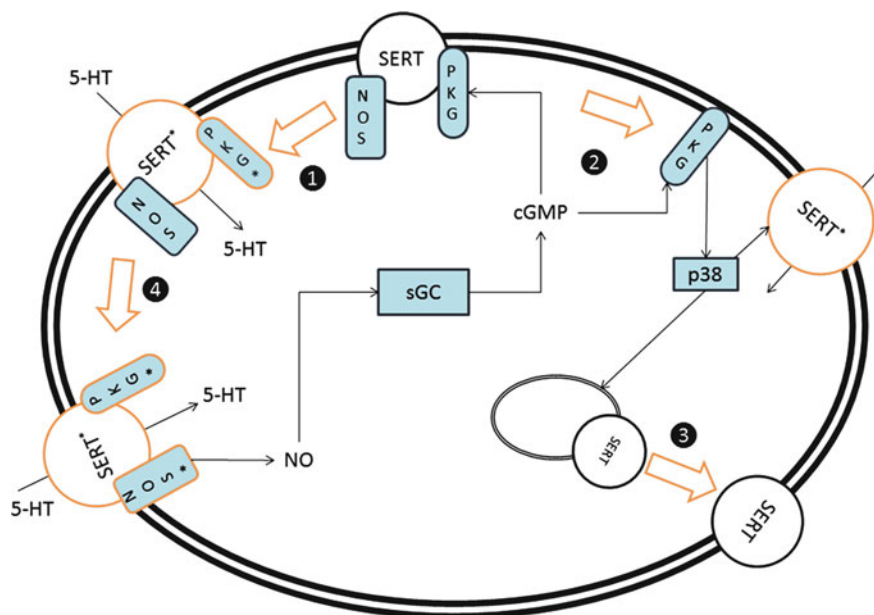


Fig. 2.2 Mechanisms of SERT regulation by the NO-cGMP pathway. 1 cGMP can activate PKGI α , which is linked to SERT via myosin; this mechanism stimulates serotonin uptake. 2 Alternatively, cGMP can activate PKG which phosphorylates p38 MAPK, leading to transport stimulation or 3 SERT membrane trafficking. SERT activation can also lead to activation of NOS-1 and subsequent production of nitric oxide 4. Abbreviations: NOS nitric oxide synthase, p38 p38 mitogen-activated protein kinase, PKG protein kinase G, SERT serotonin transporter, sGC soluble guanylate cyclase

residue is also necessary for this effect. Nonetheless, expression of PKGI α or PKGI β along with SERT in HeLa cells increases surface expression of the transporter even when the transfected PKG was mutated so as to eliminate its catalytic activity [59]. Transfection of a mutant form of SERT which lacks sites for *N*-glycosylation into Chinese hamster ovary (CHO) cells impair the association between myosin (a PKG-anchoring protein) and the transporter as well as the stimulation of uptake function by 8-bromo-cGMP, suggesting that the phosphorylation of SERT by PKG is dependent on the interaction of both proteins with myosin and on SERT being in a favorable conformation that is promoted by sialylated *N*-glycans [65] (Fig. 2.2).

Interestingly, p38 MAPK also seems to regulate the interaction between SERT and syntaxin 1A (Syn1A), a protein which determines the stoichiometry of 5-HT uptake by SERT [63]; when both proteins interact, 5-HT uptake is electroneutral, without 5-HT-induced ionic currents or 5-HT-independent sodium currents. When this interaction is broken, 5-HT uptake is electrogenic due to the appearance of a voltage-dependent influx of 12 sodium ions per 5-HT molecule (at -80 mV), which can lead to cell depolarization [66]. CaMKII inhibitors shift the affinity of

SERT for Syn1A, leading to the emergence of these SERT-mediated currents [67]. Importantly, p38 MAPK inhibitors produce the same effect [63], suggesting that p38 also regulates the conducting state of the serotonin transporter.

