


MINI-REVIEW

Open Access

Role of 5-HT₇ receptors in the immune system in health and disease



Alejandro Quintero-Villegas^{1,5} and Sergio Iván Valdés-Ferrer^{2,3,4*} 

Abstract

In mammals, serotonin (5-HT) has critical roles in the central nervous system (CNS), including mood stability, pain tolerance, or sleep patterns. However, the vast majority of serotonin is produced by intestinal enterochromaffin cells of the gastrointestinal tract and circulating blood platelets, also acting outside of the CNS. Serotonin effects are mediated through its interaction with 5-HT receptors (5-HTRs), a superfamily with a repertoire of at least fourteen well-characterized members. 5-HT₇ receptors are the last 5-HTR member to be identified, with well-defined functions in the nervous, gastrointestinal, and vascular systems. The effects of serotonin on the immune response are less well understood. Mast cells are known to produce serotonin, while T cells, dendritic cells, monocytes, macrophages and microglia express 5-HT₇ receptor. Here, we review the known roles of 5-HT₇ receptors in the immune system, as well as their potential therapeutic implication in inflammatory and immune-mediated disorders.

Keywords: 5-HT₇ receptors, Signaling pathway, 5-HT₇ effect, 5-HT₇ distribution, Inflammation, Dendritic cell, Microglia, macrophages, Lymphocytes

Introduction

Serotonin (5-hydroxytryptamine [5-HT]), a monoamine neurotransmitter discovered over seven decades ago as a vasoconstricting agent (Rapport et al. 1948), has critical -and well defined- roles in the central nervous system (CNS), including regulation of mood stability, pain tolerance, or sleep patterns to name a few. Serotonin receptors are expressed throughout the immune system (Herr et al. 2017; Ahern 2011). 5-HT₇ receptor is a member of the family of serotonin receptors, originally cloned in 1993 (Bard et al. 1993; Lovenberg et al. 1993; Ruat et al. 1993) a little more than a decade after the first receptor, 5-HT₁ receptor, was (Peroutka and Snyder 1981). Like other serotonin receptors, 5-HT₇ receptors are members of the G protein-coupled receptor superfamily. Their activation leads to the initiation of two well-characterized signaling pathways: the *canonical* signaling occurs through G_{αs}, while a *non-canonical* pathway signals through G_{α12} (Guseva et al. 2014b). Different 5-HT₇ receptor isoforms have been described (5-HT_{7a}, 5-HT_{7b},

5-HT_{7d}, all expressed in humans and rats, as well as 5-HT_{7c}, expressed only in rats) differing only on the carboxy terminus length, nonetheless, no relevant functional differences have been observed between them (Liu et al. 2001).

Distribution of 5-HT₇ receptors

5-HT₇ receptors are expressed mainly in two compartments: the CNS (Hedlund and Sutcliffe 2004) and the gastrointestinal (GI) tract (Yaakob et al. 2015), although they are also expressed in other tissues including immune cells (see below). In the CNS, the receptor is broadly expressed in the spinal cord, suprachiasmatic nucleus of the hypothalamus, antedorsal thalamus, globus pallidus, prefrontal cortex, trigeminal nucleus caudalis, raphe nuclei area, amygdala and hippocampus, particularly in pyramidal cells of *cornu ammonis* (CA)1 and CA3, where they are expressed in both, neurons and glial cells, including microglia, the CNS-specific phagocytic cell (Chapin and Andrade 2001; Dogrul and Seyrek 2006; Gill et al. 2002; Horisawa et al. 2013; Thomas and Hagan 2004; Tokarski et al. 2003; Russo et al. 2005; Hedlund and Sutcliffe 2004; Lovenberg et al. 1993).

5-HT₇ receptors are found on smooth muscle cells in several arteries, including the aorta, cerebral, coronary,

* Correspondence: sergio.valdesf@incmnsz.mx

²Departments of Neurology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

³Departments of Infectious Diseases, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Full list of author information is available at the end of the article



and pulmonary arteries, where their primary known role is to induce vasodilation (Jasper et al. 1997; Nilsson et al. 1999; Jähnichen et al. 2005; Chang Chien et al. 2015; Terrón and Falcón-Neri 1999). In the GI tract, 5-HT₇ receptors are expressed not only in gut-associated neurons, but also in enterocyte-like and immune cells in lymphatic tissues scattered all along the gut (Iceta et al. 2009; Kim et al. 2013; Guseva et al. 2014b), including monocytes, lymphocytes and dendritic cells (DCs) (León-Ponte et al. 2007; Wu et al. 2019), where it may play a crucial role in inflammation signaling (Urbina et al. 2014; Soga et al. 2007; Holst et al. 2015). Also, 5-HT₇ receptors are found in neutrophils, but the net effect of 5-HT₇ receptor signaling and modulation on neutrophil function is yet to be defined (Rapalli et al. 2016). 5-HT₇ receptors have also been identified in hepatic stellate cells and hepatocytes (Ruddell et al. 2006; Svejda et al. 2013).

Of direct relevance to the present review, 5-HT₇ receptors are also present in immune tissues, including the spleen and thymus; peripheral blood (Stefulj et al. 2000); DCs and other bone marrow-derived mononuclear cells (Shen et al. 1993; Vanhoenacker et al. 2000; Idzko et al. 2004).

Methods

We performed a comprehensive search of English language literature to identify all original research, and review articles regarding 5-HT₇ receptors, signaling pathways and the effects on the immune system; PubMed database since 1993 was used. We used the following Medical Subject Headings (MeSH) and main keywords for searches: 5-HT₇, LP-211, LP-44, LP-21, AS-19, SB 269970, 5-HT₇ physiology, 5-HT₇ receptor mechanism of action, 5-HT₇ receptor signaling pathway, 5-HT₇ receptor effect, 5-HT₇ receptor distribution, inflammation, dendritic cell, microglia, macrophages, and lymphocytes. We also reviewed the reference lists of the articles identified during the search. The authors independently reviewed the selected articles.

