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Role of platelet serotonin in innate immune cell recruitment

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Serotonin and the innate immune system: immune cell recruitment
- *3.1. Platelets release and respond to serotonin*
- *3.2. Monocytes and macrophages respond to 5-HT in a complex manner*
- *3.3. Serotonin acts as a chemoattractant on dendritic cells*
- *3.4. Serotonin promotes neutrophil recruitment in acute inflammation*
- *3.5. Eosinophil trafficking is enhanced by serotonin*
- *3.6. Basophils/Mast Cells*

4. Serotonin and the recruitment of adaptive immune cells
- *4.1. T lymphocytes*
- *4.2. B lymphocytes*
- *4.3. NK Cells*

5. Serotonin on endothelial and smooth muscle cells
6. Conclusion

1. ABSTRACT

Serotonin (5-Hydroxytryptamine, 5-HT) was discovered as a vasoconstrictor in 1937. Since its discovery, the involvement of serotonin in numerous physiological processes was described. It acts as an important neurotransmitter, regulates bowel movement, can be released as a tissue hormone and acts as a growth factor. Among the years, a link between serotonin and inflammation has been identified and further evidence suggests an important role of serotonergic components in immune responses. Peripheral serotonin is synthesized by the enzyme tryptophan hydroxylase (Tph), which exists in two different isoforms: Tph2 being responsible for serotonin synthesis in neurons and Tph1 for generation of serotonin in peripheral organs. After synthesis in intestinal enterochromaffin cells, serotonin is stored in platelets and released upon stimulation. Several immune cells express the serotonin transporter SERT and enzymes for serotonin metabolism (monoamine oxygenase, MAO). To be susceptible to changes in serotonin levels, serotonin receptors are required and almost all of the 15 receptor subtypes are represented on immune cells. In this review, we describe the distribution of serotonergic components in cells of the immune system and the impact of platelet-derived serotonin on these cells. In particular, we aim to understand the effect of serotonin on immune cell recruitment to sites of inflammation.

2. INTRODUCTION

Serotonin, 5-Hydroxytryptamine (5-HT), was first discovered by Vittorio Erspamer in 1937. The Italian pharmacologist extracted an unknown bioactive substance from enterochromaffin gut cells, which showed vasoconstrictive features when applied to smooth muscle cells (1). He called this vasoconstrictor enteramine. In the following years, Irvine Page and his colleagues discovered a serum-derived vasoconstrictor, which they called serotonin. In later years, serotonin and enteramine were found to be identical and serotonin was identified in the brain of various mammals (2). Serotonin plays a role in numerous physiological processes, especially as an important neurotransmitter in the central nervous system, but also in bowel movement, as a tissue hormone, growth factor and inflammatory modulator, among others (3–5). With the rise of molecular detection methods, the identification of various receptor types and –subtypes has begun and until today seven different serotonin receptors have been identified, resulting in 15 different subtypes in total (6).

Peripheral serotonin is produced in the enterochromaffin cells in the gut and released into the bloodstream, where it is readily sequestered by platelets via the serotonin transporter SERT. After uptake, it is either stored in subcellular compartments, the dense granules or metabolized by the enzyme monoamine oxygenase MAO.

The vast majority of peripheral serotonin is stored in circulating platelets (7). Platelets store serotonin in their dense granules at millimolar concentrations. These granules can be released upon platelet activation, thereby increasing levels of serotonin locally and systemically (7,8). These local regulations in serotonin levels not only contribute to vascular tone, haemostasis and clot formation (7), but are also thought to have a direct effect on immune functions. The effect of peripheral serotonin on immune cells has been investigated for the last two decades and increasing evidence suggests a direct effect of platelet-derived serotonin on various types of immune cells. In his comprehensive review, Gerard Ahern recapitulates effects and metabolism of serotonin in immune cells (9), considering uptake, synthesis and expression of receptors on immune cells. He describes various immune cells that produce serotonin, like mast cells, macrophages and T-cells (determined by Tph1 expression in these cells), and cells that express the serotonin transporter SERT, like dendritic cells, B cells, and possibly NK cells. Almost every receptor subtype is represented on one or more types of immune cells, e.g. the 5-HT1A receptor on mast cells, which mediates chemotaxis and contributes to several inflammatory diseases, or the 5-HT4 receptor on dendritic cells (DCs), which induces chemokine release in mature DCs in a pro-inflammatory manner. Receptors of the 5-HT1 class are expressed by mast cells, macrophages and DCs, 5-HT2 receptors were found on macrophages, DCs and eosinophils. The only 5-HT receptor of the ligand gated ion channel family, 5-HT3, was found in B cells, and the Gq-coupled serotonin receptors 5-HT4 and 7 were shown to be expressed on T cells and DCs (9). This illustrates the variety and complexity of serotonergic components on immune cells.

3. SEROTONIN AND THE INNATE IMMUNE SYSTEM: IMMUNE CELL RECRUITMENT

3.1. Platelets release and respond to serotonin

Upon activation of platelets, dense granule contents are secreted via a number of intracellular signaling mechanisms. In addition to ADP, ATP, pyrophosphate and Ca^{2+}, serotonin is thereby released into the plasma. Dense granule secretion is part of a positive feedback loop, activating passing platelets to enhance plug formation and vasoconstriction, for example at sites of vascular damage. Therefore, platelets themselves express corresponding receptors to the contents of dense granules, including the serotonin receptors 2A and 3. Activation of these receptors results in the activation of PLC-beta and subsequent intracellular Ca^{2+} release, thereby further stabilizing platelet activation. Thus, autocrine serotonin signaling contributes to the activation of the integrin alphaIIb/beta3 complex, which then in turn can bind its ligands, e.g. fibrinogen or vWF (10,11). Activation of platelets not only leads to integrin activation, but also increases surface levels of P-selectin, a membrane marker of platelet alpha-granules. In-vitro analysis of the effect of serotonin on platelet activation has shown that serotonin itself could not induce platelet aggregation or activation, but enhanced thrombin- and ADP-induced aggregation and surface expression of P-selectin (12).

Studies on $Tph1^{-/-}$ knockout mice however did not show increased levels of P-selectin on platelets in inflammatory settings, suggesting a co-stimulatory role of platelet derived serotonin on platelet P-selectin expression (13). Thus, serotonin might play a modulatory role in platelet-leukocyte and platelet-endothelial interactions via P-selectin and its corresponding ligands on other cell types, and further investigation is needed.

The first link between plasma serotonin, platelets and inflammation was found in 1960 (10, 14), but an increasing number of studies examines the link between the immune-modulatory effect of (platelet-derived) serotonin and inflammation (3,9,15,16). Both, pro- and anti-inflammatory features of peripheral serotonin signaling have been described. Platelets are the main source of serotonin for immune cells following tissue damage and activation by other disease-mediated stimuli (7,17–19).

Interestingly, recent findings show a connection between spore-forming gut bacteria and serotonin synthesis in the host individual. In their study, Yano and co-workers found that absence of spore-forming bacteria leads to decreased Tph1 levels in enterochromaffin cells in the gut, increased colonic SERT expression and decreased levels of serotonin in the serum of germ-free mice. Re-colonization with spore-forming bacteria could reverse these effects and restore normal serum serotonin levels. Experiments on platelet activation revealed decreased P-selectin expression and integrin activation in-vitro in platelets from germ-free mice with reduced serotonin levels (20). Not only does that suggest a pro-inflammatory effect of serotonin on platelets, it also links the gut microbiome to inflammatory diseases via a direct effect on circulating platelets.

