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Review

Serotonin

DOROTEA MÜCK-ŠELER
NELA PIVAC

Division of Molecular Medicine,
Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia

Correspondence:
Dorotea Mück-Šeler
Laboratory for Molecular Neuropsychiatry
Division of Molecular Medicine
Ruđer Bošković Institute
Bijenička 54, 10000 Zagreb
E-mail: seler@irb.hr

Abbreviations:
alpha-MTrp;
alpha-methyl tryptophan;
AD, Alzheimer's disease;
ADHD attention-deficit/hyperactivity disorder;
BBB, blood-brain barrier;
CSF cerebrospinal fluid;
MAO, monoamine oxidase;
PTSD, posttraumatic stress disorder;
5-HIAA, 5-hydroxyindoleacetic acid;
5-HTT, serotonin transporter;
TPH, tryptophan hydroxylase

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Abstract

Serotonin is a monoamine that could be found in plans, animals and human body. The homeostasis of serotonin is maintained by the series of interdependent processes that include synthesis, storage, transport and removal/degradation. In the human body serotonin is synthesized in two independent compartments that are separated by brain-blood barrier. The majority of serotonin is synthesized in enterochromaffin cells of the gastrointestinal tract, released in the blood stream and stored in blood platelets. About 5% of serotonin is synthesized in the brain within serotonergic neurons. As a neurotransmitter serotonin plays an important role in the regulation of physiological functions like body temperature, sleep, vomiting, sexuality, appetite, behaviour and cognitive functions such as learning and memory. The dysfunction of the serotonergic system has been implicated in the aetiology of a variety of psychiatric (depression, schizophrenia, alcoholism) and neurological (migraine, Alzheimer's disease, epilepsy) disorders. Recent genetic association studies of the neuropsychiatric disorders have focused on functional polymorphisms i.e. DNA sequence variations that alter the expression and/or functioning of the gene product in the loci encoding different genes. Some of them are genes for tryptophan hydroxylase, serotonin transporter and serotonergic receptors.

THE BEGINNINGS

Serotonin (5-hydroxytryptamine, 5-HT) was discovered 60 years ago in blood, peripheral tissues and central nervous system (*1*). It was first identified as a vasoconstrictor substance that is released from platelets during the coagulation of blood, and later as a monoamine neurotransmitter in the brain. It has been established that gastrointestinal tract, blood platelets and brain were the main locations of serotonin in the mammal's body. In addition, serotonin could be also found in plants (bananas, walnuts, tomatoes, hickories, pineapples), mushrooms, octopuses, and in poison of insects (spiders, scorpions, wasps).

Synthesis and metabolism

Serotonin is a tryptamine that consists of an indole ring with a hydroxide group on the fifth C atom, and a carboxyl-amide side chain (Figure 1).

The main precursor of serotonin is the essential amino acid L-tryptophan that must be provided by food. L-tryptophan and the other precursor, 5-hydroxytryptophan, are transported from blood to brain by the active carrier system located in the blood-brain barrier (BBB). It is believed that serotonin, due to its chemical properties, does not cross BBB, but new evidence (*2*) suggests that serotonin might cross endothelial cells of the BBB using serotonin transporter. The serotonin synthesis occurs in a two-step enzymatic procedure (Figure 2). The first

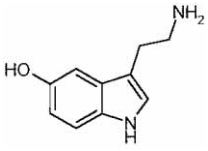

Figure 1. *The chemical structure of serotonin or 3-(2-aminoethyl)-5-hydroxyindole.*

and rate-limited step is hydroxylation of the tryptophan to 5-hydroxytryptophan. This reaction is catalyzed by tryptophan hydroxylase, a specific enzyme located only in the serotonergic neurons (*3*). The 5-hydroxytryptophan is decarboxylated by a nonspecific enzyme, aromatic amino acid decarboxylase, into serotonin. Serotonin levels could be determined in the brain and various body fluids including serum/plasma, platelets, cerebrospinal fluid (CSF) and urine. The flavine-containing mitochondrial enzyme monoamine oxidase (MAO) is the most important enzyme for degradation of serotonin. This process has two steps: first step is a degradation of serotonin into 5-hydroxyindole acetaldehyde, and the second one is degradation through aldehyde dehydrogenase regulated conversion into 5-hydroxyinoleacetic acid (5-HIAA) as the main metabolite of serotonin.

