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Beyond a neurotransmitter: The role of serotonin in inflammation and immunity

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Abstract: Serotonin (5HT), a well-known neurotransmitter in the brain, also plays an important role in peripheral tissues, including the immune system. There is a growing body of evidence suggesting that many different immune cell types express the machinery to generate, store, respond to and/or transport serotonin, including T cells, macrophages, mast cells, dendritic cells and platelets. Interestingly, the relationship between T cells, serotonin and mood disorders appears to be multidirectional. Both preclinical and clinical evidence supports a role for inflammation and T cell imbalances in the etiology of depression and at the same time, selective serotonin reuptake inhibitors (SSRIs) appear to be immunosuppressive. This review summarizes the current knowledge on the relationship between serotonin, mood disorders and the immune system, with a particular focus on T cells and the implications of these findings for drug discovery.

Keywords: Serotonin, 5HT, immune cells, lymphocytes, T cells, immunomodulation

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1. Serotonin and T cells meet in the gut

Although serotonin (5HT) is a well-known neurotransmitter in the brain, close to 95% of the 5HT in the body is synthesized, stored and released by cells in the intestinal mucosa known as enterochromaffin (EC) cells (1-3). Many different cell types are found in the gut, including immune cells, which play an important role in the gut to maintain host defense systems in the GI tract. Interestingly, recent evidence suggests that many different immune cell types express the machinery to generate, store, respond to and/or transport serotonin. This includes T cells, macrophages, mast cells, dendritic cells and platelets. In particular, T cells play an important role to regulate intestinal homeostasis (see *1.1*). A subset of effector CD4 T cells called Th17 cells reside in the intestinal lamina propria and provide protection against foreign pathogens at the mucosal border. In addition, suppressive regulatory T cells are also found in the gut and provide immune tolerance. Serotonin itself may also be directly involved in gut inflammation, as many studies suggest that gut inflammation can influence EC cells and serotonin production, which can in turn play a role in intestinal disease progression (see *1.2*). EC cells and immune cells are therefore in close contact within the epithelium of the intestines and may influence each other to alter the intestinal landscape, with 5HT playing an inflammatory role.

1.1 Role of T cells as a regulator of intestinal homeostasis

T cells constitute a major component of the adaptive immune system. They direct the immune response and provide protection against foreign pathogens. There are several subtypes of T cells, including T helper cells (CD4), T regulatory cells (Treg) and cytotoxic (CD8) T cells. CD8 T cells have toxic granules that induce the apoptosis of abnormal or infected cells. CD4 T cells, also known as "helper T cells" are pluripotent and have the ability to differentiate into a variety of effector cells, including Th1, Th2 and Th17, depending on the physical triggers or antigens and the cytokine environment. These effector T cells direct the immune response depending on the presenting pathogen. This involves diverse functions such as activating B cells, recruiting neutrophils and guiding macrophage differentiation (4). The first T cell subsets discovered, Th1 and Th2, direct cell-mediated and humoral responses, respectively. Th17 cells line the skin and gut to protect the body from extracellular bacterial and fungal infections. Naïve CD4 T cells can also differentiate into induced regulatory T cells (iTreg), which are important in immune tolerance and protection against autoimmunity, particularly in the context of gut inflammation. Additional types of regulatory T cells exist, including natural Treg (nTreg), which are generated *de novo* in the thymus. Follicular B helper T cells (Tfh) are found in Peyer's patches and the gut and one of their roles is to help establish metabolic homeostasis in the gut (5). Together, effector and regulatory T cells maintain an equilibrium to ensure a given immune response is appropriate but not excessive.

A clear example of this equilibrium is found in the intestinal mucosa. Th17 cells, in particular, are found throughout the intestinal lamina propria. They are characterized by the expression of the inflammatory cytokine IL-17 as well as the transcription factor retinoic acid receptor-related orphan receptor gamma (RORγt) and primarily function at mucosal surfaces to protect the host from microorganisms that attempt to enter through the epithelium (6). In addition to Th17 cells, FoxP3-expressing iTreg cells are also found in the intestinal mucosa and are likely present to restrain excessive inflammatory responses (7). There is increasing evidence that Th17 and Treg cells are highly related and maintain the ability to interconvert between one another (8, 9). This and other evolutionary evidence leads to the intriguing possibility that Th17 and Treg cells co-evolved for the purposes of distinguishing

between “good” and “bad” bacteria, allowing for the colonization of the gut with beneficial commensal organisms and maintaining protection against pathogens (10). Interestingly, serotonin appears to have differential effects on Th17 and Treg and it is likely that it plays a role in the balance of inflammatory Th17 and immunosuppressive Treg in the microenvironment of the intestinal mucosa (see *3.1*).

1.2 Serotonin and its role in gut inflammation

Almost all of the serotonin in the body is produced and stored in EC cells in the gut. These cells use the enzyme tryptophan hydroxylase I (TPH1) to synthesize serotonin, which is subsequently released from secretory granules. Serotonin is thought to play an important role in normal gut function and is involved in intestinal motility, absorption and transit (3). For this reason, specific 5HT receptors within the gut, including 5HT3 and 5HT4, are the targets of drugs used to treat gastrointestinal issues such as irritable bowel syndrome (11). Interestingly, studies using TPH1 knockout mice, in which the enzyme responsible for the synthesis of 5HT in the intestines is deleted, show that TPH1 knockouts do not have altered intestinal motility or transit. In contrast, mice in which the neural TPH2 isoform was deleted, as well as TPH1/2 double knockouts, did show major changes in these parameters. These and other data suggest that the peripheral function of 5HT in the gut may not be related to normal gut function but instead play a role in the context of pathophysiology and gut inflammation (12, 13).

