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Impact of 5-HT_3 receptor antagonists on peripheral and central diseases

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In this article we discuss the novel pharmacological aspects of 5-HT_3 receptor antagonists. Commonly used to counteract chemotherapy-induced emesis, these agents now appear to be reaching out for newer indications. Studies have reported neuroprotective and anti-inflammatory properties *in vitro* and *in vivo*. 5-HT_3 receptor antagonists can modulate the immune-inflammatory axis through blockade of 5-HT_3 receptors present on immune cells. We review evidence addressing the effects of these drugs on peripheral inflammatory diseases, including asthma, rheumatoid diseases, inflammatory bowel disease and sepsis in addition to diabetes and CNS disorders, including Alzheimer's disease (AD), seizure and stroke.

5-Hydroxytryptamine [5-HT (serotonin)] is a neurotransmitter and a crucial signaling molecule. It is found in the immune-inflammatory axis where it influences the immune response in mammals [1]. Of the recognized 5-HT receptor subtypes, 5-HT_3 stands out because it is a ligand-gated ion channel (LGIC) whereas others serve as G protein-coupled receptors (GPCRs) [2]. 5-HT_3 receptors occur in the central nervous system (CNS) and are widely expressed in the components of the immune system, including B cells, T cells and monocytes [3]. As can be assumed from their vast distribution, they are implicated in an array of physiologic and pathologic functions, such as emesis, cognition and pain [4]. The 5-HT_3 receptor subtype is found in both pre- and postsynaptic regions and their activation modulates the liberation of other neurotransmitters, including dopamine, acetylcholine (ACh), gamma aminobutyric acid (GABA), glutamate and 5-HT itself [5]. Gathering evidence from both human and animal studies suggests that the 5-HT_3 receptor antagonists, first developed as expeditious agents to counteract chemotherapy-induced emesis, possess a variety of neuroprotective and antiphlogistic properties. In this article we summarize state of the art on novel pharmacological effects observed with 5-HT_3 receptor antagonists and the possible underlying signaling cascades.

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Diabetes

The role of serotonin and its diverse 5-HT receptors has been investigated in glucose metabolism and pathogenesis of diabetes. In rats, activation of central serotonergic system induces hyperglycemia, which can be reverted by prior administration of a 5-HT_3 receptor antagonist such as ondansetron or LY-278584, indicating the involvement of 5-HT_3 receptor subtype in this hyperglycemic effect [6,7]. Of note, tropisetron, another 5-HT_3 receptor antagonist, was found to enhance the insulin release through insulin producing beta-cell line (INS-1) cells. The effect was more pronounced in the presence of serotonin at the highest concentration used (500 μM). Serotonin *per se* reduced the glucose-stimulated liberation of insulin in a concentration-dependent fashion whereas tropisetron abolished this inhibition [8]. Such observation points out the involvement of 5-HT_3 receptors in tropisetron-induced insulin secretion. The underlying mechanism concerning secretagogue action of 5-HT_3 antagonists is however wrapped up in obscurity because the main target for classical insulin secreting agents (sulfonylureas) is inhibition of ATP-sensitive potassium

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channels leading to Ca^{2+} entry and β cell depolarization. 5-HT_3 ion channel blockade, in contrast, is associated with a reduction in inward cation currents, in particular Ca^{+2}. Moreover, no hypoglycemic effect has been reported with therapeutic doses of 5-HT_3 receptor antagonists. Identification of targets for this class of drugs in glucose homeostasis merits more thorough research.

