CELL ADHESION & MIGRATION
2021, VOL. 15, NO. 1, 261–271
https://doi.org/10.1080/19336918.2021.1963574

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

The roles of serotonin in cell adhesion and migration, and cytoskeletal remodeling

Joe Anand Kumar John Jayakumar [a,b] and Mitradas M. Panicker [b,c]

[a]Manipal Academy of Higher Education, Manipal, India; [b]National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bengaluru, India; [c]Present Address - Department of Physiology and Biophysics, School of Medicine, University of California, Irvine, USA

ABSTRACT

Serotonin is well known as a neurotransmitter. Its roles in neuronal processes such as learning, memory or cognition are well established, and also in disorders such as depression, schizophrenia, bipolar disorder, and dementia. However, its effects on adhesion and cytoskeletal remodelling which are strongly affected by 5-HT receptors, are not as well studied with some exceptions for e. g. platelet aggregation. Neuronal function is strongly dependent on cell-cell contacts and adhesion-related processes. Therefore the role played by serotonin in psychiatric illness, as well as in the positive and negative effects of neuropsychiatric drugs through cell-related adhesion can be of great significance. In this review, we explore the role of serotonin in some of these aspects based on recent findings.

ARTICLE HISTORY
Received 20 October 2020
Revised 4 July 2021
Accepted 29 July 2021

KEYWORDS
Serotonin; cell adhesion and migration; cytoskeletal remodeling; platelet aggregation; immune cells; neuronal cells; development; antipsychotics; antidepressants; homeostasis; covid-19

Introduction

Serotonin, 5-hydroxytryptamine (5-HT), a monoamine, is involved in a wide range of functions, which include platelet aggregation, cell proliferation, cell transformation, vascular smooth muscle contraction, mood, appetite, cognition, learning and memory, thermoregulation, locomotion, sleep, sexual behavior, endocrine secretion, pain, and immune responses [1–3]. 5-HT, in the animal kingdom, is synthesized from the amino acid tryptophan by tryptophan hydroxylase (TPH) and AADC – an aromatic amino acid decarboxylase though in *Drosophila* and mouse phenylalanine hydroxylase is also known to substitute for TPH [4]. In mammals, more than 90% of the 5-HT present is produced by the enterochromaffin cells in the gastrointestinal tract and the rest is chiefly produced in the CNS by the serotonergic neurons of raphe nuclei present in the brain stem [5]. Apart from endogenous synthesis, 5-HT is supplied to the developing embryos from maternal and placental sources [6]. While 5-HT is not known to be supplied *via* dietary intake or cannot cross the blood-brain barrier, dietary supplementation with tryptophan or 5-hydroxytryptophan an intermediate precursor of 5-HT can raise the blood 5-HT, and since both of these molecules can cross the blood-brain barrier it can increase 5-HT in the brain as well [7]. Moreover, 5-HT is expressed very early in the development in various invertebrates and vertebrates even before the formation of the nervous system and is reported to play a developmental role [8–11].

5-HT can activate 14 known receptor subtypes (not including splice and edited variants), which are grouped into seven major families (Figure 1) based on their structural and functional similarities [12]. All 5-HT receptors are G-protein-coupled receptors, except those belonging to the 5-HT_3 family which are ionotropic ligand-gated ion-channels [12].

The distribution and functions of various 5-HT receptors in mammals are highly diverse and briefly noted here. These have been mostly studied in the context of the nervous system. 5-HT_{1A} is present in limbic areas, anterior raphae nuclei, and interpeduncular nucleus, and is implicated in the regulation of the cardiovascular system, neuroendocrine responses such as secretion of adrenocorticotropic hormone, regulation of body temperature, sleep states, mood, and neurogenesis. 5-HT_{1A} knockout mice are seen to exhibit anxiety, depression, and cognitive deficits [12,13]. 5-HT_{1B} is expressed in the hippocampus, striatum, cerebral cortex, cerebellum, and vascular tissues, which is associated with contraction of rat caudal arteries, inhibition of noradrenaline release, inhibition of plasma extravasation, and it plays a role in migraine [12,13]. 5-HT_{1D} present in low levels in the brain is a prime target for antimigraine drugs [12,13]. 5-HT_{2A} is present in the cortex, hippocampus, platelets, vascular smooth muscle

CONTACT Joe Anand Kumar John Jayakumar joeanandkumarj@gmail.com Manipal Academy of Higher Education, Manipal, Karnataka, India

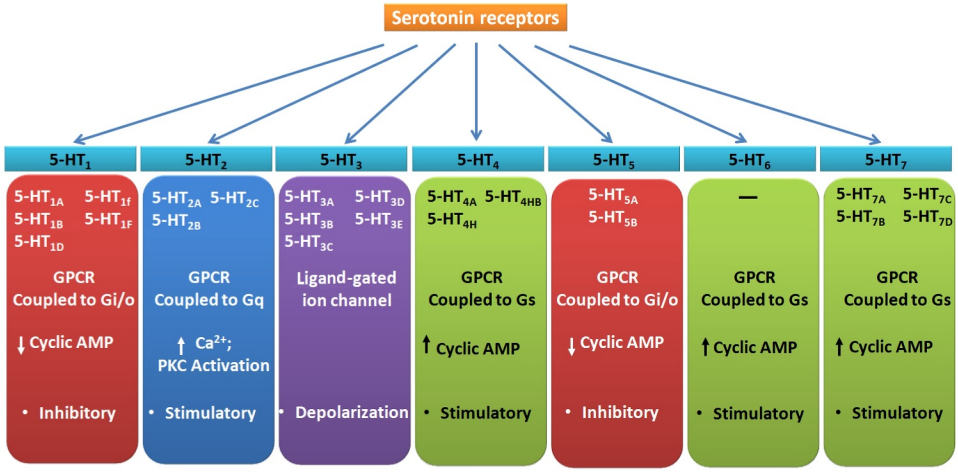

Figure 1. Classification and characteristics of serotonin receptors.

cells, and gastrointestinal tract (GIT) is associated with learning and memory, behavior, sexual functions, endocrine functions, thermoregulation, gastrointestinal motility, platelet aggregation, vascular smooth muscle contraction [14,15]. 5-$HT_{2B,}$ present in rat fundus, gut, heart, kidney, lung, cerebellum, lateral septum, dorsal hypothalamus and medial amygdala, is seen to be quintessential for the development of the cardiovascular system [14,16]. 5-HT_{2C} reported in the choroid plexus, hippocampus, amygdala, human cerebral cortex, cerebellum and substantia nigra (SN), endopiriform nuclei, cingulate, and piriform cortex, is seen to play an important role in feeding behavior[17]. 5-HT_3 receptor family subtypes 5-HT_{3A} and 5-HT_{3B}, are expressed in the amygdala, hippocampus, cortex at the CNS, peripheral autonomic ganglion and GIT, and are seen to be associated with the regulation of emetic reflex, intestinal motility and, in addition, has roles in the cardiovascular system [12]. 5-HT_4 is seen to be present in the olfactory tubercle, islands of Calleja, substantia nigra, ventral pallidum, striatum, septum, hippocampus, amygdala, heart, and GIT. 5-HT_5 is present in the cerebral cortex, dentate gyrus, pyramidal cell layer within hippocampal fields CA1-3, granule cell layer of the cerebellum, and tufted cells of the olfactory bulb, cerebral cortex, hippocampus, and cerebellum. The 5-HT_{5A} knockout mouse also shows increased exploratory activity in a novel environment. 5-HT_6 is found in the striatum, nucleus accumbens, olfactory tubercle, and cortex, is moderately expressed in the amygdala, hypothalamus, thalamus, cerebellum, and hippocampus, corpus striatum, nucleus accumbens, Islands of Calleja, olfactory tubercle, and the choroid plexus. Moderate levels are found in the hippocampal formation and cerebral cortex, thalamus, hypothalamus, and substantia nigra and is involved in various functions such as cognition, learning and memory and Alzheimer's disease [18,19]. 5-HT_7 is present in the ileum, spleen, endocrine glands, arteries, thalamus, hypothalamus, cerebral cortex, hippocampus, and amygdala [20]. It is seen to be involved in the regulation of the endocrine system, the circadian rhythm, and temperature regulation, sleep, neuropsychiatric disorders, memory and learning, locomotor functions, migraine pain, substance abuse, respiratory, cardiovascular and intestinal systems [21,22].