Platelet transmigration has been suggested in different states of disease (21–24). Especially, transmigration of platelets in allergen-induced asthma,

rheumatoid arthritis (25) or multiple sclerosis has been described (26). Moreover, platelets act as mediators for the recruitment of leukocytes to sites of inflammation (13,27–29). These platelet-leukocyte interactions are mediated via P-selectin and integrin alpha2/beta3 on platelets and corresponding ligands on leukocytes; however, the role of serotonin on these interactions is not fully understood.

3.2. Monocytes and macrophages respond to 5-HT in a complex manner

Monocytes and macrophages not only express SERT and Tph1, but also serotonin receptors and MAO. In 1986, Sternberg and coworkers performed pharmacological studies on murine macrophages, discovering the expression and specific targeting of 5-HT2 receptor on those cells (30). Two years later, Jackson and colleagues found that macrophages are able to take up serotonin by a mechanism similar to platelet serotonin uptake (SERT) and metabolize it rapidly (31). In 2005, mRNA transcripts for the receptors 5-HT1E, 5-HT2A, 5-HT3, 5-HT4 and 5-HT7 have been discovered on human monocytes. Specific activation of 5-HT4 and 5-HT7 decreased TNF alpha release under baseline condition as well as after LPS stimulation of monocytes (32).

In 1993, a Swedish research group found a link between the activation of 5-HT1A receptor on human monocytes and their capability to suppress NK cell function, indicating that higher serotonin levels lead to an increase in NK cell activity mediated by the monocytic 5-HT1A receptor (33). In addition, treatment of mice with a Tph-inhibitor showed defects in macrophage-mediated T cell activation. These studies found a defect in the macrophage-$CD4^{+}$-IL-2R alpha axis as well as defects in T cell proliferation in the spleen upon induction (34–36).

Further studies from Sternberg and his colleagues on murine macrophages showed that serotonin could suppress IFN gamma-induced macrophage activation *in vitro*. This was shown to be dependent on the dose of IFN gamma used to stimulate these cells, resulting in a co-stimulatory effect of serotonin at physiological, but highly suppressant at increased levels of IFN gamma. However, if treated with serotonin, IFN gamma-induced antigen presenting capacity of macrophages was compromised in a dose-independent manner (30,37). Other functions, such as superoxide production and cytokine release seem to be impacted by serotonin as well, and some studies indicate a 5-HT2 receptor-mediated suppression of TNF alpha release in human monocytes (38,39) as well as an increase in IL-1beta release (39). Other studies suggest a role of 5-HT3 in TNF alpha- and cytokine release (40), while basal levels of serotonin are needed for the production of IL-6 and TNF alpha. A study by Kubera and colleagues showed that increased extracellular serotonin levels could suppress pro-inflammatory cytokine release (41).

In 2016, Tong and colleagues investigated the transmigration of donor monocytes to sites of LPS-induced inflammation in the brain of mice. When they administered serotonin just before transfusion of the donor monocytes, transmigration to the inflammatory site could be increased about 1.7.-fold. However, a similar effect could be shown if other chemical agents like bradykinin or mannitol were used (42).

In conclusion, although serotonin modulates monocyte and macrophage function and cytokine release in a complex manner, little is known about serotonin effects on monocyte/macrophage migration to sites of inflammation.

3.3. Serotonin acts as a chemoattractant on dendritic cells

Dendritic cells (DCs) play an important role in presenting antigens to naïve T cells, thereby contributing to T cell activation. A variety of serotonin receptors have been described on DCs and depending on the maturation state of the cells, serotonin receptors mediate distinct cellular responses: while immature DCs were shown to express 5-HT1B, 5-HT1E and 5-HT2B receptors, all of which cause an increase of intracellular calcium upon activation, mature DCs express 5-HT4 and 5-HT7 receptors, leading to an increase in cAMP levels upon activation. The 5-HT3 receptor was expressed at all maturation states, as analyzed by agonist stimulation (43).

Other groups investigated the effect of gut serotonin on DC activation and cytokine release in a model of inflammatory bowel disease and showed that DCs isolated from $Tph1^{-/-}$ mice released significantly less IL-12p40, under baseline conditions as well as upon LPS stimulation of DCs, suggesting an pro-inflammatory effect of serotonin on DCs (44).

Besides antigen presentation, DCs can contribute to inflammation by the release of pro-inflammatory cytokines, such as TNF alpha, IL-1 beta, IL-6 and IL-8 (43,45). In his comprehensive studies on the effect of serotonin on DC cytokine release, migration and the link between serotonergic DC activation and allergic asthma, Idzko and his coworkers found in 2004, that serotonin promoted immature DC migration in-vitro, while this effect could not be seen after LPS-induced DC maturation. Pharmacological blockage of the 5-HT1B and 5-HT2 receptors could attenuate the chemotactic effect of serotonin. In-vivo experiments showed that if mice were treated with serotonin, DC migration to mediastinal lymph nodes was significantly increased compared to vehicle-treated mice (43).

Other studies published in 2015 by Holst and her colleagues showed the expression of 5-HT7 on mature DCs and a strong link between 5-HT7 receptor activation, cell morphology and cell migration via the small Rho-GTPase Cdc42 and the chemokine receptor CCR7 (46), indicating that the serotonergic activation of DCs plays an important role in inflammatory settings. In conclusion, serotonin is a chemoattractant and activator of DCs in inflammatory settings and might be a target for therapeutic interventions in inflammatory diseases, such as inflammatory bowel syndrome or asthma.

3.4. Serotonin promotes neutrophil recruitment in acute inflammation

Although neutrophils seem to be affected by serotonin levels in the plasma as suggested by several studies (47–50), it is not known whether neutrophils express serotonergic components or if secondary mechanisms impact neutrophil activation. Studies on the effect of serotonin on oxidative burst capacity in neutrophils mostly revealed an inhibitory effect for ROS production, if treated with serotonin (48). One of these studies however only showed decreased superoxide production if also stimulated with the chemotactic peptide fMLP (51).

Jancinová *et al*. observed a link between platelet-derived serotonin and decreased superoxide levels in polymorphonuclear cells (PMCs) (52). Other studies showed that serotonin inhibited ROS production in human phagocytes via the 5-HT2 receptor and linked this effect to inhibition of lysosomal myeloperoxidase in neutrophils. These studies also found that serotonin itself was able to scavenge ROS, a mechanism that had already been suggested by Schuff-Werner and coworkers in 1995 (47). While serotonin attenuated oxidative burst in total leukocyte populations, oxidative burst was not inhibited in isolated neutrophils alone (53).

Another important physiological feature of neutrophils is phagocytosis and serotonin may impact phagocytic activity of neutrophils, although the evidence is not conclusive and partly contradicting. In 1992, Nannmark and colleagues described an inhibitory effect of serotonin on tumor cell phagocytosis of human neutrophils, suggesting a negative effect of serotonin on tumor growth (54). In contrast, other studies on bacterial phagocytosis showed an increase of phagocytic activity in neutrophils, if cells were previously treated with serotonin (55). Another study revealed dose-dependent effects of serotonin on neutrophil phagocytosis: When challenged with opsonized Staphylococcus aureus, cells treated with physiological concentrations of serotonin (1 - 10 µM), showed significantly improved antibacterial defense, whereas treatment with higher concentrations (1 - 10 mM) strongly inhibited antibacterial activity (47,48). In summary, serotonin is thought to enhance phagocytosis, at least at lower concentrations, however these results are not conclusive and might depend on more complex variables than serotonin concentration alone.

