Chapter 10

Serotonin in Neurological Diseases

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Abstract

Serotonin (5-HT) is responsible for anxiety, aggression, and stress. Alterations in a serotonergic system play a significant role in pathogenesis of neurological diseases and neuropsychiatric disorders. A wide range of disturbances associated with serotonergic neurotransmission results from different functions of 5-HT in a nervous system. It is believed that 5-HT may be involved in the pathogenesis of migraine, epilepsy, Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). In these diseases, disturbances of 5-HT and its metabolites, such as 5-hydroxyindoleacetic acid (5-HIAA), were observed in the plasma, blood platelets, and cerebrospinal fluid (CSF). Changes in the level of this biogenic amine (5-HT) may be associated with malfunction of 5-HT receptors, reuptake transporter for 5-HT (5-HTT, SERT), the enzymes responsible for the synthesis and metabolism of 5-HT, and genetic variants for serotonergic system. It seems that 5-HT and its metabolites may be used as a diagnostic and prognostic marker for neurological diseases or a target for more efficient therapy in neurology in the future.

Keywords: serotonin, molecular factors, neurological diseases

1. Introduction

Serotonin (5-HT) is a neurotransmitter responsible for anxiety, aggressive behavior, stress, blood pressure regulation, peristaltic movements, heart rate, and the coagulation system. 5-hydroxytryptamine (5-HT) is produced in neurons and gut cells, as well as in the walls of blood vessels and the heart. On the periphery, 5-HT is located in platelets, which enters via 5-HT reuptake transporter (5-HTT, SERT) [1].

The level of 5-HT in whole blood is in the range of 65–250 ng/ml and in the plasma has a lower value, 5.6–23.9 ng/ml [2]. 5-HT enhances the response of the adrenal medulla, and other sympathetic ganglia using 5-HT2A/3. It has been shown that the impairment of serotonin transporter (SERT) function in addition to the increased 5-HT in the extracellular fluid and increased turnover of 5-HT and its decreased level in nerve cells causes an abnormal stress response in the form of anxiety, as well as an excessive response of the adrenal medulla, including triggered by the hypothalamic-pituitary axis (with no effects on the expression of tyrosine hydroxylase and AT_2 receptors) [3]. Furthermore, 5-HT released from the terminals of afferent vagal neurons enhances the activity of the catecholaminergic neurons of the solitary tract nucleus (pulsed through potentiation of glutamatergic) and the effect on food intake and cardiovascular reflexes [4]. 5-HT acting on 5-HT4 receptors in the human heart causes stimulation of the atrium, pro-arrhythmic effect, produces a positive inotropic effect. At the same time, stimulation of 5-HT1B/1D endings of the sympathetic cardiac causes decreased release of norepinephrine (NE) [2]. 5-HT binds competitively to the binding site of catechol-O-methyltransferase (COMT) in binding site S-adenosyl-S-methionine, inhibiting methylation substrates for this enzyme [5]. It also acts antiapoptotic by stimulating the expression of cystathionine-beta-synthase (CBS) and increases the level of hydrogen sulfide (H_2S) and antioxidant activity [6].

Currently, it is believed that disturbances in the level of 5-HT may be associated with the pathogenesis of few neurological diseases such as migraine [7], epilepsy [8], Parkinson's disease (PD) [1], multiple sclerosis (MS) [9], and amyotrophic lateral sclerosis (ALS) [10] and other disorders (attention-deficit hyperactivity disorder (ADHD) [11], autism spectrum disorder (ASD) [12]).

2. Biosynthesis and metabolism of serotonin

Biosynthesis of 5-HT is a process consisted of coupled reactions, with amino acid tryptophan (Trp) as a primary substrate. The first reaction is hydroxylation of Trp yielding 5-hydroxytryptophane (5-HTP). The next step is decarboxylation of 5-HTP to 5-hydroxytryptamine (5-HT). 5-HT is further metabolized in the body. The main metabolic pathways of 5-HT are shown in **Figure 1** [1, 13].