Serotonin and its receptors are expressed at both central nervous system and periphery and are known to modulate many functions, however, its lesser known roles in cell adhesion, migration, or cytoskeletal remodeling are recently gaining interest. The adhesion-related processes associated with the serotonergic system reviewed here are as follows. Serotonin is classically associated with platelet aggregation and inhibitors of 5-HT_{2A} are clinically used as drugs to prevent platelet aggregation. Serotonin and its receptors are also known to play a role in adhesion, migration and proliferation of vascular smooth muscle cells and pathogenesis of atherosclerosis. The adhesion-related processes mediated by serotonin in immune system are observed in mast cells, eosinophils, dendritic cells etc., for e.g in cell adhesion, migration, cytoskeletal remodeling and cell shape. Serotonin is known to augment wound healing, which is seen to be relevant for its role in fibrosis also, which is characterized by excessive extracellular matrix protein secretion. In the central nervous system, serotonin has obvious roles in the expression and modulation of adhesion molecules including NCAM, synaptic adhesion and neurite remodeling. The role of serotonin in cell adhesion is also seen in developmental processes for e.g. in gastrulation and

interneuron migration. As reviewed here, adhesion-related roles of serotonergic system are interlinked with neuropsychiatric disorders and their medication.

Examples of serotonin-mediated adhesion, migration, and remodeling of the cytoskeleton

Though the serotonergic system is mostly associated with the central nervous system and primarily recognized in neuronal signaling, emerging roles at the periphery in lesser known cellular processes related to adhesion have begun to unravel entirely novel functions. One of the well-known functions of 5-HT related to adhesion is platelet aggregation. In the neuronal context, it has also been speculated that many antidepressants and antipsychotics could mediate their roles by modulating synaptic adhesion molecules and/or the cytoskeleton. Though every detail of these studies is beyond the scope of this review, we aim to analyze in some detail adhesion-related roles of the serotonergic system in all the relevant systems, i.e. platelets, vascular smooth cells, immune cells, neuronal cells and in development, along with its clinical implications (Figure 2). It is important to note that there is a strong correlation between increased platelet aggregation and pathogenesis. For e.g. in COVID-19 patients exhibit increased thrombosis (platelet aggregation) and vascular thromboembolism (circulating platelet clots within the blood

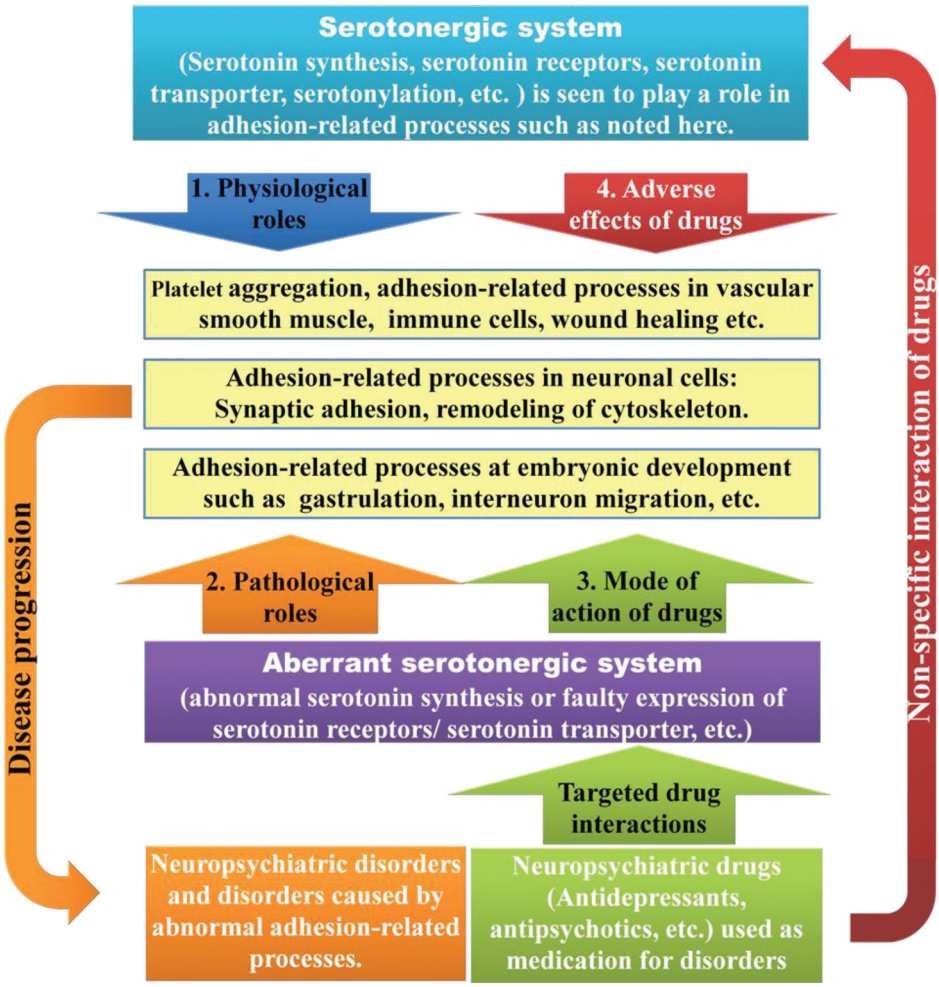

Figure 2. The schematic representation of the adhesion-related effects mediated by the serotonergic system. The link between the serotonergic system and adhesion-related processes can be depicted as follows. (1) Physiological roles: The adhesion-related processes (yellow) – platelets, vascular smooth muscle cells, immune cells, wound healing, neuronal cells, in development, etc., could be modulated by serotonergic system as its physiological role (blue). (2) Pathological roles: An aberrant serotonergic system for e.g. abnormal levels of expression of serotonin, serotonin receptors or transporter, etc., (purple) could also affect the adhesion-related processes, and such abnormal adhesion-related processes could cause the disease progression of neuropsychiatric disorders (orange). (3) Mode of action of drugs: The neuropsychiatric drugs targeting the aberrant serotonergic system could evoke its desired response of mitigating neuropsychiatric symptoms by modulating the adhesion-related processes (green). (4) Adverse effects of drugs: The neuropsychiatric drugs can also act nonspecifically on other components of serotonergic system and result in off-target adverse effects (brown).

vessels) as pathology, which is suggested to have a larger role in disease progression, including multi-organ failure and fatality [23]. The exact mechanism of increased thrombosis in COVID-19 is not fully understood, although it is speculated to be hyper-inflammation (and a subsequent cytokine storm), hypoxia and immobility. As prophylactic anticoagulants such as heparin are administered to prevent COVID-19 associated coagulopathy [24], it would be useful to know if conventional anticoagulants targeting 5-HT_{2A} antagonists such as sarpogrelate or cyproheptadine or antagonists of 5-HT_2 receptors could be employed for reducing the hyper-coagulability complication in COVID-19 [25].

