Platelet serotonin modulates immune functions

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Summary
This short review addresses immune functions of platelet serotonin. Platelets transport serotonin at a high concentration in dense granules and release it upon activation. Besides haemostatic, vasotonic and developmental modulation, serotonin also influences a variety of immune functions (mediated by different serotonin receptors). First, platelet serotonergic effects are directed against invading pathogens via activation and proliferation of lymphocytes, modulation of cytokine release, and recruitment of neutrophils to sites of acute inflammation by induction of selectin expression on endothelial cells. Second, serotonin levels are elevated in autoimmune diseases, such as asthma or rheumatoid arthritis, and during tissue regeneration after ischemia of myocardium or brain. Specific antagonism of serotonin receptors appears to improve survival after myocardial infarction or sepsis and to attenuate asthmatic attacks in animal models. It will be of great clinical relevance if these findings can be translated into human applications. In conclusion, targeting immune modulatory effects of platelet serotonin may provide novel therapeutic options for common health problems.

Keywords
Inflammatory mediators, platelet immunology, leukocyte function, leukocyte activation

Schlüsselwörter
Entzündung, Plättchen, Immunologie, Leukozytenfunktion, Leukozytenaktivierung

Zusammenfassung

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Serotonin (5-hydroxytryptamine, 5-HT) is a messenger molecule that was first described more than 60 years ago as a vasconstrictor (1). Since then a variety of different functions have been ascribed to serotonin and it keeps being at the centre of biological and medical studies (2, 3). Serotonin not only works as a neurotransmitter but it also covers regulatory functions in non-neuronal tissue (4–6). Tryptophan hydroxylase (TPH) is the rate-limiting enzyme for 5-HT synthesis. Two isoforms of this enzyme (TPH1 and TPH2) are present in the body of mammals (7): TPH2 regulates serotonin synthesis in the brain stem and TPH1 is expressed in intestinal enterochromaffine cells (EC) (6). As a neurotransmitter, 5-HT regulates various functions like sleep, mood, appetite, and sexual drive in the central nervous system (CNS) (6, 8). However, most of the serotonin circulates in platelets, modifying lung function, haemostasis, development of the heart, and immune response (6, 8, 9). After synthesis in the intestine, 5-HT is secreted into blood plasma where it is initially actively taken up by circulating platelets via the serotonin transporter (SERT) (10) and either stored in their dense granules at high concentration (65 mmol/l) or degraded by monoamine oxidases (Mercado 2000).

Interestingly, in contrast to neuronal 5-HT trafficking mediated by SERT, where an increase in extracellular serotonin reduces the number of transporter molecules on neurons (11–13), higher concentration of plasma serotonin increase SERT expression on the platelet surface initially, followed by a return to baseline levels after the initial uptake of 5-HT (14–16).

To date, 15 serotonin receptor subtypes have been identified on various cell types, like muscle cells, platelets, endothelial cells, different regions of the brain as well as in the stomach and uterus (17–22). Even...
though the influence of platelets, especially platelet serotonin, on immune functions is a very complex and dynamic process, many studies point out the importance of this aspect and its possibilities for therapeutic interventions.

**Platelets**

Serotonin-induced immune modulation is closely linked to platelets. Upon activation platelets release their dense granule contents ATP, ADP, calcium, magnesium, and serotonin (10, 23). This leads to the co-activation of other platelets in a positive feedback loop – but serotonin also affects various other cell types like smooth muscle cells, white blood cells (WBC), and endothelial cells (24–28). Multiple studies have placed 5-HT in a key regulatory position of several immune reactions, mostly due to regulation of cytokine/chemokine secretion and modification of WBC function (25, 27, 29–31).

**Platelet effect on leukocytes**

WBCs mediate many immune responses to pathogens. Interestingly, platelet-derived serotonin regulates the function of neutrophils, T and B cells, NK cells, and monocytes (24, 25, 27, 32–36). In the spleen of mice, it modulates the activation of effector T-cells via the 5-HT2A receptor (24, 34). It also affects cell growth of human T-lymphocytes and NK cells and is involved in the production of inflammatory cytokines by T cells (32, 33, 35, 36). Furthermore, it was shown that lymphocytic cytokine secretion in mice is reduced after treatment with selective serotonin reuptake inhibitors (SSRIs) (37). A similar phenomenon was also observed in women who took SSRIs during the first 5 month of pregnancy (38).