Studies with TPH1 knockout mice have also shown a potential role for peripheral serotonin in the context of inflammation and inflammatory bowel diseases (IBD), a group of autoimmune diseases characterized primarily by excessive Th1 and Th17 responses (14, 15). Dendritic cells (DCs), which present antigen and activate T cells, from TPH1 knockout mice with colitis secreted less inflammatory cytokines than DCs from control mice. T cells primed by these cells had reduced levels of the pro-inflammatory cytokines IL-17 and interferon-gamma (12). Another study showed a significant reduction in the severity of colitis in TPH1 knockout mice compared to wildtype control mice (16). Importantly, restoration of 5HT levels in TPH1 knockout mice increased disease severity, suggesting that 5HT is playing an inflammatory role in IBD. Additionally, when immune deficient mice were reconstituted with effector T cells, both the number of EC cells and the level of 5HT were significantly increased (17). Other studies have also linked EC cells and infection, with one showing that the number of EC cells and their 5HT production was increased upon infection with *Trichuris muris* (18). Further studies recently found that the fatty acid-serotonin conjugate docosahaxaenoyl-serotonin in the human gut decreased IL-17 levels and may modulate the Th17 signaling response in inflammatory disease processes of the gut (19). Peripheral serotonin may also play a role in energy homeostasis and contribute to metabolic syndrome (20). TPH1 KO mice have reduced body weight and rats fed a high fat diet showed increased expression levels of TPH1 and serotonin secretion (21). Serotonin may therefore influence obesity levels and obesity is highly linked to inflammation and inflammatory conditions in both animals and humans (22). Serotonin itself is synthesized from tryptophan and in addition to serotonin, tryptophan can be metabolized via the kynurenine pathway by the enzyme indoleamine-2, 3-dioxygenase (IDO1) into active metabolites and ultimately into nicotinamide adenine dinucleotide (NAD+). Tryptophan itself or the balance between the IDO and TPH metabolic pathways may influence inflammation, particularly in the intestines (23, 24). IDO1 expression can be induced by inflammatory cytokines and is known to play an important role in immune tolerance, particularly in regard to the maternal-fetal interface (25). In the gut, IDO inhibition worsened disease severity in a colitis model and the induction of IDO1 prevented colitis in two different mouse models (26, 27). IDO1 has also been proposed as a biomarker in

inflammatory bowel disease (28). Therefore, it appears that serotonin levels are associated with inflammation while the IDO1 pathway is associated with immune tolerance. The modulation of these two pathways may be important in the context of gut inflammation.

Interestingly, serotonin levels may also be modulated by the gut microbiota (29). Some bacteria, including *E. coli, Corynebacterium* spp. and *Streptococcus* spp., have been reported to directly synthesize serotonin and other bacterial species can synthesize tryptamine which is known to induce the release of serotonin by EC cells (30, 31). Although these bacterial species are fairly rare, at least 10% of the human population has a bacterial species with this capacity (30). Importantly, studies with pathogen-free TPH1 knockout mice suggest that less than 10% of peripheral serotonin is synthesized by microbes and instead the microbiota modulates serotonin metabolism primarily by influencing host EC cells (31). Another study demonstrated that mice treated with antibiotics to decrease their gut microbial diversity had reduced levels of both serotonin and TPH1 (32). While this a new area of research and a broader understanding of the brain-gut-microbiota axis is needed, these studies may aid in the future development of new therapeutic strategies for a variety of intestinal clinical indications.

2. Multidirectional interaction between serotonin, mood and the immune system

It is becoming increasingly clear that relationships exist between serotonin, mood and the immune response. A relationship between mood and immune function has been recognized for a number of years. Known as "sickness behavior", animals and humans present with a conserved set of behaviors and moods during a response to infection (see *2.1*). Additionally, serotonin-modulating drugs, including selective serotonin reuptake inhibitors (SSRIs) modulate a variety of immune cell functions, including cell growth and cytokine production. These drugs can decrease the clinical symptoms of certain autoimmune or inflammatory conditions in both patients and *in vivo* models (see *2.2)*. Finally, there is an abundance of evidence for the "cytokine theory" of depression, suggesting that immune dysregulation and depression are strongly linked (see *2.3*).

2.1 The relationship between the immune system and mood

One of the first hints toward a link between the immune system and mood was in animal experiments examining what is known as "sickness behavior". Numerous studies reported that sick animals display certain behavioral characteristics, and this is conserved among different mammal species (33). Virally- or bacterially-infected animals were found to be lethargic, weak, poorly groomed and hypophagic. IL-1β, in particular, has been shown to be an important inflammatory cytokine in sickness behavior (34). This sickness behavior can be induced in both animals and humans with an infusion of recombinant cytokines or lipopolysaccharide (LPS) and includes decreased activity and exploration, suppression of food intake, anxiety and impaired learning (35, 36). One such study with LPS showed that the administration of various LPS doses led to increases in inflammatory cytokines such as IL-6 and TNF-alpha as well as poor mood and increased anxiety (37). The link between cytokines and mood alterations remains to be fully elucidated but several studies suggest that the ability of inflammatory cytokines to activate IDO1 and divert tryptophan away from the serotonergic pathway may be one potential explanation (38). The depletion of tryptophan and subsequent decrease in serotonin levels is well-known in the ideology of mood disorders (39, 40).

In humans, a link between the immune system and mood was noticed in patients treated with interferon alpha. Interferon alpha is used to treat several different immune disorders and cancers, including hepatitis B and C, follicular lymphoma and malignant melanoma. During treatment with

interferon alpha, it was noted that patients would become confused, paranoid or depressed, in addition to other neuropsychiatric adverse effects, despite improvements in physiological disease symptoms (41, 42). Prescriptions for interferon alpha come with a US boxed warning to this effect. Treatment with interferon was correlated with alterations in IL-2, IL-6 and TNF-alpha expression but not cortisol levels (43). Interestingly, patients receiving interferon alpha would develop depressive symptoms which commonly disappeared after the treatment was stopped.