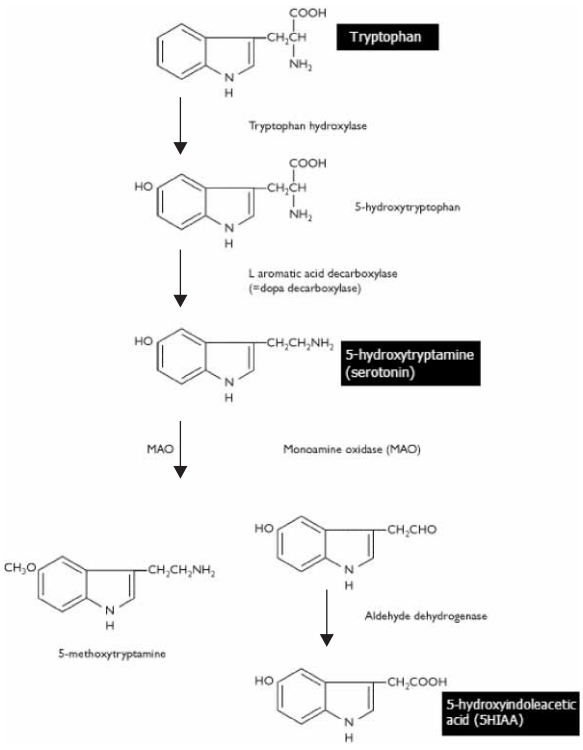

Figure 2. *Synthesis and degradation of serotonin.*

In the human body, serotonin is synthesized and located in two compartments that are separated by BBB. The first compartment, called »peripheral« compartment, contains the majority (about 95%) of serotonin in the body. Peripheral serotonin is synthesized in enterochromaffin cells of the gastrointestinal tract. The second, i.e. »central« compartment of serotonin is the central nervous system that synthesizes serotonin within serotonergic neurons. Recent studies (*3, 4*) revealed that tryptophan hydroxylase exists in two isoforms with different location within the body of mammals (Table 2). Tryptophan hydroxylase type 1 (TPH1) is responsible for the synthesis of the peripheral serotonin (*4*), while tryptophan hydroxylase type 2 (TPH2) is the predominant isoform in the brain.

Serotonergic receptors

The complex functions of serotonergic system would be impossible without a large number of serotonergic receptors (*5*). Serotonergic receptors are classified in seven different groups or »families« called 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, 5-HT7, and several subtypes (Table 1) that differ in terms of structure, action, and location. Serotonergic receptors are distributed on the presynaptic and postsynaptic neurons in the central nervous system and on the different peripheral cells and organs (Table 1). The majority of serotonin receptors are G protein-coupled receptors. The exception is 5-HT3 receptor that belongs to the ligand-gated ion channel receptors. Serotonergic receptors activate an intracellular second messenger (cAMP, IP3, DAG) cascade and produce an excitatory or inhibitory response. Serotonin receptors are very important sites of action for different classes of psychotropic drugs, like antidepressant drugs (*5*), atypical antipsychotic drugs (olanzapine, risperidone) and psychoactive compounds (LSD, DMT).

TABLE 1

The serotonergic receptors.

Type	Subtype	Distribution	Intracellular response
5-HT-1	1A, 1B, 1D, 1E, 1F	CNS, blood vessels	Inhibitory
5-HT-2	2A, 2B, 2C	CNS, platelets, blood vessels, smooth muscle	Excitatory
5-HT-3	3A, 3B	CNS, GI tract	Excitatory
5-HT-4		CNS	Excitatory
5-HT-5		CNS	Inhibitory
5-HT-6		CNS	Excitatory
5-HT-7		CNS, GI tract, blood vessels	Excitatory

Serotonin in the central nervous system

Serotonergic neurons are widely distributed throughout the mammalian brain and serotonergic system is the largest single system in the brain. The nine groups of serotonergic cell bodies are located mainly in the area of brain stem raphe nuclei. Serotonergic nerve terminals could be found in nearly all other regions of the central nervous system. The widespread distribution of the raphe projections suggests a highly collateralized axon system (*6*). The communication of serotonergic system with other important neurotransmitter systems like catecholaminergic system (*7*) is well established, although the mechanisms of interaction are not yet completely understood. Significant amounts of data have demonstrated that these interactions are very important in the mechanisms of action of antidepressant and anxiolytic drugs.

Serotonin is implicated in many physiological (body temperature, sleep, vomiting, sexuality, appetite), behavioural (aggression, mood) and cognitive (learning, memory) functions (*8*). In addition, serotonin has an important role in the growth of the central nervous system during development. It plays a critical role as a growth factor in the immature brain, directing both proliferation and maturation. This is supported by the higher serotonin turnover rate in the immature mammalian brain than at any other time in life. Recent data (*9*) suggested that an overload of serotonin during cortical development could induce abnormal distribution and incorrect positioning of cortical interneurons.

There are several methods for the determination of serotonin synthesis rate in vivo: a) pharmacological manipulation, i.e. after the administration of compound that inhibits enzyme aromatic acid decarboxylase like NSD-1015, b) the use of radiolabel tryptophan, c) the use of radiolabel alpha-methyl tryptophan (alpha-MTrp) as an analogue of tryptophan. The limitation of the pharmacological methods is that the effect of the tested compound on the serotonin synthesis could be in part influenced by the pre-pharmacological manipulation itself. Radiolabel tryptophan is an essential amino acid incorporated in proteins, while radiolabel tryptophan metabolites, like serotonin and 5-HIAA, are lost very rapidly from the brain. The use of alpha-MTrp labelled with ^{3}H or ^{14}C and the determination of serotonin synthesis by an autoradiographic method (*10*) permits the measurement of serotonin synthesis in the rat brain with high anatomical resolution and without any pharmacological pre-treatment. The disadvantages of this method are the need for special equipment and a long procedure.

The alteration of the serotonergic system has been related with the aetiology of different neurological (migraine, Alzheimer's disease, epilepsy) and psychiatric (depression, schizophrenia, mood disorders, alcoholism, ADHD, PTSD) disorders.

Peripheral serotonin

Peripheral serotonin is synthesized in enterochromaffin cells of the gastrointestinal tract. The synthesis is regulated by TPH1 (*4*). From gut serotonin is released in the blood stream and than stored mostly in blood platelets. The other peripheral cells that contain serotonin are macrophages and mast cells. Peripheral serotonin is metabolized in the liver by a MAO-A to 5-HIAA. The 5-HIAA is filtrated and excreted by the kidney. The vast increase in urine excretion of 5-HIAA was found in carcinoid syndrome, due to the pronounced production of serotonin by carcinoid cells.

In humans a direct association between neurotransmitters in the brain and those excreted in the urine is not yet defined. New evidence suggests (*2*) that neurotransmitters excretion in the urine might be used as possible biomarkers of the central nervous system activity. The study in rats treated with 5-hydroxytryptophan has shown simultaneous changes in the activity of brain serotonergic system and urinary serotonin levels.

