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Current Neuropharmacology, **2022**, *20*, 269-271

COMMENTARY

Gut Serotonin as a General Membrane Permeability Regulator

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ARTICLE HISTORY

Received: August 02, 2021
Revised: August 15, 2021
Accepted: August 15, 2021

DOI: 10.2174/1570159X19666210921100542

1. COMMUNICATION BETWEEN THE GASTROINTESTINAL SYSTEM AND THE CENTRAL NERVOUS SYSTEM

The enteric nervous system (ENS) evolved before the central nervous system (CNS) and has been considered as the "second brain" that can operate independently of the brain and spinal cord [1]. ENS may perform implicit learning and memorization, working like a little brain in the gut [2]. Perturbed gut microbiota homeostasis (dysbiosis) impairs bidirectional communication between the gastrointestinal (GI) system and the CNS (termed as the gut-brain axis) that is associated with neurodegenerative and neurological diseases [3-5].

2. SEROTONIN PRODUCED BY ENTEROCHROMAFFIN CELLS IN THE GUT

Serotonin (5-HT**)** is an evolutionarily ancient molecule that is present in a wide range of species, from nematodes to humans [6]. 5-HT has key roles in numerous normal physiological conditions and pathological processes [7-10]. 5-HT is well-known as a neurotransmitter that regulates the neural activity and a wide range of neuropsychological processes [10]. Only a small fraction of 5-HT is manufactured in the brain since about 95% of the body's 5-HT is produced by enterochromaffin cells (ECs) in the gut that acts as a hormone with autocrine, paracrine, and endocrine functions [11]. 5-HT released from ECs can mediate diverse gastrointestinal functions like peristalsis, secretion, vasodilation, and perception of pain or nausea by means of activation of 5-HT receptors on intrinsic and extrinsic afferent nerve fibers that are found in the lamina propria [12]. 5-HT from the ECs is also picked up, to a large degree, by platelets and stored in their dense bodies and distributed throughout the body as a hormone and released upon their activation [13].

Dysbiosis has been linked to numerous chronic diseases like cardiovascular disease, obesity, diabetes, urinary stone disease, asthma, and inflammatory bowel disease, among others [14]. Dysbiosis that perturbs 5-HT levels of platelets and plasma [15, 16] is also associated with autism spectrum disorder (APD), depression, anxiety, posttraumatic stress disorder (PTSD), pain, migraine, fibromyalgia, epilepsy, Parkinson's and Alzheimer's diseases, among others [17-22]. Psychological, environmental, and physical stressors also perturb the ENS and the gut microbial community that are also linked to multiple GI disorders and diverse diseases [23].

3. PLATELET AS CIRCULATING MIRRORS OF NEURONS

Almost one trillion platelets in the blood can work as immune cells and are essential mediators of hemostasis, thrombin generation, homeostasis, inflammation, and immune response [24-26]. In addition, platelets are increasingly considered a bridge between mental, immunological, and coagulation-related diseases [27]. Schizophrenia, depression, anxiety disorders, Parkinson's and Alzheimer's diseases, among others, are associated with platelet dysfunction [27]. Furthermore, platelets mimic the stable synaptic structure between neurons and mirror some features of neurons regarding protein expression [27-29]. It was proposed that platelets could be considered as circulating mirrors of neurons [28]. Both neurons and platelets have common proteins like reelin, amyloid peptides, Amyloid-beta precursor protein (APP), and Brain-derived neurotrophic factor (BDNF). Platelets contain cytokines (IL-1α, IL-1β, IL-4, TGFβ1), chemokines (CXCL4, CCL3), and neurotransmitters (serotonin, dopamine, epinephrine, histamine, gamma-aminobutyric acid (GABA)) [29, 30]. Activated platelets can also synthesize pro-inflammatory mediators such as Platelet-activating factor (PAF), Prostaglandins (PGs), and thromboxanes. Both platelets and neurons have similar secretory vesicles that contain 5-HT, dopamine, epinephrine, glutamate, GABA, calcium, adenosine 5′-diphosphate (ADP), and Adenosine 5′-triphosphate (ATP), which are released from activated platelets or neurons following an action potential [27]. Serotonin released by activated platelets and Platelet-activating factor (PAF) have key functions in the regulation of sterile neuroinflammation, hemorrhage, and neuronal plasticity after traumatic brain injury [31].

4. INTESTINAL SEROTONIN AS A HORMONE-LIKE REGULATORY SIGNAL OF MEMBRANE PERMEABILITY

Recently, we proposed [32] that serotonin - produced by ECs - may work as a continuous hormone-like regulatory signal that influences membrane permeability in host organs

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1570-159X/22 $65.00+.00

and tissues, including the brain. This signal by 5-HT is dependent on the intestine's actual health condition. Perturbed 5-HT biosynthesis in the gut may cause alterations in various platelet-dependent signal processes, including changes in vascular (membrane) permeability throughout the whole body as well as in the blood-brain barrier (BBB) [33, 34]. 5-HT induced changes in cellular permeability are able to affect many membrane-associated signaling processes. In addition, the gut microbiome influences glucose homeostasis of the whole body through gut-derived serotonin [35]. Furthermore, 5-HT has strong antioxidant and free radical scavenging ability, and its circulating levels are associated with a decrease in the plasma antioxidant capacity [36, 37]. Our concept may present an important role in which gut dysbiosis and 5-HT produced by ECs can considerably contribute to the development of a wide range of human diseases, including neurodevelopmental and neuropsychiatric disorders [32].

CONCLUSION

Cellular membrane signal processes have central roles in the regulation of cell functions and intra- and intercellular communication [38, 39]. Serotonin, produced by ECs and distributed by platelets, may work as a continuous hormone-like signal that can regulate membrane permeability in host organs and tissues, including the brain [32]. Understanding these processes could open up new opportunities in neuro(pharmacology) research. In addition, because serotonin transporters (SERTs) are present in the BBB, it suggests that 5-HT from the gut conveyed by platelets not only regulates the membrane permeability of the BBB, but 5-HT can also enter into the extracellular fluid of the CNS [40]. This 5-HT (from gut) may act by diffusion mechanism and may have a wide range of effects on the CNS via modulation of various signal and neurotransmission processes [41].

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The author, István Bókkon, gratefully acknowledge the assistance of SXM ExperiMental Ltd, Hungary, Budapest.

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