Inflammatory bowel disease

5-HT is a key enteric mucosal signaling molecule that controls peristalsis and mucosal secretion through activation of 5-HT_{1P}, 5-HT_3 and 5-HT_4 receptors on submucosal and myenteric afferent neurons [5]. Experimental colitis is associated with an increase in colonic content of 5-HT [9,10]. Enterochromaffin (EC) cells are the major 5-HT producing cell type in the bowel. An increase in number of EC cells and a decrease in the amount of serotonin reuptake transporter (SERT) are seen during conditions with gut mucosal inflammation which collectively contribute to the elevated bioavailability of 5-HT in the inflamed colon [11,12]. Such elevated content of 5-HT accounts for hypermotility and hypersecretion associated with inflammatory bowel disease (IBD). Intestinal immunocytes, through the release of various cytokines, can activate neighboring EC cells to liberate 5-HT [10]. EC cells express 5-HT_3 and 5-HT_4 receptors which act to regulate 5-HT secretion from EC cells. Activation of 5-HT_3 receptors on EC cells causes a further rise in 5-HT secretion through a positive feedback mechanism and, reasonably, Gebauer *et al.* showed the ability of granisetron to diminish 5-HT release from EC cells *in vitro* [13]. It has been shown that pharmacological inhibition or genetic deletion of tryptophan hydroxylase in mice causes a notable amelioration of murine IBD suggesting the detrimental role of 5-HT signaling in gut inflammation [14]. Indeed, 5-HT activates dendritic cell function leading to sequential T-cell activation in the context of gut inflammation [15]. Our investigations show that 5-HT_3 receptor antagonists, alongside their established therapeutic efficacy in diarrhea dominant irritable bowel syndrome (IBS), elicit beneficial effects in experimental models of IBD. Both tropisetron and granisetron were shown to protect against rat colitis associated with decreased inflammatory response and lipid peroxidation in the gut [16,17]. Regarding these findings, 5-HT_3 receptor antagonists seem to modulate 5-HT release from EC cells thereby attenuating excessive intestinal motility and secretion. In addition, 5-HT_3 receptor antagonists possibly offset neurogenic inflammation, an important component in the pathogenesis of IBD [18]. Neurogenic inflammation and the way these compounds affect it will be discussed in detail in the asthma section.

T cells have a substantial part in the pathogenesis of IBD. Interaction of T cells with antigen presenting cells leads to IL-2 secretion from T cells that in turn activate tissue macrophages to release a variety of pro-inflammatory cytokines and mediators, including TNF-α, IL-1β, nitric oxide and reactive oxygen species (ROS). These events result in tissue injury in IBD [19]. Interestingly, tropisetron can inhibit IL-2 gene transcription and activation of human T cells. In this respect, equipotent congeners ondansetron and granisetron displayed different profiles. Granisetron had no effect on IL-2 production whereas ondansetron partially inhibited T cell activation [20]. Therefore, it is plausible that tropisetron employs an additional mechanism, not shared by other 5-HT_3 antagonists to counteract T cell-induced tissue injury in IBD.

Asthma

Since the identification of numerous biologically active neuropeptides in the lungs of patients and animals with asthma, considerable attention has been drawn toward the role of neurogenic inflammation in pathogenesis of asthma, especially the late phase. Neurogenic inflammation arises from the release from airway afferent neurons of such mediators as substance P, neuropeptide Y and calcitonin gene-related peptide. 5-HT can boost sensory neuropeptide-induced neurogenic inflammatory response by acting at 5-HT_3 receptors on capsaicin-sensitive fibers [21,22]. Pharmacological blockade of 5-HT_3 receptors in this context is therefore of benefit as such inhibition precludes the release of pro-inflammatory neuropeptides and consequently ameliorates inflammation and the resulting airway hyperreactivity.

It has been demonstrated that 5-HT produces bronchoconstriction in patients with asthma, while having no effect on healthy individuals [23]. An elevated plasma level of 5-HT has been also documented in symptomatic asthmatic patients when compared with nonasthmatics. Indeed, a significant correlation was seen between 5-HT level and clinical severity rating and forced expiratory volume in one second (FEV1) in these patients [24]. Evidence supports the existence of prejunctional 5-HT_3 receptors on postganglionic cholinergic nerves. When activated, these receptors mediate the potentiating effect of 5-HT on parasympathetic-induced airway smooth muscle contraction. Using human airway *ex vivo*, 5-HT_3 antagonists ondansetron and tropisetron successfully blocked 5-HT-induced facilitation of cholinergic contraction [25]. Thus these compounds would help to combat bronchoconstriction associated with the excessive 5-HT production in asthma.

