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5-HT and the Immune System

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Abstract

The classical neurotransmitter, serotonin (5-HT), plays an important role outside of the central nervous system in immune signaling. Here I review recent studies describing 5-HT uptake in dendritic cells and B lymphocytes, 5-HT synthesis in T lymphocytes, and the role of specific 5-HT receptor subtypes in innate and adaptive immune cells. Furthermore, a recent paper describing the immune phenotype of 5-HT deficient mice is discussed.

Introduction

Although, 5-HT has a well-known signaling role in immune cells many older studies relied primarily on pharmacological tools, using agonists/antagonists that either lacked selectivity or at concentrations that are non-selective. Recent studies have identified 5-HT subtypes at the mRNA/protein level, and have used selective drugs and genetic approaches to characterize the signaling functions. These data have clarified earlier misconceptions (for example 5-HT subtypes in T cells) and revealed diverse roles for 5-HT in immune functions. Further, new data demonstrate a broad capacity for 5-HT synthesis and transport in immune cells.

5-HT Synthesis and Storage in Immune cells

Platelets, storing 5-HT synthesized by enterochromaffin cells in the gut, represent the major source of 5-HT for immune cells. In addition to platelets, rodent (but apparently not human) mast cells can both take up and synthesize 5-HT. Kushnir-Sukhov et al. (2007) [1] recently described low levels of the key peripheral 5-HT synthesizing enzyme, tryptophan hydroxylase 1 (TPH-1) in human mast cells. Whether this leads to significant 5-HT synthesis is unclear. Whole blood 5-HT levels are reported to be abnormal in a population of mastocytosis patients [2] who contain greatly increased numbers of mast cells, suggesting that mast cells may contribute to 5-HT levels. Interestingly, recent studies have revealed that 5-HT transport and synthesis is more diverse than previously appreciated. O'Connell et al. (2006) [3] showed that mouse dendritic cells (DCs; key antigen-presenting cells, see Figure 1) express the serotonin transporter (SERT), but do not express TPH-1 or TPH-2. SERT in DCs is functionally equivalent to neuronal SERT with an affinity of 85 nM for 5-HT. Of note, DC-activating stimuli such as LPS and anti-CD40 increase SERT expression. At the same time levels of monoamine oxidase A&B (MAO-A&B), the principal 5-HT catabolizing enzymes, decrease. Thus, activated DCs apparently store rather than degrade 5-

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HT. These data suggest that 5-HT uptake is optimized for late stage DC functions such as interactions with T cells in lymphoid tissues. Significantly, the authors showed that 5-HT can be rapidly secreted from DCs via Ca^{2+} dependent exocytosis. Thus, the ability of DCs to sequester and secrete 5-HT may influence T cell functions that are known to be 5-HT sensitive (see below).

Similar to DCs, Meredith et al. (2005) [4] showed that B lymphocytes exhibit a marked increase in SERT expression upon activation. SERT is barely detectable in tonsillar B cells (germinal center and extrafollicular) under resting conditions. However, mitogenic stimulation of B cells leads to a robust increase in SERT protein. Notably, high levels of SERT expression were detected in various malignant B cell lines with SERT expression positively correlated with basal cell growth.

The expression of 5-HT uptake in DCs and B cells is especially relevant given the recent discovery of 5-HT synthesis in T lymphocytes [3,5]. Although naïve splenic T cells express little TPH-1 (and no TPH-2), there is a 30-fold increase in TPH-1 transcript and a ~5-fold increase in 5-HT synthesis (measured over a 6 hour period) following T-cell activation [5]. Interestingly, the authors failed to identify SERT expression in T cells [5], although T cells nonetheless do take up 5-HT slowly [3], possibly via the dopamine transporter (DAT) that has a lower affinity for 5-HT. Thus, it is tempting to speculate that DCs and B cells rapidly sequester 5-HT from the microenvironment of activated T-cells.