Platelet aggregation and migration of vascular smooth muscle cells

Two classical functions of 5-HT also to be discovered very early on were platelet aggregation and vascular smooth muscle contraction, in part due to its initial isolation and identification from fractionated serum [26,27]. Further work established that 5-HT is synthesized and secreted into the blood by enterochromaffin cells and is subsequently taken up and stored in platelets as dense granules [28]. During vascular injury, the contact of platelets with the damaged and exposed vessel walls triggers its aggregation and release of 5-HT. The released 5-HT further stimulates 5-HT_{2A} on platelets and vascular smooth muscle cells, causing amplification of platelet aggregation and vasoconstriction, with resultant clot formation and hemostasis [29,30]. Hence, many conventional antiplatelet aggregation drugs are seen to be inhibitors of 5-HT_{2A}, such as sarpogrelate, cyproheptadine, pizotifen, which are used in major occlusive disorders, such as atherosclerosis [31,32]. While the atherosclerotic plaques trigger the first step of pathogenesis i.e. uncontrolled platelet aggregation or thrombosis [33], the associated 5-HT release also initiates a second step, the migration and proliferation of smooth muscle cells into the intima causing thickening of the vessel wall [34]. The migratory effects of 5-HT on smooth muscle cells have been experimentally demonstrated in cultured rat aortic smooth muscle cells [35] and bovine pulmonary artery smooth muscle cells [36] as well, and 5-HT_2 and 5-HT_4 receptors were seen to be involved respectively. Progress in atherosclerosis research has now shed light on 5-HT_{2A} as a significant player and potential target for drug discovery [32].

Adhesion, migration and cytoskeletal remodeling of immune cells

In the immune system, cell adhesion and migration are essential for various functions such as extravasation, chemotaxis, phagocytosis, antigen presentation, secretion of migratory cytokines & extracellular matrices [37], and 5-HT can affect many of these functions [38]. It also turns out that 5-HT plays significant adhesion-related roles in various immune cells, i.e. mast cells, eosinophils, and dendritic cells.

In mice bone marrow-derived mast cells and human CD34+ derived mast cells, 5-HT is seen to cause increased *in vitro* adhesion, migration and actin polymerization, and are dependent on 5-HT_{1A} expressed in these cells. Bone marrow-derived mast cells from 5-HT_{1A}-/- mice did not exhibit any of this increased adhesion or actin polymerization, and similarly, in wild type mice, pharmacological inhibition of 5-HT_{1A} abolished the serotonin-mediated increase in the adhesion of these cells to fibronectin substrates. Moreover, intradermal injection of 5-HT also caused migration and accumulation of mast cells to the site of injection in wild type mice, but not in 5-HT_{1A}-/- mice [39]. Mast cells are a source of 5-HT [39] and are known to cross the blood-brain barrier and release 5-HT that played a role in learning and memory [40]. Similarly its also known that mast cell-deficient C57BL/6 $^{W\ sh/sh}$ mice show impaired spatial learning and memory [41]. So mastocytosis, a condition caused by increased proliferation of mast cells that eventually accumulates in various organs such as skin, liver, etc., is associated with neuropsychiatric disorders such as depression and post-traumatic stress disorder (PTSD) [42].

5-HT is also known to act as a chemo-attractant for eosinophils [43] and causes 5-HT_{2A} dependent *in vitro* migration of human eosinophils, and *in vivo* rolling and migration of murine bone marrow-derived eosinophils within inflamed post-capillary venules [44].

Another role of 5-HT mediated adhesion in the immune system is on dendritic cells, where 5-HT is seen to promote *in vitro* and *in vivo* adhesion, migration, and cytoskeletal modulation. It is seen that 5-HT aids the migration of lung-derived dendritic cells in response to intratracheally injected FITC-labeled OVA, to crossing into mediastinal lymph nodes through epithelial tight junction barriers. Similarly, transwell migration of dendritic cells was seen to be mediated by 5-HT_{1B} and 5-HT_{2A} [45]. In colon explants, treatment with 5-HT_7 inhibitor caused reduced and diffused migration of dendritic cells,

compared to straight and long-distance migration seen with controls. 5-HT_7 activation also caused actin-mediated extensive morphological changes, *in vitro* transwell migration, and 3D collagen gel invasion of dendritic cells [46].

Moreover, it is seen with numerous studies, that 5-HT is significantly involved in immune disorders such as asthma, wheezing, allergic rhinitis, chronic pulmonary obstructive disease, arthritis, irritable bowel syndrome, Raynaud's phenomenon/scleroderma or psoriasis [47–52] and the underlying cause or mechanism could be based on adhesion-mediated effects.

A physiological process that is at the intersection of serotonin, platelets and immune cells is wound healing, and serotonin may have an augmentative role. Serotonin is seen to promote cell migration, proliferation, survival, and antiapoptotic effects in keratinocytes and fibroblasts [53]. Moreover, numerous lines of evidence also suggest that autologous platelets enhance healing of skin wounds in humans [54]. Platelets are significant reservoirs for serotonin, and the mechanism could be serotonin-mediated adhesion and migration of cells involved in tissue repair. Yet another role for serotonin is an increased risk of fibrosis with increased blood serotonin, and inhibitors of serotonin receptors such as 5-HT_{2A} and 5-HT_{2B} play protective roles [55,56].

Modulation of adhesion molecules and cytoskeleton of neuronal cells

The serotonergic system being an integral part of CNS, is known to have significant roles in neuropsychiatric disorders. Several medications are therefore targeted to 5-HT receptors. Recent results from our laboratory suggest that some of the clinically used antipsychotics may modulate adhesion-related processes and F-actin remodeling[57]. Many neuropsychiatric studies, including postmortem brain analysis of schizophrenic patients, have shown expression of synaptic adhesion molecules such as neural cell adhesion molecule (NCAM) to be significantly reduced [58]. The significance of NCAM is even more evident in its relevance in schizophrenia mouse models, such as NCAM1 null mice [59] and in the maternal deprivation mouse model [60] also NCAM expression is seen to be reduced [61]. The modulation of NCAM by 5-HT is driven by the addition of polysialic acid. It is known that non-polysialylated NCAMs are associated with robust and rigid adhesion, polysialylation decreases its adhesiveness and enables dendritic arborization, neuronal migration and synaptic plasticity [62]. Notably, in conditions of depression, in schizophrenic individuals or animal models, polysialylated-NCAMs are also seen to be decreased [63], and antipsychotics or antidepressants used in their treatment promote polysialylation of NCAM [64].