In 1996, a first link between serotonin and chemotaxis has been described by Simonenkov and coworkers, who found that addition of serotonin increased movement velocity in a chemotactic assay in-vitro (56). Other publications in contrast, found that serotonin could inhibit migration activity in mononuclear cells isolated by Ficoll-Paque, whereas PMCs did not seem to respond to this stimulus (57). While these studies investigated a direct effect on neutrophils, others looked at the interactions between neutrophils and endothelial cells and how these interactions could be modulated by serotonin. For example, Doukas *et al* discovered that if treated with serotonin, cultured calf endothelial cells increased intercellular contacts, whereas rolling velocity of neutrophils was decreased (50). Other studies investigated the impact of mast cell-derived serotonin on neutrophil recruitment to sites of acute inflammation. In 1996, Kubes and colleagues found that degranulation of mast cells in inflamed tissue could induce leukocyte rolling and adhesion on the endothelium; however, they did not establish a direct link between mast cell-derived serotonin and neutrophil recruitment in particular. An increase in vascular permeability in mesenteric venules after superperfusion with serotonin however was evident (41).

In contrast, pharmacological receptor blockade of the 5-HT2 receptor implicated an important role of serotonin for the early phase (60 min) leukocyte and neutrophil recruitment after LPS injection in rats (58). Our group also conducted studies with mice deficient of Tph1, the rate limiting enzyme for peripheral serotonin synthesis. Interestingly we found that the absence of peripheral serotonin decreased neutrophil recruitment to sites of acute inflammation, e.g. in a model of LPS-induced pneumonia and a model of sterile peritonitis. Intra-vital microscopy showed increased neutrophil rolling velocity in $Tph1^{-/-}$ mice, indicating fewer neutrophil-endothelial interactions, known to mediate slow rolling involving integrins and selectins (13). Serotonin deficiency in myocardial ischemia/reperfusion was associated with a significant decrease in transmigrated neutrophils into the affected myocardium after 24 hours, whereas other leukocyte subsets showed no alterations in transmigration (not published). Similar results were found after pharmacological depletion of peripheral serotonin depots by long term fluoxetine treatment, a potent SERT inhibitor used as an antidepressant. While long-term treatment with serotonin reuptake inhibitors depletes serotonin stores in platelets, acute fluoxetine treatment increased plasma serotonin levels, which could ameliorate the pro-inflammatory phenotype of WT mice in disease models of acute

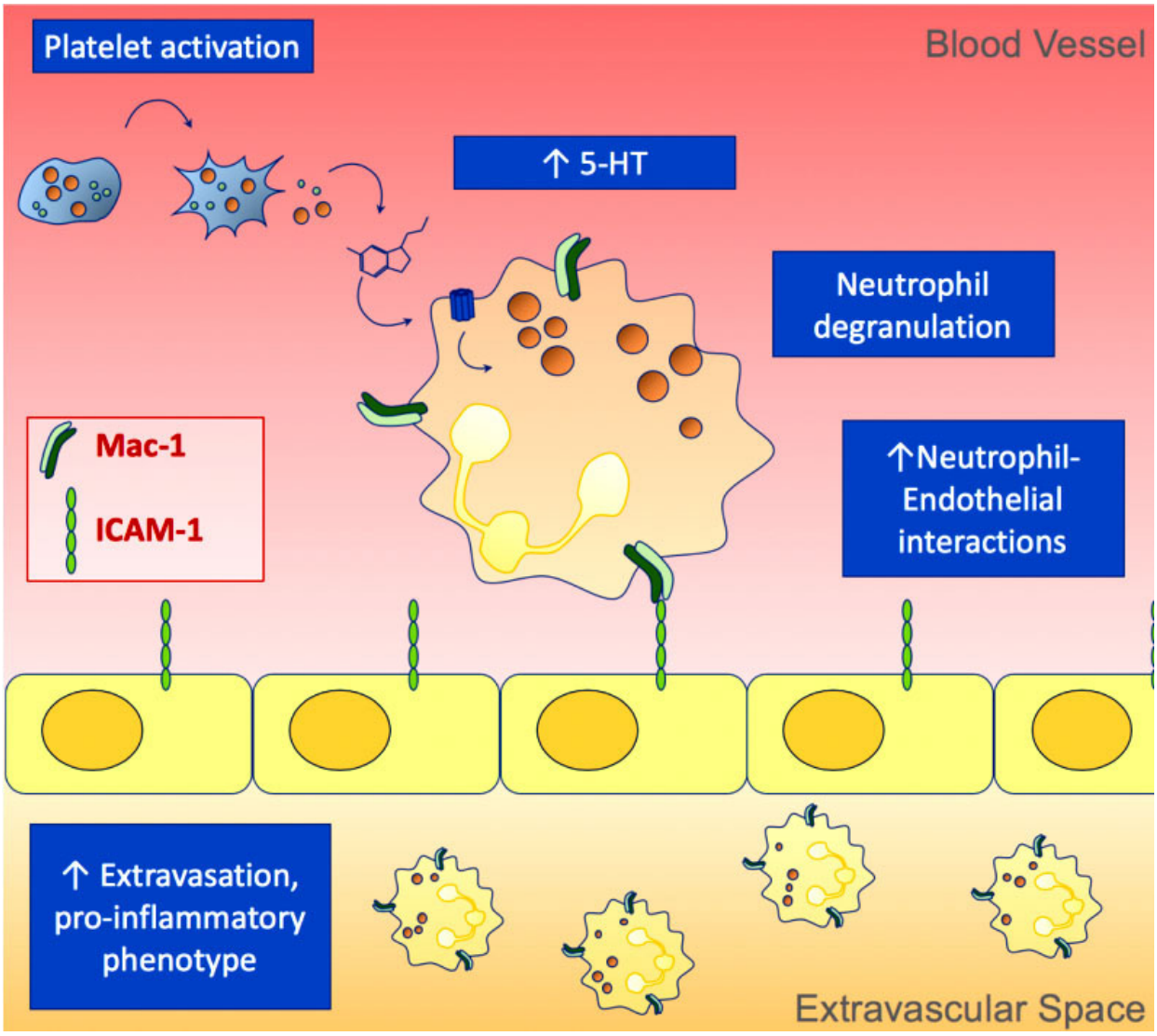

Figure 1. Simplified scheme of the influence of platelet-derived serotonin on neutrophil degranulation and extravasation.

inflammation (13). Receptor transcripts for 5-HT4 and 7 were found in murine neutrophils. Interestingly, both human and murine neutrophils in inflammatory diseases show decreased signs for degranulation, if serotonin levels were decreased or abolished (not published). The possible interaction of platelet-derived serotonin and neutrophils is displayed in Figure 1.

Taken together, there is strong evidence suggesting that serotonin promotes neutrophil recruitment in a 5-HT receptor-mediated manner, possibly by direct serotonin-induced degranulation.

3.5. Eosinophil trafficking is enhanced by serotonin

Eosinophils are mostly known for their role in parasitic infections as well as allergies and are associated with inflammatory diseases. Eosinophils express the 5-HT receptors 1A, 1B, 1E, 2A, 2B and 6, of which 5-HT2B seems to be most important for eosinophils (59).