Finally, in a recent study Nakumura et al. (2008) [6] reported expression of TPH-1 (identified by immunohistochemistry) in intestinal macrophages, but direct demonstration of 5-HT synthesis in macrophages is lacking.

The problem of contaminating 5-HT in tissue culture

Unlike neuronal 5-HT signaling, which often can be measured rapidly, many assays of immune cell functions require longer-term (>24 hr) measurement. A confound, only recently appreciated, is the presence of considerable amounts of 5-HT in tissue culture media; primarily derived from serum or from 5-HT producing cells. Indeed, 10% heat-inactivated fetal bovine serum contains ~300 nM 5-HT detected by ELISA [5]. These levels of 5-HT, assuming that immuno-reactive 5-HT is bioactive, are sufficient to activate many 5-HT receptors. Thus, there is real danger that contaminating 5-HT may confound experimental results.

5-HT and the Innate Immune Response

Recent studies have revealed effects of 5-HT on innate immune cells (see Figure 1). Kushnir-Sukhov et al. (2006) [7] showed that 5-HT induces adhesion and chemotaxis (but not degranulation) in mouse and human mast cells. Pharmacological and genetic evidence indicated that the 5-HT_{1A} receptor is critical for these processes. Importantly, 5-HT attracts mast cells to sites of inflammation; injection of 5-HT into the skin produced accumulation of mast cells in wild-type but not in 5-HT_{1A} receptor-null mice.

Similarly, Boehme et al. (2004) [8] showed that 5-HT is chemotactic for eosinophils. Allergic asthma is characterized by infiltration of eosinophils, and 5-HT could contribute to eosinophil recruitment. Indeed, plasma levels of 5-HT are greater in symptomatic compared with asymptomatic asthma patients. Boehme et al. revealed for the first time an important role for 5-HT in eosinophil migration and recruitment to the lung. Pharmacological studies suggested that 5-HT_{2A} receptors mediated these effects; the 5-HT_{2A} receptor antagonist, DPM (N-{1(S)-[4-(3,4-dichlorobenzy)]piperazin-1-yl-methyl}-2-methylpropyl}-4-

methylbenzamide dihydrochloride), significantly inhibited (by ~80%) allergen-induced pulmonary eosinophilia.

A key property of macrophages is phagocytosis. Nakumura et al. (2008) [6] showed that 5-HT enhanced phagocytosis in murine macrophages and that this effect was sensitive to WAY100635 suggesting a role for the 5-HT_{1A} receptor. In addition, Mikulski et al. (2010) [9] showed that alveolar macrophages express 5-HT_{2C} receptors. These receptors drive 5-HT-induced Ca²⁺ transients and upregulate expression of the chemokine, CCL2, a potent monocyte attractant. Both of these effects were inhibited by the selective 5-HT_{2C} receptor antagonist RS-102221 and were absent in AMs derived from 5-HT_{2C} receptor-null mice.

Natural Killer (NK) cells are innate cells with a key cytolytic function. Evans et al. (2008) [10] showed that selective serotonin reuptake inhibitors (SSRIs) enhanced this cytolytic function of NKs in vitro. Further, Hernandez et al. (2010) [11] reported that long-term treatment with SSRIs in humans increases NK proliferation. The signaling mechanisms, however, remain obscure.