In addition, there are numerous inflammatory conditions that have comorbid mood alterations. Rheumatoid arthritis, inflammatory bowel disease, psoriasis, systemic lupus erythematosus (SLE), asthma and others have a strong association with mood symptoms and disorders (44, 45). Anxiety and depression are very common in patients with inflammatory bowel disease, and increase during periods of disease flare-ups (46, 47). In particular, one study showed that after adjusting for disease activity and other parameters, patients with both depression and IBD were at increased risk for relapse, surgery and hospitalization (48). In patients with rheumatoid arthritis (RA), serum IL-17 levels were significantly higher in patients with anxiety and depression than those without and IL-17 levels independently correlated with higher anxiety scores (49). While there is a strong correlation between mood alterations and immune dysregulation, more research is necessary to determine causation and further elucidate the mechanism behind this link.

2.2 The influence of SSRIs and other serotonin modulators on the immune system

Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression and other psychiatric illnesses and are recognized to block 5HT reuptake, with some also inhibiting norepinephrine uptake (50). While there remains a debate in the field over the exact mechanism of action of SSRIs with respect to the treatment of mood disorders, the body of literature recognizing the modulatory effect of SSRIs on the immune system has been growing. SSRIs appear to affect a variety of immune cell functions, influencing proliferation, cytokine production and even modulating apoptosis (51, 52). T cell proliferation is altered in the presence of many SSRIs, including sertraline, fluoxetine and paroxetine. While most studies show an anti-proliferative effect, a few have found that low doses stimulate T cell proliferation (53). SSRIs have also been shown to play an immunosuppressive role in the context of autoimmune diseases, including inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis.

In a mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), mice treated with an SSRI showed decreased clinical symptoms, reduced cytokine production and even decreased spinal cord demyelination compared to control animals (54-56). Additionally, the antipsychotic agent clozapine attenuated EAE disease severity and enhanced Treg cell differentiation (57). Fluoxetine was found to increase apoptosis in CD4 T cells and inhibit immune cell proliferation (58). Similarly, patients with both multiple sclerosis (MS) and depression treated with SSRIs show an attenuated Th1 response and reduced new enhancing MS lesions (59, 60). In the context of inflammatory bowel disease, mice treated with fluoxetine had decreased disease burden and inhibited inflammatory signaling pathway molecules, including nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) (61). However, certain SSRIs, including fluoxetine, may modulate the immune response differently depending on whether the immune response is ongoing or inhibited (62). In a mouse model of allergic rhinitis, the tricyclic antidepressant despiramine attenuated nasal symptoms, upregulated Treg and downregulated Th17 responses. There was no effect on Th1 and IFN-gamma production in this model (63). While the exact mechanism of SSRIs remains uncertain, it is becoming

increasingly clear that altering serotonin using SSRIs has immunologic effects that could potentially be useful for the treatment of autoimmune and inflammatory diseases.

2.3 Immune dysregulation in depression; the potential for immunotherapy

Due to an abundance of evidence linking immune dysregulation and depression, a "cytokine theory" of depression has emerged in the literature. Despite elevated levels of immunosuppressive glucocorticoids, patients diagnosed with major depression have elevated levels of pro-inflammatory cytokines and increased numbers of inflammatory T cell populations (64, 65). Interestingly, there is evidence that immune dysfunction can actually precede major depressive disorder (MDD) psychopathology. Therapeutic administration of pro-inflammatory cytokines can lead to depression in cancer and hepatitis patients, despite improvements in physiological disease symptoms (42, 66). Many pro-inflammatory cytokines, including IL-1β and TNF-alpha from the innate immune system, as well as IL-6 and IFN-gamma from T cells, are associated with depressive symptoms or the severity of major depression (67-69). Single nucleotide polymorphisms (SNPs) have been found in the genes for numerous inflammatory cytokines as well as genes critical for T cell function that correlate with risk of depressive symptoms or major depression (70-72).

Increased levels of pro-inflammatory cytokines and an elevated Th17:Treg ratio in MDD patients suggest that alterations in immune function may contribute to the development of depression, with alterations in Th17 and Treg being of particular importance (64). MDD patients consistently show reduced percentages of Treg compared with healthy controls (73, 74). In another study, despite similar total T cell counts, patients with MDD had decreased Treg number and percentage (75). Remarkably, after treatment for MDD, with either medication or behavioral therapy, the Treg population increases back to normal levels. In addition, MDD patients had increased Th17 numbers as well as higher RORγt expression and elevated IL-17 compared to healthy controls (64, 76). Interestingly, mice deficient in RORγt, and therefore deficient in Th17 cells, were examined for behavioral characteristics, and showed reduced levels of learned helplessness compared with control animals (77). Th17 cell administration promoted learned helplessness and treatment with either a RORγt inhibitor or anti-IL17 antibodies to reduce the Th17 population abrogated this response. This suggests that Th17 cells promote depression-like behavior. Additionally, depletion of Treg using anti-CD25 antibody treatment increased depressive symptoms in several mouse models of depression and anxiety (78). Even the administration of high dose captopril to decrease the Treg population led to depressive-like behaviors in mice that could be rescued by SSRI administration (79). However, one study examining chronic unpredictable mild stress showed a decreased Th17/Treg ratio (80). Taken together, this work as well as data from human subjects showing an elevated Th17:Treg ratio in MDD patients strongly suggests that alterations in the balance between inflammatory Th17 and suppressive Treg populations is correlated with depression. Whether the depression and/or decreased serotonin levels lead to an alteration in T cell populations or if the inflammatory condition of an imbalance in the Th17:Treg ratio contributes to depression is an important question for the field. One study with TPH1-deficient mice with arthritis showed that these mice had increased Th17 and decreased Treg populations compared with wildtype controls, suggesting that serotonin levels may indeed alter the Th17/Treg balance (81). One might speculate that the alterations in serotonin and immune dysregulation both ultimately contribute to the progression of depression disease processes.