Serotonin has an important role in the vascular biology. It is involved in the control of vascular resistance, blood pressure, haemostasis and platelet function (*11*). One of the most important functions of the peripheral serotonin is the promotion of platelet aggregation and blood clotting. Activated 5-HT-2A receptors on platelet membrane also stimulate platelet activation and aggregation.

Blood platelets and serotonergic neurons

The function of central serotonin in mood, state of mind, and behaviour, as well as its role in cognition and memory are very difficult to establish. Literature data suggest that blood platelets can be used as an easy obtainable peripheral model for the some processes in the central serotonergic neurons (*12–14*) (Table 2). The kinetic and pharmacological characteristics of the active transport of serotonin from plasma to platelets are similar to the reuptake of serotonin from synaptic cleft into presynaptic neurons. In addition, platelet MAO type B activity corresponds to MAO-B activity in presynaptic part of neurons. There are also 5-HT2A receptors (*14*), α_2-adre-

TABLE 2

Similarities and differences between blood platelets and serotonergic synaptosomes.

Brain serotonergic neuron	Blood platelets
Similarities	
Serotonin stored in dense bodies or vesicles	
Active transport (uptake) of serotonin	
Binding sites for ^{3}H-paroxetine, ^{3}H-imipramine	
Receptors: 5-HT2A and α_2-adrenergic	
Monoamine oxidase type B	
Differences	
Serotonin synthesis	No synthesis
Function: Neurotransmission	Function: aggregation, vasoactive compound

nergic receptors (*15*) and binding sites for ^{3}H-imipramine and ^{3}H-paroxetine on the platelet membrane, which can be used as peripheral markers for the evaluation of pharmacologic and kinetic characteristics of equivalent central nervous receptors and binding sites on presynaptic or postsynaptic part of the serotonergic neurons in psychiatric and neurodegenerative disorders.

Numerous studies have tested platelet serotonin concentrations in various psychiatric disorders. Altered platelet serotonin concentrations were found in patients with different psychiatric and neurological disorders like major depression (*16*), subtype of major depression with psychotic symptoms (*17*), bipolar disorder (*18*), schizophrenia (*16*, *19–21*), postpartum depression (*22*), posttraumatic stress disorders (PTSD) with comorbid depression (*23*), PTSD with psychotic symptoms (*24*), alcoholism (25), attention-deficit/hyperactivity disorder (ADHD) with impulsive symptoms (*26*), migraine (*27*), and Alzheimer's disease (*28, 29*).

SEROTONIN AND NEUROPSYCHIATRIC DISORDERS

Preclinical and clinical investigations suggest that serotonin could be related to the aetiology and treatment of different neuropsychiatric disorders including depression, schizophrenia, PTSD, alcoholism, ADHD and Alzheimer's disease (AD).

Depression

Depression is a severe and devastating mental disorder with a high prevalence worldwide, and with twice higher risk in women than in men. Although, the pathogenesis and treatment of depression were the topics of intensive preclinical and clinical research, the complex neurobiological basis of depression is still unclear (*30*). The first hypothesis of depression was established almost forty years ago (*31*). It postulated that depression is a consequence of the low serotonin and/or noradrenalin levels and the dysfunction in the central serotonergic, noradrenergic and dopaminergic systems. These neurotransmitters interact with each other and regulate mood, sleep, anhedonia, appetite, concentration and motivation, suicidal behaviour, cognitive and autonomic functions (*8*) that are frequently disturbed in depression.

In following years numerous attempts were made to identify the reproducible neurochemical alterations in the nervous systems of patients with depression, but mostly with negative or inconsistent results. Concentrations of 5-HIAA, the major 5-HT metabolite, in CSF have been extensively studied in depressed subjects. A significant reduction in CSF 5-HIAA was found in depressed patients (*32*), but several other studies (*33*) were not able to confirm the difference in 5-HIAA levels between depressed patients and healthy controls. Recent study (*34*) described elevated brain serotonin turnover rate in medication-free patients with depression, particularly in those carrying the short form (s allele) of the gene for serotonin transporter. However it was not clear if the elevated brain serotonin turnover is a consequence of increased neuronal activity, enhanced vesicular leakage and subsequent intraneuronal metabolism or reduced brain serotonin transporter availability.

Platelet serotonin levels, platelet 5-HTT and platelet 5-HT2A receptors were also investigated in depression. The decreased (*35*) or unaltered (*19, 36*) platelet serotonin levels were found in depressive patients as well as altered number of platelet 5-HT2A receptors and the number of platelet serotonin uptake sites (*37*).

The majority of antidepressant drugs in current use, act by affecting the neurotransmitters (serotonin, noradrenalin, and dopamine), their receptors and enzymes involved in their synthesis or degradation (*38*). However, the clinical improvement after antidepressant therapy is usually observed 2–3 weeks after the beginning of the treatment. It is believed that this therapeutic delay depends on the antidepressant-induced desensitization of serotonergic or noradrenergic receptors.

Schizophrenia

Schizophrenia is a complex and multifactorial mental disorder with the prevalence of 1% worldwide. The alterations of the dopaminergic system and their receptors are the basis for the »dopaminergic hypothesis« of schizophrenia. Since this hypothesis is not able to explain the complex symptoms of disease and efficacy of atypical antipsychotics, with a higher affinity for 5-HT2A than to D2 receptors, it is supposed that schizophrenia might be associated with the dysfunction of other neurotransmitters systems like serotonergic system (*39*). In addition serotonergic system regulates some physiological and behavioural functions that are disturbed in schizophrenia (*8*). In line with this »serotonin hypothesis of schizophrenia« the alteration of serotonergic activity was found in the brain of schizophrenic patients, with the decreased serotonin neurotransmission in cortical regions, and increased in the putamen, accumbens and pallidus. The decreased or unaltered density of 5-HT2 receptors in frontal cortex (*39*), decreased density of 5-HT1A receptors and unchanged 5-HT6 receptor binding (*40*) were also found in schizophrenic patients.