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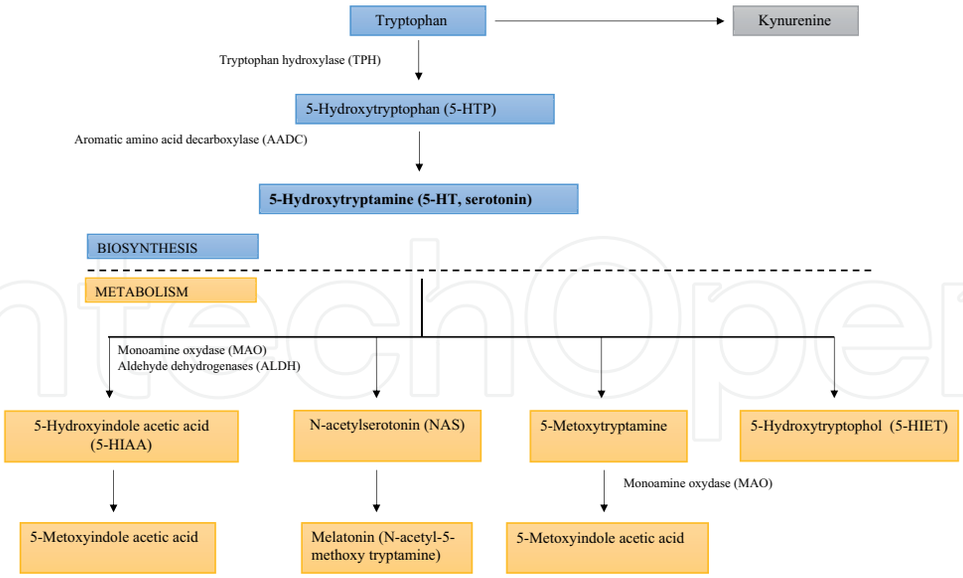

Figure 1. Biosynthesis and metabolic pathways of serotonin.

3. Serotonin and its metabolites in migraine

The disturbances in serotonergic system are a hallmark of migraine. Migraine is a common primary headache disorder that affects 11% of adult worldwide. It occurs three times more often in females (15–18%) than in males (6–8%) [14]. The disease is divided into two main clinical forms: migraine with aura (MA) and migraine without aura (MO). The exact pathomechanism of migraine is unknown, but it is postulated that disease has neurovascular origin in which cortical spreading depression (CSD) and trigeminovascular system (TGVS) play an important role [15]. The TGVS regulates vascular tone and transmission of pain signals [16]. It is believed that activation of TGVS during the head pain phase initiates a chemical cascade of vasoactive neuropeptides such as substance P, calcitonin gene-related peptide, neurokinin A, and nitric oxide. These molecules cause vasodilatation, which can contribute to headaches [17]. The TGVS transmitting migraine pain may be controlled by serotonergic neurons. 5-HT can modulate the trigeminal nerve function, as well as inhibit or promote the pain perception [18]. A decreased level of platelet 5-HT and its metabolite, N-acetylserotonin (NAS), during migraine activate TGVS by CSD [19].

It is known that migraine is a consequence of chronically low 5-HT disposition due to disturbances in its synthesis. The 5-HT metabolism has a cycling character in course of migraine. The plasma concentration of 5-HT is lower and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), is higher during attack-free period, with transient increase of 5-HT and decrease of 5-HIAA during attacks [20–22]. The changes of 5-HT and its metabolite in plasma reflect the situation in the brain as the elevated 5-HIAA level was also found in cerebrospinal fluid (CSF) of migraine suffers [23].

Although the role of 5-HT in migraine pathogenesis is known from ages, the reason of abnormalities of the central 5-HT synthesis remains unknown. The neuroimaging studies have found some answers for a serotonergic mechanism in migraine brain [24]. The electrophysiological studies of Sand et al. [25] indicated that reduced level of serotonergic neurotransmission caused the increase in visual evoked potentials (VEPs) amplitude (P100-N145) in MA patients compared with controls and individuals with MO. It may be associated with the presence of visual aura and increased sensitivity to light in patients with migraine. Authors suggested that disturbances in 5-HT metabolism may be more important in MA than in MO. Dysregulation of 5-HT in brainstem of migraine patients may be caused by a higher level of 5-HTT compared with controls. The higher the availability of 5-HTT, the lower the synaptic level of 5-HT, and in consequence, the lower the brain 5-HT level [26]. The reduction of brain 5-HT synthesis and serotonergic neurotransmission may lead to symptoms related to migraine, such as nausea, dizziness, photophobia, and pain sensitivity [27].

Numerous studies searched the polymorphisms and mutations in genes involved with 5-HT homeostasis in migraine patients. No association between migraine and polymorphisms in genes encoding tryptophan hydroxylase (TPH), aromatic l-amino acid decarboxylase (AADC), monoamine oxidase A (MAO-A), monoamine oxidase B (MAO-B), and most of 5-HT receptors (5-HT1A, 5-HT2A, 5-HT2C, 5-HT1B, and 5-HT1F) were found [13]. Genetic variants in 5-HTT gene, SLC6A4, have also been analyzed in migraine. There are two widely studied polymorphisms: the first is 5-HTTLPR insertion-deletion polymorphism located in the regulatory region of SLC6A4 and the second is STin2 VNTR (variable number of tandem repeats) with four different alleles that correspond to the number of tandem repeats (12, 10, 9, or 7). Both polymorphisms are associated with lower 5-HT reuptake. According to meta-analyses, the short allele of 5-HTTLPR is a risk factor for migraine among European women, while the non-STin2.12 alleles have the protective effect against migraine compared with STin2.12 genotype in the European population [28, 29]. According to the review of Margoob and Mushtaq [30], the S allele and S/S genotype are also associated with many neuropsychiatric diseases, such as major depressive disorder, unipolar or bipolar depression, and seasonal affective disorder. This may explain the fact that patients with migraine more often suffer from depression and anxiety disorders.