In addition, B cell proliferation and early phase activation is influenced by serotonin in mouse and rat models (24). This shows that platelet serotonin is involved in the activation and regulation of the specific immune response mediated by T and B cells (39).

Neutrophils are recruited to sites of inflammation and infections and play an important role in the defense against pathogens and intruding microorganisms (40–42). Besides phagocytosis and releasing their granule contents they are also able to generate neutrophil-extracellular-traps (NETS) to entrap microorganisms (43, 44). Platelet serotonin is crucial for the recruitment of neutrophils towards inflammatory hot-spots and pharmacological depletion of serotonin improves the outcome after endotoxic shock in mice (27). Genetically modified mice lacking the limiting enzyme for peripheral serotonin synthesis, TPH1 have been extensively used to study non-neuronal serotonin effects. Tph1-/- mice show improved wound healing and attenuated neutrophil extravasation in response to peritonitis or acute lung injury. Leukocyte rolling and adhesion on inflamed endothelial cells is impaired in Tph1-/- mice and wild-type mice after platelet serotonin depletion, which appears to be caused by reduced P- and E-selectin presentation on inflamed endothelium (27, 45). This links platelet serotonin to the innate immune response against pathogens invading the organism.

**Platelet serotonin**

**In asthma**

Allergic airway inflammation provokes a local release of platelet 5-HT in mouse models and human patients (46). After challenge with an allergen, 5-HT increase ten-fold in bronchoalveolar lavage of predisposed patients, inducing all cardinal clinical features of asthmatic attacks. Notably, serotonin is considered a key regulator of pulmonary vascular resistance and vessel wall integrity (47–49).

**In cancer**

Platelets can promote angiogenesis in tumors and metastasis. Ho-Tin-Noé et al. demonstrated a substantial role of platelets in tumor vessel physiology and depletion of platelets almost immediately lead to hemorrhage within the tumor (50). Besides other factors, serotonin contributes significantly to intratumoral homeostasis by dys-balancing permeability factors in mice. In addition, another study showed that specific blockade of the 5-HT2 receptor by ketanserin reduced circulating tumor cells in rats (51). Moreover, serotonin induced growth of cultured human hepatocellular cancer cells (52) and plasma 5-HT levels are increased in patients suffering from colorectal-, hepatic-, or intestinal cancer (53, 54). It has been suggested that inhibition of platelet-derived homeostatic factors like 5-HT might be viable to induce intratumoral bleeding subsequently decreasing tumor growth and viability, which could lead to new treatment strategies for cancer patients (50, 51).
In viral hepatitis

In a mouse model of viral hepatitis, lymphocytic choriomeningitis virus (LCMV)-induced hepatitis is altered in Tph1-/- mice (55). Hepatic infection by LCMV in mice resembles hepatitis B and C immune mechanism in humans with specific T-cell infiltration, platelet recruitment, and alteration of hepatic microcirculation. The release of serotonin by platelets was responsible for tissue damage caused by CD8(+) T-cells, aggravation of microcirculatory dysfunction, and reduced clearance and control of infiltrated viruses. Those observations were attenuated in Tph1-/- mice and in WT mice after pharmacological depletion of 5-HT by SSRIs. Even though the exact regulatory mechanisms by which platelet derived serotonin affects hepatitis remain unclear, these findings indicate that 5-HT antagonism might affect inflammatory immune responses during hepatitis. (55–57)