Signaling pathways

There are at least two separate signaling pathways downstream of 5-HT₇ receptors (Fig. 1). The activation of the *canonical* signaling pathway leads to the phosphorylation of different adenylyl cyclases (AC), specially AC1 and AC8 (Baker et al. 1998). The increased activity of AC results in an increased production of cyclic adenosine monophosphate (cAMP), activation of protein kinase type A (PKA) and subsequently the phosphorylation of different target proteins like extracellular signal-regulated kinase (ERK) and Protein kinase B (also known as Akt) (Errico et al. 2001; Johnson-Farley et al. 2005). Signaling through the *non-canonical* pathway leads to

activation of Gα12, whose downstream activity is mainly exerted by the Rho family of small guanosine triphosphate (GTP)-ases (Rho, Rac, cell division control protein 42 [Cdc-42]) (Guseva et al. 2014b).

Interestingly, 5-HT₇ receptors may interact with other members of the 5-HT family of receptors. For instance, there is a well-characterized interaction between 5HT₇ and 5-HT_{1A} receptors. 5-HT₇ receptors can form heterodimers with 5-HT_{1A} receptors, resulting in a reduction in the activity of 5-HT₇ receptor (Renner et al. 2005). Moreover, 5-HT_{1A} also inhibits the same signaling cascade as 5-HT₇ receptor-mediated Gs (Zhou et al. 2019). Although to our knowledge no study has demonstrated a biological effect of this crosstalk in the immune system, this interaction could potentially explain the neutral effect of serotonin or SSRI administration.

In neuroblastoma cells, activation of 5-HT₇ receptors induces the formation of filopodia via a Cdc-42-mediated pathway (Kvachnina 2005); in cultured hippocampal neurons, promotes the formation of dendritic spines and accelerates synaptogenesis; moreover, in cultured striatal and cortical neurons, activation of Gα12 leads to pronounced neurite growth via the activation of cyclin-dependent kinase 5 (Cdk5) and ERK (Speranza et al. 2013). All that suggests that 5-HT₇ receptor signaling is critical for synaptogenesis and cell-cell communication which may also occur between non-neuronal cells, including immune ones as will be discussed below.

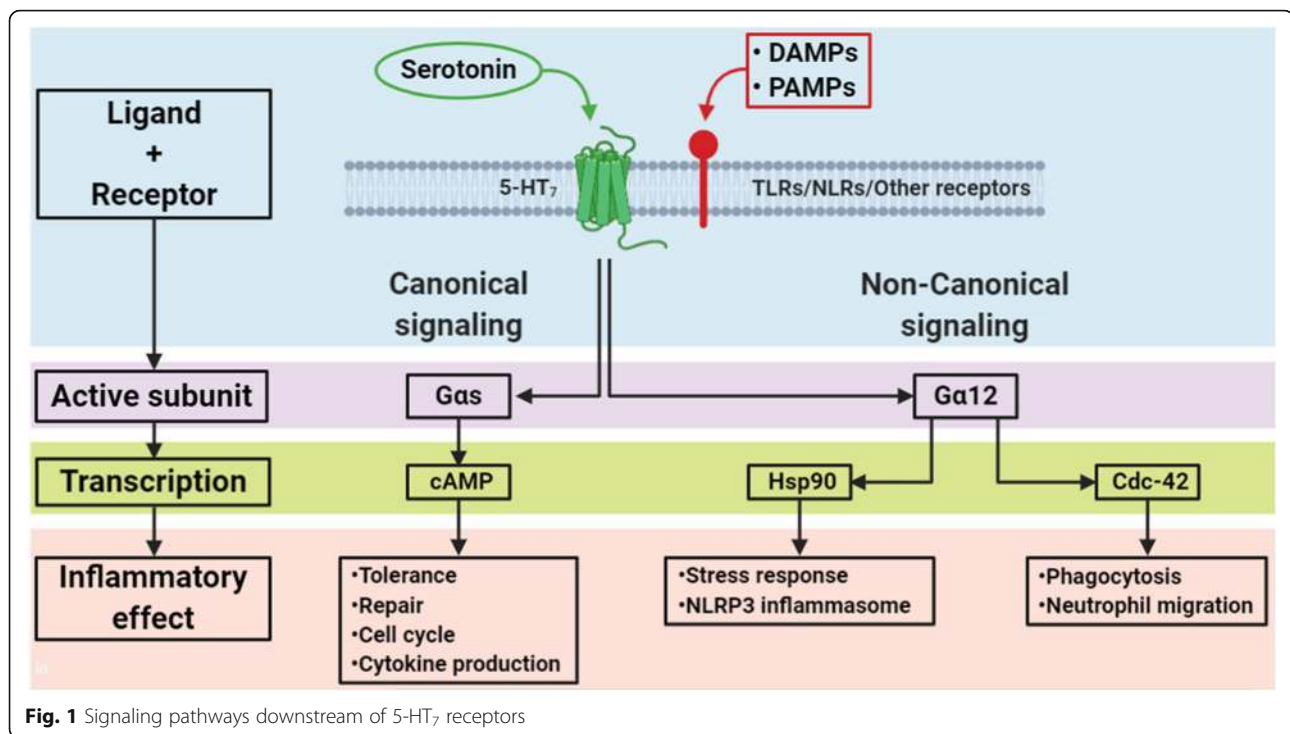
Effects of 5-HT₇ receptor signaling in immune cells

Dendritic cells

5-HT₇ receptors are highly expressed in mature, but not immature DCs (Idzko et al. 2004; Holst et al. 2015). 5-HT₇ receptor activation induces DCs to release interleukin (IL)-1β and IL-8, while reducing the secretion of IL-12 and tumor necrosis factor (TNF)-α (Idzko et al. 2004). As observed in neurons, 5-HT₇ receptor signaling in mature DCs also induces process branching and elongation via Cdc-42. While DCs do not show chemotactic response to 5-HT₇ receptors, the non-selective high-affinity agonist 5-carboxamidotryptamine enhances velocity and distance of the chemotactic response to chemokine ligand (CCL)19 (Holst et al. 2015). The above mentioned data is summarized in Table 1.