A control of the 5-HT level is a means of migraine treatment. Triptans—the 5-HT1B/1D receptor agonists—are successfully used in migraine therapy. The medications that inhibit the reuptake of 5-HT (e.g., selective 5-HT reuptake inhibitor, SSRI) are efficient in chronic pain conditions among which are chronic headaches [31].

High prevalence of migraine was noted in a population of fibromyalgia (FM) sufferers; therefore, it is suggested that both disorders share the same pathomechanism with disturbances in 5-HT metabolism [32]. FM is a chronic pain syndrome, characterized by widespread musculoskeletal pain with diffuse tenderness in specific areas. It affects 3–6% of the world population and 80% of suffers are women [33, 34]. The plasma and CSF levels of 5-HT are decreased in individuals with FM and correlate with clinical symptoms. The low level of Trp and 5-HT precursor, 5-HTTP, as well as high concentration of metabolites in the kynurenine pathway

suggest that the synthesis of 5-HT is decreased in FM. Additionally, 5-HTP supplements are recommended for people with FM. A combined therapy of 5-HTP and MAO inhibitors is more effective that each substance alone [35, 36]. The disturbances in 5-HT concentrations may be associated with changes in 5-HTT, as well. The binding capacity of 5-HTT was found to be lower in FM patients compared with controls. A negative correlation was noted between the binding capacity and rate of 5-HTT and severity of symptoms. The lower expression of 5-HTT in FM patients may be caused by genetic changes [37]. The genetic studies in FM have found that short allele of 5-HTTLPR polymorphism is associated with decline in 5-HTT expression and is a risk factor for developing the disease, similarly to migraine. The T102C polymorphism in *HTR2A* gene encoding 5-HT2A is also postulated to be a risk factor for FM [38]. As 5-HT2 and 5-HT3 are involved in pain perception, the treatment with 5-HT3 antagonist or inhibition of 5-HT reuptake is effective in FM patients [39]. The SSRI administration is necessary as depression is a common disorder among FM patients and it is present in up to 80% of individuals [34]. Participation of 5-HT in the pathogenesis of migraine attacks requires further study.

4. Serotonin levels in epileptic patients

Inhibitors of 5-HT reuptake are also used in another common neurological disorder, epilepsy. Since 1957 it is known that 5-HT can inhibit epileptic attacks [40]. Epilepsy is defined as a set of somatic, vegetative, and mental symptoms. The disease affects 1% of the world population [41]. The disease occurs with a comparable frequency in women and men. Two peaks of incidence are noted: one in childhood and the other over the age of 65 years [42]. In the pharmacotherapy of epilepsy old (e.g., carbamazepine, CBZ; valproate, VPA) and new generation (e.g., lamotrigine, LTG) of antiepileptic drugs (AEDs) are used. Their mechanisms of action among others involve also changes in serotonergic system: CBZ and VPA release the 5-HT, while LTG inhibits 5-HT uptake [8]. The increase in extracellular 5-HT level inhibits both limbic and generalized seizures [43]. Lower values of 5-HIAA concentration were observed in CSF of individuals with epilepsy; this in turns suggests hypofunctional serotonergic neurotransmission in the course of the disease [44].

Moreover, alterations in 5-HT1A, 5-HT2C, 5-HT3, and 5-HT7 receptor subtypes have been analyzed in epilepsy [8]. The binding capacity of 5-HT1A is lower in epilepsy. Reduction in 5-HT1A binding and changes in 5-HT2C and 5-HT7 are features of depression, thus it is unsurprising that 25% of epilepsy cases are accompanied by depression [45, 46]. There is also an age-related decline in 5-HT1A receptors and as it was mentioned before the onset of epilepsy increases in older people. SSRI has anticonvulsant effects because of nonspecific receptor activation, as the volume of 5-HT1A and 5-HT2C receptors is decreased in the temporal regions of brain in epileptic patients. Studies on a mouse model of epilepsy have found that disturbances in the serotonergic system may lead to postictal depression of breathing due to inadequate response to increased CO_2 blood level. Moreover, SSRI drugs are thought to be effective in prevention of hypoventilation after a seizure incident, and of sudden unexpected death in epilepsy in consequence [8, 47].