An increase in platelet serotonin concentration was observed in schizophrenic patients with predominantly chronic time course (*41*), with paranoid symptoms (*19*), positive symptoms (*42*) and in schizophrenic patients born in winter (*20*). Although there is no direct evidence that platelets serotonin concentration correlates with central serotonin levels, an abnormal tomographic brain scans were found in schizophrenic patients with high platelet serotonin levels (*43*).

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a severe psychiatric and polygenetic disease that appears in some people that survived the extremely dangerous traumatic life event like natural disasters, war or sexual abuse. PTSD could be associated with alterations in different

neuroendocrine (*44*) and neurotransmitter (*45*) systems. Despite the intensive neurobiological research, the role of serotonin in the pathophysiology of PTSD is still unclear. Some studies (*46*) suggested altered serotonergic function in PTSD that might contribute to cognitive disturbances, depressive symptoms and many physiological and pathological behaviours, such as aggression, that frequently arises in PTSD.

It is believed that serotonergic neurons from dorsal nuclei raphe with nerve terminals in hippocampus and amygdala are responsible for anxiogenic response to stress via 5-HT2A receptors, while neurons from median raphe have anxyolitic effect achieved through 5-HT1A receptors. However, a positron emission tomography study (*47*) did not find altered 5-HT1A receptors binding in patients with PTSD compared to healthy subjects. Indirect peripheral evidences for the altered efficacy of serotonergic system in PTSD are decreased serum serotonin concentration and altered number of platelet serotonin transporters *(48)*. Platelet serotonin concentration was higher in PTSD veterans with psychotic subtype of PTSD compared to platelet serotonin concentration in non-psychotic war veterans or in healthy controls (*24*). Since platelet serotonin concentrations correlated with the severity of delusions, the core psychotic symptoms, these data confirmed that platelet serotonin concentration might be used as a trait marker of psychotic symptoms in PTSD.

Alcoholism

Literature data suggest that alcohol dependence and alcohol abuse could be associated with the disturbance in serotonergic system (*49*). The role of serotonin in alcoholism is based on the data showing alterations in measures of the serotonergic function in the brain, as well as in CSF, blood precursor availability, uptake of serotonin in blood platelets and challenge studies.

Post-mortem brain analyses have found reduced serotonin transporter binding in the hippocampus (*50*) or in dorsal striatum (*51*), and decreased density of 5-HT1A receptors (*52*) in patients with alcoholism compared to non-alcoholic controls. Reduce activity of serotonergic transporter in the brain of abstinent alcoholics was confirmed in vivo using SPECT (*53*). The values of 5-HIAA concentration in CSF are in line with central serotonergic disturbances in patients with alcoholism. Low levels of 5-HIAA in CSF were found in early-onset alcoholics (*54*), in abstinent alcoholics (*55*) and in alcoholic impulsive offenders (*56*).

Decreased plasma tryptophan levels and low serotonin precursor availability suggest impaired serotonin synthesis in alcoholism (*49*). The results on the blood platelets serotonin transporter activity in patients with alcoholism are inconsistent. Lower (*57*), increased (*58*), or unaltered (*59*) serotonin uptake into platelets were found in alcoholics when compared to healthy controls. Alcoholism-induced fall of serotonin transporter activity has been related to a decreased platelet serotonin content observed in male and female alcoholic patients, independently on the presence of comorbid psychiatric disorders (*60*).

It has been shown that prolactin or cortisol response to administration of serotonergic drugs like fenfluramine, m-clorophenylpiperazine, 6-chloro-2-1-piperazinylpyrazine, and adrenocorticotropic hormone (ACTH) response to m-chlorophenylpiperazine, was lower in alcoholics than in non-alcoholic patients (*61*), suggesting also altered central serotonergic function in alcoholism.

ADHD

Serotonin dysfunction has been implicated also in ADHD, although the primary neurotransmitter that is altered in ADHD is dopamine, and to a lesser extent, noradrenalin (*62*). However, besides the classical characteristics symptoms of ADHD (such as hyperactivity, inattention and impulsivity), aggression, as well as disturbances in the cognition, are also frequent in ADHD. These findings confirmed also the role of serotonin in ADHD (*63*). The concentration of serotonin was found to be lower in ADHD (*64*), or unaltered in ADHD (*26*). Since ADHD is a multifactorial and clinically heterogeneous psychiatric disorder, platelet serotonin concentration was found to be increased in children with ADHD with pronounced impulsive symptoms (*26*) suggesting that higher platelet serotonin concentration in impulsive compared to non-impulsive children with ADHD might be used as a possible trait marker of impulsivity in ADHD. The impulsivity is associated with serotonin function in non-clinical sample (*65*). There is a significant correlation between impulsivity and lower serotonergic function (*66*). On the other hand, the opposite data exist, and therefore impulsivity has been associated also with the increased serotonergic functioning (*67*) in children and adolescents.

Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized with a progressive loss of cognitive functions such as learning and memory. The aetiology and pathophysiology of AD is still unclear. The neurobiological alterations in AD include accumulations of amyloid plagues outside and neurofibrillary tangles inside neurons and the dysfunctions of cholinergic, catecholaminergic and serotonergic systems. The decrease in the brain concentration of serotonin and 5-HIAA was found in AD (*68*). The loss of presynaptic somatodendritic 5-HT1A autoreceptors and postsynaptic 5-HT1A heteroreceptors (*68*), and 5-HT2 receptors in cerebral cortex (*69*), were also found in patients with AD. It seems that the development of behavioural and psychological symptoms in AD (*70*) is related to the genetic variants of 5-HT2A and 5-HT2C receptors. In addition, daily living and functioning was improved in patients with AD treated with combination of rivastigmine and selective serotonin reuptake inhibitor, fluoxetine.

The reduced serotonin concentration in platelets (*29*), CSF (*71*) and brain (*72*) of patients with AD would sug-

gest the decrease in serotonin synthesis. The main factors that influence serotonin synthesis are plasma availability of its precursor tryptophan and the activity of the rate-limiting enzyme TPH. Plasma level of tryptophan depends on the dietary intake and feeding behaviour that could be also changed in AD. In patients with AD low tryptophan concentrations in serum *(73),* plasma (*74*) and CSF (*71*) was found in some, but not all studies (*75*). The alterations in serotonergic and kynuramine pathways of tryptophan metabolism have been connected to pathophysiology of AD (*76*), suggesting that low plasma tryptophan concentration in AD might be also a consequence of the enhanced tryptophan degradation via the kynuramine pathway (*73*). In addition, tryptophan depletion in healthy volunteers (*77*) or in patients with mild to moderate AD (*78*) induced changes in cognitive performance.

Altered serotonin synthesis in AD (*72*) might be a consequence of reduced TPH activity in particular brain areas of patients with AD (*79*) or the lack of the TPH cofactors tetrahydrobiopterin and folic acid. Since TPH activity is sensitive to reactive oxygen species, the tetrahydrobiopterin deficiency could also impair serotonin synthesis through oxidative damage of TPH (*80*).

A decreased platelet serotonin concentration observed in patients with AD in the late phase of disease (*29*), might be related to the reduced serotonin active transport through platelet membrane. This finding is in line with the decrease in the maximum number (Vmax) of serotonin transporters found in severely ill patients with AD compared to both patients with mild AD and healthy controls (*81*).

CANDIDATE GENES OF THE SEROTONERGIC SYSTEM

Recent genetic association studies of the neuropsychiatric disorders have focused on functional polymorphisms i.e. DNA sequence variations that alter the expression and/or functioning of the gene product in the loci encoding different genes. Some of them are genes for TPH, serotonin transporter (5-HTT) and serotonin type 1A (5-HT1A), 1B (5-HT1B), 2A (5HTR2A) receptors.

Tryptophan hydroxylase

Tryptophan hydroxylase (EC 1.14.16.4) is a key enzyme in the synthesis of serotonin. It metabolizes the essential amino acid L-tryptophan, by hydroxylation at the position 5, to the serotonin precursor L-5-hydroxytryptophan (Figure 3.). The cofactors are O_2 (dioxygen), BH_4 /(6R)-L-erythro-5,6,7,8-tetrahydrobiopterin/ and Fe^{2+}. TPH is a specific and selective enzyme that is only located in the serotonin producing cells like serotonergic neurons, pineal gland and enterocromaffine cells of the gut. It exists in two isoforms (*3*), with different location within the body of mammals (Table 3). One isoform is TPH1 that is responsible for the synthesis of the peripheral serotonin (*4*), while TPH2 is the predominant isoform in the brain.

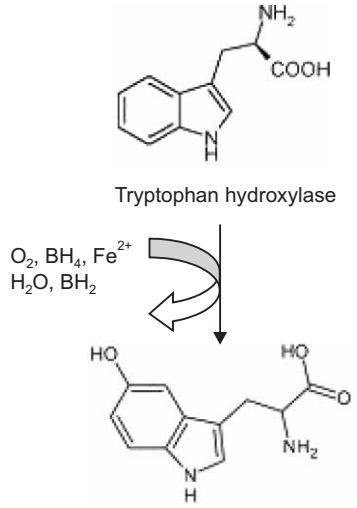

Figure 3. *Tryptophan hydroxylase catalyzes tryptophan to 5-hydroxytryptophan.*

In humans, the genes for TPH1 (MIM *191060) and TPH2 (MIM *607478) are located on chromosomes 11 at position 11p14-p15.3 and 12 (12q21), respectively. The human TPH2 gene spans 97 kilobases (kb) and consists of 11 exons. The sequence identity between two homologous TPH is 71% (*121*). In TPH1 knockout mice the concentration of peripheral serotonin was reduced to 6% (blood), 1.5% (jejunum) and 0.1% (colon) as compared to serotonin concentration in wild type mice (*3, 82*). However, genetically modified mice without TPH1 isoform had normal serotonin concentration in hippocampus and frontal cortex (*82*), and similar development, appearance and behaviour as mice with TPH1 gene. Those results suggested that serotonin synthesis in the brain depends mostly on the TPH2 isoform activity. Recently, Savelieva *et al.* (*3*) reported the phenotypic evaluation of TPH2 knockout mice and double knockout mice without both TPH1 and TPH2 gene. They have found the pronounced decrease in serotonin levels in cortex, thalamus/hypothalamus, olfactory bulb, cerebellum hippocampus, brainstem and striatum in both groups of knockout mice compared to wild type mice. The lowest serotonin concentration was determined in double knockout mice without TPH1 and TPH2 gene. Although genetically modified mice were similar in appearance, or histological analysis with no loss of the serotonergic cell bodies in raphe nucleus, there were differences in the body weight, body size and percent of body fat in male, and percent of body fat in female double knockout mice compared to wild type mice (*3*). There were a few effects of *TPH* genotype on behaviour. Mutant mice had similar exploratory behaviour and locomotor activity and showed increased anxiety-like behaviour (*3*).