In spite of the fact that most of these observations were made in transfection systems, the regulation of SERT by the PKG-p38 MAPK pathway is of physiological significance. A non-synonymous single-nucleotide polymorphism in human SERT (I425 V) has high rates of serotonin uptake in relation to wild-type transporters, an effect which is associated with insensitivity to treatment with nitric oxide donors [68]. Isoform α of p38 MAPK is widely distributed in tryptophan hydroxylase 2-expressing cells in the mouse DRN [69], and social defeat stress leads to p38 phosphorylation in this region [70]. Adenoviral deletion of p38 α in the DRN abolishes stress-induced reinstatement of cocaine seeking behavior, and blocks the acquisition of conditioned place avoidance of a context which has been paired with a κ -opioid receptor agonist, effects which are also observed with conditional deletion of p38 α in SERT-expressing cells in the whole CNS but not in astrocytes. Also, whole-brain synaptosomes of mice injected with a κ -opioid receptor agonist show increased rate of SERT-specific serotonin uptake than synaptosomes of control animals; this effect, however, is not observed in the synaptosomes of mice with conditional deletion of p38 α in SERT-expressing cells [70].

SERT is the target of serotonin selective reuptake inhibitors (SSRIs), and acute administration increases serotonin release preferentially in the raphe nuclei [71–74]. Genetic ablation of SERT results in elevated anxiety-like behavior in adult mice, an effect which is modulated by differences in genetic background [75] and is accompanied by fivefold increases in extracellular 5-HT concentrations [76], desensitization and downregulation of 5-HT_{1A}Rs in the raphe, hypothalamus, septum, and amygdala [77], 5-HT_{1A}R-dependent reduction in spontaneous firing rates in 5-HTergic neurons in the DRN [78], downregulation of 5-HT_{1B}Rs in serotonergic axon terminals [79], and disorganization of vibrissae-stimulated barrel fields in the somatosensory cortex [80]. Early blockade of SERT by chronic SSRI treatment mimics the effect of knocking out the transporter [81]. SERT overexpression, on the other hand, results in decreased anxiety [82].

Wistar-Zagreb 5-HT rats selected for extreme values of peripheral (platelet) transporter activity [83, 84] show discordant brain 5-HT turnover and extracellular concentrations, for animals with high peripheral SERT activity (high WZ-5HT) presenting normal serotonin levels in the brain, slightly lower [³H]citalopram binding sites and increased serotonin release after potassium chloride or citalopram infusion in a microdialysis probe on the ventral hippocampus [85]. Thus, high WZ-5HT rats are not exactly hyperserotonergic, in the sense that their baseline serotonergic “tone” is not different from control populations or from low WZ-5HT rats; nonetheless, their serotonergic system is “hyperresponsive” to stimulation [84]. Interestingly, there are no differences between both lines of Wistar-Zagreb rats and control populations in terms of 5-HT_{1A}R, 5-HT_{1B}R, or 5-HT_{2A}R mRNA or protein expression, nor of binding sites or affinity to radioligands, in the hippocampus, striatum, or cortex [84, 86], in opposition to the

compensatory changes observed in SERT knockout mice [77, 79]. High WZ-5HT rats show increased anxiety in the elevated plus-maze and social interaction tests, as well as diminished exploratory activity in the elevated zero-maze plus-maze and in the holeboard [87], as well as increased freezing to context [84], resembling SERT knockout animals [75].

These WZ-5HT animals have been proposed as a rodent model of human serotonergic dysfunctions associated with SERT genetic polymorphisms [84]. In humans (as well as in rhesus macaques [88, 89]), an important genetic polymorphism rests in a promoter region of the *slc6a4* gene. This polymorphic region (5-HTTLPR) consists of a 44 base-pair insertion/deletion event expressed as a short (*s*) or long (*l*) allele [90]; the long allele, with 16 repeat elements, leads to increased SERT expression than the short allele, with 14 repeat elements [90]. In immortalized lymphoblast B cell lines which express SERT in an allele-specific fashion, cells with the *l/l* genotype show higher 5-HT uptake and SERT protein expression than cells with the *l/s* or *s/s* genotypes [91], and brain-derived neurotrophic factor (BDNF) [92] and the adenylate cyclase activator forskolin [91] decrease 5-HT uptake in *l/l* lymphoblasts. The absence of an effect of these treatments on 5-HT uptake in *l/s* or *s/s* genotype lymphoblasts reinforces the idea of a decreased regulatory capacity of SERT in these genotypes.