Monocytes and macrophages

Experimental evidence has shown an *in vitro* effect of 5-HT₇ receptors on these cells, but the net effect is still incompletely understood. Monocytes treated with serotonin, or methiothepin maleate (a non-specific 5-HT_{1/6/7} receptor agonist), exhibit an inflammatory and anti-apoptotic polarization, including upregulation of TNF-α and IL-6, as well as upregulation of the transcription factors B-cell lymphoma 2 (Bcl-2), nuclear



factor kappa-light-chain-enhancer of activated B cells (NF- κ B); and inhibition of caspase-3. Moreover, treating monocytes with serotonin resulted in increased expression of the costimulatory molecules cluster of differentiation (CD) 40, CD80, and CD86, but not of MHC class II molecules (Soga et al. 2007). In contrast, the selective 5-HT₇ receptor antagonist SB 269970 reverts the anti-inflammatory effect of serotonin on dextran sodium sulfate (DSS)-stimulated M2 macrophages, increasing the production of TNF- α and IL-12, while also interfering with polarization (de las Casas-Engel et al. 2013).

In human and murine macrophages, it has been recently shown that serotonin (as well as AS19, a selective 5-HT₇ receptor agonist) decrease inflammatory priming, in part by reducing the production of IL-12, TNF- α , and type 1 interferons, as well as enhancing the production of transforming growth factor β 1 (TGF- β 1). Moreover, 5-HT₇ receptor signaling promotes pro-fibrotic gene signature in a 5-HT₇ and PKA-dependent manner (Dominguez-Soto et al. 2017).

A role for 5-HT₇ receptors has been experimentally observed in murine models of skin fibrosis and DSS-induced colitis. In the former, macrophage infiltration and collagen deposition are blunted by genetically or chemically interfering with 5-HT₇ receptor signaling (Dominguez-Soto et al. 2017). Oral administration of DSS results in a well-characterized model of gastrointestinal inflammation. Interestingly, DSS also results in increased expression of 5-HT₇ receptors in a subset of

anti-inflammatory myeloid (CD11b⁺CD68⁺) cells, suggesting that myeloid expression of 5-HT₇ receptors may also –under specific insults– attenuate the inflammatory response (Guseva et al. 2014a).










Microglia

These, CNS-specific phagocytic mononuclear cells (Wolf et al. 2017), are produced in the yolk sac and migrate during early CNS development, before the blood brain barrier is formed. In adult life, microglia are involved in a number of homeostatic functions, including neurogenesis, synaptogenesis and synapsis remodeling, as well as neuronal apoptosis and removal (Li and Barres 2018). Microglia also actively survey the CNS for preserved molecular patterns suggestive of infection (pathogen-associated molecular patterns [PAMPs]) and tissue injury (damage-associated molecular patterns [DAMPs]) (Sankowski et al. 2015; Salter and Stevens 2017). Adult microglia express several serotonin receptors, including 5-HT_{2a}, 5-HT_{2b}, 5-HT_{5a}, and 5-HT₇ receptors (Krabbe et al. 2012). Microglia express at least two splice variants of the 5-HT₇ receptor: 5-HT_{7(a/b)}. In these cells, the administration of serotonin, as well as 5-carboxamidotryptamine (5-CT) induces an inflammatory priming and IL-6 production, indicating that these receptors may play a role in CNS inflammation and repair (Mahé et al. 2005).

T cells

Lymphocytes express functional serotonin receptors (Cedeño et al. 2005; Müller et al. 2009). However,

Table 1 Effect of 5-HT₇ receptor signaling on different immune cells and inflammatory conditions

Cell Type		5-HT ₇ Effect
Dendritic cells		<ul style="list-style-type: none"> ●Induces secretion of IL-1β and IL-8; reduces secretion of IL-12 and TNF-α ●Induces process branching and elongation
Monocytes, Macrophages, Microglia		<ul style="list-style-type: none"> ●Pro- and anti-inflammatory <ul style="list-style-type: none"> ○Anti-apoptotic ○Increase in TNF-α, IL-6, Bcl-6, NF-κB ○AS-19 (agonist) decreases IL-12, TNF-α, and type 1 interferons; enhances production of TGF-β1 ○SB-269970 (antagonist) increases TNF-α and IL-12
Lymphocyte		<ul style="list-style-type: none"> ●Concanavalin A, reserpine, and physical restraint increased expression of 5-HT₇ ●Increase in proliferation rate, expression of CD25
Disease Model		5-HT ₇ Effect
Inflammatory Bowel Disease		<ul style="list-style-type: none"> ●5-HT₇ expression increased in DSS-induced colitis ●5-HT₇ blockade/ablation results in increased severity of acute and chronic colitis ●5-HT₇ agonists have anti-inflammatory effect
Lung Injury		<ul style="list-style-type: none"> ●5-HT₇ antagonists decrease lung fluid content, TNF-α, IL-6, oxidative stress in bleomycin-induced lung injury ●5-HT₇ antagonists reduce collagen deposition, expression of TGF-β1 and procollagen type I
Central nervous system inflammation		<ul style="list-style-type: none"> ●LP-211 (agonist) reduces neurotoxic effect of β-amyloid in a model of Alzheimer disease ●AS-19 (agonist) reduces pro-apoptotic effect of streptozotocin
Sepsis		<ul style="list-style-type: none"> ●In LPS-induced sepsis, 5-HT₇ mRNA increases in parallel to TNF-α, IL-1β, NF-κB ●LP-44 (agonist) attenuates cell injury and reduces iNOS and TNF-α ●In a CLP-induced sepsis, AS19 increases survival; reduces tissue injury, inflammatory cytokines, lung NF-κB
Liver Injury		<ul style="list-style-type: none"> ●5-HT₇ signaling induced during chronic liver injury <ul style="list-style-type: none"> ○Reduced ALT and AST levels ○Increased superoxide dismutase ○Reduced TNF-α, IL-6, TGF-β1
Soft tissue inflammation		<ul style="list-style-type: none"> ●In carrageenan-induced paw inflammation, 5-HT₇ agonists reduce cyclooxygenase mRNA expression; decrease oxidative stress, serum cytokine levels

information on the role of 5-HT₇ receptors in lymphoid cells is scant. However, preliminary evidence indicates that lymphocytes obtained from rats exposed to either concanavalin A, reserpine, or physical restraint have an increase in number of 5-HT₇ receptor-positive lymphocytes, as well as increased expression of 5-HT₇ mRNA (Urbina et al. 2014). Naïve splenic T cells express 5-HT₇ receptors; their ex vivo exposure to serotonin leads to a rapid 5-HT₇ receptor-dependent phosphorylation of ERK 1/2, increased proliferation rate, and increased expression of CD25; that response is abrogated by the 5-HT₇ receptor antagonist SB 269970 (León-Ponte et al. 2007). Together, this suggests that 5-HT₇ receptors play a role in T cell responses to inflammatory stimuli.