Numerous studies have investigated serotonin and eosinophil recruitment. Boehme and colleagues showed that serotonin is a strong chemoattractant for eosinophils and that 5-HT2 receptor activation on these cells contributes to the development and severity of allergy-induced asthma (60). Other groups investigated the effect of serotonin on eosinophil migration and intracellular signaling and found that serotonin as well as 5-HT2A activation induced eosinophil transmigration in-vitro. In addition to increased migratory behavior, activation of 5-HT receptors induced morphology changes and intracellular signaling pathways linked to cellular shape change, cytoskeletal reorganization and polarization, ultimately promoting eosinophil trafficking

Table 1. Summary of serotonergic components on immune cells and the effect on recruitment or migration behavior

Cell Type	5-HT receptors	SERT	Tph1	MAO	Effect of 5-HT on recruitment	Cytokine response to 5-HT	References
Platelets	2A, 3	+		+			7
Monocytes and Macrophages	1A, 1E, 2A, 3, 4, 7	+	+	+	Enhanced - possibly through vascular permeability	↑ IL-1 beta, IL-6, IL-8/ CXCL8; IL-12p40 ↓ TNF alpha	30 - 42
Dendritic Cells	1B#, 1E#, 2B#, 3, 4*, 7*	+	+	+	Enhanced - acts a chemoattractant and activator, promotes proliferation	↑ IL-1 beta, IL-6, IL-8/ CXCL8; IL-12p40 ↓ TNF alpha	43, 44, 46
Neutrophils	(1A, 1B, 2) 4, 7				Enhanced - promotes recruitment to sites of acute inflammation	-	13, 41, 50, 58
Eosinophils	1A, 1B, 1E, 2A, 2B, 6	+			Enhanced - promotes transmigration via 5-HT2A	Not affected	17, 59, 60
Basophils						Not affected	61, 62
Mast Cells	1A	+	+		Enhanced - induction of adhesion in-vitro, might contribute to mast cell accumulation in tissues	Not affected	
T Cells	1B, 2A, 3, 7	+	+	+	Enhanced - proliferation, possibly enhances migration	↑ IFN gamma, IL-2, IL-16	63, 64
B Cells	1A, 3A	+				-	65 - 69
NK Cells					Enhanced - possibly enhances adhesion/ migration	↑ pro-inflammatory	33, 71
Endothelial Cells	1B, 2B, 4	+	+			↑ eNOS	72, 77 - 80
VSMCs	5-HT2A				Regulation of IL-6, ICAM-1 and VCAM-1	↑ IL-6?	72 - 77

Reproduced with permission from Herr *et al*. 2017 (81).

and transmigration in a model of allergic asthma (59). Supporting the work of Boehme *et al*, other studies have found that blockade of 5-HT2 receptors could significantly reduce ovalbumin-induced allergic asthma in mice, notably eosinophilia in lungs of these animals (17). Therefore, strong evidence suggests that serotonin enhances eosinophil transmigration in a 5-HT2A-dependent manner, thereby contributing to the development and severity of allergy-induced asthma and possibly in other inflammatory diseases.

3.6. Basophils/Mast Cells

Murine and human mast cells express Tph1 and SERT and storage of serotonin in mast cell granules have been shown, and - at least in rodents - are believed to be an important source of peripheral serotonin (61).

Kushnir-Sukhov and colleagues discovered that serotonin did not induce mast cell degranulation or cytokine release, but it induced adhesion to fibronectin *in vitro*, which could be directly linked to the 5-HT1A receptor. They also showed serotonin-mediated mast cell accumulation, if 5-HT was injected into the skin of mice, suggesting that serotonin can induce mast cell adhesion and transmigration (62). There is a lack of studies examining the effect of serotonin on basophil recruitment or activation.

4. SEROTONIN AND THE RECRUITMENT OF ADAPTIVE IMMUNE CELLS

4.1. T lymphocytes

T cells express the serotonergic components Tph1, SERT and MAO as well as a variety of 5-HT receptors. Comprehensive studies on T cells and serotonin revealed the expression of 5-HT7 receptor in naïve and activated T cells, which also showed additional expression of 5-HT1B and 5-HT2A receptors. T cell proliferation depends on serotonin as shown in a model of impaired serotonin synthesis, where regular T cell proliferation could be restored by addition of a selective 5-HT7 receptor agonist (63). Other studies investigating 5-HT receptors on T cells suggest a role of 5-HT1B and 5-HT2A in T helper cell proliferation whereas blocking of the 5-HT2A receptor resulted in

decrease of pro-inflammatory cytokine release from T cells. A study from Magrini and co-workers found, that if treated with serotonin, human primary T cells show decreased responsiveness to CXCL12 in a 5-HT3 receptor-mediated manner, suggesting an inhibitory role of serotonin on T cell migration (64). However, this effect was only seen in activated T cells towards a gradient of CXCL12 but not CCL2 or CCL5 respectively. Thus, it is not fully understood, if serotonin modulates T cell migration into inflamed tissues and if so, which mechanisms are involved.

4.2. B lymphocytes

Two studies have suggested that serotonin has an anti-apoptotic effect on malignant B cells, which depends on serotonin uptake into these cells. This effect could be reversed by pharmacological inhibition of SERT (65,66). On the contrary, another study conducted by Meredith and colleagues in 2005 found the opposite effect: If malignant B cells were treated with drugs targeting SERT, a pro-apoptotic effect could be observed. They also stated that SERT expression was most predominant on malignant B cells whereas non-malignant B cells seem to express SERT to a much lesser extent (67). More evidence is needed to understand the role of serotonin in B cell proliferation, especially in the state of disease.

Other than SERT, B cells were shown to express the 5-HT receptors 1A and 3A, as demonstrated by Iken and Rinaldi, respectively (68,69). These receptors however are mostly linked to B cell proliferation and little is known about the effect of serotonin on B cell migration or tissue infiltration.

4.3. NK Cells

Serotonin suppresses interactions between monocytes and NK cells, leading to increased cytotoxic activity and release of pro-inflammatory mediators (33). When patients with depressive disorder were treated with SSRIs, increased numbers of NK cells were found in the blood of these patients (70). In addition, Zimmer *et al* performed a small study on a NK cell line, in which serotonin increased migratory behavior of NK cells in-vitro (71). However, since there is no evidence for 5-HT receptor expression on NK cells and a direct effect of serotonin has not been shown so far, more studies are needed to understand interactions of serotonin and NK cells.

5. SEROTONIN ON ENDOTHELIAL AND SMOOTH MUSCLE CELLS

Recruitment of immune cells to sites of inflammation directly depends on interactions between leukocytes and the vascular cell compartment. To understand these mechanisms, it is important to also consider the effects of serotonin on endothelial cells (ECs) as well as vascular smooth muscle cells (VSMCs), both of which are described to be susceptible to local changes in serotonin levels. Receptor transcripts of 5-HT1, 2, 4 and 7 have been found on ECs and VSMCs (72) and recent studies by Ni and colleagues showed the presence of Tph1, SERT and MAO in rat endothelial and smooth muscle cells (73,74).