Importantly, the presence of the short allele of the 5-HTTLPR polymorphism has been associated with anxiety symptoms in adult humans [91], and there are evidences of associations between this polymorphism and certain physiological and behavioral endophenotypes of anxiety. Carriers of the short allele exhibit increased startle responses to unexpected loud sounds [93], risk aversion [94–97], amygdala activity to fearful faces and to novel neutral stimuli [98–100], and functional coupling between amygdala and ventromedial prefrontal cortex when viewing positive or negative emotionally charged images [101, 102].

The rhesus macaque 5-HTTLPR also contains a polymorphism consisting on a 21 base-pair insertion/deletion event expressed as short or long alleles [89]. The presence of two copies of the *s* allele leads to ~50 % less serotonin transporters and is associated with lower 5-HIAA levels [103]. Importantly, it also produces behavior that is indicative of higher anxiety levels [104]. Infant macaques carrying the *s* allele who underwent short maternal separation periods showed higher levels of circulating ACTH during separation [105]. ACTH responses were higher in female *l/s* than *l/l* macaques only if they were allowed sensory contact with other subjects in addition to the maternal separation event, [106]. By contrast, *s* carrier males showed increased ACTH secretion regardless of rearing background [105]. Likewise, *s* carrier macaques also show greater sensitivity to intravenous injections of alcohol when adolescent [105], and female *s* carrier macaques spontaneously consume more alcohol when exposed to maternal separation [107].

In addition to the high-affinity sodium-dependent SERT, a low-affinity sodium-independent transporter has been described, a system called uptake₂. Uptake₂ is a high-capacity, low-affinity transport system for monoamines that is acutely inhibited by corticosteroids [108, 109]. Two proteins mediate uptake₂ in the CNS, the plasma membrane monoamine transporter (PMAT) and the organic cation

transporter 3 (OCT3) [110]. Human OCT3 is the major uptake₂ transporter of histamine, epinephrine, and norepinephrine, while human PMAT is the major uptake₂ transporter for serotonin and dopamine [110]. Nonetheless, the affinity of corticosteroids to OCT3 is much higher than to PMAT [111, 112]. While PMAT is highly expressed in the mouse cortex, olfactory tubercle and hippocampus [113], OCT3, is expressed in highest densities in the colliculi islands of Calleja, subiculum, lateral septum, lateral and dorsomedial hypothalamic nuclei, and retrosplenial cortex [114]. Despite the low selectivity for serotonin, OCT3 has been implicated in 5-HT transport, as SERT-deficient mice show upregulation of OCT3 expression in the hippocampus [115], and inhibition of OCT3 in the rat dorsomedial hypothalamus dramatically increases extracellular serotonin levels in this structure [116]. The effects of OCT3 deletion on anxiety-like behavior are not contradictory, and probably dependent on the targeting mechanism and on background genotype. For example, in mice from a 129/Ola-FVB/N genetic background (25 %:75 %), deletion of exons 1 and 2 produce animals with increased anxiety-like behavior in the elevated Y-maze and open-field [117]; deletion of exons 6 and 7 in a C57BL/6 genetic background leads to decreased anxiety-like behavior in the elevated plus-maze and open-field [118].

2.3 Serotonin Receptors

Up to 14 distinct human serotonin receptors have been cloned [119], and most of these receptors present post-transcriptional modifications [120]. While the 5-HT₃ receptor is ionotropic, all other receptor classes (5-HT₁-5-HT₇) are metabotropic. Canonical transduction pathways for these receptors have been described as positive (5-HT₄, 5-HT₆, 5-HT₇) or negative (5-HT₁, 5-HT₅) coupling to adenylyl cyclase and positive coupling to phosphatidyl inositide turnover (5-HT₂) [121]. Non-canonical transduction pathways have also been described, including nitric oxide synthase and phospholipase A₂ activation (Table 2.1) [122, 123].

Specific serotonin receptors have been linked to anxiety by pharmacological [124] and genetic [125] experiments. Among those, evidence for important roles in anxiety has been gathered for the 5-HT_{1A} and 5-HT_{2C} receptors. The main difficulty in evaluating these results is that these receptors are located both presynaptically at the raphe nuclei and postsynaptically at its targets. In the raphe, 5-HT_{1A} receptors are somatodendritic, while 5-HT_{1B} receptors show a preterminal axonal localization [126, 127]. 5-HT_{1A} receptors are also enriched in limbic regions of the brain, while 5-HT_{1B} receptors are located mainly on the basal ganglia [128, 129].