In support of immunotherapy for depression, a recent study showed that psoriasis patients treated with the TNF-alpha inhibitor etanercept showed decreased depressive symptoms (82). The

lessening of depressive symptoms was not correlated with measurements of joint pain, suggesting that increased mood was not simply due to symptom alleviation. Non-steroidal anti-inflammatory drugs (NSAIDs), including celecoxib, have also been shown to decrease depressive symptoms (83, 84). The safety of treating a population of patients that may have co-morbid depression and cardiovascular symptoms requires additional research, although at least one meta-analysis showed that celecoxib decreased depressive symptoms without increasing the risk of adverse effects (85, 86). While this remains an area of active research, future research examining the specific mechanisms underlying the relationship been inflammation and depression may lead to the development of anti-inflammatory drugs that could be used in the treatment of depression and other mood disorders.

3. The immunomodulatory role of serotonin in immune cells

Many *in vivo* disease models and human clinical studies suggest that serotonin may modulate the immune system. This raises important questions about the capacity of different immune cells to generate, store, respond to and/or transport serotonin. There is currently a growing body of evidence suggesting that many different cell types, including T cells, macrophages, mast cells, dendritic cells and platelets have one or more of these capacities. Interestingly, of the major tissues in the body, serotonin uptake is the highest in the spleen (87). Additionally, many studies have shown that SSRIs can alter immune cell function depending on the specific cell type. The findings of these studies are summarized in the sections below.

3.1 T cells

Over four decades ago, scientists started to examine the potential role of serotonin signaling in the activation of lymphocytes by mast cells and platelets, predicated on the existence of a 5HT receptor or binding site on lymphocytes (88-92). Studies were performed revealing that the noradrenergic system could modulate peripheral immune function through 5HT (93). In 1989, researchers proposed that antigen-sensitized effector T cells release inflammatory cytokines in response to 5HT released by murine platelets and mast cells. This was shown to occur via the 5HT2 receptor (94). Subsequently, functional 5HT1 and 5HT2 receptors were found on Jurkat cells, a transformed human T lymphocyte line. Activation of the 5HT2 receptor family in Jurkats resulted in the stimulation of phosphatidylinositol turnover and mobilization of intracellular calcium (95). 5HT1A receptors were also found on mitogen-activated human T cells and treatment with 5HT1A receptor antagonists blocked T cell proliferation. In murine models, 5HT1A receptor decreased T cell cytokine production *in vitro* and decreased cell-mediated immunity and contact sensitivity responses *in vivo* (96, 97). Subsequently, 5HT3 receptors were also found to be expressed in T cells, the activation of which facilitated the progression of T cells from S to G2/M phase of the cell cycle and promoted cell growth and proliferation (98). More recently, 5HT7 receptors and TPH1 were found in rat lymphocytes and both were shown to be significantly increased upon T cell activation (99).

The specific role of 5HT in T cells remains unclear, while it is largely described as immunostimulatory, a few studies show an immunosuppressive role. Stefulj *et al* pointed out this discrepancy after finding in their own experiments that low concentrations of 5HT had no effect on mitogen-induced lymphocyte proliferation but was inhibitory at high concentrations (100). Yin *et al* showed that the activation of 5HT1B receptors increased T cell proliferation and other studies have

found increased expression of the 5HT1A receptor on peripheral blood lymphocytes of patients with systemic lupus erythematosus, even suggesting that this increase contributed to the autoimmune process (101, 102). Subsequent studies have expanded on this, showing the presence of 5HT2A receptors on both CD4 and CD8 T cells. In 5HT-depleted mouse T cells, treatment with a selective 5HT2AR agonist enhanced T cell activation. These data suggest a role for 5HT as an immunoactivator at the 5HT2A receptor (103). However, Davydova *et al* showed that stimulation of 5HT2A receptors resulted in an immunosuppressive response defined by a reduction of CD8 T cells in the spleen and peripheral blood (104). Overall, many serotonin receptor subtypes have been found to be expressed in T cells, including 5HT1, 5HT2, 5HT3 and 5HT7. However, it is important to point out that most of this work was performed using artificial stimulation protocols and does not distinguish between CD4 and CD8 T cells or their specific subtypes, such as Th17 and Treg. An increased understanding of the expression profile of different serotonin receptors is critical to fully elucidate the role of serotonin in T cell biology. It is possible that the apparent conflicting immunostimulatory and immunosuppressive role of 5HT on T cells is due to different expression levels of receptor or transporters in the different T cell subsets and their opposing actions.

In addition to 5HT receptor expression in T cells, a high affinity transporter of 5HT analogous to the serotonin transporter (SERT or 5HTT) in neurons was found on blood lymphocytes from patients with major depression (105). SERT numbers were significantly reduced in depressed patients compared to healthy subjects and this was partially rescued upon SSRI administration (105, 106). The role of SERT in T cells was further examined using SSRIs. In one study, the role of fluoxetine appeared to depend on the activation status of the T cell; in the presence of fluoxetine, stimulation of T cells with Concanavalin A (Con A) at mitogenic concentrations decreased T cell proliferation, but at submitogenic concentrations of Con A fluoxetine stimulated proliferation (107). Treatment of rat CD4 and CD8 T cells with fluoxetine increased the expression of SERT and decreased cyclic adenosine monophosphate (cAMP) levels, inhibiting T cell activation and proliferation. In the same study, the ratio of CD4/CD8 T cells was significantly decreased, suggesting that fluoxetine plays an immunosuppressive role in T cells (108). Treatment with SSRIs was also shown to slow the progression of graft vs host disease by reducing the expansion of alloreactive T cells. This reduction was thought to be mediated through increased apoptosis in activated T cells and a suppression of calcium signaling (53). Another SSRI, citalopram, was also shown to suppress the production of IL-2, IL-4 and IL-17 in the thymus of wildtype C57BL/6 mice (109). In addition, fluoxetine and 5HT2 receptor agonists were shown to be involved in the modulation of taurine transport, which plays a protective role against reactive oxygen species in T cells (110, 111). More recently, studies have found that T cells also have the potential for serotonin storage, degradation and synthesis, as they express type 1 vesicular monoamine transporter (VMAT1), monoamine oxidase A (MAO-A) and TPH1 (112). Interestingly, MAO-A and TPH1 expression, as well as 5HT levels, were higher in CD8 T cells compared to CD4 T cells. A study by O'Connell *et al* suggests that activated T cells release 5HT, which is then taken up by dendritic cells to be stored and subsequently released to signal other naïve T cells, modulating their proliferation and differentiation (113). The potential autocrine and paracrine role of 5HT in T cell proliferation, function and activity has been described elsewhere (62). Overall, the studies described above suggest a role for SERT and other serotonin-related machinery in T cell function, although one study argues that the role of serotonin uptake and SERT function in T cells may be limited (114). A broader understanding of the function of SERT, MAO and TPH1 in T cells is needed to fully understand the role of serotonin in T cell biology.