DCs are professional antigen-presenting cells, with the unique capacity to activate naïve T cells. Several studies have identified roles for 5-HT in DC function. Idzko et al. (2004) [12] described the expression of numerous 5-HT receptors in human monocyte-derived DCs. Immature DCs primarily expressed mRNA for 5-HT_{1B}, 5-HT_{1E} and 5-HT_{2B} receptors that mediated Ca²⁺ mobilization, whereas mature DCs expressed 5-HT₄ and 5-HT₇ receptors that signaled a rise in cAMP. The 5-HT₃ receptor ion channel was detected at all maturation stages and was functionally characterized with the agonist 2-methyl 5-HT and by chelating extracellular Ca²⁺. It should be noted that the Ca²⁺ chelation results are inconclusive since this treatment would disrupt entry through other channels including Orai proteins (Store-operated entry) and Transient Receptor Potential channels. Further, 5-HT altered the cytokine profile of DCs, enhancing IL-1 β and IL-8 and decreasing IL-12 and TNF- α . Muller et al. (2009) [13] explored the functional consequences of 5-HT signaling in DCs. 5-HT acting through 5-HT₁ and 5-HT₂ receptors induced chemotaxis in immature human DCs and enhanced the migration of pulmonary DCs to draining lymph nodes in mice. Further, 5-HT enhanced production of the pro-inflammatory cytokine, IL-6, and the Th2 cytokine, IL-10, while reducing the Th1 cytokine, IL-12p70. In addition, 5-HT treated DCs increased their production of the Th2 attracting chemokine CCL22, while decreasing the Th1 chemokine, CXCL10. These effects were mediated through 5-HT₄ and 5-HT₇ receptors. Consequently, DCs treated with 5-HT induced a Th2 polarization in naïve CD4 T cells. Interestingly, in another study Katoh et al. (2005) [14] showed that 5-HT modulated the differentiation of DCs from human monocytes. Monocytes cultured with 5-HT produced DCs with enhanced IL-10 production but reduced antigen-presenting capacity. Taken together, these data have potentially important implications for the pathogenesis of allergic disease, in particular asthma, where DCs play a critical role [15].

5-HT and Adaptive Immunity

For nearly 20 years, 5-HT has been proposed as a T-cell modulator. The results of early studies showed that 5-HT could stimulate T-cell proliferation and implicated (albeit based on limited pharmacological tools) a key role for the 5-HT_{1A} receptor. Recently, Leon Ponte et al. (2007) [5] completed a comprehensive analysis of 5-HT receptor expression in naïve and activated murine splenic T cells. Importantly, the authors showed that naïve T cells selectively express the 5-HT₇ receptor. Although mRNA for 5-HT_{1B} receptor was found in naïve T cells, only 5-HT₇ protein was reliably detected by Western blot. Following T-cell activation, T cells enhanced expression of 5-HT₇ receptors, along with the 5-HT_{1B} and 5-HT_{2A} receptors. To confirm a role for 5-HT₇ receptors in naïve T cell signaling, the authors

used the selective 5-HT₇ receptor antagonist, SB 269970 (10-100nM). This inhibitor fully blocked 5-HT induced ERK activation and phosphorylation of I κ B α , whereas SB 216641 (100 nM), a selective inhibitor of 5-HT_{1B} receptors had little effect. Further, impaired T-cell proliferation due to blockade of 5-HT synthesis, was restored by treatment with the 5-HT₇ receptor agonist, AS19. Thus, 5-HT appears to exert an autocrine signaling role acting, at least in naïve T cells, through the 5-HT₇ receptor. Other studies have addressed a role for the 5-HT_{1B} and 5-HT_{2A} receptors that are expressed upon T-cell activation. Yin et al. (2006) [16] showed that 5-HT_{1B} receptor antagonists impaired the proliferation of helper CD4⁺ T cells. Inoue et al. (2011) [17] showed that a 5-HT_{2A} agonist enhanced Concanavalin-A induced activation whereas a 5-HT_{2A} antagonist blocked T-cell receptor mediated interleukin-2 and interferon-gamma production. Consistent with these data, Akiyoshi et al. (2006) [18] showed that treatment with a 5-HT_{2A} antagonist enhanced the survival of cardiac allograft in mice.

