Journal of Community Medicine & Public Health
Kilic F. J Community Med Public Health 7: 389
www.doi.org/10.29011/2577-2228.100389
www.gavinpublishers.com

Review Article

Serotonin Signaling and the Hyperpermeable Endothelial Barrier in Sepsis: Clues to a Molecular Mechanism

Fusun Kilic*

Biology Department, Merced College, Merced, California, USA

***Corresponding author:** Fusun Kilic, Ph.D. Biology Department, Merced College, Merced, California, USA

Citation: Kilic F (2023) Serotonin Signaling and the Hyperpermeable Endothelial Barrier in Sepsis: Clues to a Molecular Mechanism. J Community Med Public Health 7: 389. DOI: https://doi.org/10.29011/2577-2228.100389

Received Date: 20 November, 2023; **Accepted Date:** 27 November, 2023; **Published Date:** 30 November, 2023

Short Summary

Sepsis is a serious medical condition characterized by a severe systemic inflammatory response caused by a microbial infection. This review evaluates a novel approach to therapy, which targets serotonin (5-HT) and its transporter, SERT.

Abstract

Sepsis is characterized by a severe systemic inflammatory response caused by hyperpermeability of the endothelial barrier resulting microvascular leakage, which is a leading factor to multiorgan failure. In sepsis, the hyperpermeable endothelial cells contribute to the activation of platelets, which release numerous mediators that affect coagulation, inflammatory response and are believed to directly or indirectly affect the integrity of the endothelial barrier. One such mediator is serotonin (5-hydroxytryptamine, 5-HT), a signaling molecule which mediates a number of cellular functions including regulation of cytoskeletal dynamics associated with barrier function of endothelial cells. The actions of 5-HT are mediated by different types of receptors and terminated via an uptake mechanism of a 5-HT transporter (SERT) on the platelet and endothelial cell. Earlier studies revealed unexpected discoveries concerning the impact of 5-HT signaling on the permeability of the endothelial barrier. These findings have been supported by the clinical reports on the anti-inflammatory property of 5-HT reuptake inhibitor, SSRIs in treating sepsis-related morbidity and mortality. This review focuses on a wide-range of literature to pinpoint cellular and molecular mechanisms that mediate 5-HT-induced microvascular injury in sepsis pathogenesis.

Keywords: Sepsis; Platelets; Endothelial Barrier; Serotonin; Serotonin transporter; Serotonin signaling; SSRIs

Introduction

Sepsis is a medical condition characterized by a severe systemic inflammatory response caused by a microbial infection. In the U.S., sepsis causes ~270,000 deaths annually and a health care burden of ~$41.8 billion [1-3]. Sepsis is an important cause of morbidity and mortality in the older population (greater than 80 years) [2,3]. Patients with severe sepsis have a poor prognosis with mortality rates of 40%-60% when one or more organs are affected [2-4]. Yet, there are no effective therapies to treat sepsis [4-6], and clinicians rely only on supportive care [6-9] usually initiated after the presence of symptoms, and not necessarily improve the microcirculatory function [9].

Clinical studies reported the anti-inflammatory property of SSRIs, the serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors [10-14], in treating infectious disease-related morbidity and mortality [15-18]. The traditional view of the SSRIs invokes a functional stratification of serotonin transporter, SERT which is responsible for accumulation of 5-HT by neurons, platelets, and other cells. SSRIs reduces the reuptake rates of 5-HT into serotonergic neurons through acting on SERT and to increase the synaptic 5-HT levels. Because, the downregulation of 5-HT in synaptic cleft is the foundation of a variety of neuropsychiatric disorders, including affective disorder, anxiety disorders, obsessive-compulsive disorder, and autism [19-21]. Due to these characteristics, SSRIs have been used to treat the neuropsychiatric disorders [20].

5-HT can involve in numerous biological processes in the cell cytoplasm, and in extracellular compartments through receptor-dependent and receptor-independent (transporter, SERT-dependent) signaling pathways (Figure 1); for the stability of cellular events, extracellular vs cytoplasm ratio of 5-HT should be regulated [22-24].

Receptor-dependent pathway is related with the plasma 5-HT signaling, which is initiated by an interaction between plasma 5-HT and 5-HT receptors such as 5- HT2A, or 5-HT2B, on platelets or endothelial cells, respectively. 5-HT signaling transduced by 5-HT2A mobilizes calcium from intracellular stores to trigger the vesicular release of pro-coagulant molecules from granules [24-26]. SERT- dependent (receptor-independent) pathway is related the free level of 5-HT in cell cytoplasm which binds to small GTPases, such as Rab4 and regulates the membrane trafficking of granules as well as SERT [22,27-31]. Thus, SSRIs downregulate the cellular 5-HT uptake rates which elevates the plasma 5-HT concentration [29,30]. These studies emphasize the importance of plasma vs. platelet 5-HT ratio in platelet physiology [32].