Interestingly, serotonin may influence T cell function by altering metabolism. Serotonin itself may have evolved in the mitochondria, and the monoamine oxidase enzyme is localized to the inner surface of the mitochondrial outer membrane (87, 115). There is evidence that serotonin or its metabolite melatonin influence the electron transport chain and acts as powerful antioxidants (116, 117). In addition, serotonin can alter glycolytic enzymes to up- or downregulate glycolysis (87, 118, 119). In T cells, there is increasing evidence that the balance between glycolytic and oxidative metabolism is a critical regulator of CD4 T cell differentiation and function (120, 121). Effector T cells such as Th1 and Th17 utilize aerobic glycolysis for energy while Treg rely on the oxidation of glucose and lipids (120-124). Importantly, these metabolic programs are critical for the function of each cell type and alterations in these pathways inhibit CD4 T cell cytokine production, proliferation and function. Future studies are needed to determine the mechanism by which serotonin influences the CD4 T cell compartment, but it is possible that serotonin alters T cell metabolism and thereby influences T cell function.

3.1.1 The role of serotonin in the balance of T cell subsets

The ratios between different T cell subsets have been shown to be important clinically and may be altered by 5HT. The role of 5HT in the Th17:Treg balance was described in detail above (see *2.3*). While the Th17:Treg balance has been more recently studied as a measure of autoimmunity, both the CD4: CD8 T cell ratio and Th1:Th2 ratio have both been used as measures of immune status in a variety of disease settings. Healthy adults have about a 2:1 ratio of CD4:CD8 T cells, although it can vary (125-128). A reduced ratio, particularly < 1, is associated with states of immunodeficiency and autoimmunity. Interestingly, differences in serotonin machinery have been found between these two cell types. In one study, CD8 T cells were found to possess more SERT than CD4 T cells in both depressed patients and controls (106). Another study showed that IL-2R expression was lower in mouse splenic CD8 T cells but not CD4 T cells, after treatment with drug that depleted intracellular serotonin (129). Furthermore, Chen *et al* found that TPH1 and MAO-A and 5HT production were significantly greater in CD8 T cells than in CD4 T cells (112).

Similarly, the balance between Th1 and Th2 is important to provide an adequate and productive immune response (130-132). The Th1:Th2 ratio and the cytokine profiles of each have been studied in a variety of diseases including systemic lupus erythematosus, schizophrenia, depression, autism, pregnancy, asthma, hepatitis B, and rheumatoid arthritis (131, 133-138). Th1 secretes the inflammatory cytokine IL-2, while Th2 secretes the anti-inflammatory IL-4. Interestingly, the levels of both of these cytokines may be altered in the context of depression. Patient with MDD had higher levels of inflammatory cytokines and lower levels of anti-inflammatory ones compared to controls, and this imbalance was rescued upon treatment with SSRIs (131). Another study showed that antidepressant treatment may affect Th1:Th2 balance through the action of the anti-inflammatory cytokine, transforming growing factor beta 1 (TGF-beta1) (136). Overall, these and other studies further suggest a link between T cell subtype imbalances, serotonin, and mood alterations. It will be important to further examine the serotonergic machinery in specific T cell subsets and whether drugs that alter 5HT signaling have differential effects on the balance of specific T cell subtypes in different disease settings.

3.2 Monocytes and macrophages

Macrophages are a type of white blood cell that play an important role in the immune system, specifically by means of their phagocytic (literally "cell eating") function (139). Macrophages engulf and destroy foreign materials and pathogens in virtually all tissues. They are part of the innate immune system and have the ability to respond to and migrate towards chemotactic agents as well as recruit lymphocytes to affected tissues (140). Monocytes are leukocytes that can differentiate into macrophages as well as a few other immune cell types. Monocytes can fulfill many of the same functions as dendritic cells and macrophages, while retaining their ability to give rise to new macrophages and various monocyte subpopulations (141). Like T cells, monocytes and macrophages express some serotonin-related machinery. The mRNA for several serotonin receptors have been found in both macrophages (5HT1A, 5HT2A, 5HT2B, 5HT2C, 5HT3, and 5HT7) and monocytes (5HT1E, 5HT2A, 5HT3, 5HT4, and 5HT7), suggesting that these cells can respond to serotonin signaling (142, 143). SERT has also been shown to be expressed in macrophages and allow for the uptake of extracellular serotonin (144). However, unlike other immune cells, neither cell type has been shown to express TPH, suggesting that macrophages and monocytes are incapable of *de novo* serotonin synthesis. The presence of serotonin degradation machinery is less clear; while some studies have reported that monocytes and a subset of macrophages express MAO-A, other studies have not found MAO-A expression (145, 146). Macrophages can, however, degrade serotonin to 5-hydroxyindole acetic acid via another metabolic pathway (147).