The management of refractory asthma seen in a subgroup of patients remains a compelling clinical problem that contributes appreciably to both the patients' morbidity and health care costs. Persistent airways inflammation, despite corticosteroid therapy, can be treated with alternative broad-spectrum anti-inflammatory treatments, such as calcineurin inhibitors, which act to prevent T lymphocyte activation by blocking the activation of nuclear factor of activated T cells (NFAT) [26]. We have recently shown that tropisetron can potently inhibit calcineurin activity in cerebellar granule cells and that the effect is exerted independent of 5-HT_3 receptor [27]. Although the responsible mechanism is not investigated yet, the calcineurin inhibitory effect of tropisetron might arise from its interaction with immunophilins, such as FKBP12 or cyclophilin. Calcineurin itself could be a suspect; this phosphatase possesses regulatory and catalytic domains, both of which could be targeted by tropisetron. This property of tropisetron can thus be exploited to control persistent airway inflammation in refractory asthma.

Taken together, 5-HT_3 antagonists appear to be of relevance for targeting both aspects of asthma, namely inflammation and bronchoconstriction, while some can also help overcome glucocorticoid resistance.

Arthritis

Rheumatic diseases are painful conditions characterized by aberrant production of manifold mediators that trigger cartilage erosion and osteodestruction [28]. Among them, 5-HT is a modulator of various immune functions, released by activated platelets in

sites of inflammation leading to an elevation in its local concentration and is found in synovial inflammation [1]. 5-HT induces synovial plasma extravasation through release of prostaglandins (PGs) and leukotrienes [29]. 5-HT level was found elevated in affected joint perfusates of antigen-induced arthritis. In addition, 5-HT evoked joint inflammation and pain, when injected intra-articularly [30]. Attenuation of the disease severity in adjuvant-induced arthritis by pharmacological depletion of 5-HT reflects its pro-inflammatory role in this model [31]. In clinical setting, high plasma levels of 5-HT are linked to progression of erosions in patients with rheumatoid arthritis (RA) [32]. Ample evidence implicates the 5-HT_3 receptor subtype in pain and inflammation. The efficacy of 5-HT_3 antagonists in rheumatic diseases is now well-documented. In human monocytes, tropisetron inhibited lipopolysaccharides (LPS)-stimulated secretion of TNF-α and IL-1β [33]. In human macrophage-like synovial cells, tropisetron completely blocked the serotonin-evoked overexpression of prostaglandin E2 (PGE_2) [28]. In pilot studies, local injection of tropisetron potently relieved inflammation and pain in RA, activated osteoarthritis (OA) and tendinopathies [34,35]. In a double-blinded study, a single intra-articular injection of tropisetron yielded comparable clinical benefits to methylprednisolone in RA and OA which lasted for at least three weeks following its administration [36]. By contrast, Granisetron displayed an immediate, short-lasting alleviation in temporomandibular joint inflammatory arthritis. Of note, the effect was greater in patients with higher levels of circulating 5-HT [37] indicating the crucial role of 5-HT_3 receptor subtype in antiphlogistic properties repeatedly reported with this class of drugs. The analgesic effect of 5-HT_3 antagonists emerges from their aptitude to inhibit the release of sensory neuropeptides which trigger the development of neurogenic inflammation.

Given their effects on various disease processes and a broad therapeutic window, 5-HT_3 receptor antagonists merit consideration for larger-scale clinical trials to closely scrutinize their potential efficacy in pain and inflammation related to rheumatic diseases.

Sepsis

Further evidence for the antiphlogistic actions of 5-HT_3 receptor antagonists comes from a recent investigation demonstrating inhibitory effects of tropisetron on proinflammatory cytokine production in an experimental model of sepsis [38]. Such effect can have an enormous therapeutic outcome because, according to the 'cytokine theory of disease', excessive production of cytokines has a substantial role in development of the complications secondary to sepsis and/or septic shock [39]. Sympathetic overstimulation during sepsis has been alleged to amplify the observed inflammatory response [40]. Intriguingly, tropisetron could in parallel curtail the sympathetic outflow as verified by the decreased serum level of noradrenaline in this sepsis model [38]. These preliminary findings propose the efficacy of 5-HT_3 receptor antagonists in counteracting both disproportionate cytokine release and sympathetic overstimulation in sepsis.