Several studies analyzed the association between genetic variants of the TPH in neuropsychiatric disorders and emotion-related personality traits, but with inconsistent results. Zhang *et al.* (*83*) reported that allele A of the functional polymorphism G1463A at TPH2 gene could

TABLE 3

Two tryptophan hydroxylase isoforms, their location and function of the corresponding central or peripheral serotonin.

Tryptophan hydroxylase isoform	
TPH1	TPH2
Location	
Peripheral tissue	Brain
Serotonin functions	
Migraine	Migraine
Vasoconstriction	Sleep
Haemostasis	Behaviour
Immune system	Mood
Intestinal motility	Food intake and body weight
Melatonin synthesis	Neuropsychiatric disorders

be related to the low TPH2 activity and consequently to the impaired brain serotonin synthesis in depressed patients. Their suggestion that 1463A allele could be a risk factor for unipolar major depression were not confirmed in the larger number of patients of the West European Caucasian origin with affective disorders (*84*), or in Chinese population with unipolar depression (*85*). Recent, haplotype analysis of the eight polymorphisms: rs4448731 (intergenic), rs4565946 (intron 2), rs11179000 (intron 4), rs7955501 (intron 5), rs10506645 (intron 7), rs4760820 (intron 8), rs1487275 (intron 8) and rs10879357 (intron 8) of the human TPH2 (*86*) has shown no association between TPH2 polymorphisms and bipolar depression and suicidal behaviour in Brazilian population. There were also no significant differences in genotype or allele frequencies of the TPH2 -703G/T polymorphism between bipolar patients and healthy subjects of the Korean origin (*87*). The meta-analysis of *TPH1* and *TPH2* gene variants in the large number of subjects with ADHD from four independent European Caucasian samples have shown no consistent evidence for common genetic variants in the *TPH1* and *TPH2* regions in ADHD (*88*).

It has been hypothesized that smaller volumes of the amygdala and hippocampus are related to the presence of the T allele of the TPH2 (rs4570625; G-703T) polymorphism in Japanese subjects. This was the first study that compared personality traits (harm avoidance, reward dependence, novelty seeking, persistence, self directedness, cooperativeness, self-transcendence) assessed with the Temperamental and Character Inventory (*89*), with the volume of amygdala and hippocampus (determined using magnetic resonance imaging) in T allele carriers and GG individuals. The results suggested that regional brain volume could be a brain structural intermediate phenotype between genetic variations in THP2, i.e. between serotonin synthesis and personality traits related to mood or anxiety disorders (*89*).

Serotonin Transporter-Linked Polymorphic Region

The serotonin transporter (5-HTT) is an important protein responsible for the active transport of serotonin into neurons, enterochromaffin cells and platelets. In the brain 5-HTT is localized in membrane of presynaptic nerve terminals and in dendritic arbors close to serotoninergic cell bodies. 5-HTT regulates serotonin levels in the synaptic cleft following neuronal stimulation, and consequently the magnitude and duration of its effect on postsynaptic serotonergic receptors. It terminates the action of serotonin by rapid reuptake of released serotonin from synaptic cleft into presynaptic neuron by means of an active transport process that depends upon maintenance of ion gradients across the cell membrane by Na^+-K^+--ATPase (*90*). The *in vitro* and *in vivo* (*91*) studies have shown that 5-HTT is not only a protein with important role in the homeostatic regulation of the serotonergic function, but also a site of action for several classes of antidepressant drugs including classical tricycle compounds and novel selective serotonin reuptake inhibitors (*91*).

Among a number of genes involved in the synthesis of protein related to metabolism and function of serotonergic system, gene encoding the 5-HTT (*SLC6A4*) is the most extensively investigated. The 5-HTT gene (OMIM *182138) is located on chromosome 17 at position 17q11.1--17q12 and consisted of fifteen axons encoding a protein of 630 amino acids with 12 transmembrane domains (*90*, *92*). The most studied variants in the *5-HTT* gene are the serotonin transporter-linked polymorphic region (5-HTT gene-linked polymorphic region, 5-HTTLPR; rs795541) and a functional variable number of tandem repeats (VNTR) polymorphism in intron 2. 5HTTLPR is a repetitive element of varying length in the 5' flanking region located č1.4kb upstream of the transcription start site that modulates transcriptional activity of human 5--HTT (*90*). A deletion/insertion in the 5-HTTLPR creates two alleles (each of 20 to 23 bp): short or *S* allele and long or *L* allele made up of fourteen and sixteen repeated elements, respectively. Some studies have found that long allele results in higher serotonin transporter mRNA transcription in human cell lines. The uptake of serotonin is two-fold higher in cells containing the homozygous *L/L* form of the *SLC6A4* than either the *L/S* or *S/S* forms. On the other hand, *S* allele is associated with reduced transcriptional efficiency and decreased 5-HT expression and uptake (*92*).

It has been suggested that this 5-HTTLPR polymorphism alters the promoter activity and consequently serotonergic functions (*93*). In this respect, a significantly higher maximal number (Bmax) of platelet serotonin uptake sites was found in subjects carrying the L/L genotype as compared with Bmax of platelet serotonin uptake sites in individuals with L/S or S/S genotype (*94*). Additionally, the uptake of serotonin is approximately two--fold higher in cells containing the homozygous *L/L* form of the *5-HTT,* while *S* allele is related to reduced transcriptional efficiency and therefore decreased serotonin uptake (*92*). Volumetric neuroimaging studies have

shown that the *S* allele is associated with reduced grey matter volume in the limbic system and disrupted amygdala-cingulate coupling (*95*).