Table 2.1 Major signaling pathways of G-protein coupled 5-HT receptors

Receptor	Canonical transduction pathway	Secondary transduction pathways
5-HT_{1A}	AC inhibition	MAPK cascade activation
	GIRK modulation	PLC activation
	HVA inhibition	PLA ₂ activation/inhibition
		NOS-1 activation/inhibition
5-HT_{1B}	AC inhibition	Jak cascade activation
		MAPK cascade activation
		PLC activation
		NOS-1 activation
5-HT_{1D}	AC inhibition	GIRK modulation
		HVA inhibition
		GIRK activation
5-HT_{1E}	AC inhibition	AC activation (weak)
5-HT_{1F}	AC inhibition	PLC activation
5-HT_{2A}	PLC activation	PLA ₂ activation
		Jak cascade activation
		GPase activation (astroglia)
		MMP activation (astroglia)
5-HT_{2B}	PLC activation	NOS-2 activation
		MAPK cascade activation
		PLA ₂ activation
		Na ⁺ /Ca ²⁺ exchanger activation
5-HT_{2C}	PLC activation	GIRK inhibition
		PLA ₂ activation
5-HT₄	AC activation	
5-HT_{5A}	AC inhibition	PLC activation (transient)
		GIRK activation
		ADP-ribosyl cyclase inhibition
5-HT_{5B}	Unknown	
5-HT₆	AC5 activation	
5-HT₇	AC5 activation	MAPK cascade activation
		cAMP-GEF cascade activation

Abbreviations: *AC* adenylyl cyclase, *cAMP-GEF* cyclic adenosine monophosphate-binding guanine nucleotide exchange factor, *GIRK* G-protein coupled inward rectifying potassium channel, *GPase* glycogen phosphorylase, *HVA* high-voltage activated calcium channel, *NOS* inducible nitric oxide synthase, *MAPK* mitogen-activated protein kinase, *MMP* matrix metallo-proteinase, *NOS* nitric oxide synthase, *PLA₂* phospholipase A₂, *PLC* phospholipase C

2.3.1 5-HT_{1A} Receptors

Different transduction mechanisms mediate 5-HT_{1A}R activation in presynaptic (DRN) and postsynaptic sites: in the raphe, activation of 5-HT_{1A}Rs inhibits high-voltage activated currents (*I_{HVA}*), but do not couple to adenylyl cyclase [130]. Knockout animals in which the 5-HT_{1A} receptor is absent from birth show increased anxiety-like behavior [131] that is rescued after normalizing expression

of 5-HT_{1A}Rs in forebrain areas in adulthood [132]. Conversely, decreasing the density of 5-HT_{1A} autoreceptors in adulthood in normal animals does not affect baseline anxiety-like behavior but leads to exaggerated behavioral despair in the tail suspension and forced swim tests after prolonged stress [133]. When this suppression is made at birth and maintained throughout life, however, increased anxiety-like behavior is observed in the open-field and light/dark box tests, while behavioral despair remains normal [134]. It seems that the developmental maintenance of a serotonergic “tone”, mediated by 5-HT_{1A} autoreceptors, has an important role in the organization of defensive behavior.

5-HT_{1A} receptor expression, activity, and/or trafficking are regulated by a plethora of mechanisms. The coupling of 5-HT_{1A} receptors to different transduction mechanisms depend on its interaction with G $\alpha_{i/o}$ or G $\beta\gamma$ proteins, with the latter being necessary for I_{HVA} inhibition [135]. Coupling to G $\alpha_{i/o}$ (and, therefore, to adenylyl cyclase) is tightly regulated by regulator of G protein signaling (RGS) proteins, which function as GTPase accelerating proteins (GAPs) that bind to and rapidly deactivate G α subunits [136]. Mice with a point mutation in G α_{i2} that renders this protein insensitive to RGS protein regulation show less neophobia and reduced anxiety in the elevated plus-maze and marble burying test. They also show a dramatically increased response to treatment with 8-OH-DPAT or fluvoxamine in the tail suspension test [137]. Interestingly, RGS4 expression in serotonergic neurons is dependent on the activity of the transcription factor *Sim1*, which is enriched in lateral wings of the dorsal raphe nucleus [22].