5. Serotonin and Parkinson's disease

PD was first described in 1817 by an English physician James Parkinson. PD is still an incurable neurological disease, and its pathological mechanism is not fully explained. It is known that in PD there is an imbalance of motor and nonmotor functions, including the autonomic system [1]. Biogenic amines: catecholamines and 5-HT are involved in the regulation of autonomic functions such as blood pressure. In PD degeneration of serotonergic system may also result in depression, psychiatric, and sleep disorders [48]. Moreover, factors regulating levels of biogenic amines such as COMT [49], MAO-A [50], and *5-HTT* gene encoding SERT [51], and bradykinin [52] are involved in the regulation of pain sensation involving neuropeptide Y (NPY). Neuropeptides, Y_1 and Y_2, are also involved in controlling the level of calcium ions regulating by calbindin-B and inflammatory conditions, underlying degenerative changes in the course of PD [1].

Moreover, so far the participation of MAO-B enzyme in the pathogenesis of PD is well known. While the role of MAO-A enzyme in this pathogenesis is not clear. The results of association studies between genetic variants of the *MAO-A* gene and the disclosure of PD are divergent. Hotamisligil and Breakefield [53] have shown that *Eco*RV and *Msp*I polymorphisms of the *MAO-A* gene occurred with threefold higher frequency in patients with PD compared with controls. In contrast, the study of Costa-Mallen et al. [50] did not confirm this association. It was also shown that *MAO-A* polymorphism in the intron 1 in both Japanese population [54] and Caucasians [55] was not associated with PD. On the other hand, a study of Parsian et al. [56] confirmed that *MAO-A* polymorphism was linked to the general population of patients with PD but it did not demonstrate significant differences between familiar PD (FPD) and sporadic PD (SPD).

Preliminary study of Dorszewska et al. [1] indicated that the use of selective MAO inhibitors for depression treatment (by increasing the levels of biogenic amines) in PD may be a particularly effective therapy for patients with genotype *MAO-A* TT (c.1460C>T) and lower levels of NA and 5-HT. Antidepressant MAO inhibitors lead to an inactivation of MAO-A and they promote an increase of 5-HT concentration [57].

It has been shown that SERT (or 5-HTT) is involved in regulating of 5-HT level. SERT is encoded by *5-HTT* gene (SLC6A4, SLC6 member 4) located on the long arm of chromosome 17 in the region 17q11.1-q12 [58]. The *5-HTT* gene may play an important role in revealing and development of mental illness, depression, and feeling of pain as well as SPD [51, 59–63]. In SPD, changes in the SERT level are observed within the raphe nuclei, cingulate, and hypothalamus, as well as increase of SERT activity and decrease of 5-HT level in the striatum, thus leading to depression in these patients [64, 65]. It has been shown that depressive symptoms occur in 50% of patients with PD [1].

Influence of genetic variants of the *5-HTT* gene on SERT concentrations in specific brain structures in PD is not clear. The literature data indicated that 5-HTTLPR polymorphisms and the *5-HTR2* gene lead to lower SERT expression in the dentate rim and caudate nucleus. There was no correlation between the *5-HTT* polymorphism and disclosure of SPD [66]. In contrast,

the study conducted on 393 Caucasian PD patients indicated the influence of 5-HTTLPR polymorphism on a risk of SPD disclosure [67]. Mutations in the *5-HTT* gene related to pathogenesis SPD are summarized in the work of Dorszewska et al. [1].

It seems that in patients with PD, there are many mechanisms involved in controlling levels of biogenic amines, including catecholamines and 5-HT, associated with the appearance of motor and nonmotor symptoms and impaired blood pressure regulation. Furthermore, changes in levels of biogenic amines may also be a consequence of genetic variants influencing their level and the activity of enzymes responsible for the metabolism.

6. Disturbances of serotonin levels in multiple sclerosis

MS is a complex and not fully recognized neurological disorder. Both the environmental and genetic factors are a probable cause of this disease. MS is mainly characterized by myelin destruction and a consequent dysfunction of the central nervous system (CNS). This disease is caused by inflammatory processes, linked with increased levels of Th17 and Th1 cells and decreased levels of regulatory T cells. All the MS patients are at risk of disease progression over time. This progression affects not only physical ability but also mental functions. The disease may have different forms, such as relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), primary progressive multiple sclerosis (PPMS), and progressive relapsing multiple sclerosis (PRMS). Serotonergic system disturbances are one of the studied areas in MS patients [68].