Secondly, remodeling cytoskeleton is integral to neuronal events such as spinogenesis, axonal guidance, growth cone or neurite maturation, synaptogenesis, and plasticity [65]. For these functions, 5-HT is generally seen to have an augmentative role, for e.g. treatment with fluoxetine and vortioxetine, which increases 5-HT concentrations in the synapse, is seen to promote spine enlargement, synaptic contacts and dendritic density [66,67]. Nevertheless, the effects of individual 5-HT receptors are highly variable, based on the receptor type, site of expression, and/or time. For e.g. in rat embryonic neuron culture, 5-HT_{1A} is seen to increase dendritic filopodia density and 5-$HT_{2A/2C}$ is seen to increase the puncta and spine density on embryonic day 11, but on embryonic day 15 they are seen to negate each other's effects [68]. In another study 5-HT_{1A} has been reported to restrict dendritic growth cone formation [69] while it has also been shown to increase spinogenesis in a similar context [70]. Moreover, 5-HT_{2A} [68,71–73], and 5-HT_7[46] [74–77], has been reportedly seen to cause neurite elongation, spinogenesis and synaptogenesis, while 5-HT_3 is believed to cause a decrease in total axon length and dendritic branching in cultured neurons [78].

Adhesion and migration in embryonic development

In invertebrates, such as sea urchins, mollusks, starfish, planaria and *Drosophila*, 5-HT is expressed early in the development and is ascribed various pre-nervous roles [8,11,79–82]. In mammals, 5-HT is expressed at different time points in development, for e.g. in rodents 5-HT is expressed in preimplantation embryos and embryonic stem cells [9,83] and in primates it is shown to be present at least from the first month of gestation [84].

Development is a process crucially dependent on differential adhesion, and 5-HT and its receptors play significant roles, which are directly or indirectly related to adhesion. For e.g. HToin *Drosophila*, 5-HT_{2Dro}, is seen to play a very important role in its gastrulae, where 5-HT_{2Dro} knockout causes lethally abnormal ectoderm extension due to aberrant adherence junctions, while disruption of 5-HT synthesis also results in similar condition [81,85]. Curiously, mice that lack TPH1 and TPH2 enzymes (involved in the synthesis of 5-HT in the periphery and CNS respectively) are quite normal at birth but does show retarded development initially, and then recovers [86,87]. Such retarded growth could also be attributed to highly deficient maternal care exhibited by dams that lack serotonin [88,89]. It is interesting to

note that in mice that lack TPH1 and TPH2 there does not seem to be a total loss of serotonin [90]. One of the possible reasons could be Phenylalanine hydroxylase taking the role of TPH1 in converting tryptophan to 5-hydroxytryptophan the rate-limiting step of serotonin synthesis [4]. 5-HT receptors when globally knocked out, are seen to exhibit a fairly robust survival also suggesting redundancy of functions among 5-HT receptors, which seem to obviate the adverse effects due to absence of individual receptors [10]. These observations suggest that the serotonergic system in development is highly buffered, that even when serotonin synthesis in the developing embryo is inadequate or individual 5-HT receptors are absent, there is some level of compensation. Curiously, when whole embryo cultures were exposed to pharmacological agents, such as inhibitors of SERT, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} or 5-$HT_{2A,}$ 5-$HT_{2B,}$ or 5-HT_{2C}, severe embryonic malformations were observed, and some of them seem to be directly related to adhesion and/or migration [16,91–95]. Moreover, in humans also antipsychotics or antidepressants at pregnancy are seen to be associated with an increased risk of spontaneous abortions, stillbirths or malformations [96,97].

Another adhesion-related process during development, i.e. interneuron migration is also seen to be significantly regulated by 5-HT receptors. 5-HT_{3A} expressed in caudal ganglionic eminence-derived interneurons, plays a role in their migration and laminar positioning to specified cortical plates [98,99]. 5-HT_6 is also known to affect migration of PC12 and neuronal cells [100–102], and is present in the proliferative zones i.e. subventricular zones (SVZ) and intermediate zone (IZ) of developing mice embryos, and aids interneuron migration [103,104]. Interneuron migration is very important for the spatiotemporal formation of brain regions for e.g. laminar positioning of cortex and formation of neuronal circuits [105,106107–108]. It is known that faulty interneuron migration results in neuronal migration disorders (National Institute of Neurological Disorders and Stroke information page), which could lead to neuropsychiatric disorders such as autism and schizophrenia. One could perhaps also speculate on interneuron connectivity being affected by 5-HT-mediated adhesion.

The clinical implication of an aberrant serotonergic system and adverse effects pertinent to cell adhesion and migration, and cytoskeletal remodeling

The role of 5-HT in the central nervous system and neurological disorders such as schizophrenia, anxiety, autism, depression, and bipolar disorders are well known [107–109], and so are the roles of antidepressant and antipsychotic drugs known to effectively relieve neuropsychiatric complaints [110,111]. However, the other roles that the serotonergic system is involved in, especially at the periphery, and in events such as adhesion, migration, and cytoskeletal remodeling have only received moderate attention, despite its significant clinical implications.

Although 5-HT is perceived to be majorly associated with a large number of functions in the CNS, more than 90% of 5-HT is present at the periphery, and is likely to play significant roles. As the 5-HT receptors are present both at the CNS as well as periphery, many neuropsychiatric drugs targeted to affect the CNS are, not so surprisingly, seen to have off-target adverse effects at the periphery. As expected, serotonin is associated with many disorders at the periphery especially in conditions known to increase 5-HT levels in the blood, such as administration of antidepressants. Platelet aggregation, a serotonin-affected phenomenon, also has a strong correlation with atherosclerosis, fibrosis and psoriasis [33,55,112,113]. In conditions such as mastocytosis, atherosclerosis, pulmonary hypertension, or psoriasis, we also see an associated elevated blood level of 5-HT [39,114,115]. In particular, the significance of 5-HT in cardiac fibrosis became evident, from the infamous use of a weight-loss drug Fen-Phen, where the main anorexine fenfluramine, a serotonin reuptake inhibitor, and an agonist of 5-HT_{2B} and caused fibrosis of the heart valve which led to significant mortality [116,117]. Curiously other serotonin reuptake inhibitors have not been reported to cause a similar valvular defect until now. In pulmonary artery hypertension, there is also an over-expression of SERT [48] and maternally administered SSRIs are known to result in pulmonary hypertension in offsprings [118]. Similarly, an increase or decrease in 5-HT is seen to result in the increase or decrease in bone resorption respectively, and humans on SSRI administration are prone to bone fractures [119]. On the contrary, antipsychotics are seen to be beneficial in all of the aforementioned complications, e.g. in delaying the onset of atherosclerosis and fibrosis and for treating pulmonary hypertension, multiple sclerosis, cystic fibrosis, and psoriasis [32,120–122], but is seen to be counter-effective in bone mineralization [123]. Interestingly, in carcinoid syndrome i.e. cancer of the enterochromaffin cells associated with high secretion of 5-HT, as expected, high levels of metastasis are observed [124]. While 5-HT/SSRIs have been linked to promoting metastasis antipsychotics are seen to inhibit it [125,126].