The intron 2 VNTR contains nine, 10, or 12 copies of a sixteen- or seventeen-base pair repeat (*96*). A stronger expression and greater enhancer activity was observed by the 12-copy allele than by the 10-copy allele in the hindbrain of transgenic embryonic mice (*97*) and in embryonic stem cells (*98*) suggesting its functionality. Very poor linkage disequilibrium was found between 5HTTLPR and the intron 2 VNTR (*99*).

A lot of studies conducted in healthy individuals and in patients with psychiatric and neurological disorders suggested that 5-HTTLPR could be considered as a candidate gene for depression (*99*), mood disorders (*100*), alcoholism, autism and stress related psychiatric disorders, while other studies did not replicate these data (*101*). An association between early stressful life event (childhood maltreatment, abuse, lack of social support) and increasing risk for the development of depression in subjects carrying short alleles was found (*102*). In addition, there is a growing body of literature suggesting the connection between stressful life events and occurrence of depression that may be dependent on variation at the 5-HTTLPR locus of the *5-HTT* (*102*). However, recent meta-analysis (*103*) did not confirm that the 5-HTTLPR genotype and stressful life events, alone or in combination, are risk factors for the development of depression in both male and female subjects.

Different findings related to the association between 5HTTLPR and psychiatric disorders might be induced by differences in population genetic structure and substructure between cases and controls, and to ancestry differences corresponding to ethnic groups. There are significant differences in the allele frequencies in 5-HTTLPR between Caucasian and Asian populations, since *S* allele is found in 42% of Caucasians and in 79% of Asians (*104*). In the large groups of healthy subjects from Croatia and the Russian federation (Russians, Bashkirs and Tatars) there were significant ethnic differences in allele and genotype frequencies of the 5-HTTLPR (*104*). These finding might explain the contradictory results showing the positive or negative or no association between various psychiatric disorders, treatment outcomes and 5-HTTLPR across different populations.

The association between 5HTTLPR and s platelet serotonin concentration was also studied, but the findings were contradictory, showing positive, negative or a lack of association (*105–107*). The study including large groups of healthy male and smaller groups of female Caucasian subjects of Croatian origin, free of neuro-psychiatric disorders, showed also a lack of association between 5--HTTLPR genotypes and platelet 5-HT concentration, and failed to detect the functional relevance of the 5--HTTLPR variants on platelet 5-HT concentration (*107*). Therefore, since a positive significant association between *L/L* and *L/S* genotypes and increased blood serotonin levels was detected in patients with obsessive-compulsive disorder, the results of the lack of association between 5HTTLPR and platelet serotonin concentration suggest that genotype-induced changes in 5-HTT transcription and consequent changes in platelet serotonin concentration might be differently regulated in healthy subjects and psychiatric patients (*107*).

The relationship between the changes in serotonin uptake and 5-HTT gene in patients with AD is inconsistent. A study (*108*) failed to find the difference in the allelic distribution on the deletion/insertion polymorphism of the 5-HTT gene between patients and controls. In contrast, an association between long allele of the 5-HTT gene and development of aggressive behaviour in AD was found (*109*).

Serotonin type 1A receptor

Serotonegic receptor type 1A (5-HT1A) is one of the most investigated and characterized serotonergic receptors. The 5-HT1A receptors were found in a variety of human brain regions (*110*). They are subdivided according to their location in a) presynaptic somatodendritic 5-HT1A autoreceptors located on cell bodies and dendrites of serotonergic neurons in dorsal and median raphe nuclei and b) 5-HT1A heteroreceptor positioned postsynaptically in the pyramidal cells and interneurons of cortico-limbic regions (hippocampus, cerebral cortex and lateral septum) that received serotonergic input from the raphe nuclei (*5*). The activation of presynaptic 5-HT1A autoreceptors by serotonin or its agonists inhibits the firing rate of the serotonergic neuron and reduces serotonin synthesis, turnover and release (*111*) and thus affects the serotonergic activity in projection areas. In addition, 5-HT1A receptors have an important role in the neurodevelopmental processes such as synapse formation, neurite outgrowth and neuronal migration (*112*). Due to their wide distribution and multitude of functions, 5--HT1A receptors are associated with aetiology and treatment of mental disorders (*113*), especially major depressive disorder.

Post-mortem evaluation of the number and/or affinity of 5-HT1A receptors in the brain of depressed patients revealed different results among studies. Reduced 5-HT1A ligand binding or receptor gene expression was found in cortico-limbic regions of the suicide depressed victims with or without medication at the time of death (*114*). The increase in 5-HT1A receptor binding (*115*) and negative results (*116*) were also reported. This lack of consistency between studies can be due to the variety of factors including sex, comorbidities (substance abuse, alcohol dependence and other psychiatric diagnoses), post-mortem delay and to the different methods used for the measurement of the 5-HT1A ligand binding. The desensitization of presynaptic 5-HT1A autoreceptors, but not postynaptic receptors was observed after chronic treatment with antidepressants like serotonin reuptake inhibitors and monoamine oxidase inhibitors.