Serotonin may also alter phagocytosis in macrophages. The 5HT1A receptor was shown to enhance phagocytosis and was potentiated by the activation of NFκB, which in turn upregulated the expression of 5HT1A (148). Interestingly, the modulation of phagocytosis by serotonin may be variable depending on other stimuli. In murine macrophages, serotonin augmented phagocytosis at low concentrations of IFN-gamma, whereas serotonin suppressed phagocytosis at high concentrations of IFN-gamma (149). Monocyte function may also be altered by the activation of the 5HT1A receptor, as one study showed that the stimulation of the 5HT1A receptor on monocytes inhibited the release of hydrogen peroxide, an inhibitor of natural killer cell activity (150). Serotonin may therefore upregulate natural killer cell activity via monocyte suppression, playing a pro-inflammatory role.

Macrophages are also known to differentiate into two subclasses, the M1 and M2 phenotypes, each of which plays a unique function in immunity; M1 macrophages are pro-inflammatory whereas M2 macrophages are largely anti-inflammatory. This is similar to the dual role of effector and regulatory CD4 T cells. Interestingly, serotonin may have differential functions within each subtype. Serotonin has been shown to induce and maintain the differentiation of the M2 phenotype, as well as inhibit genes related to the M1 phenotype, likely through 5HT2B and 5HT7 receptor-mediated responses (143). The 5HT7 receptor, in particular, may be primarily responsible for upregulating the M2 phenotype and suppressing M1-related pro-inflammatory gene expression. There is increasing evidence that imbalances in M1 and M2 macrophage populations promote autoimmune disease states and tumorigenesis (151). Overall, these studies suggest that serotonin is playing an immunomodulatory role in macrophages, with activation of the 5HT1A receptor enhancing phagocytosis while other 5HT receptors appear to induce the anti-inflammatory M2 phenotype. A better understanding of the role of serotonin in macrophage differentiation will be important to determine the potential use of serotonergic-modulating drugs in this setting.

3.3 Dendritic cells

Dendritic cells (DCs) are professional antigen presenting cells that facilitate the bridge between innate and adaptive immunity (152). Their functions include phagocytosis and subsequent presentation of co-stimulatory molecules to T cells and the secretion of cytokines to stimulate immune responses. One such cytokine, IL-6, is secreted by DCs and is thought to promote CD4 T cell survival, Th17 differentiation and inhibit the action of Treg, thereby increasing the inflammatory response and decreasing immune tolerance (153, 154). Alternatively, a similar process of antigen presentation also enables dendritic cells to decrease autoimmunity by presenting self-antigens to T cells, leading to central and peripheral tolerance (155, 156).

Like in other immune cells, 5HT has recently been shown to be an important regulatory molecule in DCs. 5HT appears to be able to exert its modulatory effects on DCs depending on the maturity of the DC. While both immature and mature DCs expressed mRNA for the 5HT2A and 5HT3 receptors, the expression of other 5HT receptors depended on the maturation status of the DC. Immature DCs were shown to express mRNA for the 5HT1B, 5HT1E, and 5HT2B receptors while mature DCs preferentially expressed mRNA for the 5HTR4 and 7 receptors. Thus, it is likely that the function of 5HT in DCs may depend on the maturity status of the DC (157, 158). The activation of 5HT4 and 5HT7 receptors via 5HT agonists was shown to increase the expression of IL-1β and IL-8 and decreased the expression of IL-12 and TNF-α in mature DCs, altering migration patterns and growth (157, 159). Interestingly, rats with carrageenan-induced inflammation showed increased expression of the 5HT7 receptor compared to rats without inflammation (160). More recently, another study showed that activation of the 5HT7 receptor altered DC morphology in LPS-induced DCs (161). Additionally, stimulation of the 5HT7 receptor upregulated the expression of C-C chemokine receptor type 7 (CCR7), an important receptor involved with DC migration. Inhibition of the 5HT7 receptor decreased DC migration and altered DC morphology, inhibiting both chemotactic migration direction and velocity (161). Cytokine production can also be altered by 5HT signaling, as IL-6 signaling appears to be controlled by the 5HT3, 4, and 7 receptors in DCs (152, 153, 162). In addition to IL-6, another study found a decrease in the levels of a Th1 chemoattractant in mature DC and an increase in a chemokine involved in trafficking of Th2 cells in cells treated with 5HT, suggesting a potential immunomodulatory role of 5HT in the Th1:Th2 balance (162). Additionally, in LPS-matured DCs, 5HT upregulated the release of IL-10 and downregulated IL-12p70, a cytokine that favors Th1 polarization (162). Overall, these studies suggest that 5HT increases DC migration and alters cytokine production to indirectly modulate T cell differentiation toward Th2 responses.

In addition, limited data suggests that SSRIs can attenuate the function of DCs, at least *in vitro*, as DC antigen presentation was inhibited when fluoxetine was added to the cultures (163). The expression of the co-stimulatory molecule inducible T cell costimulatory-L (ICOS-L) on DC was also downregulated in cultures containing fluoxetine, leading to antigen presentation and proliferation defects. Fluoxetine also inhibited DC maturity, decreasing antigen presentation and thereby immune function (163). DCs have also been shown to express SERT, the expression of which increased upon DC maturation and activation. The majority of 5HT entering the cell via SERT appears to be stored in intracellular vesicles and can be released extracellularly via calcium-dependent exocytosis (113, 164). In addition, bone marrow-derived DCs expressed both MAO-A and MAO-B, however their expression decreased substantially upon DC activation (113). MAO expression was not detected in splenic DCs. Together, these data suggest that 5HT is taken up by DCs, sequestered in intracellular vesicles and likely not degraded, but instead released into the microenvironment. Therefore, DCs appear to have the

capacity to modulate 5HT levels in the environment and potentially target other cell types, including T cells, and modulate their function