Vascular smooth muscle cells are susceptible to serotonin via 5-HT2A receptors: Upon activation by serotonin or a selective 5-HT2A receptor agonist, VSMCs can increase IL-6 production in humans (75), whereas IL-6 production, ICAM-1 and VCAM-1 expression and NOS activity was reduced in rats (76). Since contradictory effects of serotonin on VSMCs have been published, it is not clear how serotonin affects VSMCs in-vivo. However, it was shown that 5-HT2A receptor activation has an impact on multiple intracellular signaling pathways in VSMCs, thereby modulating immune cell adhesion and vascular reactivity in a complex manner (77).

Endothelial cells respond to platelet-derived serotonin by activation of endothelial nitric oxide synthase (eNOS), an important vasodilator. Serotonin was shown to modulate EC migration and proliferation, therefore playing a role in angiogenesis (77). In relation to immune cell recruitment, serotonin was shown to impact vascular integrity in the context of acute inflammation: Kubes *et al*. showed that increased serotonin levels mediated vascular leakage in rat mesenteric vessels, underlining the role of serotonin in early edema formation, even though leukocyte adhesion was not altered (78).

In 1994, Katz and coworkers found that serotonin induced EC-mediated adhesion of T cells (79). We found evidence, that EC activation was attenuated in mice lacking peripheral serotonin, and higher in mice with increased plasma serotonin levels, but are unsure, whether these are direct serotonin effects or mediated by leukocytes (80). More scientific evidence is needed to fully understand the complex mechanisms of serotonin-mediated interactions between circulating blood cells and ECs.

6. CONCLUSION

Serotonin plays an important role in immune cell activation and regulation. This is reflected by the variety of serotonergic components that are expressed by immune cells of the innate and adaptive immune system. Serotonin released by activated platelets at sites of inflammation, basal plasma serotonin - or tissue serotonin released by other cells can modulate immune cells. Mostly, serotonin is considered a pro-inflammatory modulator that promotes the invasion

of neutrophils and other cells in acute inflammation. More evidence is needed, however, to fully understand the complex effects of serotonin in inflammation and immune cell recruitment.

7. REFERENCES

1. M. Vialli, V. Erspamer: Ricerche sul secreto delle cellule enterocromaffini: Nota VII Osservazioni critiche su alcuni problemi inerenti alla istochimica delle enterocromaffini. *Zeitschrift fuer Zellforschung und Mikroskopische Anatomie* 27, 81–99 (1937)
DOI: 10.1007/BF00391792

2. B.M. Twarog, I.H. Page: Serotonin Content of Some Mammalian Tissues and Urine and a Method for Its Determination. *American Journal of Physiology-Legacy Content* 175, 157–161 (1953)
DOI: 10.1152/ajplegacy.1953.175.1.157
PMid:13114371

3. M. Berger, J.A. Gray, B.L. Roth: The Expanded Biology of Serotonin. *Annual Review of Medicine* 60,355–366 (2009)
DOI: 10.1146/annurev.med.60.042307.110802
PMid:19630576 PMCid:PMC5864293

4. D. Duerschmied, M. Canault, D. Lievens, A. Brill, S.M. Cifuni, M. Bader, D.D. Wagner: Serotonin stimulates platelet receptor shedding by tumor necrosis factor-alpha-converting enzyme (ADAM17). *Journal of Thrombosis and Haemostasis* 7, 1163–1171 (2009)
DOI: 10.1111/j.1538-7836.2009.03476.x
PMid:19426283 PMCid:PMC3244876

5. R. Mössner, K.P. Lesch: Role of Serotonin in the Immune System and in Neuroimmune Interactions. *Brain, Behavior, and Immunity* 12, 249–271 (1998)
DOI: 10.1006/brbi.1998.0532
PMid:10080856

6. G.J. Siegel ed: *Basic neurochemistry: molecular, cellular, and medical aspects*. 6th ed. Philadelphia: Lippincott Williams & Wilkins (1999).

7. A. McNicol, S.J. Israels: Platelet Dense Granules. *Thrombosis Research* 95, 1–18 (1999)
DOI: 10.1016/S0049-3848(99)00015-8

8. P. Golino, F. Piscione, C.R. Benedict, H.V. Anderson, M. Cappelli-Bigazzi, C. Indolfi, M. Condorelli, M. Chiariello, J.T. Willerson: Local Effect of Serotonin Released during Coronary Angioplasty. *New England Journal of Medicine* 330, 523–528 (1994)
DOI: 10.1056/NEJM199402243300802
PMid:8043066

9. G.P. Ahern: 5-HT and the immune system. *Current Opinion in Pharmacology* 11, 29–33 (2011)
DOI: 10.1016/j.coph.2011.02.004
PMid:21393060 PMCid:PMC3144148

10. J.S. Bennett: Structure and function of the platelet integrin IIb 3. *Journal of Clinical Investigation* 115, 3363–3369 (2005)
DOI: 10.1172/JCI26989
PMid:16322781 PMCid:PMC1297263

11. Y.Q. Ma, J. Qin, E.F. Plow: Platelet integrin alpha2b beta3: activation mechanisms. *Journal of Thrombosis and Haemostasis* 5,1345–1352 (2007)
DOI: 10.1111/j.1538-7836.2007.02537.x
PMid:17635696

12. N. Li, N.H. Wallén, M. Ladjevardi, P. Hjemdahl: Effects of serotonin on platelet activation in whole blood. *Blood Coagul Fibrinolysis* 8, 517–523 (1997)
DOI: 10.1097/00001721-199711000-00006
PMid:9491270

13. D. Duerschmied, G.L. Suidan, M. Demers, N. Herr, C. Carbo, A. Brill, S.M. Cifuni, M. Mauler, S. Cicko, M. Bader: Platelet serotonin promotes the recruitment of neutrophils to sites of acute inflammation in mice. *Blood* 121, 1008–1015 (2013)
DOI: 10.1182/blood-2012-06-437392
PMid:23243271 PMCid:PMC3567335

14. R.B. Davis, W.R. Meeker, D.G. McQuarrie: Immediate Effects of Intravenous Endotoxin on Serotonin Concentrations and Blood Platelets. *Circulation Research* 8, 234–239 (1960)
DOI: 10.1161/01.RES.8.1.234
PMid:13814510

15. Á Domínguez-Soto, A Usategui, M. de las Casas-Engel, M. Simón-Fuentes, C. Nieto, V. Cuevas, M.A. Vega, J. Luis Pablos, Á.L. Corbí: Serotonin drives the acquisition of a profibrotic and anti-inflammatory gene profile through the 5-HT7R-PKA signaling axis. *Scientific Reports* 7, (2017)

16. M. Pelletier, R.M. Siegel: Wishing Away Inr flammation? New Links between Serotonin and TNF Signaling. *Molecular Interventions*

9, 299–301 (2009)
DOI: 10.1124/mi.9.6.5
PMid:20048135 PMCid:PMC2861806

17. J.J. De Bie, P.A.J. Henricks, W.W. Cruikshank, G. Hofman, E.H. Jonker, F.P. Nijkamp, A.J.M. Van Oosterhout: Modulation of airway hyperresponsiveness and eosinophilia by selective histamine and 5-HT receptor antagonists in a mouse model of allergic asthma. *British Journal of Pharmacology* 124, 857–864 (1998)
DOI: 10.1038/sj.bjp.0701901
PMid:9692769 PMCid:PMC1565459