As in neuropsychiatric disorders, the level of 5-HT becomes an important factor in development of various diseases. Once SSRIs are in the system, they target all the SERT proteins at neuronal and peripheral systems and SSRIs change the ratio of 5-HT in blood plasma vs cell cytoplasm. Therefore, any attempt to build a link between the anti-inflammatory role of SSRIs and sepsis must start with a detail analysis of cellular mechanisms to learn more about the mechanism if it is through elevating the extracellular 5-HT, or reducing the cytoplasmic 5-HT levels. Here, the reader is referred to a number of publications on detail background and additional perspective on 5-HT signaling pathway and the hyperpermeability of the endothelial barrier [33-39].

At elevated levels, 5-HT in blood plasma are associated with increases in G protein-coupled receptors signaling and serotonylation of small GTPases [25-28], which in turn lead to remodeling of cytoskeletal elements to enhance granule secretion and promote unique expression of sialylated N-glycan structures on smokers' platelets [30-33]. In receptor-dependent pathway, 5-HT signaling elevates resting concentrations of intracellular Ca2+ and transglutaminase (TGase) activity which in turn accelerates the cellular trafficking dynamics and remodels the surface proteins and glycans [25-28]. MALDI/MS and LC/MS/MS analyses of the membrane proteins and glycans identified an elevation in the number of sialylated N-glycans [31], as well as the appearance of certain enzymes and proteins on the plasma membrane [32-34], included in membrane trafficking of secretory vesicles (via altering the actin-myosin network), that bind G-protein–coupled receptors, or that activate small GTPases [28]. These studies suggest a link between 5-HT signaling and its downstream effectors—including phospholipase C (PLC) and inositol-1,4,5-triphosphate (IP3) pathways, in receptor-dependent pathways (Figure 1). When the blood plasma 5-HT concentration is elevated, the 5-HT receptor on the endothelial cells, 5-HT2B sends the signal to activate PLC and produce IP3 (Figure 1). Rac-GTP is formed when TGase transamidates 5-HT. Binding to Rac-GTP activates PAK1, which phosphorylates vimentin. PAK1 is a Rac1 effector and its activation leads to multiple phosphorylations that commonly occur at the plasma membrane [35].

Additionally, 5-HT-induced permeability of endothelial cells was associated with the phosphorylation of p21 activating kinase (PAK1), PAK1-dependent phosphorylation of vimentin (P-vimentin) filaments [22,28,29,36,37]. Following phosphorylation, the curved filamentous structure of vimentin undergoes reorganization and straightens [22,28,29]. These findings need to be confirmed by further investigations with preclinical and *in vitro* study models, for example, if SSRI application restores internal organ damage in preclinical sepsis-induced mouse model. What is the mechanism that SSRI rescue the sepsis-associated endothelial hyperpermeability? Does SSRI act as an anti-inflammatory agent through elevating the extracellular 5-HT, or reducing the cytoplasmic 5-HT levels? Addressing these issues will advance our understanding of the mechanisms underlying cellular responses to refine current views of 5-HT signaling processes during sepsis.

While all *in vitro* models of sepsis have essential limitations, it is still necessary to investigate molecular mechanisms to develop effective therapies to treat sepsis. For these purposes, the preclinical models were developed to study sepsis mediate microvascular injury [38,47]. These include intravascular infusion of endotoxin or live bacteria, soft tissue infection, cecal ligation and puncture (CLP)-induced murine, rats or rabbit models. In lipopolysaccharide (LPS)-induced sepsis mouse model [43-47], Huang et al showed that the elevated 5-HT in blood plasma aggravated sepsis-induced acute lung injury by promoting neutrophil extracellular trap formation in the lungs of LPS-sepsis mouse [48]. LPS murine model uses younger mice which do not mimic the age of the human population that incurs sepsis [48,49]. In contrast, CLP murine model [43-47] uses older mice to more closely mimic the age of the human population that incurs sepsis, and the mice receive fluids and antibiotics to mimic the basic supportive therapy afforded patients with sepsis [50]. In between all other sepsis-induced animal models, CLP is generally accepted to be a relevant rodent model of bacterial sepsis because it exhibits many of the key pathogenic features observed in humans with severe sepsis during the hypotensive periods of cold shock [46]. Additionally, CLP-model is easy to monitor the steps in the development of sepsis such as the early failure of the

renal microcirculation [45,47]. In CLP-sepsis mice, the decreased perfusion and leakage, which are a leading acute kidney injury and directly related to changes in organ function were observed by intravital microscopy [45,47]. Based on all these characteristics, CLP-induced sepsis mice model is accepted as a good model to learn more about sepsis.

In a recent study, Zhang, et al. used 5-HT deficient mouse model, TPH1-knockout (KO) mice in to develop sepsis [43]. TPH1 is the rate-limiting enzyme in the biosynthesis of 5-HT [25,51]. TPH1-KO mice do not have 5-HT in their blood system Zhang et al., the survival rates of CLP-induced wild-type with the CLP-induced TPH1-KO mice [43]. Interestingly, the CLP-induced wild-type mice had a significantly lower survival rate than the CLP-induced TPH1-KO group. The tissue histopathology analysis revealed that 5-HT markedly exacerbated histological damages in the peritoneum, lung, liver, kidney, intestinal tissue, and heart in sepsis. In this study, Zhang, et al. proposed that the initial elevation of plasma 5-HT promoted serum cytokines and bacteria as well as facilitating oxidative stress in sepsis [43]. It will be interesting to investigate if SSRI treatment will be able to recover the elevated 5-HT-associated damages.