In MS, the level of 5-HT precursor, Trp, is reduced in both plasma and CSF [68–70]. Monaco et al. [68] found that not only the Trp level in plasma was decreased, but also the level of leucine and valine was decreased. The neutral amino acids to Trp ratio were found to be significantly higher in MS than in other analyzed neurological diseases. The low concentration of Trp in CSF and plasma of MS patients stays in line with decreased of brain 5-HT synthesis and overactivation of kynurenine pathway of Trp metabolism. The kynurenine pathway competes with the melatonin pathway for Trp. Moreover, overactivation of the kynurenine pathway leads to severe imbalance between emerging neuroprotective and neurotoxic metabolites [6, 71, 72].

It is known, that in MS, the decreased of 5-HT synthesis in the brain may lead to the local 5-HT-deficit. A significant role in this deficit may play 5-HT metabolites, N-acetylserotonin (NAS) and melatonin. The levels of these metabolites are dependent on availability of 5-HT. NAS and melatonin exhibit antioxidant and anti-inflammatory properties. It also acts as immune signaling agents [73]. NAS exerts similar as a brain-derived neurotrophic factor (BDNF), activating the brain-derived neurotrophic factor (BDNF) receptor. However, melatonin decreases the number of Th1 and Th17 cell populations and the cytokines synthetized [74]. It also exerts a positive effect on mitochondrial function and reduces oxidative stress [74, 75]. It has been shown that NAS and melatonin in experimental autoimmune encephalomyelitis (EAE) in mice reduce clinical scores and the loss of mature oligodendrocytes, demyelination, and axon injury [74].

Literature data indicate that both synthesis and metabolism of 5-HT are disrupted in patients with MS. The low level of 5-HIAA was found in CSF of MS patients [9, 76]. Moreover, Markianos et al. [77] presented a negative correlation between 5-HIAA CSF level in RRMS patients and scores of disability scales: expanded disability status scale (EDSS) and multiple sclerosis severity scale (MSSS). What is interesting, the negative correlation was stronger between 5-HIAA level and MSSS than EDSS. MSSS scores not only disability status as EDSS, but also time of disease duration. Markianos et al. [77] also suggest that 5-HT turnover is more affected by the rate of accumulation of disability rather than disability itself. Reduced serotonnergic activity may lead to axonal loss. Therefore, it seems that 5-HIAA may be considered as a biomarker of severity and duration in RRMS.

It is believed that the serotonergic system also may be a target for therapy in MS. It has been shown that fluoxetine, a represent of SSRIs, reduces the formation of new enhancing lesions in magnetic resonance imaging (MRI) of nondepressed patients with RRMS. This explains the reason of elevated astrocyte-cAMP levels. The elevated levels of intracellular cAMP levels inhibit interferon-gamma induction of MHC class II in astrocytes. Normally, the MHC class II expressed on astrocytes in MS acts as antigen-presenting cells and take part in inflammation [78]. What is more, fluoxetine also promotes disease remission in acute EAE [79]. Moreover, escitalopram belonging to SSRI lowered the risk of stress-related relapse in women with MS [80]. Those studies implicated fluoxetine, and perhaps other SSRIs, may be analyzed as candidate drugs in MS.

The altered of 5-HT activity is linked not only to MS symptoms, but also to mental changes in these patients. For instance, the low concentration of platelet 5-HT may correlate with fatigue symptoms in MS [81]. Other studies have shown that SSRIs and duloxetine, which is 5-HT and NE reuptake inhibitor, are effective in depression treatment in MS [82]. Depression in MS is explained among others, as due to decreased 5-HT and melatonin synthesis.

Many studies suggested that platelet 5-HT may be used to estimate brain 5-HT level. Platelet 5-HT was found to strongly correlate with 5-HT level in CSF [83]. There are many similarities in serotonergic mechanisms in platelets and serotonergic neurons. The 5-HT uptake from plasma to platelets is similar to neuronal 5-HT uptake [84]. It is known that SERT transports 5-HT through the membrane. This transporter is encoded by the same single copy gene in platelets and neurons [85]. The 5-HT uptake in platelets and neurons is inhibited by the same drugs, tricyclic antidepressants and neuroleptics. Furthermore, 5-HT is stored in dense granules in both platelets and synaptic vesicles in neurons. Moreover, both types of cells contain MAO-B in a greater amount than MAO-A. This fact allows them to storage 5-HT which is not metabolized by MAO-B. These similarities justify treating platelets as models of serotonergic neurons [83]. Moreover, 5-HT in the blood is concentrated mainly in platelets what underlines their significant function in the serotonergic system. The 5-HT level in platelets is 24,000 times higher than in plasma [86] and the platelet 5-HT accounts for 98% of its total circulating amount [87].