The 5-HT1A receptor is coded by the *HTR1A* gene (OMIM *109760) located on chromosome 5 at position

5q11.2-q13. Recently, the 27 single nucleotide polymorphisms of the *HTR1A* gene were described (*113*). Among them the most investigated, and the most prevalent in normal human population is a functional polymorphism C-1019G (rs6295), located within the promoter region of the gene. It has been shown that this polymorphism regulates gene expression (*117*). Genetic studies suggested that the G allele of the C-1019G is associated with an increase in presynaptic 5-HT1A receptor expression and lowered expression of the postsynaptic 5-HT1A receptor. These opposite effects could be related to two transcription factors: epidermal autoregulatory factor-1 (Deaf-1 or NUDR) and Hes5 that are co-localized on both, presynaptic and postsynaptic 5-HT1A receptors (*117, 118*). Deaf-1 is a repressor at somatodendritic 5-HT1A receptor, but enhances the transcription in non-serotonergic neurons that express postsynaptic 5-HT1A receptors.

Several studies investigated the association between C-1019G *HT1A* promoter polymorphism and regional binding potential of two selective 5-HT1A antagonists ^{11}C-WAY100635 or ^{18}F-MPPF using Positron Emission Tomography (PET) in healthy subjects, but with inconsistent results (*119*). Concerning response to treatment, the C-1019G variant seems to be of primary interest in antidepressant response: C allele carriers generally show a better response to treatment, especially in Caucasian samples (*113*).

Serotonin type 1B receptor

Serotonergic receptors type 1B (5HT1B) were found to be rodent specific and similar to the human serotonergic receptor type 1D (5-HT1D). Since these two types of 5-HT1 receptors share similar brain distribution, transductional features and function, it has been suggested that they are species homologues with 97% overall sequence homology (*5*).

Serotonergic receptors type 1B (5HT1B) are terminal autoreceptors and postsynaptic heteroreceptors (*5*), located in the central nervous system in the basal ganglia, striatum, hippocampus and cortex. 5-HT1B receptors were also found on the variety of vascular tissues including cerebral arteries. The main function of autoreceptors located on the nerve terminals is the control of serotonin release, but they may act as terminal heteroreceptors controlling the release of other neurotransmitters like catecholamine and GABA (*5*).

A recent study *(120)* has shown the co-localization and interaction of 5-HT1B receptors and protein p11 at the cell surface in vitro. The p11 knockout mice exhibited a depression-like phenotype and had reduced responsiveness to 5HT1B receptor agonists and reduced behavioural reactions to antidepressants. The decrease in brain p11 expression was found in the animal model of depression and in the brain tissue from depressed patients, while an over expression in p11 and the increase in 5HT1B receptor function was observed in rodent brains after antidepressants or electroconvulsive therapy *(120)*.

Animal studies suggested that 5-HT1B receptors have a role in aggressive behaviour related to alcoholism. Knockout mice showed increased alcohol intake and more propensities to aggressive behaviour, although other studies (*121*) did not confirm the relationship between 5-HT1B receptors and alcoholism. The 5-HT1B receptor gene has been postulated to play a modulatory role in alcohol consumption and alcohol dependence, and was considered as candidate gene for alcoholism (*122*).

In humans 5-HT1B receptor is encoded by the gene *HTR1B* (OMIM*182131) located on chromosome 6 within the region 6q13-q26 at position 6q14.1. Intronless *HTR1B* gene consists of a single exon, encoding a 390 amino acid peptide (*123*). A number of polymorphisms has been discovered in the coding sequence and surrounding 5' and 3' untranslated regions. 5*HTR1B gene* is an attractive candidate for studies of the genetic basis of ADHD (*124*). The most widely studied polymorphism of the *HTR1B gene* in and around the *HTR1B* locus is relatively common synonymous G861C polymorphism (*124*).

Serotonin type 2A receptor

Serotonin type 2A receptor (5HT2A) is a G protein coupled serotonergic receptor located on the membrane of postsynaptic serotonergic neurons. High concentrations of 5-HT2A receptors were found on the apical dendrites of pyramidal cells in layer V in cortex (prefrontal, parietal, somatosensory), claustrum and basal ganglia *(5)*. In the brain 5-HT2A receptors mediate hormone secretion, mood and perception, and regulate different behaviours. 5-HT2A receptors are highly expressed in blood platelets, fibroblasts, and many cell types of the cardiovascular system. Widely distributed peripheral 5-HT2A receptors are involved in the platelet aggregation (*14*), capillary permeability and vascular smooth muscles contraction. 5-HT2A receptors are molecular target for many atypical antipsychotic drugs like olanzapine or risperidone.

The loci encoding the serotonin type 2A receptor (*HTR2A*) are located on the long arm of the chromosome 13q14-q21 in man, and on chromosome 14 in the mouse *(125)*. The *HTR2A* gene consists of 3 exons separated by 2 introns and spans over 20 kb (*126*). A number of polymorphisms encoding for *HTR2A* gene was found, including A-1438G (rs6311), T102C (rs6313) and His452Tyr (rs6314). Several genetic studies investigated the association of *HTR2A* genetic variants and vulnerability to psychiatric disorders like schizophrenia (*127*), suicide (*128*), panic disorder, alcoholism (*129)* and AD (*130*), with inconsistent and mostly negative results. Several studies reported that particular polymorphism in *HTR2A* gene may, to some extent, account for the difference in treatment response to risperidone (*131*), clozapine (*132*) and antidepressants (*133*).

IN CONCLUSION

Since serotonin discovery in the gastrointestinal tract *(1)*, the comprehensive investigations enlarge its first role as a hormone to the neurotransmitter function in the central nervous system that has a myriad of central and peripheral functions. However, serotonin has an important role in the modulation the effects of other neurotransmitters. In the words of Thomas Carew, a Yale researcher, »Serotonin is only one of the molecules in the orchestra. But rather than being the trumpet or the cello player, it is the band leader who choreographs the output of the brain.«

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