There is a growing appreciation to the importance of microcirculatory failure in the development of organ injury during sepsis [52,53]. Indeed, microvascular dysfunction, increased microvascular permeability is a hallmark of sepsis and recognized now as a strong predictor of death among patients with severe sepsis [54,55]. We observed the declined renal microcirculation in mice few hours after CLP was induced [42]. Using CLP-induced mice model, we investigated the mechanism by which 5-HT regulates the microvascular permeability in development of sepsis [42]. Additionally, these studies addressed if clinically relevant delayed therapy with a SERT inhibitor restore microcirculatory perfusion and renal function [42]. When the CLP was induced on mice that lack the SERT gene (SERT-KO mouse [34]), the impact of CLP-sepsis on microvascular perfusion of these mice were much better than the only CLP-induced wild-type mice [42]. Also, mice treated with the SERT inhibitor, paroxetine, had better microvascular perfusion following CLP. Overall, reducing the 5-HT uptake rates via targeting SERT, either genetically or through SSRI could reduce sepsis induced microvascular leakage and help restore microvascular perfusion [42]. These findings appear to agree with the clinical reports on anti-inflammatory role of SSRIs in sepsis through reducing the cytoplasmic 5-HT levels.

The relationship between platelets and the endothelia is another case of the chicken-and-egg paradox. While the platelets are one of the major contributors to the endothelial damage [56-59], the hyperpermeable endothelial cells contribute to the activation of platelets [54]. There are several studied proposing the role of platelets in this major issue. Specifically, *in vitro* studies in the absence of tissue and endothelial wall injury demonstrated platelets responses to systemic immune complexes [56]. Based on these, platelets were proposed as a crucial mediator of the inflammatory response in sepsis [56]. Once it is activated, platelets release numerous mediators that affect coagulation, inflammatory response and are believed to directly or indirectly affect the integrity of the endothelial barrier [60]. One such mediator is 5-HT because platelets are the major storage for 5-HT in blood [39,61-63]. Therefore, in sepsis the initial elevation of plasma 5-HT is associated with the elevation of the serum cytokines, bacteria and oxidative stress. CLP-sepsis mice showed a significant elevation in 5-HT concentration in blood plasma [64,65]; furthermore, the 5-HT uptake rates of the renal endothelial cells exposed to septic serum or 5-HT showed an elevation in cellular 5-HT uptake rates [42].

In contrast to the relationship between the blood plasma 5-HT levels and the cellular 5-HT uptake rates in sepsis, our earlier studies reported that the cellular 5- HT uptake rates depended on the number of SERT molecules on the plasma membrane [22-24,27-31]. Moreover, an increase in extracellular 5-HT concentration reduced the cellular 5-HT uptake rates by decreasing the number of SERT molecules on the plasma membrane [22,29]. Like the other membrane proteins, SERT is translocated to the plasma membrane of the cells in a substrate- dependent manner [29]. Once 5-HT is removed from the extracellular matrix into the cytoplasm, SERT is rerouted from the plasma membrane to the cytoplasmic compartments. 5-HT signaling accomplishes this by altering membrane trafficking of small GTPases and the structure of cytoskeletal proteins [27]. Interestingly, in CLP-sepsis mouse, the relationship between the blood plasma 5-HT level and the cellular 5-HT uptake rates did not agree with these earlier reports [28]. The impact of the elevated serum cytokines, bacteria and oxidative stress on structure and function of SERT must be investigated to learn about the upregulation of 5-HT uptake rates in sepsis.

The impact of 5-HT on weakening the endothelial barrier was first described in the late 1950's [61,62]. In this line, studies demonstrated that 5-HT increases the permeability of blood vessels [61,62], microvascular leakage [45,47,66] or recruitment of neutrophils [67]. Lately, a strong link was built between the anti-inflammatory property of the SSRIs with the concentration of 5-HT in extracellular compartment [10-15]. What is the mechanism by which septic conditions upregulate platelet and endothelial SERT and lead to loss of the endothelial barrier?

The findings from various laboratories propose that elevated 5-HT level activates PAK and disassembly and spatial reorientation of vimentin filaments [36,37,68-70] (Figure 1). Interestingly, these associations were found by an immunoprecipitation assay, only in