Thus, we see that the adverse effects of abnormal levels of serotonin or faulty expression of receptors/transporter are not confined to just CNS, but are pervasive across multiple systems in the body. Similarly, neuropsychiatric medications such as SSRIs (antidepressants) or antipsychotics are seen to have huge off-target effects outside the CNS. This is one of the major reasons why neuropsychiatric treatment remains a tightrope walk, with specificity largely remaining elusive, often necessitating 'risk versus benefit', and limiting the usage of available drugs. As the mode of action of many antidepressants and antipsychotics at the CNS includes replenishing inadequate synthesis, controlling the excessive production of neurotransmitters or modulation of signaling of receptors [127], many of these drugs require chronic administration. This, unfortunately, paves way for several side effects for e.g. agranulocytosis, extrapyramidal symptoms, dyskinesia, weight gain, etc. [128]. In the case of serotonin syndrome, a life-threatening complication arising from increased serotonergic activity following clinical administration of serotonergic agents, SSRIs and many drugs that affect the serotonin metabolism, exhibit symptoms which are termed as the classical triad of cognitive-behavioral changes, neuromuscular excitability, and autonomic instability [129].

Despite significant advances in neuropsychiatry especially serotonin biology, the adverse effects of medications targeting the serotonergic system remain severe. Hence, the path forward in clinical interventions involving the serotonergic system needs to be holistic and multi-targeted, for gaining specificity to minimize off-target effects. To achieve that, it would be imperative to also unravel the complex links between serotonergic systems and lesser-known cellular processes such as cell adhesion and cytoskeletal remodeling, which could aid in understanding the effects of these drugs thereby design optimal drugs with improved clinical results.

The link between the serotonergic system and adhesion-related processes can be depicted as follows. (1) Physiological roles: The adhesion-related processes (yellow) – platelets, vascular smooth muscle cells, immune cells, wound healing, neuronal cells, in development, etc., could be modulated by serotonergic system as its physiological role (blue). (2) Pathological roles: An aberrant serotonergic system for e.g. abnormal levels of expression of serotonin, serotonin receptors or transporter, etc., (purple) could also affect the adhesion-related processes, and such abnormal adhesion-related processes could cause the disease progression of neuropsychiatric disorders (orange). (3) Mode of action of drugs: The neuropsychiatric drugs targeting the aberrant serotonergic system could evoke its desired response of mitigating neuropsychiatric symptoms by modulating the adhesion-related processes (green). (4) Adverse effects of drugs: The neuropsychiatric drugs can also act nonspecifically on other components of serotonergic system and result in off-target adverse effects (brown).

Acknowledgments

The authors wish to thank Department of Biotechnology, Government of India for the Grant BT/PR10961/MED/30/1310/2014 and the National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bengaluru, India for intramural grants to MMP. The fellowship of JJ was supported by the Union Grants Commission, Government of India. JJ thanks Ramanathan Sowdhamini, and Shaon Chakrabarti, National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bengaluru, India.

Disclosure statement

The authors declare no competing interests.

Funding

This work was supported by the Department of Biotechnology, Government of India [Grant BT/PR10961/MED/30/1310/2014].

ORCID

Joe Anand Kumar John Jayakumar http://orcid.org/0000-0003-3414-8188
Mitradas M. Panicker http://orcid.org/0000-0002-0782-6222

References

[1] Berger M, Gray JA, Roth BL. The expanded biology of serotonin. Annu. Rev. Med. 2009;60(1):355–366.
[2] Mohammad-Zadeh LF, Moses L, Gwaltney-Brant SM. Serotonin: a review. J Vet Pharmacol Ther. 2008;31:187–199.
[3] Švob Štrac D, Pivac N, Mück-Šeler D. The serotonergic system and cognitive function. Transl Neurosci. 2016;7:35–49.
[4] Mordhorst A, Dhandapani P, Matthes S, et al. Phenylalanine hydroxylase contributes to serotonin synthesis in mice. FASEB J. 2021;35(6):(e21648).
[5] Mosienko V, Beis D, Pasqualetti M, et al. Life without brain serotonin: reevaluation of serotonin function with mice deficient in brain serotonin synthesis. Behav Brain Res. 2015;277:78–88.
[6] Kliman HJ, Quaratella SB, Setaro AC, et al. Pathway of Maternal Serotonin to the Human Embryo and Fetus. Endocrinology. 2018;159(4):1609–1629.
[7] Turner EH, Loftis JM, Blackwell AD. Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. Pharmacol Ther. 2006;109:325–338.