3.4 Mast cells

Mast cells are another vital component of the immune system. Mast cells contain secretory granules, intracellular vesicles filled with chemotactic agents, proteases and histamine which are used to target pathogens and foreign compounds (165). The signaling cascades involved in mast cell degranulation and chemotaxis rely on a diverse set of signaling molecules, thus enabling mast cells to respond to a myriad of different signals (166). Until recently, it was thought that serotonin did not play a role in mast cell function. However, the presence of serotonin was detected in human mast cells from patients with mastocytosis, a set of conditions characterized by aberrant proliferation and accumulation of mast cells in one or more organ systems (167). In addition, mast cells have been shown to express TPH1, suggesting that they are capable of *de novo* serotonin production (168). Importantly, one study suggests that mast cells express TPH1 at a higher level than any other immune cell type and that its presence in mast cells may actually be independent of serotonin and instead function to deplete tryptophan in the microenvironment (169). Furthermore, rat mast cells appear to be capable of serotonin uptake via SERT *in vitro*, and the serotonin-modulating drugs clomipramine and fluoxetine were shown to inhibit this process. Mast cells may also respond to serotonin, as studies have detected the mRNA for the serotonin receptors 5HT1A, 5HT1B, 5HT1E, 5HT2A, 5HT2B, 5HT2C, 5HT3, 5HT4, and 5HT7. Notably, 5HT1A was found to be the principal receptor involved in inducing mast cell adhesion to fibronectin, a component of tissue matrix (170). Mast cells have not been found to express MAO (171). Overall, these data suggest that mast cells have the machinery to generate, transport and respond to serotonin (172, 173).

The presence of serotonergic cellular machinery prompts the question of what the role of serotonin is in mast cells. One study showed that the concentration of extracellular serotonin increased when human mast cells were cultured with IgE and activated with streptavidin *in vitro*. This corresponded to a concomitant increase in beta-hexosaminidase, a common degranulation marker, suggesting that serotonin may actually be degranulated by mast cells in conjunction with other components of secretory granules (168). Other studies using murine mast cells have revealed that the packaging of serotonin into secretory granules is dependent on serglycin, a proteoglycan found in mast cell granules; the mechanism by which this occurs is currently unknown (174). Certain vesicle-associated membrane proteins, including vesicle-associated membrane protein-8 (VAMP-8), are believed to alter the exocytosis of serotonin-containing granules by mast cells, as mice deficient in VAMP-8 showed a drastic decrease in serotonin release *in vitro* (175-177). Immature mast cells also migrated toward serotonin across an artificial membrane in a dose-dependent manner. Together, these findings suggest that serotonin is involved in degranulation and promotes mast cell migration. Whether serotonin actively triggers degranulation or cytokine production is unknown, and further studies will be required to further elucidate the role of serotonin and 5HT receptors in mast cells (170).

Since altered mast cell activity plays such an important role in pathological conditions such as angioedema, interstitial cystitis, irritable bowel disease, allergic responses, and everyday immunological function, pharmacological options continue to be explored to mitigate or potentiate their activity (178-181). As the function of serotonin in mast cells appears to be largely inflammatory, serotonin receptor antagonists are hypothesized to be anti-inflammatory in this setting. Indeed, the use of 5HT antagonists

suppressed mast cell activation in rat mast cells *in vivo*, likely via the 5HT2A receptor (182, 183). Like in other immune cells, serotonin-modulating drugs and SSRIs appear to be immunosuppressive in mast cells, inhibiting their proliferation, activation and granule formation (184). Amitriptyline, clomipramine, and maprotiline were all capable of preventing mast cell degranulation in rat mast cells from the mesentery, particularly when a high drug concentration was used (185). Amitriptyline was also shown to decrease intracellular calcium, which disrupted signal transduction required for degranulation (186). Fluoxetine and clomipramine also prevented mast cell serotonin reuptake, increasing the extracellular serotonin concentration (172). In addition, complications of mast cell deficiency, such as dysfunctional hippocampal neurogenesis, can be rescued, in part, by SSRI treatment and this process was shown to be dependent on the serotonin made in mast cells (187). Hormone-based drugs also show some influence on the degranulation of both serotonin and histamine from mast cells. Estradiol, the most potent form of estrogen in humans, was shown to enhance serotonin degranulation by rat mast cells. Interestingly, this augmentation of degranulation was inhibited by tamoxifen, an estrogen receptor antagonist. This suggests that selective estrogen receptor modulators (SERMs) may have immunotherapeutic benefits related to regulation of serotonin output by mast cells (188).

3.5 Platelets and the role of platelet-derived serotonin on the immune system

Platelets are blood cells that aid in hemostasis, thrombosis and immunity (189). In addition to these roles, platelets also play an important role in conjunction with serotonin. Many studies have shown that the peripheral serotonin synthesized from enterochromaffin cells appears to be stored almost entirely by platelets (190-192). Thus, the concentration of serotonin in the periphery appears to be largely dependent on the uptake and storage of serotonin by platelets via the serotonin transporter SERT (189-191). Using the intracellular transporter VMAT2, platelets transport serotonin into dense granules and their activation leads to the release of the contents of the granules (193, 194). Once released, serotonin was shown to interact with the 5HT2 receptor on the platelet itself, causing platelet aggregation. The addition of a 5HT antagonist prevented platelet aggregation, further confirming the role of serotonin in platelet function. Additionally, serotonin levels appear to be controlled by the downregulation of SERT at the plasma membrane (195). Initially, the presence of extracellular serotonin upregulates the number of vesicles delivering SERT to the membrane, but at higher levels, small GTPases are modified by serotonylation and SERT-containing vesicles are subsequently internalized and trapped within the cell (195, 196).