endothelial cells grown in CLP-mouse, not in SHAM-mouse serum [42]. These findings also confirm the impact of the level of 5- HT in extracellular compartment, which is elevated in CLP-sepsis serum. Vimentin is a type III intermediate filament involved in cytoplasmic trafficking in cells of mesenchymal (e.g., endothelium, fibroblasts, megakaryocytes) and myogenic origin [71,72]. Vimentin participates in a network of intermediate filaments that extends beneath the cell membrane and regulates the activity of PAK, which functions in the transduction of diverse extracellular signals to alter intracellular pathways [28,36,37]. Significantly, vimentin is a substrate of PAK, and PAK becomes activated in cells that are exposed to 5-HT. Following phosphorylation of the Serine at position 56, the curved filamentous structure of vimentin undergoes reorganization and straightens (37). As mentioned above, elevated 5-HT activates PAK to phosphorylate vimentin via changing the organization of this intermediate filament [22,29,36,37]. Following phosphorylation, the curved filamentous structure of vimentin undergoes reorganization and straightens. As a part of actin- myosin bundle, the structural change on P56-vimentin could also change the actin- myosin-vimentin cytoskeletal network [22,72,73]. Based on these data, we propose that during sepsis increased endothelial uptake of platelet-derived 5-HT together with 5-HT signaling leads to changes in the cytoskeletal network and its partner, endothelial (ve-cadherin), which in turn disrupts the endothelial barrier (Figures 1 & 2). Thus, agents targeting SERT could reduce sepsis induced microvascular leakage and help restore microvascular perfusion.

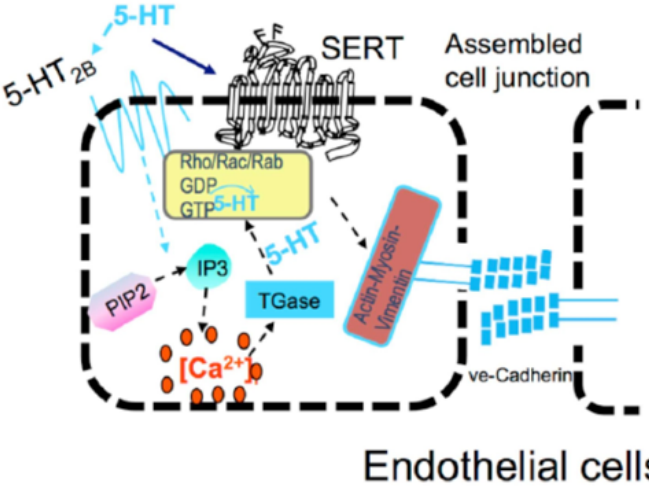

Figure 1: Proposed mechanisms by which 5-HT signaling and SERT-mediatedincreases in cytoplasmic 5-HT lead to weakening of the permeability barrier.

An association between P-vimentin and ve-cadherin involves in endothelial dysfunction during sepsis. This was deduced through our studies [42] where P- vimentin levels were highly increased in 5-HT pretreated platelets of wild-type mice however, SERT-KO mice could not phosphorylate vimentin even after 5-HT treatment. These findings suggest that phosphorylation of vimentin requires 5-HT uptake ability of SERT which upregulates the intracellular free 5-HT concentration [42] (Figure 2).

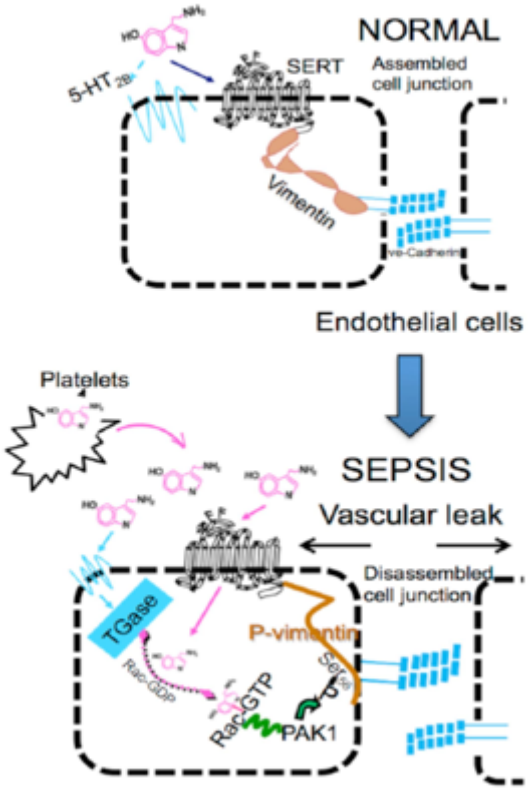

Figure 2: During sepsis, platelets release 5-HT which is taken up by endothelial SERT. Increased intracellular 5-HT along with extracellular 5-HT signaling lead to phosphorylation of vimentin and weakening of the tight junction. PAK1- dependent phosphorylation of vimentin produces a strong association between P-vimentin and ve-cadherin.

All these findings from clinical, preclinical, and *in vitro* studies build a strong link between blood plasma 5-HT level and sepsis-associated endothelial damage which suggest a facilitative role to the cytoplasmic 5-HT in sepsis-associated endothelial hyperpermeability. The following sections will summarize how SSRIs act an anti-inflammatory agent during sepsis. Addressing this gap is a crucial step in understanding of the existing body of knowledge in sepsis.

SSRI Protects Endothelial Barrier against Cytoplasmic 5-HT-Associated Damage

The endothelial membrane - cytoskeletal interactions play important role in the integrity of endothelial barrier function [71-75]. The interactions between complex sets of proteins that comprise tight junctions, adherens junctions, and gap junctions provide a barrier ability to the endothelial cells. Adherens junctions form pericellular zipperlike structures along the cell border through their transmembrane homophilic adhesion [73]. The adherens junctions in endothelial cells contain vascular endothelial (ve)-cadherin as the major structural protein that mediates homophilic binding and adhesion of adjacent cells in a Ca2--dependent manner. ve-Cadherin is required for the proper assembly of adherens junctions and development of normal endothelial barrier function [71-75].