18. Y. Odaka, J. Takahashi, R. Tsuburaya, K. Nishimiya, K. Hao, Y. Matsumoto, K. Ito, Y. Sakata, S. Miyata, D. Manita: Plasma concentration of serotonin is a novel biomarker for coronary microvascular dysfunction in patients with suspected angina and unobstructive coronary arteries. *European Heart Journal* ehw448 (1998)

19. P. Hervé, J.M. Launay, M.L. Scrobohaci, F. Brenot, G. Simonneau, P. Petitpretz, P. Poubeau, J. Cerrina, P. Duroux, L. Drouet: Increased plasma serotonin in primary pulmonary hypertension. *Am J Med* 99, 249–254 (1995)
DOI: 10.1016/S0002-9343(99)80156-9

20. J.M. Yano, K. Yu, G.P. Donaldson, G.G. Shastri, P. Ann, L. Ma, C.R. Nagler, R.F. Ismagilov, S.K. Mazmanian, E.Y. Hsiao: Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. *Cell* 161, 264–276 (2015)
DOI: 10.1016/j.cell.2015.02.047
PMid:25860609 PMCid:PMC4393509

21. A. Lellouch-Tubiana, J. Lefort, E. Pirotzky, B.B. Vargaftig, A. Pfister: Ultrastructural evidence for extravascular platelet recruitment in the lung upon intravenous injection of platelet-activating factor (PAF-acether) to guinea-pigs. *Br J Exp Pathol* 66, 345–355 (1985)

22. C.P. Page, W. PauL, J. Morley: Platelets and bronchospasm. *Int Arch Allergy Appl Immunol* 74, 347–350 (1984)
DOI: 10.1159/000233571
PMid:6735490

23. S.C. Pitchford, S. Momi, S. Baglioni, L. Casali, S. Giannini, R. Rossi, C.P. Page, P. Gresele: Allergen Induces the Migration of Platelets to Lung Tissue in Allergic Asthma. *American Journal of Respiratory and Critical Care Medicine* 177, 604–612 (2008)
DOI: 10.1164/rccm.200702-214OC
PMid:18096710

24. S.C. Pitchford, H. Yano, R. Lever, Y. Riffo-Vasquez, S. Ciferri, M.J. Rose, S. Giannini, S. Momi, D. Spina, B. O'connor: Platelets are essential for leukocyte recruitment in allergic inflammation. *J Allergy Clin Immunol* 112, 109–118 (2003)
DOI: 10.1067/mai.2003.1514
PMid:12847487

25. G.K. Endresen, O. Forre: Human platelets in synovial fluid. A focus on the effects of growth factors on the inflammatory responses in rheumatoid arthritis. *Clin Exp Rheumatol* 10, 181–187 (1992)

26. H.F. Langer, E.Y. Choi, H. Zhou, R. Schleicher, K.J. Chung, Z. Tang, K. Gobel, K. Bdeir, A. Chatzigeorgiou, C. Wong C: Platelets Contribute to the Pathogenesis of Experimental Autoimmune Encephalomyelitis. *Circulation Research* 110, 1202–1210 (2012)
DOI: 10.1161/CIRCRESAHA.111.256370
PMid:22456181 PMCid:PMC3382058

27. C. Hillgruber, A.K. Steingräber, B. Pöppelmann, C.V. Denis, J. Ware, D. Vestweber, B. Nieswandt, S.W. Schneider, T. Goerge: Blocking Von Willebrand Factor for Treatment of Cutaneous Inflammation. *Journal of Investigative Dermatology* 134, 77–86 (2014)
DOI: 10.1038/jid.2013.292
PMid:23812299

28. I. Slaba, J. Wang, E. Kolaczkowska, B. McDonald, W.Y. Lee, P. Kubes: Imaging the dynamic platelet-neutrophil response in sterile liver injury and repair in mice: HEPATOLOGY, Vol. XX, No. X, 2015. *Hepatology* 62, 1593–1605 (2015)
DOI: 10.1002/hep.28003
PMid:26202541

29. T.G. Diacovo, S.J. Roth, J.M. Buccola, D.F. Bainton, T.A. Springer: Neutrophil rolling, arrest, and transmigration across activated, surface-adherent platelets via sequential action of P-selectin and the beta 2-integrin CD11b/CD18. *Blood* 88, 146–157 (1996)

30. E.M. Sternberg, H.J. Wedner, M.K. Leung, C.W. Parker: Effect of serotonin (5-HT) and other monoamines on murine macrophages:

modulation of interferon-gamma induced phagocytosis. *J Immunol* 138, 4360–4365 (1987)

31. J.C. Jackson, R.F. Walker, W.H. Brooks, T.L. Roszman: Specific uptake of serotonin by murine macrophages. *Life Sciences* 42, 1641–1650 (1988)
DOI: 10.1016/0024-3205(88)90443-2

32. T. Dürk, E. Panther, T. Müller, S. Sorichter, D. Ferrari, C. Pizzirani, F. Di Virgilio, D. Myrtek, J. Norgauer, M. Idzko: 5-Hydroxytryptamine modulates cytokine and chemokine production in LPS-primed human monocytes via stimulation of different 5-HTR subtypes. *International Immunology* 17, 599–606 (2005)
DOI: 10.1093/intimm/dxh242
PMid:15802305

33. K. Hellstrand, S. Hermodsson: Serotonergic 5-HT1A receptors regulate a cell contact-mediated interaction between natural killer cells and monocytes. *Scand J Immunol* 37, 7–18 (1993)
DOI: 10.1111/j.1365-3083.1993.tb01658.x
PMid:7678181

34. J.L. Kut, M.R.I. Young, J.W. Crayton, M.A. Wright, M-E. Young: Regulation of Murine T-Lymphocyte Function by Spleen Cell-Derived and Exogenous Serotonin. *Immunopharmacology and Immunotoxicology* 14, 783–796 (1992)
DOI: 10.3109/08923979209009235
PMid:1294623

35. M.R. Young, J.L. Kut, M.P. Coogan, M.A. Wright, M.E. Young, J. Matthews: Stimulation of splenic T-lymphocyte function by endogenous serotonin and by low-dose exogenous serotonin. *Immunology* 80, 395–400 (1993)

36. M.R. Young, J.P. Matthews: Serotonin regulation of T-cell subpopulations and of macrophage accessory function. *Immunology* 84, 148–152 (1995)

37. E.M. Sternberg, J. Trial, C.W. Parker: Effect of serotonin on murine macrophages: suppression of Ia expression by serotonin and its reversal by 5-HT2 serotonergic receptor antagonists. *J Immunol* 137, 276–282 (1986)

38. E. Arzt, M. Costas, S. Finkielman, V.E. Nahmod: Serotonin inhibition of tumor necrosis factor-alpha synthesis by human monocytes. *Life Sciences* 48, 2557–2562 (1991)
DOI: 10.1016/0024-3205(91)90612-F

39. I. Cloëz-Tayarani, A.F. Petit-Bertron, H.D. Venters, J.M. Cavaillon: Differential effect of serotonin on cytokine production in lipopolysaccharide-stimulated human peripheral blood mononuclear cells: involvement of 5-hydroxytryptamine2A receptors. *Int Immunol* 15, 233–240 (2003)
DOI: 10.1093/intimm/dxg027
PMid:12578853

40. B.L. Fiebich, R.S. Akundi, K. Lieb, E. Candelario-Jalil, D. Gmeiner, U. Haus, W. Müller, T. Stratz, E. Muñoz: Antiinflammatory effects of 5-HT3 receptor antagonists in lipopolysaccharide-stimulated primary human monocytes. *Scand J Rheumatol Suppl* 119, 28–32 (2004)
DOI: 10.1080/03009740410006998
PMid:15515409