Alzheimer's disease

Cholinergic axon terminals in the human cerebral cortex possess 5-HT_3 receptors that mediate the tonic inhibitory control of 5-HT on ACh release. 5-HT_3 receptor antagonists tropisetron and ondansetron enhanced ACh release in human cortical tissue by blocking the inhibitory effect of 5-HT [41]. Such facilitation of cholinergic function conforms to the clinical finding that ondansetron ameliorates age-related memory impairment [5]. Likewise, in numerous experimental studies, hippocampal 5-HT_3 antagonism has proved promising in attenuating scopolamine-induced memory disturbances [42,43]. Given the high density of 5-HT_3 receptors in the limbic system and cortex, regions implicated in learning and memory [44], their antagonists can emerge as potential cognitive enhancers for the treatment of memory deficiencies associated with neurodegenerative disorders, especially AD. Amyloid-β peptide (Aβ) deposits in AD brain probably cause alterations in cellular signaling pathways that trigger caspase activation, ROS production, excessive glutamate release, sustained rise in intracellular [Ca^{2+}] and ensuing activation of such transcription factors as nuclear factor-κB (NF-κB) [45]. These events eventually culminate in progressive dysfunction and loss of neurons in the limbic and association cortices that underlie deterioration of memory and psychomotor abilities. When administered to Aβ-challenged rat cortical neurons, 5-HT_3 receptor antagonists substantially abated apoptosis, elevation of cytosolic Ca^{2+}, glutamate release, ROS generation and caspase-3 activity. The observed neuroprotective properties were mediated through 5-HT_3 receptor antagonism as they were completely blocked by concurrent treatment with a 5-HT_3 receptor agonist [46]. Alongside, tropisetron, *in vitro*, was

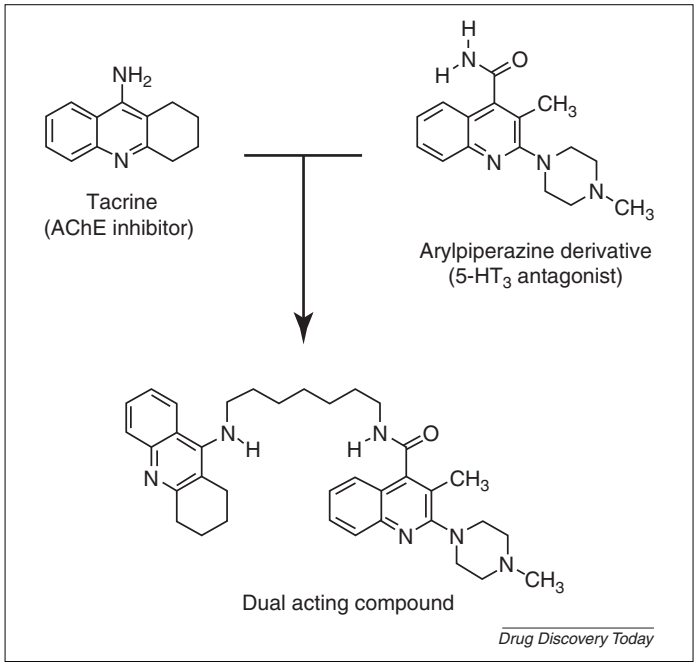

FIGURE 1

Simplified scheme illustrating the innovative synthesis of a high-affinity 5-HT_3 receptor antagonist with potent acetylcholinesterase (AChE) inhibitory activity. This heterobivalent ligand displays a nanomolar affinity for both the 5-HT_3 receptor (*Ki*: 5.6 ± 0.02 nM) and the human AChE (IC50: 4.1 ± 0.6 nM), and a tenfold lower potency in inhibiting butyrylcholinesterase (BuChE, IC50: 40 ± 5.0 nM). To achieve this goal, an optimized 5-HT_3 receptor ligand was conjugated by means of a spacer to tacrine, an AChE inhibitor.
Adapted from Cappelli *et al.*, 2005 [47], where a detailed description of the synthesis can be found.

found to be an efficacious inhibitor of signaling pathway leading to the activation of pro-inflammatory NF-κB, a transcription factor pivotal to the upregulation of several neuroinflammatory mediators in AD brain. This effect, nonetheless, appears to occur independently of 5-HT_3 receptor interaction [20]. Recently, in an attempt to restore the normal cholinergic tone in AD patients, a novel molecule was synthesized which possess both 5-HT_3 receptor blocking and cholinesterase inhibitory properties (Fig. 1) [47]. In light of the aforementioned findings, theoretically these compounds might act synergistically to enhance ACh bioavailability, which is progressively disturbed in the AD brain and meanwhile interfere with the pathological events underlying the neurodegeneration associated with the disorder. Figure 2 summarizes the sites targeted by 5-HT_3 receptor antagonists in AD. The results of a recent study demonstrated that the novel 5-HT_3 antagonist with alpha7 nicotinic acetylcholine receptor (α7nAChR) partial agonist properties, R3487/MEM3454 significantly improved attentional performance in rats. R3487/MEM3454 is currently in Phase 2 clinical trial for the treatment of AD and cognitive impairment associated with schizophrenia [48].