[8] Sarkar A, Mukundan N, Sowndarya S, et al. Serotonin is essential for eye regeneration in planaria Schmidtea mediterranea. FEBS Lett. 2019;593(22):3198–3209.
[9] Basu B, Panicker MM Serotonin in pre-implantation mouse embryos is localized to the mitochondria and can modulate mitochondrial potential. 2008;135(5):657-69. http://www.reproduction-online.org/content/135/5/657.short
[10] Gaspar P, Cases O, Maroteaux L. The developmental role of serotonin: news from mouse molecular genetics. Nat. Rev. Neurosci. 2003;4(12):1002–1012.
[11] Buznikov GA, Nikitina LA, Voronezhskaya EE, *et al.* Localization of serotonin and its possible role in early embryos of Tritonia diomedea (Mollusca: nudibranchia). Cell Tissue Res. 2003;311(2):259–266. .
[12] Hannon J, Hoyer D. Molecular biology of 5-HT receptors. Behavioural Brain Research. 2008;195 (1):198–213.
[13] Lanfumey L, Hamon M. 5-HT1 Receptors. <![CDATA[Current Drug Target -CNS & Neurological Disorders]]>. 2004;3(1):1–10.
[14] Bonhaus DW, Bach C, DeSouza A, *et al.* The pharmacology and distribution of human 5-hydroxytryptamine2B (5-HT2b) receptor gene products: comparison with 5-HT2a and 5-HT2c receptors. British Journal of Pharmacology. 1995;115 (4):622–628. .
[15] Schmidt CJ, Sorensen SM, Kenne JH, et al. The role of 5-HT2A receptors in antipsychotic activity. Life Sci. 1995;56:2209–2222.
[16] Lauder JM, Wilkie MB, Wu C, et al. Expression of 5-HT2A, 5-HT2B and 5-HT2C receptors in the mouse embryo. Int J Dev Neurosci. 2000;18:653–662.
[17] Chagraoui A, Thibaut F, Skiba M, et al. 5-HT2C receptors in psychiatric disorders: a review. Prog Neuropsychopharmacol Biol Psychiatry. 2016;66:120–135.
[18] Helboe L, Egebjerg J, de Jong IEM. Distribution of serotonin receptor 5-HT6 mRNA in rat neuronal subpopulations: a double in situ hybridization study. Neuroscience. 2015;310:442–454.
[19] Pereira M, Martynhak B, Andreatini R, et al. 5-HT6 receptor agonism facilitates emotional learning. Front Pharmacol. 2015;6:200.
[20] Thirumaran S-L, Lepailleur A, Rochais C. Structure-activity relationships of serotonin 5-HT7 receptors ligands: a review. Eur J Med Chem. 2019;111705. DOI:10.1016/j.ejmech.2019.111705
[21] Shahidi S, Asl SS, Komaki A, et al. The effect of chronic stimulation of serotonin receptor type 7 on recognition, passive avoidance memory, hippocampal long-term potentiation, and neuronal apoptosis in the amyloid β protein treated rat. Psychopharmacol (Berl). 2018;235:1513–1525.
[22] Shahidi S, Mahmoodi M, Sadeghimehr N. Involvement of Serotonin 5-HT7 Receptors in Learning and Memory in Mice. Neurophysiology. 2019;51:77–82.
[23] Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135:2033–2040.
[24] Riker RR, May TL, Fraser GL, et al. Heparin-induced thrombocytopenia with thrombosis in COVID-19 adult respiratory distress syndrome. Res Pract Thromb Haemost. 2020;4(5):936–941.
[25] Kuindersma M, Spronk PE. Ketanserin as potential additive drug to improve V/Q mismatch in COVID-19? Crit Care. 2020;24(1):526.
[26] Erspamer V, Asero B. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. Nature. 1952;169:800–801.
[27] Rapport MM, Green AA, Page IH. Serum vasoconstrictor (serotonin) III. chemical inactivation. J Biol Chem. 1948;176:1237–1241.
[28] McNicol A, Israels SJ. Platelet Dense Granules: structure, Function and Implications for Haemostasis. Thromb Res. 1999;95:1–18.
[29] Li Z, Delaney MK, O'Brien KA, et al. Signaling during platelet adhesion and activation. Arterioscler Thromb Vasc Biol. 2010;30:2341–2349.
[30] McNicol A, Israels SJ. Platelets and anti-platelet therapy. J Pharmacol Sci. 2003;93:381–396.
[31] Lin OA, Karim ZA, Vemana HP, et al. The Antidepressant 5-HT2A Receptor Antagonists Pizotifen and Cyproheptadine Inhibit Serotonin-Enhanced Platelet Function. PLoS ONE. 2014;9(1):e87026.
[32] Watada S, Harada H, Matsubara K, et al. Effect of sarpogrelate hydrochloride, a 5-hydroxytryptamine2 receptor antagonist, on allograft arteriosclerosis after aortic transplantation in rats. Transpl Immunol. 2013;29(1-4):162–166.
[33] Reininger AJ, Bernlochner I, Penz SM, et al. A 2-Step Mechanism of Arterial Thrombus Formation Induced by Human Atherosclerotic Plaques. J Am Coll Cardiol. 2010;55(11):1147–1158.
[34] Nemecek GM, Coughlin SR, Handley DA, et al. Stimulation of aortic smooth muscle cell mitogenesis by serotonin. Proc Natl Acad Sci. 1986;83:674–678.
[35] Tamura K, Kanzaki T, Saito Y, et al. Serotonin (5-hydroxytryptamine, 5-HT) enhances migration of rat aortic smooth muscle cells through 5-HT 2 receptors. Atherosclerosis. 1997;132(2):139–143.
[36] Day RM, Agyeman AS, Segel MJ, et al. Serotonin induces pulmonary artery smooth muscle cell migration. Biochem Pharmacol. 2006;71(3):386–397.
[37] Mackay CR, Imhof BA. Cell adhesion in the immune system. Immunol Today. 1993;14:99–102.
[38] Arreola R, Becerril-Villanueva E, Cruz-Fuentes C, et al. Immunomodulatory Effects Mediated by Serotonin. J Immunol Res. 2015;2015:1–15.
[39] Kushnir-Sukhov NM, Brown JM, Wu Y, et al. Human Mast Cells Are Capable of Serotonin Synthesis and Release. J Allergy Clin Immunol. 2007;119:498–499.
[40] Silverman A-J, Sutherland AK, Wilhelm M, et al. Mast cells migrate from blood to brain. J Neurosci. 2000;20:401–408.
[41] Nautiyal KM, Dailey CA, Jahn JL, et al. Serotonin of mast cell origin contributes to hippocampal function. Eur J Neurosci. 2012;36(3):2347–2359.
[42] Georgin-Lavialle S, Gaillard R, Moura D, et al. Mastocytosis in adulthood and neuropsychiatric disorders. Transl Res. 2016;174:77–85.e1.
[43] Boehme SA, Lio FM, Sikora L, et al. Cutting edge: serotonin is a chemotactic factor for eosinophils and