As it has been mentioned that plasma 5-HT is transported to platelets by SERT. SERT is a member of the Na+/Cl-dependent solute carrier 6 (SLC6) family. In platelets, 5-HT may be deposited in dense vesicles by vesicular monoamine transporter (VMAT) or degraded by MAO [88]. Although the mechanisms of transport are recognized, the relations between 5-HT

plasma level, SERT, and platelets are still not fully understood. SERT is found to compete with dopamine transporter (DAT). Moreover, the SERT expression in relation to the 5-HT plasma level seems to be complicated and biphasic [86, 88]. These facts may play a significant role in regulation of SERT in platelets.

The similarities between neurons and platelets are mainly the complex transport regulation and lack of 5-HT synthesis in platelets. Despite that it can be used to estimate the brain 5-HT in many studies of neurological diseases, such as ALS and MS. These studies will be discussed further.

7. Amyotrophic lateral sclerosis and serotonin level

ALS is a neurodegenerative disease that affects upper and lower motor neurons. The etiology and pathogenesis of motor neuron degeneration are still not elucidated. Many of motor neuron functions are altered in ALS, especially motor neuron excitability and synaptic glutamate release. Due to disappointing results of treatment with riluzole, a glutamate action modulator, new mechanisms are under research. 5-HT system alterations may also be involved in ALS pathogenesis. The alterations of this system affect 5-HT synthesis and release. There are reports suggesting that some changes in serotonergic system may be used in clinical laboratory tests in ALS [89].

The role of 5-HT in ALS progression may be related to many mechanisms. 5-HT facilitates motor neuron activity by strengthening weak inputs—electrical impulses or excitatory neurotransmitters, such as glutamate. As in ALS 5-HT neurons are degenerated, the amount of glutamate needed to excitation of motor neuron increases. This leads to the pathological glutamate overexpression and neurotoxicity [10]. Moreover, in the brain 5-HT inhibits the glutamatergic system as a precursor of melatonin, which inhibits glutamate neurotoxicity. El Oussini et al. [89] have also indicated that 5-HT2B receptor limits degeneration of mononuclear phagocytes in CNS, which accompanied neurodegeneration in the disease.

Disturbances of serotonergic system in ALS may be found in studies of 5-HT precursor, Trp. Monaco et al. [68] shown that CSF and plasma level of Trp are reduced in ALS patients. Moreover, plasma levels of leucine and valine, which compete with Trp for uptake into the brain [90], were increased in ALS patients as a result of a larger uptake of neutral amino acids. However, its ratio was increased not only in patients with ALS, but also in patients with some other neurological diseases, such as MS. The authors of the study suggest that its different levels may be possibly used to differentiate these diseases.

The level of 5-HT itself may also have a prognostic value. Dupuis et al. [87] have shown that platelet 5-HT level is not only significantly decreased in ALS compared with controls, but it also predicts survival in ALS. In the study, the level of 5-HT was measured at one single time point in patients with diagnosed disease. The authors calculated the difference between platelet and plasma unconjugated 5-HT concentrations. The level of platelet 5-HT was more decreased in patients with bulbar onset, what corresponds with less 5-HT1A receptor binding in imaging studies [91]. Moreover, in all ALS patients, the platelet 5-HT level corresponded

with survival, from time of test to death. This can be related to some role of 5-HT alterations in the disease progression [87].

As it has been mentioned before, the serotonergic receptors can also play a significant neuroprotective role and its expression may be altered in ALS. The study of El Oussini et al. [89] has shown that the 5-HT2B receptor may limit progression in ALS by some mechanisms related to mononuclear phagocytes. On the other hand, the test of *5HT2B* gene, which encodes 5-HT2B receptors, may have some value as a survival predictor. Moreover, in the same study, patients carrying the C allele of single nucleotide polymorphism (SNP) rs10199752 in *5HT2B* gene, which encodes the 5-HT2B receptor, had a longer survival than patients carrying the more common A allele. This was also accompanied by decreased mononuclear phagocyte degeneration and increased concentrations of 5-HT2B mRNA in the spinal cord.

However, the imaging studies showed also decreased concentration of 5-HT1A receptors in the brain raphe and the cortex in ALS, even more decreased in patients with bulbar ALS onset [92]. The studies showed also alterations in concentration of 5-HIAA. This can be treated as evidence of 5-HT metabolism alterations in ALS. The *postmortem* studies of ALS patients showed decreased levels of 5-HIAA and 5-HT in the spinal cord and the brain tissue. The alterations were found particularly in the cervical and thoracic level of the spinal cord. One single study showed that concentrations of 5-HIAA were lower in the cervical spine of ALS patients with no difference in 5-HT level compared with controls [93]. However lower 5-HIAA concentration may be still linked to weak 5-HT metabolism.