The endothelium of the vessel wall functions as a semi-permeable barrier between the blood and interstitial space and is important for tissue/fluid homeostasis. The loss of barrier function is a hallmark of sepsis and contributes significantly to overall microvascular failure [45,47,66]. Based on the literature and our findings [42], we propose that sepsis-associated elevation in 5-HT level in blood plasma leads to endothelial barrier disruption once it is taken in the cells. In cytoplasm, free 5-HT causes a structural reorganization of the vimentin, actin-myosin cytoskeleton leads an alteration in the conformation of cadherin, this weakens the endothelial cell barrier. However, if the uptake of 5-HT from extracellular compartments to the cytoplasm is hampered via SERT inhibitors like SSRIs, this rescues cytoplasmic 5-HT-associated damage on the endothelial barrier (Figure 2).

The endothelial cell lining of the vessel wall is the first line of defense against organ injury and functions as a semi-permeable barrier between the blood and interstitial space. As such, it is susceptible to injury from microbial virulence factors, proinflammatory mediators released from activated blood cells, and oxidative stress [44]. Briefly, microbial virulence factors, proinflammatory mediators in circulation, and oxidative stress promote the activation of endothelia in which the barrier function is impaired [54-56]. Endothelial hyperpermeability allows the neutrophil adhesion and infiltration into tissues [76], coagulation abnormalities [77], microvascular leakage [78], and hypoperfusion associated with sepsis- induced multiorgan failure [79] morbidity and mortality [80]; finally, endothelia cannot defense against organ injury anymore.

Based on the literature, it appears that the microbial virulence factors in circulation activates the endothelial cells which contributes to the activation of blood cells such as platelets. These white blood cells participate in the inflammatory response, hemostasis, host response, and microvascular permeability. Yet, a direct link between platelets and sepsis on an increased blood plasma 5-HT level has not been built until the clinical studies reported the advantageous of SSRIs in sepsis development [10-17]. Before this review, it was generally accepted that an environment favoring pathophysiological activation of platelets is related with the development of sepsis.

Platelets are derived from the fragmented cytoplasm of megakaryocytes and enter the circulatory system in an inactive form. In sepsis, the hyperpermeable endothelial cells contribute to the activation of platelets which accelerates the exocytosis of platelet cytoplasm located granules, dense and a-granules [9,10]. Notably, blood plasma 5-HT concentration is in the low nanomolar range, but the dense granules of resting platelets store millimolar concentrations of 5-HT [22-24,51,81]. Thus, platelets apparently are designed to tightly control the cytoplasmic free 5-HT concentration. However, secretion of dense granules from platelets increase the 5-HT concentration in the blood plasma several folds and in cytoplasm if SERT on platelet surface reuptake them [22-24]. In summary, there is a biphasic relationship between blood plasma 5-HT elevation, loss of surface SERT, and depletion of platelet 5-HT [51]. Specifically, in platelets, plasma membrane SERT levels and platelet 5-HT uptake initially rise as plasma 5-HT levels are increased, but then fall below normal as the plasma 5-HT level continues to rise. The actions of 5-HT are mediated by receptors, and terminated by a single 5-HT transporter, SERT, on the platelet and endothelial cell, through an uptake mechanism [28-34].

This Review summarizes the available literature on the anti-inflammatory roles of SSRIs in sepsis. Several evidences are provided demonstrating how sepsis- induced elevation in 5-HT levels in blood plasma, or in cell cytoplasm reorganize the intracellular factors to produce hyperpermeable endothelial barrier through engaging in receptor-dependent and -independent signaling pathways. Also, a crosstalk between the platelet and endothelia in sepsis was depicted. Based on existing evidences and emerging mechanistic insights, novel therapeutics targeting to stabilize the 5-HT level in endothelial cell cytoplasm in sepsis should be designed.

Acknowledgements

The author wishes to thank her collaborators, colleagues, and the students who have contributed across disciplines to the understanding of the serotonin signaling in sepsis.

Source of Funding

This work was supported by the NIH Child Health and Human Development HD058697, and HD053477grants and Heart Lung and Blood Institute HL091196 and the Minnie Merrill Sturgis

Diabetes Research Fund, and the Sturgis Charitable Trust to FK.

Disclosure

The author declares no competing financial interests.