The 5-HT_{1A} gene promoter possesses a negative glucocorticoid response element (GRE) that is highly sensitive to binding of a mineralocorticoid-glucocorticoid receptor heterodimer, less sensitive to binding of the mineralocorticoid receptor (MR), and weakly sensitive to binding of the glucocorticoid receptor (GR) [138]. Additionally, activation of GRs represses an NF- κ B-induced 5-HT_{1A} promoter activity [139]. In rats, adrenalectomy is followed by a rapid upregulation of 5-HT_{1A} mRNA expression and 5-HT_{1A}R binding sites in the septo-hippocampal system, but not in the raphe [140–144]; this effect is reversed by treatment with low doses of corticosterone which preferentially bind MRs [140, 145–147]. Since both types of receptors are expressed in the septo-hippocampal system, while only GR is expressed in the DRN [139, 148] this affinity profile of the negative GRE in the 5-HT_{1A}R promoter could explain the lack of effect of manipulations of corticosteroid levels on autoreceptors in the raphe. In contrast, local activation of GRs in the DRN, as well as chronic mild stress, decreases the potency of 5-HT_{1A} receptor agonists to inhibit cell firing [144, 149–151]. These effects are not observed with acute stressors, however [152, 153], suggesting that corticosteroid effects on the raphe are due to a desensitization of 5-HT_{1A} autoreceptors [154].

The 5-HT_{1A} receptor gene is also negatively controlled by two calcium-dependent transcription factors, Freud-1 and Freud-2 (Five repressor element under dual binding protein) [155, 156]. In raphe cells, binding of Freud-1 in the dual repressor element (DRE) in the 5-HT_{1A} promoter region is sufficient to repress transcription; however, in postsynaptic cells, a second protein complex

(Freud-2) is necessary to reach the same effect [138, 156]. After chronic restraint stress, Freud-1 levels are reduced in the prefrontal cortex of male Sprague–Dawley rats, upregulating 5-HT_{1A}R mRNA expression; however, 5-HT_{1A}R protein levels are downregulated, suggesting post-transcriptional receptor downregulation [157]. Conversely, social defeat downregulates 5-HT_{1A} mRNA levels in the prefrontal cortex of Wistar rats, but no effect is seen in Freud-1 mRNA levels [158].

2.3.2 5-HT_{1B} Receptors

The primarily preterminal axonal localization of 5-HT_{1B} autoreceptors suggests that they may also have a role in the control of serotonergic “tone” [127]. Nonetheless, the effects of knocking down 5-HT_{1B}Rs are opposite to those observed after genetic manipulation of 5-HT_{1A}Rs. 5-HT_{1B}R knockout mice show increased exploratory activity in an open field that disappears after multiple expositions [159]; 5-HT_{1A}Rs, on the other hand, show decreased exploratory activity in the open field [131]. Moreover, while 5-HT_{1A} knockouts show increased anxiety in an elevated plus-maze and in the novelty-suppressed feeding test, 5-HT_{1B} knockouts show decreased anxiety [131, 159]. 5-HT_{1B} knockouts show decreased serotonin levels in the nucleus accumbens, locus coeruleus, and spinal cord, but not in regions associated with anxiety- or fear-like behavior [160]. Increasing expression of 5-HT_{1B}Rs in the dorsal raphe nucleus increases anxiety-like behavior in the elevated plus-maze and open field following inescapable stress, but decreased it in the absence of prior stress [161]; a similar effect is seen in the fear-potentiated startle paradigm, where 5-HT_{1B}R-overexpressing animals show decreased potentiation in the absence of prior stress, and this effect is abolished by inescapable stress [162]. Specific overexpression in the caudal DRN decreases immobility in the Porsolt forced swim test and freezing in contextual fear conditioning [163].