Stroke

Stroke represents a major medical problem in the Western world and the leading cause of permanent disability. Cerebral cortex and hippocampus are the brain regions with highest vulnerability to ischemia. 5-HT_3 receptor antagonists have been shown to prevent oxidative stress-induced injury to rat cortical neurons as evidenced by abolished neuronal apoptotic death, $[Ca^{2+}]i$ elevation, glutamate release, ROS generation and caspase-3 activation. Using selective 5-HT_3 agonists, the authors showed the protection to be mediated by blockade of 5-HT_3 receptors [49]. In rat hippocampal slices, stimulation of 5-HT_3 receptors exacerbated the ischemia-induced decrease in CA_1 field potential, whereas antagonism of the 5-HT_3 receptor produced dose-dependent neuroprotection against the ischemia-induced neuronal injury [50]. However, *in vivo* observations are controversial. We have recently found that tropisetron improves neurological deficits and inflammation in a murine embolic stroke. Interestingly, granisetron did not mimic these beneficial effects. In the same way, co-administration of tropisetron and a selective 5-HT_3 receptor agonist failed to reverse the effects of the former [51]. These findings imply that, contrary to the data *in vitro*, the observed neuroprotection was not a class effect and occurred in a 5-HT_3 receptor-independent manner. Nonetheless, other research described a lack of protection by tropisetron against ischemia and/or reperfusion model of stroke [52]. Such discrepancy might emerge from the differences in the nature of the employed experimental models and doses.

The protection conferred by 5-HT_3 antagonists can be explained as follows: being a ligand gated ion channel, the 5-HT_3 receptor