References

1. Paoli CJ, Reynolds MA, Sinha M, Gitlin M, Crouser E (2018) Epidemiology and Cost of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. Crit Care Med. 46: 1889-1897.
2. Rudd KE, Johnson C, Agesa KM, Shackelford KA, Tsoi D, et al., (2020) Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 395: 200-211.
3. Kramarow, EA (2021) Sepsis-related Mortality Among Adults Aged 65 and over: United States, 2019. NCHS Data Brief. 422: 1-8.
4. Guarino M, Perna, B, Cesaro AE, Maritati M, Spampinato MD, et al. (2023) Update on Sepsis and Septic Shock in Adult Patients: Management in the Emergency Department. J. Clin Med. 12: 3188.
5. Schortgen F, Asfar P (2015) Update in sepsis and acute kidney injury 2014. Am. J. Respir. Crit. Care Med. 191: 1226-1231.
6. Zarbock A, Gomez H, Kellum JA (2014) Sepsis-induced acute kidney injury revisited: pathophysiology, prevention and future therapies. Curr. Opin. Crit. Care. 20: 588-595.
7. Wenzel RP, Edmond MB (2012) Septic shock--evaluating another failed treatment. N Engl J Med 366: 2122-2124.
8. Schrier RW, Wang W (2004) Acute renal failure and sepsis. N Engl J Med 351: 159-169.
9. Van Haren FM, Sleigh J, Boerma EC, La Pine M, Bahr M, et al. (2012) Hypertonic fluid administration in patients with septic shock: a prospective randomized controlled pilot study. Shock. 37: 268-275.
10. Meikle CKS, Creeden JF, McCullumsmith C, Worth RG (2021) SSRIs: Applications in inflammatory lung disease and implications for COVID-19. Neuropsychopharmacol Rep. 41: 325–335.
11. Hillhouse TM, Porter JH (2015) A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol. 23: 1-21.
12. Wong DT, Perry KW, Bymaster FP (2005) Case history: the discovery of fluoxetine hydrochloride. Nat Rev Drug Discov. 4: 764–74.
13. Walker FR (2013) A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? Neuropharmacology. 67: 304–17.
14. Kroeze Y, Zhou H, Homberg JR. (2012) The genetics of selective serotonin reuptake inhibitors. Pharmacol Ther. 136: 375–400.
15. Gałecki P, Mossakowska-Wójcik J, Talarowska M (2018) The anti-inflammatory mechanism of antidepressants - SSRIs, SNRIs. Prog Neuropsychopharmacol Biol Psychiatry. 80: 291-294.
16. Colantuoni A, Martini R, Caprari P, Ballestri M, Capecchi PL, et al. (2020) COVID-19 Sepsis and Microcirculation Dysfunction. Front Physiol. 11: 747.
17. Foletto VS, da Rosa TF, Serafin MB, and Horner R (2022) Selective serotonin reuptake inhibitor (SSRI) antidepressants reduce COVID-19 infection: prospects for use Eur J Clin Pharmcol. 78: 1601–1611.
18. Dorian A Rosen, Scott M Seki, Anthony Fernández-Castañeda, Rebecca M Beiter, et al. (2019) Modulation of the sigma-1 receptor–IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. Science Translational Medicine. 11: eaau5266
19. Kilic F, Rudnick G (2000) Oligomerization of the serotonin transporter and its functional consequences. P.N.A.S, U.S.A. 97: 3106-3111.
20. Kilic F, Murphy D, Rudnick G (2003) A human serotonin transporter mutation cau- ses constitutive activation of transport activity. Mol. Pharm. 64: 446-6.
21. Kocabas AM, Rudnick G, Kilic F (2003) Functional consequences of homo- but not hetero-oligomerization between transporters for the biogenic amine neurotransmitters. J. Neurochem. 85: 1513-1520.
22. Mercado CP, Kilic F (2010) Molecular mechanisms of SERT in platelets: regulation of plasma serotonin levels. Molecular Interventions. 10: 231-241.
23. Brenner B, Harney JT, Ahmed BA, Jeffus BC, et al. (2007) Plasma serotonin levels and the platelet serotonin transporter. J Neurochem. 102: 206-215.
24. Ziu E, Mercado CP, Li Y, Singh P, Ahmed BA, et al. (2012) Downregulation of the serotonin transporter in hyperreactive platelets counteracts the pro-thrombotic effect of serotonin. J Mol Cell Cardiol. 52: 1112-1121.
25. Walther DJ, Peter JU, Winter S, Höltje M, Paulmann N, et al. (2003) Serotonylation of small GTPases is a signal transduction pathway that triggers platelet alpha-granule release. Cell. 115: 851-862.
26. Shirakawa R, Yoshioka A, Horiuchi H, Nishioka H, Tabuchi A, et al. (2000) Small GTPase Rab4 regulates Ca2+-induced α-granule secretion in platelets. J. Biol. Chem. 275: 33844–33849.
27. Mercado C, Ziu E, Kilic F (2011) Communication between 5-HT and small GTPases. Current Opinion in Pharmacology. 11: 23-28.
28. Cooper A, Woulfe DS and Kilic F (2018) Post-translational modifications of serotonin transporter. Pharmacological Research. 140: 7-13.
29. Kilic, F, Ziu E, and Freyaldenhoven S "Plasma Serotonin and Platelet Serotonin Transporter: Molecular and Cellular Aspects in Cardiovascular Research." In Brataas, J. and Nanstveit, V. (eds.): Handbook of Cardiovascular Research. 2009. Nova Science Publishers, Inc. Hauppauge, NY. ISBN: 978-1-60741-792-7.
30. Lowery III CL, Woulfe DS, and Kilic F (2019) The responses of the plasma serotonin and the platelet serotonin transporter to cigarette smoking. Front Neurosci. 13: 32.
31. Lowery III CL, Elliott C, Cooper A, Hadden C, Sonon RN, et al. (2017) Cigarette Smoking- Associated alterations in Serotonin/Adrenalin Signaling Pathways of Platelets. J Am Heart Assoc. 6: e005465.
32. Mercado CP, Kilic F (2010) The Elevated Extracellular/Intracellular Serotonin Ratio Alters the Propensity of Platelet Aggregation AHA-Arteriosclerosis Thrombosis and Vascular Biology. 30: E219-E219
33. Mercado CP, Quintero MV, Li Y, Singh P, Byrd AK, et al. (2013) serotonin-induced N-glycan switch regulates platelet aggregation. Sci Rep. 3: 2795.