41. M. Kubera, M. Maes, G. Kenis, Y.K. Kim, W. Lasoń: Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor α and interleukin-6. *Psychiatry Research* 134, 251–258 (2005)
DOI: 10.1016/j.psychres.2004.01.014
PMid:15892984

42. H.I. Tong, W. Kang, P.M.C. Davy, Y. Shi, S. Sun, R.C. Allsopp, Y. Lu: Monocyte Trafficking, Engraftment, and Delivery of Nanoparticles and an Exogenous Gene into the Acutely Inflamed Brain Tissue – Evaluations on Monocyte-Based Delivery System for the Central Nervous System. *PLOS ONE* 11, e0154022 (2016)

43. M. Idzko, E. Panther, C. Stratz, T. Muller, H. Bayer, G. Zissel, T. Durk, S. Sorichter, F. Di Virgilio, M. Geissler: The Serotoninergic Receptors of Human Dendritic Cells: Identification and Coupling to Cytokine Release. *The Journal of Immunology* 172, 6011–6019 (2004)
DOI: 10.4049/jimmunol.172.10.6011
PMid:15128784

44. N. Li, J.E. Ghia, H. Wang, J. McClemens, F. Cote, Y. Suehiro, J. Mallet, W.I. Khan: Serotonin Activates Dendritic Cell Function in the Context of Gut Inflammation. *The American Journal of Pathology* 178, 662–671 (2011)
DOI: 10.1016/j.ajpath.2010.10.028
PMid:21281798 PMCid:PMC3069907

45. N. Katoh, F. Soga, T. Nara, R. Tamagawa-Mineoka, M. Nin, H. Kotani, K. Masuda, S. Kishimoto: Effect of serotonin on the

differentiation of human monocytes into dendritic cells. *Clinical and Experimental Immunology* 146, 354–361 (2006)
DOI: 10.1111/j.1365-2249.2006.03197.x
PMid:17034589 PMCid:PMC1942053

46. K. Holst, D. Guseva, S. Schindler, M. Sixt, A. Braun, H. Chopra, O. Pabst, E. Ponimaskin: The serotonin receptor 5-HT7R regulates the morphology and migratory properties of dendritic cells. *Journal of Cell Science* 128, 2866–2880 (2015)
DOI: 10.1242/jcs.167999
PMid:26092936

47. P. Schuff-Werner, W. Splettstösser, F. Schmidt, G. Huether: Serotonin acts as a radical scavenger and is oxidized to a dimer during the respiratory burst of human mononuclear and polymorphonuclear phagocytes. *Eur J Clin Invest* 25, 477–484 (1995)
DOI: 10.1111/j.1365-2362.1995.tb01733.x
PMid:7556365

48. P. Schuff-Werner, W. Splettstoesser: Antioxidative properties of serotonin and the bactericidal function of polymorphonuclear phagocytes. *Adv Exp Med Biol* 467, 321–325 (1999)
DOI: 10.1007/978-1-4615-4709-9_41
PMid:10721072

49. P.J. Simpson, J.A. Schelm, J.A. Jakubowski, J.K. Smallwood: The role of serotonin (5HT2) receptor blockade in myocardial reperfusion injury: effects of LY53857 in a canine model of myocardial infarction. *J Pharmacol Exp Ther* 258, 979–985 (1991)

50. J. Doukas, H.B. Hechtman, D. Shepro: Vasoactive amines and eicosanoids interactively regulate both polymorphonuclear leukocyte diapedesis and albumin permeability *in vitro*. *Microvascular Research* 37, 125–137 (1989)
DOI: 10.1016/0026-2862(89)90032-0

51. V. Jancinová, K. Drábiková, R. Nosál', M. Petríková, M. Cíz, A. Lojek, E. Danihelová: Inhibition of FMLP-stimulated neutrophil chemiluminescence by blood platelets increased in the presence of the serotonin-liberating drug chloroquine. *Thromb Res* 109, 293–298 (2003)
DOI: 10.1016/S0049-3848(03)00239-1

52. V. Jancinová, R. Nosál, K. Drábiková, E. Danihelováa: Cooperation of chloroquine and blood platelets in inhibition of polymorphonuclear leukocyte chemiluminescence ☆1☆ This work was supported in part by grants No. 2/1012/21 (Scientific Grant Agency VEGA), No. 28/2001 (Slovak-Czech Intergovernmental Research-Technical Cooperation).1Abbreviations: CAT, catalase; HRP, horseradish peroxidase; PBS, phosphate-buffered saline; PMNL, polymorphonuclear leukocytes; PRP, platelet rich plasma; SOD, superoxide dismutase. *Biochemical Pharmacology* 62, 1629–1636 (2001)
DOI: 10.1016/S0006-2952(01)00811-5

53. L. Prachařov, K. Okénková, A. Lojek, M. Číž: Serotonin and its 5-HT2 receptor agonist DOI hydrochloride inhibit the oxidative burst in total leukocytes but not in isolated neutrophils. *Life Sciences* 86, 518–523 (2010)
DOI: 10.1016/j.lfs.2010.02.003
PMid:20149804

54. U, Nannmark, L. Sennerby, L.M. Bjursten, G. Skolnik, U. Bagge: Inhibition of leukocyte phagocytosis by serotonin and its possible role in tumour cell destruction. *Cancer Letters* 62, 83–86 (1992)
DOI: 10.1016/0304-3835(92)90202-7

55. B.J. Northover: The effect of histamine and 5-hydroxytryptamine on phagocytosis of staphylococci *in vitro* by polymorphs and macrophages. *J Pathol Bacteriol* 82, 355–361 (1961)
DOI: 10.1002/path.1700820213
PMid:14480422

56. A.P. Simonenkov, V.D. Fedorov, A.A. Galkin: (Serotonin deficiency in neutrophils). *Biull Eksp Biol Med* 121, 467–469 (1996)
DOI: 10.1007/BF02446749
PMid:8829471

57. L. Bondesson, K. Nordlind, S. Lidén, E. Sundström: Inhibiting Effects of Serotonin and Serotonin Antagonists on the Migration of Mononuclear Leucocytes. *Immunopharmacology and Immunotoxicology* 15, 243–250 (1993)
DOI: 10.3109/08923979309025997
PMid:8349951

58. A. Walther, E. Petri, C. Peter, M. Czabanka, E. Martin: Selective Serotonin-Receptor Antagonism and Microcirculatory Alterations During Experimental Endotoxemia. *Journal of Surgical Research* 143, 216–223 (2007)
DOI: 10.1016/j.jss.2006.08.021
PMid:17825323

59. B.N. Kang, S.G. Ha, N.S. Bahaie, M.R. Hosseinkhani, X.N. Ge, M.N. Blumenthal, S.P. Rao, P. Sriramarao: Regulation of Serotonin-Induced Trafficking and Migration of Eosinophils. *PLoS ONE* 8, e54840 (2013) DOI: 10.1371/journal.pone.0054840 PMid:23372779 PMCid:PMC3553162

60. S.A. Boehme, F.M. Lio, L. Sikora, T.S. Pandit, K. Lavrador, S.P. Rao, P. Sriramarao: Cutting edge: serotonin is a chemotactic factor for eosinophils and functions additively with eotaxin. *J Immunol* 173, 3599–3603 (2004) DOI: 10.4049/jimmunol.173.6.3599 PMid:15356103