functions additively with eotaxin. J Immunol. 2004;173 (6):3599–3603.
[44] Kang BN, Ha SG, Bahaie NS, et al. Regulation of serotonin-induced trafficking and migration of eosinophils. PLoS One. 2013;8(1):1.
[45] Müller T, Dürk T, Blumenthal B, et al. 5-hydroxytryptamine modulates migration, cytokine and chemokine release and T-cell priming capacity of dendritic cells in vitro and in vivo. PloS One. 2009;4 (7):e6453.
[46] Holst K, Guseva D, Schindler S, et al. The serotonin receptor 5-HT7R regulates the morphology and migratory properties of dendritic cells. J Cell Sci. 2015;128(15):2866–2880.
[47] Lechin F, Dijs BVD, Lechin AE. Plasma serotonin, pulmonary hypertension and bronchial asthma. Clin Sci. 2002;103:345–346.
[48] Eddahibi S. Polymorphism of the Serotonin Transporter Gene and Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease. Circulation. 2003;108:1839–1844.
[49] Boilard E, Blanco P, Nigrovic PA. Platelets: active players in the pathogenesis of arthritis and SLE. Nat Rev Rheumatol. 2012;8:534–542.
[50] Crowell MD. The role of serotonin in the pathophysiology of irritable bowel syndrome. Am J Manag Care. 2001;7(8 Suppl):S252–60.
[51] Rey J, Cretel E, Jean R, et al. Serotonin reuptake inhibitors, Raynaud's phenomenon and erythromelalgia. Rheumatology. 2003;42:601–602.
[52] Ronpirin C, Psoriasis: TT. A review of the role of serotonergic system. Afr J Biotechnol. 2010;9:1528–1534.
[53] Sadiq A, Shah A, Jeschke MG, et al. The Role of Serotonin during Skin Healing in Post-Thermal Injury. Int J Mol Sci. 2018;19(4):1034.
[54] Slaninka I, Fibír A, Kaška M, et al. Use of autologous platelet-rich plasma in healing skin graft donor sites. J Wound Care. 2020;29:36–41.
[55] Dees C, Akhmetshina A, Zerr P, et al. Platelet-derived serotonin links vascular disease and tissue fibrosis. J Exp Med. 2011;208(5):961–972.
[56] Fabre A, Marchal-Sommé J, Marchand-Adam S, et al. Modulation of bleomycin-induced lung fibrosis by serotonin receptor antagonists in mice. Eur Respir J. 2008;32(2):426–436.
[57] John Jayakumar JAK, Panicker MM, Basu B. Serotonin 2A (5-HT2A) receptor affects cell-matrix adhesion and the formation and maintenance of stress fibers in HEK293 cells. Sci Rep. 2020 Dec 10;10(1):21675
[58] Ayalew M, Le-Niculescu H, Levey DF, et al. Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. Mol Psychiatry. 2012;17(9):887–905.
[59] Albrecht A, Are SO. NCAM deficient mice an animal model for schizophrenia? Front Behav Neurosci. 2012;6:43.
[60] Ellenbroek BA, Riva MA. Early maternal deprivation as an animal model for schizophrenia. Clin Neurosci Res. 2003;3:297–302.
[61] Chocyk A, Dudys D, Przyborowska A, et al. Impact of maternal separation on neural cell adhesion molecules expression in dopaminergic brain regions of juvenile, adolescent and adult rats. Pharmacol Rep. 2010;62:1218–1224.
[62] Angata K, Fukuda M. Polysialyltransferases: major players in polysialic acid synthesis on the neural cell adhesion molecule. Biochimie. 2003;85:195–206.
[63] Gnanapavan S, Giovannoni G. Neural cell adhesion molecules in brain plasticity and disease. Mult Scler Relat Disord. 2013;2:13–20.
[64] Frasca A, Fumagalli F, Ter Horst J, et al. Olanzapine, but not haloperidol, enhances PSA-NCAM immunoreactivity in rat prefrontal cortex. Int J Neuropsychopharmacol. 2008;11(5):591-5.
[65] Gordon-Weeks PR, Fournier AE. Neuronal cytoskeleton in synaptic plasticity and regeneration. J Neurochem. 2014;129:206–212.
[66] Chen F, du Jardin KG, Waller JA, et al. Vortioxetine promotes early changes in dendritic morphology compared to fluoxetine in rat hippocampus. Eur Neuropsychopharmacol. 2016;26(2):234–245.
[67] Waller JA, Chen F, Sánchez C. Vortioxetine promotes maturation of dendritic spines in vitro: a comparative study in hippocampal cultures. Neuropharmacology. 2016;103:143–154.
[68] Yoshida H, Kanamaru C, Ohtani A, et al. Subtype specific roles of serotonin receptors in the spine formation of cortical neurons in vitro. Neurosci Res. 2011;71(3):311–314.
[69] Ferreira TA, Iacono LL, Gross CT. Serotonin receptor 1A modulates actin dynamics and restricts dendritic growth in hippocampal neurons: htr1a and dendritic growth. Eur J Neurosci. 2010;32:18–26.
[70] Mogha A, Guariglia SR, Debata PR, et al. 1A receptor-mediated signaling through ERK and PKCα is essential for normal synaptogenesis in neonatal mouse hippocampus. Transl Psychiatry. 2012;2(1):e66.
[71] Xia Z, Hufeisen SJ, Gray JA, et al. The PDZ-binding domain is essential for the dendritic targeting of 5-HT 2A serotonin receptors in cortical pyramidal neurons in vitro. Neuroscience. 2003;122:907–920.
[72] Jones KA, Srivastava DP, Allen JA, et al. Rapid modulation of spine morphology by the 5-HT2A serotonin receptor through kalirin-7 signaling. Proc Natl Acad Sci. 2009;106(46):19575–19580.
[73] Roppongi RT, Kojima N, Hanamura K, et al. Selective reduction of drebrin and actin in dendritic spines of hippocampal neurons by activation of 5-HT2A receptors. Neurosci Lett. 2013;547:76–81.
[74] Speranza L, Labus J, Volpicelli F, et al. Serotonin 5-HT7 receptor increases the density of dendritic spines and facilitates synaptogenesis in forebrain neurons. In J. Neurochem. 2017;141(5):647-661.
[75] Volpicelli F, Speranza L, Di Porzio U, et al. The serotonin receptor 7 and the structural plasticity of brain circuits. Front Behav Neurosci. 2014;8:318.
[76] Lippiello P, Hoxha E, Speranza L, et al. The 5-HT7 receptor triggers cerebellar long-term synaptic depression via PKC-MAPK. Neuropharmacology. 2016;101:426–438.