There is emerging evidence demonstrating a role for 5-HT signaling in B lymphocytes. SERT was identified in the mid 1990s. Serafeim et al. (2002) [19] showed that uptake of 5-HT drives apoptosis of Burkitt lymphoma (BL) cells, and that blockade of SERT ameliorates this effect. Accordingly, Hernandez et al. (2010) [11] showed that long-term treatment with SSRIs in humans enhances B cell numbers by ~30%. The mechanism for 5-HT-induced apoptosis is unclear. It appears to be independent of oxidative signaling but potentially could involve the intracellular serotonylation signaling pathway. Interestingly, Serafeim et al. (2003) [20] showed that higher doses of SSRIs directly promote BL cell apoptosis, by inhibiting DNA synthesis and locking cells in G0/G1 phase. In contrast normal peripheral and tonsillar B cells were resistant to SSRI-induced apoptosis. The authors speculated that this differential sensitivity opens the door for selective therapeutic treatment of BL with SSRIs, while preserving normal B cell function. In a follow-up paper the same group detected SERT in a variety of B cell lines [4], indicating SERT as a potential target for a broad range of B-cell malignancies.

Interestingly, there are several reports of 5-HT₃ receptor expression in B cells. High levels of mRNA are detected in B cells in the germinal phase. In contrast, mRNA is much lower in naïve B cells and mantle cell lymphomas [21,22]. Rinaldi et al. (2010) [23] recently corroborated these findings at the protein level.

Immune Phenotype of TPH1-null mice

Genetic approaches are key to deciphering the immune functions of 5-HT. Lang et al. (2008) [24] using mice lacking TPH-1 (essential for most peripheral 5-HT synthesis) reported a critical role for platelet-derived serotonin in a viral hepatitis model. The authors found in wild-type mice that 5-HT released from platelets recruited to the liver, exacerbated hepatitis by reducing liver microcirculation and delaying the early recruitment of cytotoxic (CD8⁺) T cells. In contrast, TPH-1 null mice exhibited normal microcirculation and less hepatocyte injury. Notably, the functions of CD8⁺ and helper (CD4⁺) T cells (measured by cytotoxicity assays and production of IFN- γ) were normal in the TPH1-null mice. Thus, these results suggest that 5-HT does not directly affect immune cells, but instead affects T cells indirectly by regulating the vasculature. Additionally, the authors reported that innate immune responses (clearance of murine hepatitis) were unaffected in TPH-1-null mice.

Peripheral 5-HT synthesis is mostly absent in TPH-1 null mice, save for a small residue in the enteric nerves of the gut. Thus, these data might suggest that 5-HT is not critical for intrinsic innate and adaptive immune responses. Indeed, TPH-1-null mice do not appear to be overtly immune compromised [24]. On the other hand, one could argue that 5-HT has an immunomodulatory role independent of viral infection, for example, in allergic disease. In

addition, it should be noted that the *ex vivo* measures of T cell function in this study were performed in serum/media that likely contained contaminating 5-HT. Thus, this could have nullified any differences in T-cell function between wild-type and TPH1-null animals.

Conclusions

Recent studies have revealed that the synthesis and transport of 5-HT in immune cells is much more diverse than previously realized. Thus, 5-HT levels in the microenvironment of immune cells (for example DCs and T cells) may be dynamically regulated even in the absence of platelet-derived 5-HT. In practical terms, the discovery of 5-HT synthesis in T lymphocytes, behooves the experimentalist to control for this newly identified source of 5-HT, in addition to the contaminating 5-HT in serum. Importantly, new data have revealed 5-HT receptor subtypes and their signaling roles in numerous immune cells. In the future genetic approaches are needed to confirm the roles of 5-HT in general (TPH-1 null mice) and 5-HT receptor subtypes in animal disease models.

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Cell Type	5-HT Synthesis	5-HT Transporters	5-HT Receptor Subtypes
Neurons	Yes	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Neurons	Yes	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Glial Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Endothelial Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Smooth Muscle Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Mast Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Macrophages	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric T Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric B Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Dendritic Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Natural Killer Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7
Enteric Stem Cells	No	SERT, VMAT2	5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7

Figure 1. Summary of 5-HT synthesis, 5-HT transport and 5-HT receptor subtypes in different immune cells. The known signaling roles for SERT (effects of SSRIs) and 5-HT receptors are listed for each cell.