34. Mercado CP, Byrum S, Beggs ML, Ziu E, Raj VR, et al. (2013) Impact of Elevated Plasma Serotonin on Global Gene Expression of Murine Megakaryocytes PLoS ONE. 8: e72580.

35. Bokoch GM (2003) Biology of the p21-activated kinases. Annu Rev Biochem 72: 743-781.

36. Li QF, Spinelli AM, Wang R, Anfinogenova Y, Singer HA, et al. (2006) Critical role of vimentin phosphorylation at Ser-56 by p21-activated kinase in vimentin cytoskeleton signaling. J. Biol. Chem. 281: 34716-34724.

37. Tang DD, Bai Y, Gunst SJ (2005) Silencing of p21-activated kinase attenuates vimentin phosphorylation on Ser-56 and reorientation of the vimentin network during stimulation of smooth muscle cells by 5-hydroxytryptamine. Biochem. J. 388: 773-783.

38. Remick, DG, Ayala A, Chaudry IH, Coopersmith CM, Deutschman C, et al. (2019) Premise for Standardized Sepsis Models. Shock. 51: 4–9.

39. Rowley DA, Benditt EP (1956) 5-Hydroxytryptamine and histamine as mediators of the vascular injury produced by agents which damage mast cells in rats. J Exp Med. 103: 399-412.

40. De Backer D, Donadello K, Sakr Y, Ospina-Tascon G, Salgado D, et al. (2013) Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. Crit. Care Med. 41: 791-799.

41. Spanos A, Jhanji S, Vivian-Smith A, Harris T, Pearse RM (2010) Early microvascular changes in sepsis and severe sepsis. Shock 33: 387-391.

42. Cooper A, Mayeux P, Kilic F (2016) A novel signaling mechanism for plasma serotonin and the serotonin transporter in the remodeling of cell-cell junctions during microvascular leakage. Mol Biol Cell 27: 2202.

43. Zhang J, Bi J, Liu S, Pang Q, Zhang R, et al. (2017) 5-HT Drives Mortality in Sepsis Induced by Cecal Ligation and Puncture in Mice. Mediators Inflamm 2017: 6374283.

44. de Stoppelaar SF, van 't Veer C, Claushuis TA, Albersen BJ, Roelofs JJ, et al. (2014) Thrombocytopenia impairs host defense in gram-negative pneumonia-derived sepsis in mice. Blood 124: 3781-3790.

45. Holthoff JH, Wang Z, Patil NK, Gokden N, Mayeux PR (2013) Rolipram improves renal perfusion and function during sepsis in the mouse. J Pharmacol Exp Ther 347: 357-364.

46. Doi K, Leelahavanichkul A, Yuen PS, Star RA (2009) Animal models of sepsis and sepsis-induced kidney injury. J Clin Invest 119: 2868-2878.

47. Wang Z, Holthoff JH, Seely KA, Pathak E, Spencer HJ, et al. (2012) Development of oxidative stress in the peritubular capillary microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. Am J Pathol 180: 505-516.

48. Cloutier N, Allaeys I, Marcoux G, Machlus KR, Mailhot B, et al. (2018) Platelets release pathogenic serotonin and return to circulation after immune complex-mediated sequestration. Proc Natl Acad Sci U S A 115: E1550-E1559.

49. Huang Y, Ji Q, Zhu Y, Fu S, Chen S, et al. (2022) Activated platelets autocrine 5-Hydroxytrypthophan aggravates sepsis-induced acute lung injury by promoting neutrophils extracellular traps formation. Front Cell Dev Biol 9: 777989.

50. Miyaji T, Hu X, Yuen PS, Muramatsu Y, Iyer S, et al. (2003) Ethyl pyruvate decreases sepsis induced acute renal failure and multiple organ damage in aged mice. Kidney Int 64: 1620-1631.

51. Ziu E, Hadden C, Li Y, Lowery III CL, Singh P, et al. (2014) Effect of serotonin on platelet function in cocaine exposed blood. Sci Rep 4: 5945.

52. Aird WC (2003) The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood 101: 3765-3777.

53. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL (2013) Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 5: 73-79.

54. Lee WL, Liles WC (2011) Endothelial activation, dysfunction and permeability during severe infections. Curr Opin Hematol 18: 191-196.