Neutrophils

While neutrophil migration can be regulated through the effect of serotonin in other receptors, current evidence suggest that 5-HT₇ receptor has no role on neutrophil recruitment (Rapalli et al. 2016).

Hepatocyte response to injury

The above mentioned data is summarized in Table 1. Serotonin has been observed to play a role in liver remodeling in response to inflammatory injury, but the mechanism is incompletely understood. Current evidence suggests that hepatocyte proliferation may be regulated by 5-HT receptors at a number of levels. An in vitro study on rat hepatocytes showed that 5-HT₇ receptor activation by serotonin dose-dependently increases cAMP and PKA signaling, whereas the pharmacological blockade by SB 269970 (a highly specific antagonist) reverted this effect, an observation with potential implications for extra-hepatic tumor seeding to the liver (Svejda et al. 2013).

Organ and disease specific effects of 5-HT₇

Sepsis

In lipopolysaccharide (LPS)-induced sepsis, lung expression of 5-HT₇ receptors increases in parallel to the increased expression of TNF- α , IL-1 β , and NF- κ B. Moreover, in that model, activating 5-HT₇ receptors with LP44 attenuates LPS-induced cell injury, reducing the levels of inducible nitric oxide synthase (iNOS) and TNF- α in a dose-dependent manner (Ayaz et al. 2017).

Cecal ligation and puncture (CLP) is a well validated model of severe poli-microbial sepsis that results in acute and chronic inflammation (Valdés-Ferrer 2014; Buras et al. 2005; Valdés-Ferrer et al. 2013). Administration of a selective 5-HT₇ receptor agonist (AS19) in a rat model of CLP-induced sepsis results in increased survival, decreased tissue injury, a reduction in circulating inflammatory cytokines (IL-1 β , IL-6 and TNF- α), an increase in antioxidant mediators (superoxide dismutase and glutathione), and a

reduction in lung NF- κ B (Cadirci et al. 2013). The above mentioned data is summarized in Table 1.

Inflammatory bowel disease

5-HT₇ receptors are expressed in enteric neurons and CD11c⁺ DCs in the colon; as mentioned above, 5-HT₇ receptor expression is significantly increased after the induction of colitis by DSS (Domínguez-Soto et al. 2017). In that model, the blockade or genetic ablation of 5-HT₇ receptors results in increased severity of acute and chronic colitis; in contrast, 5-HT₇ receptor agonists result in an anti-inflammatory effect (Guseva et al. 2014a; Kim et al. 2013). However, pharmacological blockade of 5-HT₇ receptors has no effect in 2, 4, 6 trinitrobenzene sulfonic acid-induced colitis (Rapalli et al. 2016), suggesting that the inflammatory effect of 5-HT₇ receptors is model-specific. More studies of the downstream-signaling mediators are needed to further understand the therapeutic potential of 5-HT₇ receptors in experimental inflammatory bowel disease.

Lung inflammation

Bleomycin induces experimental pulmonary fibrosis (Adamson and Bowden 1974). During the acute inflammatory phase, 5-HT₇ receptor antagonists decrease lung fluid content, inflammatory cytokines (TNF- α , IL-6) and oxidative stress burden. In the chronic fibrogenic phase, 5-HT₇ receptor antagonism reduces collagen deposition, and mRNA expression of TGF- β 1 and procollagen type I (Tawfik and Makary 2017). In contrast, in CLP-induced sepsis, 5-HT₇ receptor agonists reduce pro-inflammatory mediators and increase survival (Cadirci et al. 2013). Altogether, the current evidence is ambivalent regarding the usefulness of pharmacologically interfering with 5-HT₇ receptor signaling in experimental lung injury.

Liver disease

To our knowledge only one study has focused on the effect of 5-HT₇ receptor signaling during chronic liver injury induced by carbon tetrachloride. There, 5-HT₇ receptor agonists reduced alanine transaminase (ALT) and aspartate transaminase (AST) levels; increased the level of superoxide dismutase; and decreased the levels of TNF- α , IL-6 and TGF- β 1. By the same token, 5-HT₇ receptor antagonism increases cytokines levels. In their histopathological analysis, the carbon tetrachloride group showed severe vacuolar degeneration, necrosis, irregular walls of the vena centralis and lytic areas. In contrast, the administration of the 5-HT₇ receptor agonist LP-44 partially rescued animals from liver damage. This suggests that 5-HT₇ receptors may be a potential therapeutic target for chronic liver inflammation (Polat et al. 2017).

Alzheimer disease (AD)

Immune activation in response to inflammatory insults is a key mediator of neurodegeneration in AD, depression, as well as other CNS disorders (Baganz and Blakely 2013; Strasser et al. 2016). Microglia engulf and degrades β -amyloid, leading to an excessive release of inflammatory cytokines that further propagate inflammatory damage (Holmes and Butchart 2011). Also, β -amyloid binds to receptors for advanced glycation end products (RAGE), resulting in further microglia activation (Querfurth and Laferla 2018). In an AD animal model, the intracerebroventricular (ICV) administration of LP-211 (a 5-HT₇ receptor specific agonist) inhibited the neurotoxic effect of β -amyloid in hippocampus (Quintero-Villegas et al. 2018). In a rat model of streptozotocin-induced AD, ICV administration of the 5-HT₇ receptor-selective agonist AS19 rescued neuronal apoptosis and synaptic dysfunction (Hashemi-Firouzi et al. 2017). Altogether, available preliminary evidence derived from animal models indicates that pharmacological manipulation of the 5-HT₇ receptor may have a niche in the treatment of AD.

Soft-tissue inflammation

The above mentioned data is summarized in Table 1. In a carrageenan-induced paw inflammation model, 5-HT₇ receptor agonists reduced cyclooxygenase mRNA expression, decreased oxidative stress and serum cytokine levels (Albayrak et al. 2013).