[77] Kvachnina E, Liu G, Dityatev A, et al. 5-HT7 receptor is coupled to Gα subunits of heterotrimeric G12-protein to regulate gene transcription and neuronal morphology. J Neurosci. 2005;25(34):7821–7830.
[78] Hayashi T, Ohtani A, Onuki F, et al. Roles of serotonin 5-HT 3 receptor in the formation of dendrites and axons in the rat cerebral cortex: an in vitro study. Neurosci Res. 2010;66(1):22–29.
[79] Shmukler YB, Buznikov GA, Whitaker MJ. Action of serotonin antagonists on cytoplasmic calcium levels in early embryos of sea urchin Lytechinus pictus. Int J Dev Biol. 2002;43:179–182.
[80] Nikitina LA, Buznikov GA, Galanov AY, et al. The control of oocyte maturation in the starfish and amphibians by serotonin and its antagonists. Int J Dev Biol. 2002;37:363–364.
[81] Colas J-F, Launay J-M, Maroteaux L. Maternal and zygotic control of serotonin biosynthesis are both necessary for Drosophila germband extension. Mech Dev. 1999;87:67–76.
[82] Toneby M. Functional aspects of 5-hydroxytryptamine in early embryogenesis of the sea urchinParacentrotus lividus. Wilhelm Rouxs Arch Dev Biol. 1977;181:247–259.
[83] Walther DJ, Bader M. Serotonin synthesis in murine embryonic stem cells. Mol Brain Res. 1999;68:55–63.
[84] Bonnin A, Levitt P. Fetal, maternal, and placental sources of serotonin and new implications for developmental programming of the brain. Neuroscience. 2011;197:1–7.
[85] Colas J-F, Launay J-M, Vonesch J-L, et al. Serotonin synchronises convergent extension of ectoderm with morphogenetic gastrulation movements in Drosophila. Mech Dev. 1999;87:77–91.
[86] Vitalis T, Cases O, Passemard S, et al. Embryonic depletion of serotonin affects cortical development. Eur J Neurosci. 2007;26:331–344.
[87] Vitalis T, Parnavelas JG. The role of serotonin in early cortical development. Dev Neurosci. 2003;25:245–256.
[88] Angoa-Pérez M, Kane MJ, Sykes CE, et al. Brain serotonin determines maternal behavior and offspring survival. Genes Brain Behav. 2014;13(7):579–591.
[89] Alenina N, Kikic D, Todiras M, et al. Growth retardation and altered autonomic control in mice lacking brain serotonin. Proc Natl Acad Sci. 2009;106 (25):10332–10337.
[90] Savelieva KV, Zhao S, Pogorelov VM, et al. Genetic Disruption of Both Tryptophan Hydroxylase Genes Dramatically Reduces Serotonin and Affects Behavior in Models Sensitive to Antidepressants. PLoS ONE. 2008;3(10):e3301.
[91] Il'ková G, Rehák P, Veselá J, et al. Serotonin localization and its functional significance during mouse preimplantation embryo development. Zygote. 2004;12(3):205–213.
[92] Veselá J, Rehák P, Mihalik J, et al. Expression of serotonin receptors in mouse oocytes and preimplantation embryos. Physiol Res. 2003;52(2):223–228.
[93] Moiseiwitsch JRD. The Role of Serotonin and Neurotransmitters During Craniofacial Development. Crit Rev Oral Biol Med. 2000;11:230–239.
[94] Choi DS, Ward SJ, Messaddeq N, et al. 5-HT2B receptor-mediated serotonin morphogenetic functions in mouse cranial neural crest and myocardiac cells. Development. 1997;124:1745–1755.
[95] Shuey DL, Sadler TW, Lauder JM. Serotonin as a regulator of craniofacial morphogenesis: site specific malformations following exposure to serotonin uptake inhibitors. Teratology. 1992;46:367–378.
[96] Sørensen MJ, Kjaersgaard MIS, Pedersen HS, et al. Risk of fetal death after treatment with antipsychotic medications during pregnancy. PloS One. 2015;10(7): e0132280.
[97] Hemels ME, Einarson A, Koren G, et al. 2.1 Antidepressant use during early pregnancy and the rates of spontaneous abortions: a meta-analysis. Antidepressant Use Pregnancy Knowl Transf Transl. Res Find. 2015;39:23.
[98] Frazer S, Otomo K, Dayer A. Early-life serotonin dysregulation affects the migration and positioning of cortical interneuron subtypes. Transl Psychiatry. 2015;5(9):e644.
[99] Murthy S, Niquille M, Hurni N, et al. Serotonin receptor 3A controls interneuron migration into the neocortex. Nat Commun. 2014;5:5524.
[100] Riccio O, Potter G, Walzer C, et al. Excess of serotonin affects embryonic interneuron migration through activation of the serotonin receptor 6. Mol Psychiatry. 2009;14(3):280–290.
[101] Vitalis T, Ansorge MS, Dayer AG Serotonin homeostasis and serotonin receptors as actors of cortical construction: special attention to the 5-HT3a and 5-HT 6 receptor subtypes. (2013).
[102] Koizumi K. Serotonin induces the migration of PC12 cells via the serotonin receptor 6/cAMP/ERK pathway. Biomed Rep. 2013. DOI:10.3892/br.2013.203
[103] Dayer AG, Jacobshagen M, Chaumont-Dubel S, et al. 5-HT 6 Receptor: a New Player Controlling the Development of Neural Circuits. ACS Chem. Neurosci. 2015;6(7):951–960.
[104] Jacobshagen M, Niquille M, Chaumont-Dubel S, et al. The serotonin 6 receptor controls neuronal migration during corticogenesis via a ligand-independent Cdk5-dependent mechanism. Development. 2014;141 (17):3370–3377.
[105] Kepecs A, Fishell G. Interneuron cell types are fit to function. Nature. 2014;505(7483):318–326.
[106] Marín O, Rubenstein JLR. Cellmigration in the Forebrain. Annual Review of Neuroscience. 2003;26 (1):441–483.
[107] González-Maeso J, Sealfon SC. Psychedelics and schizophrenia. Trends Neurosci. 2009;32:225–232.
[108] Roth BL, Hanizavareh SM, Blum AE. Serotonin receptors represent highly favorable molecular targets for cognitive enhancement in schizophrenia and other disorders. Psychopharmacol (Berl). 2004;174(1):17–24.
[109] Meltzer HY, Li Z, Kaneda Y, et al. Serotonin receptors : their key role in drugs to treat schizophrenia. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2003;27(7):1159–1172.
[110] Nash J, Nutt D. Antidepressants. Psychiatry. 2007;6 (7):289–294.

[111] Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. Bmj. 2000;321(7273):1371–1376.
[112] Singh TP, Huettner B, Koefeler H, *et al.* Platelet-Activating Factor Blockade Inhibits the T-Helper Type 17 Cell Pathway and Suppresses Psoriasis-Like Skin Disease in K5.hTGF-β1 Transgenic Mice. The American Journal of Pathology. 2011;178(2):699–708.
[113] Doeing D, Patel S, Takahashi S, et al. Antidepressants and Idiopathic Pulmonary Fibrosis: prevalence and Association with Lung Function. in *C23. ILD: MANAGEMENT AND COMORBIDITIES* A4061 (American Thoracic Society, 2009). doi:10.1164/ajrccm-conference.2009.179.1_MeetingAbstracts.A4061.
[114] Kushnir-Sukhov NM, Brittain E, Scott L, et al. Clinical correlates of blood serotonin levels in patients with mastocytosis. European Journal of Clinical Investigation. 2008;38(12):953–958.
[115] Kereveur A, Callebert J, Humbert M, *et al.* High plasma serotonin levels in primary pulmonary hypertension. . Arteriosclerosis, Thrombosis, and Vascular Biology. 2000;20(10):2233–2239. .
[116] Fitzgerald LW, Burn TC, Brown, et al. Possible Role of Valvular Serotonin 5-HT2B Receptors in the Cardiopathy Associated with Fenfluramine. Mol Pharmacol. 2000;57(1):75–81.
[117] Rothman RB, Baumann MH, Savage JE, *et al.* Evidence for Possible Involvement of 5-HT 2B Receptors in the Cardiac Valvulopathy Associated With Fenfluramine and Other Serotonergic Medications. Circulation. 2000;102(23):2836–2841. .
[118] Kieler H, Artama M, Engeland A, *et al.* Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ. 2011;344(jan12 3):d8012–d8012. .
[119] Ducy P. 5-HT and bone biology. Current Opinion in Pharmacology. 2011;11(1):34–38.
[120] Ploessl C, Pettit RS, Donaldson J. Prevalence of Depression and Antidepressant Therapy Use in a Pediatric Cystic Fibrosis Population. Annals of Pharmacotherapy. 2014;48(4):488–493.
[121] MacLean M. The serotonin hypothesis in pulmonary hypertension revisited: targets for novel therapies (2017 Grover Conference Series). . Pulmonary Circulation. 2018;8(2):2045894018759125.
[122] Davids E, Hartwig U, Gastpar M. Antipsychotic treatment of psychosis associated with multiple sclerosis. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2004;28(4):743–744.
[123] Wang M, Hou R, Jian J, *et al.* Effects of antipsychotics on bone mineral density and prolactin levels in patients with schizophrenia: a 12-month prospective study. Human Psychopharmacology: Clinical and Experimental. 2014;29(2):183–189. .
[124] Shi DD, Yuppa DP, Dutton T, *et al.* Retrospective review of serotonergic medication tolerability in patients with neuroendocrine tumors with biochemically proven carcinoid syndrome. Cancer. 2017;123(14):2735–2742. .
[125] Herr MM, Mohile NA, van Wijngaarden WE. E. B. & Rich, D. Q. Antidepressant use and risk of central nervous system metastasis. Journal of Neuro-Oncology. 2016;129(1):179–187.
[126] Pulkoski-Gross A, Li J, Zheng C, *et al.* Repurposing the Antipsychotic Trifluoperazine as an Antimetastasis Agent. Molecular Pharmacology. 2015;87(3):501–512. .
[127] Daubert EA, Condron BG. Serotonin: a regulator of neuronal morphology and circuitry. Trends Neurosci. 2010;33(9):424–434.
[128] Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018;17(3):341–356.
[129] Simon LV, Keenaghan M. Serotonin Syndrome. [Updated 2021 Jan 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482377/