8. Neuropsychiatric disorders and serotonin

ADHD, one of the most common childhood conditions, is categorized as a neurodevelopmental disorder. The group of behavioral symptoms of ADHD broadly encompasses inattentiveness, hyperactivity, and impulsiveness. The exact causes of ADHD remain unknown, but 5-HT plays a potential role in its pathomechanism. Studies provide evidence that altered availability and metabolism of 5-HT may lead to impulsivity [94]. Moreover, studies indicate that 5-HT deficiency leads to a failure of 5-HT-mediated inhibitory control of aggressive behavior and can occur also in adults [11]. Some of the studies have demonstrated decreased levels of 5-HT and 5-HIAA, in the blood, urine, and CSF in individuals with ADHD compared with in healthy controls, but other studies found no differences. However, the studies indicate that 5-HT levels in the platelets are much higher in impulsive children. There was no correlation between the platelet 5-HT concentration and other common ADHD symptoms, neither any significant difference between platelet 5-HT concentrations in ADHD children compared with controls [12].

Abnormalities in 5-HT receptors were observed in patients with ADHD: the aggression and impulsiveness are linked to increased 5-HT2A and decreased 5-HT1A receptor binding. Moreover, underexpression of 5-HT1B is a predictor of increased impulsive behavior, but not of impulsive choice [95]. Changes in 5-HTT activity in various brain regions are thought to be associated with ADHD [96, 97]. Alterations in the 5-HT level may also be caused by low activity of MAO-A and lead to impulsivity and aggressive tendencies in ADHD [98].

Disturbances in serotonergic system may be a result of many polymorphisms. Animal model studies have found that inactivation of the brain-specific Trp hydroxylase-2 (TPH2) gene leads to increased aggression due to impaired synthesis of neuronal 5-HT in the raphe neurons of the brain stem [99]. The several SNPs of the TPH2 gene are found to be strongly associated with altered functions of the prefrontal cortex during a response inhibition task in adults with ADHD [100].

Hyperserotonemia is one of the biomarkers of another neuropsychiatric condition, the ASD, and is presented in approximately 30% of patient. ASD is a group of neurodevelopmental disturbances, characterized by communication difficulties, social deficits, and repetitive behaviors, and associated by mental health issues, poor motor skills, gastrointestinal symptoms, and sleep problems [101]. The range of the symptoms varies from mild to severe. The pathomechanism of ASD is unknown, as well as the contribution of the 5-HT system to its pathophysiology.

One of the consequences of hyperserotonemia is increased catabolism of 5-HT. Blood 5-HT concentrations are regulated by the activity of peripheral 5-HT-associated proteins. It is suggested that an increased velocity of kinetics of MAO-B might be an answer to high 5-HT concentrations in the platelets [102, 103]. The hyperserotonemia in platelets in autism could be due to an increased uptake of 5-HT into the platelet. Children with autism carrying the short allele of 5-HTTLPR polymorphism associated with decreased 5-HTT expression showed better connectivity than youth with autism and long allele of this polymorphism [104].

Changes in 5-HT receptors were noted in patients with Asperger's syndrome. The abnormalities in 5-HT2A receptor density and reduction in 5-HT1A receptor binding density in several brain regions were demonstrated [105, 106].

Future studies are needed to understand the role of serotonergic system in ASD.

9. Summary

Neurological diseases, such as migraine, epilepsy, PD, MS, ALS, and neuropsychiatric disorders (ADHD, ASD) may be connected to abnormal 5-HT levels in a variety of mechanisms, as shown in **Figure 2**. Synthesis and metabolism efficiency of 5-HT is changed in neurodegeneration. Patients with ALS and MS present with reduced both plasma and CSF levels of Trp, what can be linked with a decreased 5-HT synthesis. Moreover, in MS 5-HT synthesis is decreased because of overactivation of kynurenine pathway, which drives Trp away from 5-HT synthesis. This pathway is overactivated by inflammatory molecules, such as tumor necrosis factor alpha (TNF-alpha) and interferon-gamma (IFN). In MS, 5-HT concentration is decreased due to production of its neuroprotective metabolites, such as NAS and melatonin.

In ALS, the platelet 5-HT level is decreased compared with controls and there is a positive relation between platelet 5-HT and survival. In MS, a lower platelet 5-HT level was found in patients with a more severe fatigue syndrome.