Conclusions

5-HT₇ receptors are widely expressed in a vast repertoire of immune and non-immune cells. The receptor has diverse -and even discrepant- roles in the immune response, probably a reflection of at least two clearly defined signaling pathways: in dendritic cells it induces the secretion of IL-1 and IL-6; in monocytes, for instance, it may either be pro- or anti-inflammatory; while in lymphocytes it increases the proliferation rate, suggesting a proinflammatory pattern.

Regarding an organ-specific effect, in CNS, soft tissue, and liver inflammatory injury, the net effect of 5-HT₇ receptors is anti-inflammatory (reducing cell death, inflammatory cytokine release, and oxidative stress). In models of severe sepsis, 5-HT₇ receptor agonists have resulted in a net anti-inflammatory effect. In contrast, bleomycin-induced lung injury is the only experimental model where 5-HT₇ receptors seems to be pro-inflammatory. In experimental murine inflammatory bowel disease, the effect of 5-HT₇ receptors has shown contradictory results.

While our understanding of the connection between 5-HT₇ receptors and inflammation is still limited, significant advances have emerged in the past two decades. Nonetheless, current evidence suggests that pharmacological

interventions targeting 5-HT₇ receptors may be potentially useful for treating inflammatory conditions.

Abbreviations

5-HT: Serotonin; 5-HTRs: 5-HT receptor family; AC: Adenylyl cyclase; ALT: Alanine transaminase; AST: Aspartate transaminase; Bcl-2: B-cell lymphoma 2 transcription factor; CA: *Cornu ammonis* region of the hippocampus; cAMP: Cyclic adenosine monophosphate; CCL: Chemokine ligand; CD: Cluster of differentiation; Cdc-42: Cell division control protein 42; Cdk5: Cyclin-dependent kinase 5; CLP: Cecal ligation and puncture; CNS: Central nervous system; DAMPs: Damage-associated molecular patterns; DCs: Dendritic cells; DSS: Dextran sodium sulfate; ERK: Extracellular signal-regulated kinase; GI: Gastrointestinal; GTP: Guanosine triphosphate; ICV: Intracerebroventricular; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LPS: Lipopolysaccharide; mRNA: Messenger RNA; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; PAMPs: Pathogen-associated molecular patterns; PKA: Protein kinase type A; TGF- β 1: Transforming growth factor beta 1; TNF: Tumor necrosis factor

Acknowledgements

The figures on this manuscript were done using biorender.com software.

Authors' contributions

All authors read and approved the final manuscript.

Funding

This manuscript was supported by a grant (FOSISS-289788 to SIVF) from Consejo Nacional de Ciencia y Tecnología (CONACYT), Mexico.

Availability of data and materials

Not applicable (other than the referenced publications).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Escuela de Medicina, Universidad Panamericana, Mexico City, Mexico.

²Departments of Neurology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico. ³Departments of Infectious Diseases, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico. ⁴Center for Biomedical Science, Feinstein Institute for Medical Research, Manhasset, NY, USA. ⁵Department of Medicine, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico.

Received: 22 October 2019 Accepted: 6 December 2019

References

- Adamson IY, Bowden DH. The pathogenesis of bleomycin-induced pulmonary fibrosis in mice. *Am J Pathol.* 1974;77:185–97.
- Ahern GP. 5-HT and the immune system. *Curr Opin Pharmacol.* 2011;11:29–33. <https://doi.org/10.1016/j.coph.2011.02.004>.
- Albayrak A, Halici Z, Cadirci E, Polat B, Karakus E, Bayir Y, Unal D, Atasoy M, Dogrul A. Inflammation and peripheral 5-HT7 receptors: the role of 5-HT7 receptors in carrageenan induced inflammation in rats. *Eur J Pharmacol.* 2013;715:270–9. <https://doi.org/10.1016/j.ejphar.2013.05.010>.
- Ayaz G, Halici Z, Albayrak A, Karakus E, Cadirci E. Evaluation of 5-HT7 receptor trafficking on in vivo and in vitro model of lipopolysaccharide (LPS)-induced inflammatory cell injury in rats and LPS-treated A549 cells. *Biochem Genet.* 2017;55:34–47. <https://doi.org/10.1007/s10528-016-9769-2>.
- Baganz NL, Blakely RD. A dialogue between the immune system and brain, spoken in the language of serotonin. *ACS Chem Neurosci.* 2013;4:48–63. <https://doi.org/10.1021/cn300186b>.