In ischemic events

Myocardial infarction is the leading cause of death worldwide (58). After myocardial infarction, it is crucial to restore blood flow as soon as possible to prevent further myocardial necrosis. However, this comes at the cost of reperfusion injury (RI), which contributes to the final extent of necrosis in the heart (58). Whether platelet serotonin is involved in myocardial RI and via which mechanism is currently under investigation. It has been shown in animal models that serotonin levels are drastically increased during myocardial ischemia (59) and specific blockade of the 5-HT2 receptor improves the outcome after myocardial infarction (60). Serotonin also promotes survival of isolated mouse cardiomyocytes via the 5-HT2B receptor signalling pathway (61). These observations combined with the fact that neutrophils migrate into affected myocardium within the first hours of reperfusion suggest that platelets and platelet serotonin in particular may promote RI. A mouse model of hepatic ischemia revealed that platelets promote tissue repair and it was shown that proliferation of hepatocytes after ischemia is partly mediated by platelet serotonin (62, 63). These findings indicate that platelets have an impact on RI after ischemic events and that locally released serotonin may mediate neutrophil migration in RI.

Serotonin-related drugs

SSRIs are widely used as antidepressants in psychiatric related disorders to increase synaptic serotonin content. But there is also evidence, that targeting 5-HT receptors or using serotonin-like molecules is effective to treat non-neuronal diseases. For instance, it was shown that triptans, which are commonly used to treat migraine and are based on the chemical structure of serotonin, can reduce natural killer cell (NK) activity in purified peripheral blood mononuclear cells (PBMCs) and partly inhibit anti-inflammatory neutrophil secretion (64). Interestingly, serotonin in its pure form has been shown to enhance NK cytotoxic activity in PBMCs which could be completely abolished by addition of specific 5-HT1/2 receptor antagonism (65).

Sundar et al. 2014
Lee et al. 2000
Hara et al. 2004
Lederer et al. 2008
Kereveur et al. 2000
Lechin et al. 1996
Hara et al. 2004
Lee et al. 2000
Sundar et al. 2014

Tab. 1 Average plasma serotonin levels in patients with different diseases

<table>
<thead>
<tr>
<th>medical condition</th>
<th>number of patients</th>
<th>average 5-HT levels ng/ml</th>
<th>related publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>chronic obstructive pulmonary disease</td>
<td>11</td>
<td>5 ± 5</td>
<td>Sundar et al. 2014</td>
</tr>
<tr>
<td>cancer*</td>
<td>40</td>
<td>6 ± 1.6</td>
<td>Lee et al. 2000</td>
</tr>
<tr>
<td>VAP</td>
<td>15</td>
<td>18 ± 9</td>
<td>Figueras et al. 2005</td>
</tr>
<tr>
<td>healed myocardial infarction</td>
<td>10</td>
<td>5.4 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>angina pectoris effort-induced</td>
<td>53</td>
<td>1.23 ± 0.17</td>
<td>Hara et al. 2004</td>
</tr>
<tr>
<td>angina pectoris unstable</td>
<td>11</td>
<td>1.76 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>allergic airway inflammation</td>
<td>57</td>
<td>10</td>
<td>Lechin et al. 1996</td>
</tr>
<tr>
<td>pulmonary hypertension</td>
<td>21</td>
<td>0.15 ± 0.3</td>
<td>Lederer et al. 2008</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>5.9 ± 3.7</td>
<td>Kereveur et al. 2000</td>
</tr>
</tbody>
</table>

Tab. 1: Average plasma serotonin levels in patients with different diseases

1. mean value of hepatic and intestinal cancer patients; VAP: variant angina pectoris, received coronary angiography

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Conclusion
Platelet serotonin has been recognised as an important immunomodulator, regulating acute inflammation, sepsis, ischemia-reperfusion injury, and also cancer. Platelets secrete serotonin locally, after inflammatory activation, to enhance the recruitment of neutrophils and to modulate the function of monocytes, macrophages, lymphocytes, and endothelial cells. Serotonin-mediated effects are complex and other vascular, endothelial, and immune cell-derived factors influence these effects. Serotonergic intervention is therefore challenging and may not be successful without considering other immunomodulation. However, the impact of platelet-derived serotonin on immune functions appears to be so important that future therapeutic strategies in the battle against asthma, sepsis, myocardial infarction, cancer, or viral infections may include either serotonin receptor antagonism or serotonin-like derivatives.

Conflict of interest
The authors declare that there is no conflict of interest.

References