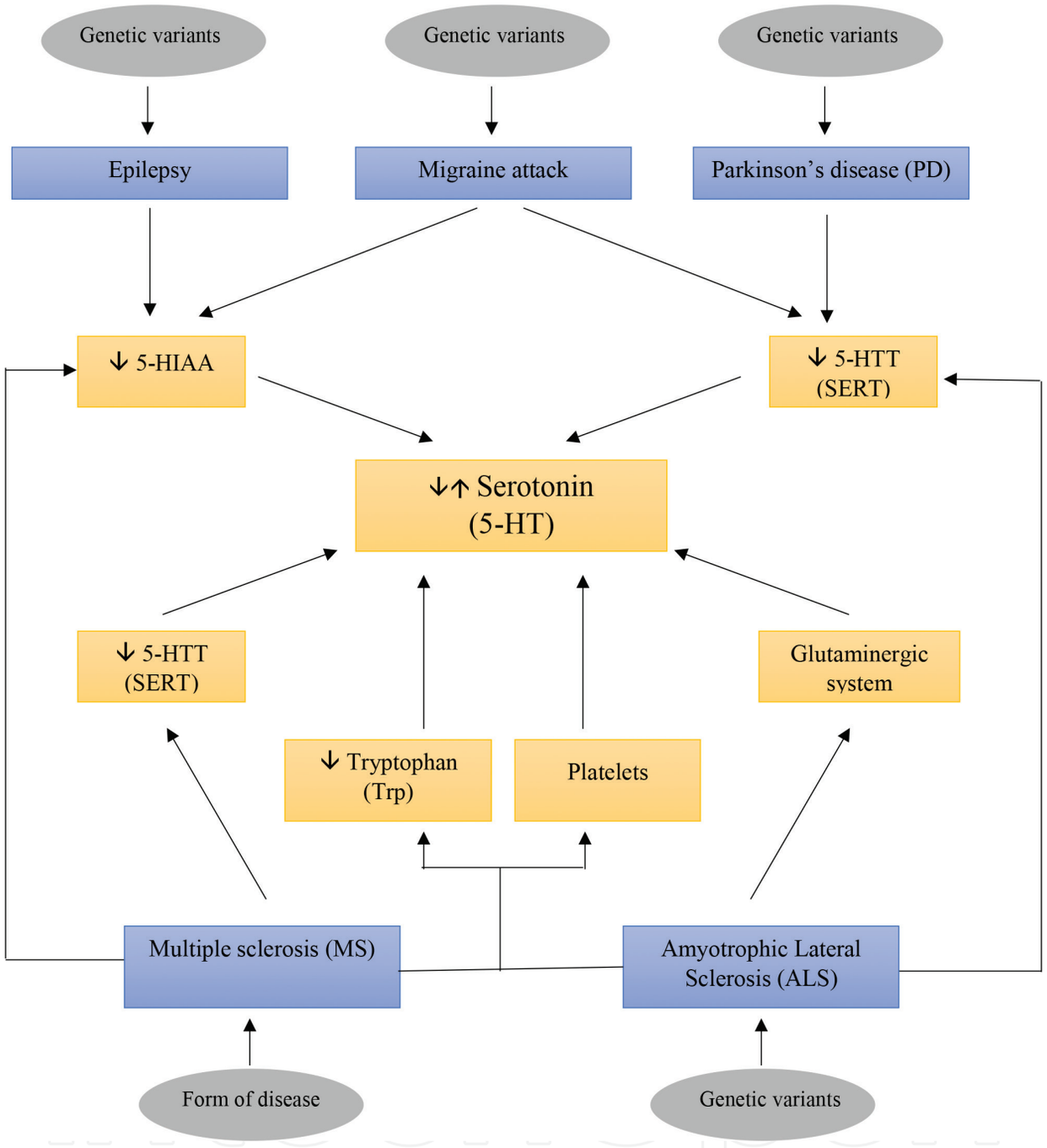

Figure 2. Disturbances of serotonin levels in neurological diseases.

Simultaneously, *postmortem* studies of ALS patients showed decreased levels of 5-HIAA and 5-HT in the spinal cord and brain tissue. However, in MS patients, lower levels of 5-HIAA were found in CSF. Moreover, in RRMS there was a negative correlation between 5-HIAA CSF level and scores of disability scales. A lower 5-HIAA level was also observed in CSF of epileptic patients as well as in migraine during attacks. However, a lower level of 5-HTT in FM and PD patients is associated with genetic variants.

Understanding the mechanisms of changes in the level of 5-HT and its precursors/metabolites in neurological diseases may contribute to finding new biomarkers relevant to the diagnosis and treatment of these diseases.

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