- Baker LP, Nielsen MD, Impey S, Metcalf MA, Poser SW, Chan G, Obrietan K, Hamblin MW, Storm DR. Stimulation of type 1 and type 8 Ca²⁺/Calmodulin-sensitive adenylyl Cyclases by the G_s-coupled 5-Hydroxytryptamine subtype 5-HT_{7A} receptor. *J Biol Chem*. 1998;273:17469–76. <https://doi.org/10.1074/jbc.273.28.17469>.
- Bard JA, Zgombick J, Adham N, Vaysse P, Branchek TA, Weinshank RL. Cloning of a novel human serotonin receptor (5-HT₇) positively linked to Adenylate Cyclase. *J Biochem Chem*. 1993;268:2342–6.
- Buras JA, Holzmann B, Sitkovsky M. Animal models of sepsis: setting the stage. *Nat Rev Drug Discov*. 2005;4:854–65. <https://doi.org/10.1038/nrd1854>.
- Cadirci E, Halici Z, Bayir Y, Albayrak A, Karakus E, Polat B, Unal D, Atamanalp SS, Aksak S, Gundogdu C. Peripheral 5-HT₇ receptors as a new target for prevention of lung injury and mortality in septic rats. *Immunobiology*. 2013;218:1271–83. <https://doi.org/10.1016/j.imbio.2013.04.012>.
- Cedeño N, Urbina M, Obregón F, Lima L. Characterization of serotonin transporter in blood lymphocytes of rats. Modulation by in vivo administration of mitogens. *J Neuroimmunol*. 2005;159:31–40. <https://doi.org/10.1016/j.jneuroim.2004.09.010>.
- Chang Chien CC, Hsin LW, Su MJ. Activation of serotonin 5-HT₇ receptor induces coronary flow increase in isolated rat heart. *Eur J Pharmacol*. 2015;748:68–75. <https://doi.org/10.1016/j.ejphar.2014.08.027>.
- Chapin EM, Andrade R. A 5-HT₇ receptor-mediated depolarization in the anterodorsal thalamus. II. Involvement of the hyperpolarization-activated current I(h). *J Pharmacol Exp Ther*. 2001;297:403–9.
- de las Casas-Engel M, Domínguez-Soto A, Sierra-Filardi E, Bragado R, Nieto C, Puig-Kroger A, Samaniego R, Loza M, Corcuera MT, Gómez-Aguado F, Rostros M, Sánchez-Mateos P, Corbí AL. Serotonin skews human macrophage polarization through HTR_{2B} and HTR₇. *J Immunol*. 2013;190:2301–10. <https://doi.org/10.4049/jimmunol.1201133>.
- Dogrul A, Seyrek M. Systemic morphine produce antinociception mediated by spinal 5-HT₇, but not 5-HT_{1A} and 5-HT₂ receptors in the spinal cord. *Br J Pharmacol*. 2006;149:498–505. <https://doi.org/10.1038/sj.bjp.0706854>.
- Domínguez-Soto Á, Usategui A, Las Casas-Engel MD, Simón-Fuentes M, Nieto C, Cuevas VD, Vega MA, Luis Pablos J, Corbí AL. Serotonin drives the acquisition of a profibrotic and anti-inflammatory gene profile through the 5-HT_{7R}-PKA signaling axis. *Sci Rep*. 2017;7:1–15. <https://doi.org/10.1038/s41598-017-15348-y>.
- Errico M, Crozier RA, Plummer MR, Cowen DS. 5-HT₇ receptors activate the mitogen activated protein kinase extracellular signal related kinase in cultured rat hippocampal neurons. *Neuroscience*. 2001;102:361–7. [https://doi.org/10.1016/S0306-4522\(00\)0460-7](https://doi.org/10.1016/S0306-4522(00)0460-7).
- Gill CH, Soffin EM, Hagan JJ, Davies CH. 5-HT₇ receptors modulate synchronized network activity in rat hippocampus. *Neuropharmacology*. 2002;42:82–92. [https://doi.org/10.1016/S0028-3908\(01\)00149-6](https://doi.org/10.1016/S0028-3908(01)00149-6).
- Guseva D, Holst K, Kaune B, Meier M, Keubler L, Glage S, Buettner M, Bleich A, Pabst O, Bachmann O, Ponimaskin EG. Serotonin 5-HT₇ receptor is critically involved in acute and chronic inflammation of the gastrointestinal tract. *Inflamm Bowel Dis*. 2014a;20:1516–29. <https://doi.org/10.1097/MIB.000000000000150>.
- Guseva D, Wirth A, Ponimaskin E. Cellular mechanisms of the 5-HT₇ receptor-mediated signaling. *Front Behav Neurosci*. 2014b;8:1–8. <https://doi.org/10.3389/fnbeh.2014.00306>.
- Hashemi-Firouzi N, Komaki A, Soleimani Asl S, Shahidi S. The effects of the 5-HT₇ receptor on hippocampal long-term potentiation and apoptosis in a rat model of Alzheimer's disease. *Brain Res Bull*. 2017;135:85–91. <https://doi.org/10.1016/j.brainresbull.2017.10.004>.
- Hedlund P, Sutcliffe J. Functional, molecular and pharmacological advances in 5-HT₇ receptor research. *Trends Pharmacol Sci*. 2004;25:481–6. <https://doi.org/10.1016/j.tips.2004.07.002>.
- Herr N, Bode C, Duerschmied D. The effects of serotonin in immune cells. *Front Cardiovasc Med*. 2017;4:1–11. <https://doi.org/10.3389/fcvm.2017.00048>.
- Holmes C, Butchart J. Systemic inflammation and Alzheimer's disease. *Biochem Soc Trans*. 2011;39:898–901. <https://doi.org/10.1042/BST0390898>.
- Holst K, Guseva D, Schindler S, Sixt M, Braun A, Chopra H, Pabst O, Ponimaskin E. The serotonin receptor 5-HT_{7R} regulates the morphology and migratory properties of dendritic cells. *J Cell Sci*. 2015;128:2866–80. <https://doi.org/10.1242/jcs.167999>.
- Horisawa T, Ishiyama T, Ono M, Ishibashi T, Tajiri M. Binding of lurasidone, a novel antipsychotic, to rat 5-HT₇ receptor: analysis by [³H]SB-269970 autoradiography. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2013;40:132–7. <https://doi.org/10.1016/j.pnpbp.2012.08.005>.