61. N.M. Kushnir-Sukhov, J.M. Brown, Y. Wu, A. Kirshenbaum, D.D. Metcalfe: Human mast cells are capable of serotonin synthesis and release. *Journal of Allergy and Clinical Immunology* 119, 498–499 (2007) DOI: 10.1016/j.jaci.2006.09.003 PMid:17291861

62. N.M. Kushnir-Sukhov, A.M. Gilfillan, J.W. Coleman, J.M. Brown, S. Bruening, M. TotH, D.D. Metcalfe: 5-Hydroxytryptamine Induces Mast Cell Adhesion and Migration. *The Journal of Immunology* 177, 6422–6432 (2006) DOI: 10.4049/jimmunol.177.9.6422 PMid:17056574

63. M. Leon-Ponte, G.P. Ahern, P.J. O'Connell: Serotonin provides an accessory signal to enhance T-cell activation by signaling through the 5-HT7 receptor. *Blood* 109, 3139–3146 (2007) DOI: 10.1182/blood-2006-10-052787 PMid:17158224 PMCid:PMC1852236

64. E. Magrini, I. Szabò, A. Doni, J. Cibella, A. Viola: Serotonin-Mediated Tuning of Human Helper T Cell Responsiveness to the Chemokine CXCL12. *PLoS ONE* 6, e22482 (2011) DOI: 10.1371/journal.pone.0022482 PMid:21853036 PMCid:PMC3154189

65. A. Serafeim: 5-Hydroxytryptamine drives apoptosis in biopsylike Burkitt lymphoma cells: reversal by selective serotonin reuptake inhibitors. *Blood* 99, 2545–2553 (2002) DOI: 10.1182/blood.V99.7.2545 PMid:11895792

66. T. Nguyen, J. Kramer, R. Vallejo, G. Stanton, B.A. Heidenreich, R. Benyamin, L.A. Vogel. Citalopram Enhances B Cell Nume bers in a Murine Model of Morphine-Induced Immunosuppression. *Pain Practice* 9, 195–205 (2009) DOI: 10.1111/j.1533-2500.2009.00259.x PMid:19226315

67. E.J. Meredith, M.J. Holder, A. Chamba, A. Challa, A. Drake-Lee, C.M. Bunce, M.T. Drayson, G. Pilkington, R.D. Blakely, M.J.S. Dyer: The serotonin transporter (SLC6A4) is present in B-cell clones of diverse malignant origin: probing a potential anti-tumor target for psychotropics. *The FASEB Journal* 19, 1187–1189 (2005) DOI: 10.1096/fj.04-3477fje PMid:15870169

68. K. Iken, S. Chheng, A. Fargin, A.C. Goulet, E. Kouassi: Serotonin Upregulates Mitogen-Stimulated B Lymphocyte Proliferation through 5-HT1AReceptors. *Cellular Immunology* 163, 1–9 (1995) DOI: 10.1006/cimm.1995.1092 PMid:7758118

69. A. Rinaldi, A.M. Chiaravalli, M. Mian, E. Zucca, M.G. Tibiletti, C. Capella, F. Bertoni: Serotonin Receptor 3A Expression in Normal and Neoplastic B Cells. *Pathobiology* 77, 129–135 (2010) DOI: 10.1159/000292646 PMid:20516728

70. M.E. Hernandez, D. Martinez-Fong, M. Perez-Tapia, I. Estrada-Garcia, S. Estrada-Parra, L. Pavón: Evaluation of the effect of selective serotonin-reuptake inhibitors on lymphocyte subsets in patients with a major depressive disorder. *European Neuropsychopharmacology* 20, 88–95 (2010) DOI: 10.1016/j.euroneuro.2009.11.005 PMid:20005081

71. P. Zimmer, W. Bloch, M. Kieven, L. Lövenich, J. Lehmann, M. Holthaus, S. Theurich, A. Schenk: Serotonin Shapes the Migratory Potential of NK Cells – An *in vitro* Approach. *International Journal of Sports Medicine* 38, 857–863 (2017) DOI: 10.1055/s-0043-113042 PMid:28783845

72. C. Ullmer, K. Schmuck, H.O. Kalkman, H. Lübbert: Expression of serotonin receptor mRNAs in blood vessels. *FEBS Letters* 370, 215–221 (1995) DOI: 10.1016/0014-5793(95)00828-W

73. W. Ni, T.J. Geddes, J.R.C. Priestley, T. Szasz, D.M. Kuhn, S.W. Watts: The

existence of a local 5-hydroxytryptaminergic system in peripheral arteries. *British Journal of Pharmacology* 154, 663–674 (2008)
DOI: 10.1038/bjp.2008.111
PMid:18414394 PMCid:PMC2439511

74. W. Ni, J.M. Thompson, C.A. Northcott, K. Lookingland, S.W. Watts: The serotonin transporter is present and functional in peripheral arterial smooth muscle. *J Cardiovasc Pharmacol* 43, 770–781 (2004)
DOI: 10.1097/00005344-200406000-00006
PMid:15167270

75. T. Ito, U. Ikeda, M. Shimpo, K. Yamamoto, K. Shimada: Serotonin increases interleukin-6 synthesis in human vascular smooth muscle cells. *Circulation* 102, 2522–2527 (2000)
DOI: 10.1161/01.CIR.102.20.2522
PMid:11076827

76. B. YU, J, Becnel, M. Zerfaoui, R. Rohatgi, A.H. Boulares, C.D. Nichols: Serotonin 5-Hydroxytryptamine 2A Receptor Activation Suppresses Tumor Necrosis Factor-alpha-Induced Inflammation with Extraordinary Potency. *Journal of Pharmacology and Experimental Therapeutics* 327, 316–323 (2008)
DOI: 10.1124/jpet.108.143461
PMid:18708586

77. T. Machida, k. Iizuka, M. Hirafuji: 5-Hydroxytryptamine and Its Receptors in Systemic Vascular Walls. *Biological and Pharmaceutical Bulletin* 36, 1416–1419 (2013)
DOI: 10.1248/bpb.b13-00344
PMid:23995652

78. P. Kubes, D.N. Granger: Leukocyte-endothelial cell interactions evoked by mast cells. *Cardiovasc Res* 32, 699–708 (1996)
DOI: 10.1016/S0008-6363(96)00118-6

79. M.F. Katz, H.W. Farber, Z. Dodds-Stitt, W.W. Cruikshank, D.J. Bear: Serotonin-stimulated aortic endothelial cells secrete a novel T lymphocyte chemotactic and growth factor. *Journal of Leukocyte Biology* 55, 567–573 (1994)
DOI: 10.1002/jlb.55.5.567
PMid:7514199

80. N. Herr, M. Mauler, T. Witsch, D. Stallmann, S. Schmitt, J. Mezger, C. Bode, D. Duerschmied: Acute Fluoxetine Treatment Induces Slow Rolling of Leukocytes on Endothelium in Mice. *PLoS ONE* 9, e88316 (2014)
DOI: 10.1371/journal.pone.0088316
PMid:24520366 PMCid:PMC3919751

81. N. Herr, C. Bode, D. Duerschmied D: The Effects of Serotonin in Immune Cells. *Frontiers in Cardiovascular Medicine* 4, (2017)

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