55. Lee WL, Slutsky AS (2010) Sepsis and endothelial permeability. N Engl J Med 363: 689-691.

56. Cloutier N, Pare A, Farndale RW, Schumacher HR, Nigrovic PA, et al. (2012) Platelets can enhance vascular permeability. Blood 120: 1334-1343.

57. Vincent JL, Yagushi A, Pradier O (2002) Platelet function in sepsis. Crit Care Med 30: S313-S317.

58. Ho-Tin-Noe B, Demers M, Wagner DD (2011) How platelets safeguard vascular integrity. J Thromb Haemost 9: 56-65.

59. Schouten M, Wiersinga WJ, Levi M, van der Poll T (2008) Inflammation, endothelium, and coagulation in sepsis. J Leukoc Biol 83: 536-545.

60. Shannon O (2021) The role of platelets in sepsis. Res Pract Thromb Haemost 5: 27-37.

61. Majno G, Palade GE (1961) Studies on inflammation. 1. The effect of histamine and serotonin on vascular permeability: an electron microscopic study. J Biophys Biochem Cytol 11: 571-605.

62. Majno G, Palade GE, Schoefl GI (1961) Studies on inflammation. II. The site of action of histamine and serotonin along the vascular tree: a topographic study. J Biophys Biochem Cytol 11: 607-626.

63. Spector WG (1958) Substances which affect capillary permeability. Pharmacol Rev 10: 475-505.

64. Tanaka T, Mori M, Sekino M, Higashijima U, Takaki M, et al. (2021) Impact of plasma 5- hydroxyindoleacetic acid, a serotonin metabolite, on clinical outcome in septic shock, and its effect on vascular permeability. Sci Rep 11: 14146.

65. Zhang J, Bi J, Liu S, Pang Q, Zhang R, et al. (2017) 5-HT Drives Mortality in Sepsis Induced by Cecal Ligation and Puncture in Mice. Mediators Inflamm 2017: 6374283.

66. Wang Z, Sims CR, Patil NK, Gokden N, Mayeux PR (2015) Pharmacologic targeting of sphingosine-1-phosphate receptor 1 improves the renal microcirculation during sepsis in the mouse. J Pharmacol Exp Ther 352: 61-66.

67. Duerschmied D, Suidan GL, Demers M, Herr N, Carbo C, et al. (2013) Platelet serotonin promotes the recruitment of neutrophils to sites of acute inflammation in mice. Blood 121: 1008-1015.

68. Liu T, Ghamloush MM, Aldawood A, Warburton R, Toksoz D, et al. (2014) Modulating endothelial barrier function by targeting vimentin phosphorylation. J Cell Physiol 229: 1484-1493.

69. Mendez MG, Kojima S, Goldman RD (2010) Vimentin induces changes in cell shape, motility, and adhesion during the epithelial to mesenchymal transition. FASEB J 24: 1838-1851.

70. Helfand BT, Mendez MG, Murthy SN, Shumaker DK, Grin B, et al. (2011) Vimentin organization modulates the formation of lamellipodia. Mol Biol Cell 22: 1274-1289.

71. Podor TJ, Singh D, Chindemi P, Foulon DM, McKelvie R, et al. (2002) Vimentin exposed on activated platelets and platelet microparticles localizes vitronectin and plasminogen activator inhibitor complexes on their surface. J Biol Chem 277: 7529-7539.

72. Shasby DM, Ries DR, Shasby SS, Winter MC (2002) Histamine stimulates phosphorylation of adherens junction proteins and alters their link to vimentin. Am J Physiol Lung Cell Mol Physiol 282: L1330-L1338.

73. Mehta D, Malik AB (2004) Signaling mechanisms regulating endothelial permeability. Physiol Rev 86: 279-367.

74. Dejana E (2004) Endothelial cell-cell junctions: happy together. Nat Rev Mol Cell Biol 5: 261-270.

75. Eriksson JE, Dechat T, Grin B, Helfand B, Mendez M, et al. (2009) Introducing intermediate filaments: from discovery to disease. J Clin Invest 119: 1763-1771.

76. Schmidt EP, Lee WL, Zemans RL, Yamashita C, Downey GP (2011) On, around, and through: neutrophil-endothelial interactions in innate immunity. Physiology (Bethesda) 26: 334-347.

77. Dumnicka P, Maduzia D, Ceranowicz P, Olszanecki R, Drożdż R, et al. (2017) The Interplay between Inflammation, Coagulation and Endothelial Injury in the Early Phase of Acute Pancreatitis: Clinical Implications. Int J Mol Sci 18: 354.

78. Claesson-Welsh L, Dejana E, McDonald DM (2021) Permeability of the Endothelial Barrier: Identifying and Reconciling Controversies. Trends Mol Med 27: 314-331.

79. Ince C, Mayeux PR, Nguyen T, Gomez H, Kellum JA, et al. (2016) The Endothelium in Sepsis. Shock 45: 259-270.

80. Dolmatova EV, Wang K, Mandavilli R, Griendling KK (2021) The effects of sepsis on endothelium and clinical implications. Cardiovasc Res 117: 60-73.

81. McNicol A, Israels SJ (2003) Platelets and anti-platelet therapy. J Pharmacol Sci 93: 381-396.