- Iceta R, Mesonero JE, Aramayo JJ, Alcalde AI. Expression of 5-HT_{1A} and 5-HT₇ receptors in caco-2 cells and their role in the regulation of serotonin transporter activity. *J Physiol Pharmacol*. 2009;60:157–64.
- Idzko M, Panther E, Stratz C, Müller T, Bayer H, Zissel G, Dürk T, Sorichter S, Di Virgilio F, Geissler M, Fiebich B, Herouy Y, Elsner P, Norgauer J, Ferrari D. The serotonergic receptors of human dendritic cells: identification and coupling to cytokine release. *J Immunol*. 2004;172:6011–9. <https://doi.org/10.4049/jimmunol.172.10.6011>.
- Jähnichen S, Glusa E, Pertz HH. Evidence for 5-HT_{2B} and 5-HT₇ receptor-mediated relaxation in pulmonary arteries of weaned pigs. *Naunyn Schmiedeberg's Arch Pharmacol*. 2005;371:89–98. <https://doi.org/10.1007/s00210-004-1006-6>.
- Jasper JR, Kosaka A, Z.P. To, Chang DJ, Eglén RM. Cloning, expression and pharmacology of a truncated splice variant of the human 5-HT₇ receptor (h5-HT_{7(b)}). *Br J Pharmacol*. 1997;122:126–32. <https://doi.org/10.1038/sj.bjp.0701336>.
- Johnson-Farley NN, Kertesz SB, Dubyak GR, Cowen DS. Enhanced activation of Akt and extracellular-regulated kinase pathways by simultaneous occupancy of G_q-coupled 5-HT_{2A} receptors and G_s-coupled 5-HT_{7A} receptors in PC12 cells. *J Neurochem*. 2005;92:72–82. <https://doi.org/10.1111/j.1471-4159.2004.02832.x>.
- Kim JJ, Bridle BW, Ghia J-E, Wang H, Syed SN, Manocha MM, Rengasamy P, Shajib MS, Wan Y, Hedlund PB, Khan W. Targeted Inhibition of Serotonin Type 7 (5-HT₇) Receptor Function Modulates Immune Responses and Reduces the Severity of Intestinal Inflammation. *J Immunol*. 2013;190:4795–804. <https://doi.org/10.4049/jimmunol.1201887>.
- Krabbe G, Matyash V, Pannasch U, Mamer L, Boddeke HWGM, Kettenmann H. Activation of serotonin receptors promotes microglial injury-induced motility but attenuates phagocytic activity. *Brain Behav Immun*. 2012;26:419–28. <https://doi.org/10.1016/j.bbi.2011.12.002>.
- Kvachnina E. 5-HT₇ receptor is coupled to G subunits of Heterotrimeric G12-protein to regulate gene transcription and neuronal morphology. *J Neurosci*. 2005;25:7821–30. <https://doi.org/10.1523/JNEUROSCI.1790-05.2005>.
- León-Ponte M, Ahern GP, O'Connell PJ. Serotonin provides an accessory signal to enhance T-cell activation by signaling through the 5-HT₇ receptor. *Blood*. 2007;109:3139–46. <https://doi.org/10.1182/blood-2006-10-052787>.
- Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. *Nat Rev Immunol*. 2018;18:225–42. <https://doi.org/10.1038/nri.2017.125>.
- Liu H, Irving HR, Coupar IM. Expression patterns of 5-HT₇ receptor isoforms in the rat digestive tract. *Life Sci*. 2001;69:2467–75. [https://doi.org/10.1016/S0024-3205\(01\)01318-2](https://doi.org/10.1016/S0024-3205(01)01318-2).
- Lovenberg TW, Baron BM, de Lecea L, Miller JD, Prosser RA, Rea MA, Foye PE, Racke M, Slone AL, Siegel BW, Danielson PE, Sutcliffe JG, Erlander MG. A novel adenylyl cyclase-activating serotonin receptor (5-HT₇) implicated in the regulation of mammalian circadian rhythms. *Neuron*. 1993;11:449–58. [https://doi.org/10.1016/0896-6273\(93\)90149-L](https://doi.org/10.1016/0896-6273(93)90149-L).
- Mahé C, Loetscher E, Dev KK, Bobinac I, Otten U, Schoeffter P. Serotonin 5-HT₇ receptors coupled to induction of interleukin-6 in human microglial MC-3 cells. *Neuropharmacology*. 2005;49:40–7. <https://doi.org/10.1016/j.neuropharm.2005.01.025>.
- Müller T, Dürk T, Blumenthal B, Grimm M, Cicko S, Panther E, Sorichter S, Herouy Y, Di Virgilio F, Ferrari D, Norgauer J, Idzko M. 5-hydroxytryptamine modulates migration, cytokine and chemokine release and T-cell priming capacity of dendritic cells in vitro and in vivo. *PLoS One*. 2009;4:1–8. <https://doi.org/10.1371/journal.pone.0006453>.
- Nilsson T, Longmore J, Shaw D, Pantev E, Bard JA, Branchek T, Edvinsson L. Characterisation of 5-HT receptors in human coronary arteries by molecular and pharmacological techniques. *Eur J Pharmacol*. 1999;372:49–56. [https://doi.org/10.1016/S0014-2999\(99\)00114-4](https://doi.org/10.1016/S0014-2999(99)00114-4).
- Peroutka SJ, Snyder SH. Two distinct serotonin receptors: regional variations in receptor binding in mammalian brain. *Brain Res*. 1981;208:339–47. [https://doi.org/10.1016/0006-8993\(81\)90562-X](https://doi.org/10.1016/0006-8993(81)90562-X).
- Polat B, Halici Z, Cadirci E, Karakus E, Bayir Y, Albayrak A, Unal D. Liver 5-HT₇ receptors: a novel regulator target of fibrosis and inflammation-induced chronic liver injury in vivo and in vitro. *Int Immunopharmacol*. 2017;43:227–35. <https://doi.org/10.1016/j.intimp.2016.12.023>.
- Querfurth HW, Laferla FM. Alzheimer's disease; 2018. p. 329–44.
- Quintero-Villegas A, Álvarez-Manzo HS, Bernal-Mondragón C, Guevara-Guzmán R, Valenzuela-Almada MOA. *SciFed journal of Alzheimer's and dementia*. SF J Alzh Dement. 2018;1:1–10.
- Rapalli A, Bertoni S, Arcaro V, Sacconi F, Grandi A, Vivo V, Cantoni AM, Barocelli E. Dual role of endogenous serotonin in 2,4,6-Trinitrobenzene