In normal animals, selection for increased learned helplessness decreases the expression of 5-HT_{1B} mRNA in the dorsal raphe nucleus; an opposite phenomenon is observed in animals which have been separated from their mothers for 15 min/day between postnatal days 2–14, but not in animals which have been separated for 180 min/day for the same period [164]. 5-HT_{1B} receptors interact with an S100 EF hand protein, S100A10, which increases membrane trafficking for this receptive protein. In a mouse line which has been selected for readiness of establishment of learned helplessness (H/Rouen mice), S100A10 mRNA is greatly diminished in the forebrain, and treatment with imipramine or electroconvulsive therapy increases S100A10 mRNA in the forebrain of rats. Overexpression of S100A10 in African Green monkey kidney COS-7 cells co-expressing 5-HT_{1B} receptors increases the amount of these receptors at the cell surface and increases the efficacy of adenylyl cyclase coupling. When S100A10 is overexpressed in the brains of mice, decreased thigmotaxis is seen in the open field, and animals spend less time immobile in the tail suspension test. S100A10 knockout mice show decreased

5-HT_{1B} receptor binding and decreased G-protein coupling efficacy in the globus pallidus in response to anpirtoline, a 5-HT_{1B} agonist. Primary cortical cultures from S100A10 knockout mice also lose their ability to respond to serotonin or anpirtoline with decreased extracellular signal-regulated kinase (ERK) phosphorylation. Finally, in S100A10 knockout mice treated chronically with imipramine, anpirtoline does not decrease thigmotaxis in an open field [165]. Overall, these results point to an important modulation of 5-HT_{1B} receptor function by S100A10 that is associated with stress reactivity, but not anxiety-like behavior. These results are also consistent with a role for the 5-HT_{1B} receptor in stress reactivity.

2.3.3 5-HT_{2C} Receptors

5-HT_{2C} receptors are located in raphe GABAergic interneurons [166] as well as in the nucleus accumbens, olfactory tubercle, claustrum, septum, cingulate cortex, amygdala, hippocampus, periaqueductal gray, habenula, and entorhinal cortex [128]. These receptors have been implicated in anxiety-like behavior, as *htr2c*^{-/-} mice show decreased anxiety-like behavior [167], and the mixed 5-HT_{1B}/5-HT_{2A}/5-HT_{2C} agonists mCPP and 1-(3-trifluoromethylphenyl)piperazine (TFMPP) have anxiogenic effects in human subjects with anxiety disorders [168–170] and in animal models [171]. The discriminative stimulus effects of mCPP are mediated by 5-HT_{2C} receptors, as other 5-HT_{2C} agonists fully substitute for mCPP on drug discrimination assays, and 5-HT_{2C} antagonists block this effect [172]; thus, it seems that the interoceptive cues of this drug is 5-HT_{2C}R-specific.

5-HT_{2C}Rs are the most “variable” among the serotonergic receptors, being associated with “collateral efficacy” or agonist-directed trafficking of receptor stimulus. In 5-HT_{2C} receptors transfected with CHO-derived cells, agonists activate two signal transduction pathways (phospholipase C-mediated inositol phosphate accumulation and phospholipase A₂-mediated arachidonic acid release) differentially; some drugs, such as TFMPP (3-trifluoromethylphenyl-piperazine), preferentially activate the PLC pathway, while others, such as LSD (lysergic acid diethylamide), preferentially activate the PLA₂ pathway [173]. Serotonin itself has a similar efficacy at each pathway, but is more potent at producing a response for inositol phosphate accumulation [173]. Importantly, agonist-directed trafficking is dependent on post-transcriptional-edited variants. 5-HT_{2C} receptors undergo adenosine-to-inosine editing events at five sites located within the second intracellular loop [174]. Two important isoforms (5-HT_{2C-VSV} and 5-HT_{2C-VGV}) have been confirmed in the central nervous system [174, 175], and, in relation to non-edited isoforms exhibit decreased constitutive activity, agonist affinity, and internalization [175–179]. Importantly, in edited isoforms, no difference in the efficacies of TFMPP or bufotenin for the PLC and PLA₂ pathways is observed [180]. The full significance of these findings is yet to be assessed *in vivo*, but it is known that the amount of RNA editing in the medial prefrontal cortex and amygdala is positively associated with anxiety-like traits in rodents [181, 182].

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