Although platelet function in hemostasis is well understand, more recently, the role of platelets and serotonin in the immune system has been a point of interest (197). More specifically, PDS may play an important role in both innate and adaptive immune regulation. In innate immunity, PDS acts by recruiting and regulating neutrophil, monocyte, and macrophage activity, while in adaptive immunity it regulates the activation, growth, and cytokine production from T and B cells. In particular, the role of PDS in neutrophil function has been partially elucidated. PDS appears to regulate the expression of P- and E-selectins on endothelial cells, thus regulating rolling and adhesion of neutrophils (192, 198). Platelet aggregation could also be induced by the addition of collagen and serotonin, and the addition of a 5-HTR2 antagonist reduced P-selectin levels, suggesting that serotonin plays a role in neutrophil adhesion (199). Additionally, when PDS was either depleted via TPH1 knockout mice or by pharmacologic means, neutrophil extravasation and rolling were attenuated (198, 200, 201).

PDS has also been shown to play a role in a variety of pathologic states including viral hepatitis, reperfusion, and cancer. In the context of viral hepatitis, platelets are recruited to the liver and, along with CD8 T cells, induced immunopathological liver damage (202-205). Reperfusion injury within the liver and heart have also been studied and linked to PDS. Reperfusion injury is thought to occur by platelet aggregation and microcirculatory vasoconstriction via serotonin. Other studies demonstrate that post-ischemic myocardial injury may be due to serotonin-induced oxidative stress via MAO (206). Overall, PDS appears to directly regulate peripheral serotonin levels and altered serotonin levels can modulate immune function by a variety of different means.

4. Concluding remarks

Serotonin is most commonly known as a neurotransmitter, but brain-derived serotonin accounts for only 5% of the serotonin the body. It is becoming increasingly clear that peripheral serotonin plays an important role in many different contexts, including inflammation and immunity (144). Within the immune system, platelets, monocytes, mast cells, and antigen presenting cells are able to assess the health status of the body, release inflammatory cytokines, as well as signal T cells, the major interpreters and modulators of the adaptive immune system. Perhaps surprisingly, many of these immune cell types possess the ability to synthesize, transport, store and/or respond to serotonin (see *Figure 1*) (112, 147, 151, 168, 182). The role of serotonin in the intrinsic function of these cell types and its role in intercellular signaling is not fully elucidated, but has been described to both facilitate physiologic immune function as well as prevent autoimmunity. In addition, in disease states of altered serotonin, such as major depressive disorder, there is also dysregulation of the immune system, suggesting a possible correlation between serotonin and immune function (86, 106, 131, 136). Conversely, conditions that are traditionally thought of as primarily autoimmune disorders, such as inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematous, have altered levels of serotonin-processing machinery such as SERT and TPH1. Additionally, serotonin-modulating drugs, such as SSRIs, play an immunosuppressive role in many of the examined immune cell types (see *Table 1*) (51).

While the presence of serotonin machinery and function has been examined in different immune cell types, more studies are needed to elucidate the specific role of serotonin in regard to its immunomodulatory role in both physiologic and pathologic states. T cells are of particular interest, as they play an important role to direct the immune response. Specifically, the balance between Th17 and Treg appears to be important for many disease states. Alterations in serotonin levels may play a role in the balance between different T cell subsets, including Th17:Treg (75, 78, 108). Importantly, the finding that SSRI treatment in MDD patients decreases IL-6 levels and increases Treg, normalizing the Th17:Treg back to that of healthy subjects, suggests that T cells can be influenced by pharmacotherapy, and that this immune change may contribute to treatment efficacy (186-189). If so, manipulation of the Th17:Treg balance may provide a new therapeutic strategy for major depressive disorder. In support of this, the compound rapamycin may be of interest. Rapamycin an immunosuppressant drug, and is used clinically to selectively increase Treg and suppress Teff, suppressing graft-versus-host and other inflammatory conditions (190, 191). Interestingly, mice treated with rapamycin showed enhanced cognitive function and increased dopamine and serotonin levels (192). Using immune-modulating drugs to treat mood disorders remains an intriguing possibility, just as serotonin-modulating drugs are being examined as immunosuppressants in the context of inflammation and autoimmunity.

While the expression profile of serotonergic-related machinery is known in total T cell populations, to our knowledge the expression of 5HT receptors, SERT and TPH1 in specific T cell subtypes remains unknown. Comprehensive profiling of the types and relative levels of serotonin machinery in specific T cell subtypes and a better understanding of the role of serotonin in these different cell types are needed. Importantly, previous studies describing discrepancies between immunostimulatory or immunosuppressive effects of serotonin may be due to the fact that immune cells can differentiate and specialize once activated. It is unlikely, for instance, that serotonin plays the same role in both Th17 and Treg. In addition, previous studies using chemical mitogens (e.g. Con A) to activate T cells may not represent *in vivo* T cell activation, which requires interaction with antigen presenting cells and signaling with cytokines in the microenvironment.

Overall, many open questions remain. The presence of different receptor subtypes on a single immune cell, for example, begs the question of what the specific function of each receptor subtype might be. Complicating the role of serotonin in immunity, certain subtypes of immune cells can go on to activate other immune cells. Even within a single cell, the synthesis and subsequent breakdown of serotonin into alternate metabolic pathways like kynurenine or melatonin may influence immune cell function as well. Intriguingly, serotonylation of GTPases has been shown to occur within platelets, and it is possible to imagine that serotonylation of additional intercellular signaling molecules may alter other signaling pathways in immune cells (196). Serotonin, originally thought of as simply a neurotransmitter in the brain, has now been shown to play a crucial role in the periphery through alterations in immune function. The bidirectional relationship between the central nervous system and immune system is an exciting new frontier for the potential use of serotonin-modifying treatments to alter immune response and immunosuppressants to alter CNS function. Ultimately, a complete understanding of the role of serotonin in inflammation and immunity has the potential to change how we model and treat both neurocognitive and immune dysfunction.

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