- sulfonic acid-induced colitis. *Front Pharmacol*. 2016;7. <https://doi.org/10.3389/fphar.2016.00068>.
- Rapport MM, Green AA, Page IH. Partial purification of the vasoconstrictor in beef serum. *J Biol Chem*. 1948;174:735–41.
- Renner U, Zeug A, Woehler A, Niebert M, Dityatev A, Dityateva G, Gorinski N, Guseva D, Abdel-Galil D, Fröhlich M, Döring F, Wischmeyer E, Richter DW, Neher E, Ponimaskin EG. Heterodimerization of serotonin receptors 5-HT1A and 5-HT7 differentially regulates receptor signalling and trafficking. *J Cell Science*. 2012;125:2486–99. <https://doi.org/10.1242/jcs.101337>.
- Ruat M, Traiffort E, Leurs R, Tardivel-Lacombe J, Diaz J, Arrang JM, Schwartz JC. Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT7) activating cAMP formation. *Proc Natl Acad Sci U S A*. 1993;90:8547–51. <https://doi.org/10.1073/pnas.90.18.8547>.
- Ruddell RG, Oakley F, Hussain Z, Yeung J, Bryan-Lluka LJ, Ramm GA, Mann DA. A role for serotonin (5-HT) in hepatic stellate cell function and liver fibrosis. *Am J Pathol*. 2006;169:861–76. <https://doi.org/10.2353/ajpath.2006.050767>.
- Russo A, Pellitteri R, Monaco S, Romeo R, Stanzani S. "In vitro" postnatal expression of 5-HT7 receptors in the rat hypothalamus: an immunohistochemical analysis. *Dev Brain Res*. 2005;154:211–6. <https://doi.org/10.1016/j.devbrainres.2004.11.002>.
- Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med*. 2017;23:1018–27. <https://doi.org/10.1038/nm.4397>.
- Sankowski R, Mader S, Valdés-Ferrer SI. Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration. *Front Cell Neurosci*. 2015;9:1–20. <https://doi.org/10.3389/fncel.2015.00028>.
- Shen Y, Monsma FJ, Metcalf MA, Jose PA, Hamblin MW, Sibley DR. Molecular cloning and expression of a 5-hydroxytryptamine7 serotonin receptor subtype. *J Biol Chem*. 1993;268:18200–4.
- Soga F, Katoh N, Inoue T, Kishimoto S. Serotonin activates human monocytes and prevents apoptosis. *J Invest Dermatol*. 2007;127:1947–55. <https://doi.org/10.1038/sj.jid.5700824>.
- Speranza L, Chambery A, Di Domenico M, Crispino M, Severino V, Volpicelli F, Leopoldo M, Bellenchi GC, di Porzio U, Perrone-Capano C. The serotonin receptor 7 promotes neurite outgrowth via ERK and Cdk5 signaling pathways. *Neuropharmacology*. 2013;67:155–67. <https://doi.org/10.1016/j.neuropharm.2012.10.026>.
- Stefulj J, Jernej B, Cicin-Sain L, Rinner I, Schauenstein K. mRNA expression of serotonin receptors in cells of the immune tissues of the rat. *Brain Behav Immun*. 2000;14:219–24. <https://doi.org/10.1006/brbi.1999.0579>.
- Strasser B, Gostner JM, Fuchs D. Mood, food, and cognition: role of tryptophan and serotonin. *Curr Opin Clin Nutr Metab Care*. 2016;19:55–61. <https://doi.org/10.1097/MCO.0000000000000237>.
- Svejda B, Kidd M, Timberlake A, Harry K, Kazberouk A, Schimmack S, Lawrence B, Pfragner R, Modlin IM. Serotonin and the 5-HT7 receptor: the link between hepatocytes, IGF-1 and small intestinal neuroendocrine tumors. *Cancer Sci*. 2013;104:844–55. <https://doi.org/10.1111/cas.12174>.
- Tawfik MK, Makary S. 5-HT7 receptor antagonism (SB-269970) attenuates bleomycin-induced pulmonary fibrosis in rats via downregulating oxidative burden and inflammatory cascades and ameliorating collagen deposition: comparison to terguride. *Eur J Pharmacol*. 2017;814:114–23. <https://doi.org/10.1016/j.ejphar.2017.08.014>.
- Terrón JA, Falcón-Neri A. Pharmacological evidence for the 5-HT7 receptor mediating smooth muscle relaxation in canine cerebral arteries. *Br J Pharmacol*. 1999;127:609–16. <https://doi.org/10.1038/sj.bjp.0702580>.
- Thomas D, Hagan J. 5-HT7 Receptors. *Curr Drug Target -CNS Neurol Disord*. 2004;3:81–90. <https://doi.org/10.2174/1568007043482633>.
- Tokarski K, Zahorodna A, Bobula B, Hess G. 5-HT7 receptors increase the excitability of rat hippocampal CA1 pyramidal neurons. *Brain Res*. 2003;993:230–4. <https://doi.org/10.1016/j.brainres.2003.09.015>.
- Urbina M, Arroyo R, Lima L. 5-HT7 receptors and tryptophan hydroxylase in lymphocytes of rats: mitogen activation, physical restraint or treatment with reserpine. *Neuroimmunomodulation*. 2014;21:240–9. <https://doi.org/10.1159/000357148>.
- Valdés-Ferrer SI. The challenges of long-term sepsis survivors: when surviving is just the beginning. *Rev Investig Clin*. 2014;66:439–49.
- Valdés-Ferrer SI, Rosas-Ballina M, Olofsson PS, Lu B, Dancho ME, Ochani M, Li JH, Scheinerman JA, Katz DA, Levine YA, Hudson LK, Yang H, Pavlov VA, Roth J, Blanc L, Antoine DJ, Chavan SS, Andersson U, Diamond B, Tracey KJ. HMGB1 mediates splenomegaly and expansion of splenic CD11b⁺ Ly-6C^{high} inflammatory monocytes in murine sepsis survivors. *J Intern Med*. 2013;274. <https://doi.org/10.1111/joim.12104>.
- Vanhoeacker P, Haegeman G, Leysen JE. 5-HT 7 receptors: current knowledge and future prospects. *Trends Pharmacol Sci*. 2000;21:70–7. [https://doi.org/10.1016/S0165-6147\(99\)01432-7](https://doi.org/10.1016/S0165-6147(99)01432-7).
- Wolf SA, Boddeke HWGM, Kettenmann H. Microglia in physiology and disease. *Annu Rev Physiol*. 2017;79:619–43. <https://doi.org/10.1146/annurev-physiol-022516-034406>.
- Wu H, Denna TH, Storkersen JN, Gerriets VA. Beyond a neurotransmitter: the role of serotonin in inflammation and immunity. *Pharmacol Res*. 2019;140:100–14. <https://doi.org/10.1016/j.phrs.2018.06.015>.
- Yaakob NS, Chinkwo KA, Chetty N, Coupar IM, Irving HR. Distribution of 5-HT 3 , 5-HT 4 , and 5-HT 7 Receptors Along the Human Colon. *J Neurogastroenterol Motil*. 2015;21:361–9. <https://doi.org/10.5056/jnm14157>.
- Zhou X, Zhang R, Zhang S, Wu J, Sun X. Activation of 5-HT1A receptors promotes retinal ganglion cell function by inhibiting the cAMP-PKA pathway to modulate presynaptic GABA release in chronic glaucoma. *J Neurosci*. 2019;39:1484–504. <https://doi.org/10.1523/JNEUROSCI.1685-18.2018>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

