HHS Public Access

Author manuscript

Front Biosci (Landmark Ed). Author manuscript; available in PMC 2021 September 15.

Published in final edited form as:

Front Biosci (Landmark Ed). 2021 August 30; 26(8): 253–254. doi:10.52586/4939.

Serotonin is a multifaceted player in the immune response

Ling Lin[1], **Kebin Hu**[1,2]

[1]Division of Nephrology, Department of Medicine, Penn State University College of Medicine, Hershey, PA 17033, USA,

[2]Department of Cellular and Molecular Physiology, Penn State University College of Medicine, Hershey, PA 17033, USA

Serotonin (5-hydroxytryptamine, 5-HT) was initially isolated from extracts of gut enterochromaffin (EC) cells causing smooth muscle cell contraction. It was named enteramine by the Erspamer group in 1937 [1]. In the central nervous system, serotonin is produced by neurons within the raphe nuclei of brainstem, regulating various brain functions such as mood, perception, memory and stress responses [2]. Peripheral serotonin accounts for about 95% of total serotonin, is synthesized by EC cells and is subsequently released into the circulation. Platelets take it up via membrane serotonin reuptake transporter (SERT) and store it in their dense granules [2–4]. Synthesis of 5-HT is limited by two enzymatic steps: (1) generation of 5-hydroxytryptophan by tryptophan hydroxylase (TPH); and (2) conversion to 5-HT by aromatic l-amino acid decarboxylase. Degradation of 5-HT into 5-hydroxyindoleacetic acid (5-HIAA), the urine excretable form, is mediated by monoamine oxidase (MAO) [2, 3].

Serotonin executes its functions through one of 15 receptors derived from 7 receptor families (5-HTR1–7). These 5-HTRs, except the 5-HTR3 nonselective cation channel, are G-protein receptors and are involved in gua-nine nucleotide-binding protein (GTPase)-mediated signal pathways [5]. Many immune cells, including monocytes/macrophages, dendritic cells (DCs), neutrophils, mast cells, eosinophils, T cells and B cells express various different 5-HTRs [6]. Thus, peripheral serotonin plays an important role in modulating both innate and adaptive immune responses and inflammation. Most recently, serum serotonin levels have been considered a good predictor for the outcome of SARS-CoV-2 infection [7] and its potential role as a therapeutic target for COVID-19 treatment is being explored [8].

In a recent issue of this journal, Dr. Schoenichen and colleagues provided a comprehensive review of the role of peripheral serotonin in the immune response and in particular the role of platelets in its regulation [9]. They discuss the functions of serotonin in

Send correspondence to: Ling Lin, Division of Nephrology, Department of Medicine, Penn State University College of Medicine, Hershey, PA 17033, USA, llin1@pennstatehealth.psu.edu, Kebin Hu, Division of Nephrology, Department of Medicine, Penn State University College of Medicine, Hershey, PA 17033, USA, Department of Cellular and Molecular Physiology, Penn State University College of Medicine, Hershey, PA 17033, USA, kebinhu@pennstatehealth.psu.edu.

Author contributions

LL and KH wrote and revised the manuscript.

Conflict of interest

The authors declare no conflict of interest.

the innate and adaptive immune systems, as well as in non-immune endothelial (ECs) and smooth muscle cells (SMCs). Monocytes/macrophages, DCs, neutrophils, eosinophils, and basophils/mast cells are essential components of innate immunity. Serotonin clearly modulates multiple functions of monocytes/macrophages and promotes their production and release of chemokines. However, its effects on migration remain largely unknown. Immature and mature DCs express different 5-HTRs. Serotonin has been found to promote migration of both immature and mature DCs through different receptor-mediated pathways. The authors also discuss strong evidence that serotonin promotes neutrophil recruitment, and eosinophil and mast cell transmigration in a receptor-mediated manner. For the role of serotonin in adaptive immunity, the authors describe the complex effects of serotonin on the proliferation, survival, and migration of T cells, B cells and NK cells. However, the specific mechanisms remain to be elucidated. Non-immune cells, such as ECs and SMCs, also express various 5-HTRs and respond to serotonin to trigger contraction or modulate immune adhesion. Notably, the authors also briefly discuss the connection between the microbiome and serotonin synthesis, which is a current topic of great interest.

In summary, there is strong evidence supporting the multifaceted roles of serotonin in regulation of the immune response. However, underlying mechanisms remain to be elucidated, and more mechanistic studies are warranted in order to further our understanding of the complex effects of serotonin on immune responses and inflammation.

Funding

LL is supported by the Department of Medicine Inspiration Polit Award (INSPIRELINFall2020). KH is supported by grants from NIH (DK102624), Pennsylvania Department of Health (4100085731), and Barsumian Trust (209023).

References

[1]. Vialli M, Erspamer V. Ricerche sul secreto delle cellule enterocromaffini. Zeitschrift für Zellforschung und Mikroskopische Anatomie. 1937; 27: 81–99.

[2]. Kanova M, Kohout P. Serotonin-Its Synthesis and Roles in the Healthy and the Critically Ill. International Journal of Molecular Sciences. 2021; 22: 4837. [PubMed: 34063611]

[3]. Berger M, Gray JA, Roth BL. The Expanded Biology of Serotonin. Annual Review of Medicine. 2009; 60: 355–366.

[4]. Wu H, Denna TH, Storkersen JN, Gerriets VA. Beyond a neuro-transmitter: the role of serotonin in inflammation and immunity. Pharmacological Research. 2019; 140: 100–114. [PubMed: 29953943]

[5]. Shajib MS, Khan WI. The role of serotonin and its receptors in activation of immune responses and inflammation. Acta Physiologica. 2015; 213: 561–574. [PubMed: 25439045]

[6]. Wan M, Ding L, Wang D, Han J, Gao P. Serotonin: A Potent Immune Cell Modulator in Autoimmune Diseases. Frontiers in Immunology. 2020; 11: 186. [PubMed: 32117308]

[7]. Soria-Castro YG, Meneses-Preza GM, Rodriguez-Lopez S, Romero-Ramirez VA, Sosa-Hernandez R, Cervantes-Diaz A, et al.Severe COVID-19 is marked by dysregulated serum levels of carboxypeptidase A3 and serotonin. Journal of Leukocyte Biology. 2021. (in press)

[8]. Pashaei YDrug repurposing of selective serotonin reuptake inhibitors: could these drugs help fight COVID-19 and save lives?Journal of Clinical Neuroscience. 2021; 88: 163–172. [PubMed: 33992179]

[9]. Schoenichen C, Bode C, Duerschmied D. Role of platelet serotonin in innate immune cell recruitment. Frontiers in Bioscience (Landmark Edition). 2019; 24: 514–526. [PubMed: 30468670]