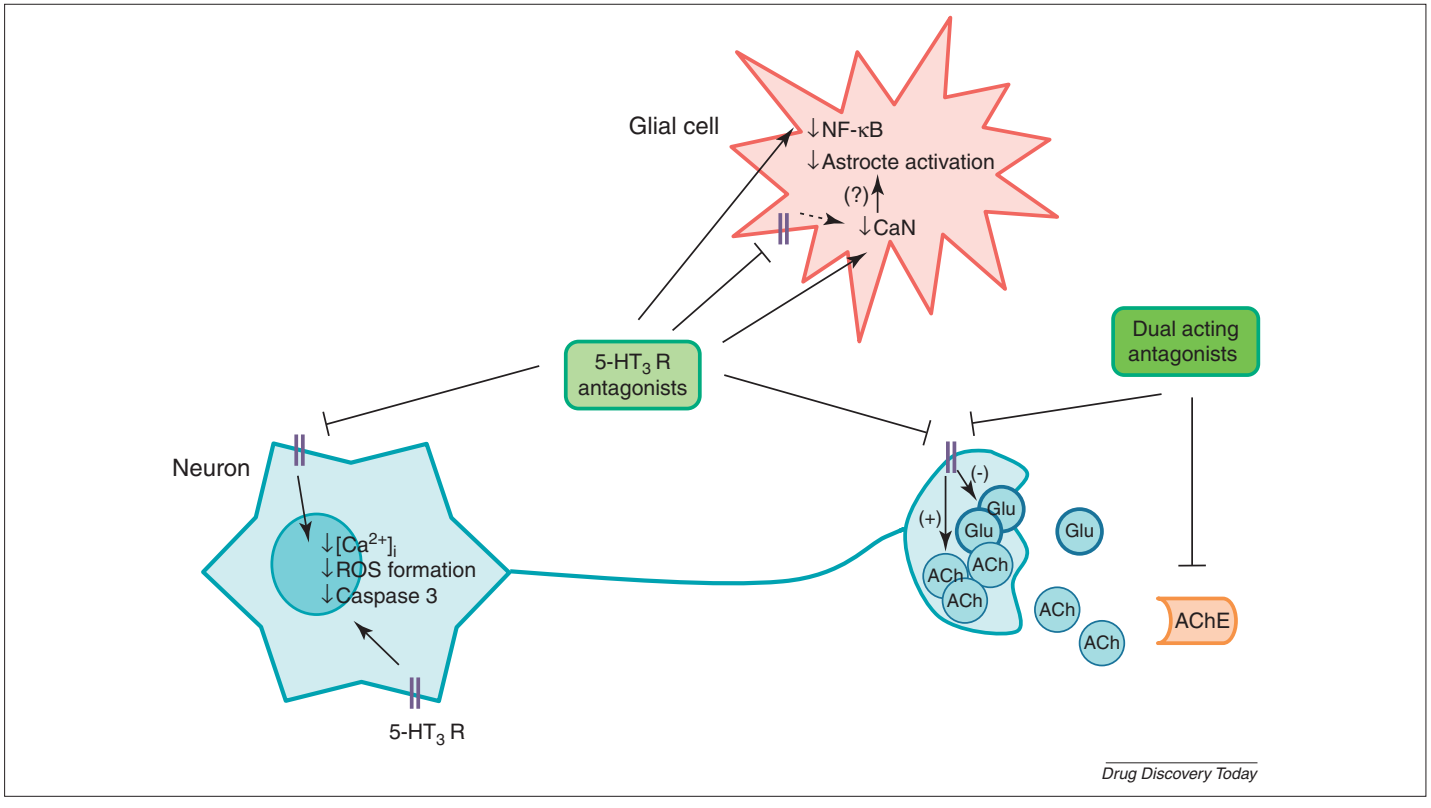

FIGURE 2

Potential sites targeted by 5-HT_3 receptor antagonists in the management of Alzheimer's disease. In neurons, blockade of the 5-HT_3 receptors diminishes intracellular Ca^{2+} concentration ($[Ca^{2+}]i$), decreases the formation of reactive oxygen species (ROS), reduces caspase-3 activity, offsets excitotoxicity by inhibition of glutamate (Glu) release and increases acetylcholine (ACh) release thereby protecting neurons against β amyloid-induced neurotoxicity and ACh deficit. In glia, 5-HT_3 antagonists abate inflammatory cascade through inhibition of nuclear factor-κB (NF-κB) and could inhibit calcineurin (CaN) activity leading to a decrease in astrocyte activation. These effects could take place independent of 5-HT_3 receptor. Dual acting antagonists can confer additional benefit by inhibiting the catalytic site of ACh esterase (AChE) thus amplifying cholinergic enhancing property of plain antagonists.

allows Ca^{2+} influx, leading to Ca^{2+} overload, mitochondrial instability, ROS production and aberrant glutamate release when disproportionately activated. The use of 5-HT_3 antagonists can nullify these events. In case of tropisetron, as mentioned above, in primary cerebellar granule neurons tropisetron elicits a potent inhibitory action on calcineurin activity which does not require the presence of 5-HT_3 receptors [27]. This finding could explain the aptitude of tropisetron to attenuate embolic stroke and potentiate the neuroprotective effects of FK506, a potent immunophilin ligand and calcineurin inhibitor [51]. Tropisetron was also found to be a partial agonist of α7nAChR [53] an essential mediator of the cholinergic anti-inflammatory pathway [54]. The α7nAChR is expressed in a wide spectrum of immune cells, and its activation is shown to inhibit pro-inflammatory cytokine production from macrophages and microglia, adhesion molecule expression and T cell proliferation [55]. *In vivo*, α7nAChR stimulation effectively attenuates immune responses and ameliorated disease severity in various experimental settings [54]. The antiphlogistic potential of the α7nAChR is supposedly mediated by interaction with two crucial signaling routes: inhibition of the transcription factor NF-κB, thereby suppressing inflammatory molecules, and activation of Jak2-STAT3 (signal transducer and activator of transcription) pathway that subsequently induces the expression of anti-inflammatory proteins [55].

Seizure

The part played by 5-HT as an important neurotransmitter in epileptogenesis is drawing attention in the scientific literature. Accumulating evidence suggests that attenuation of serotonergic neurotransmission in the brain induces or amplifies epileptic seizures while augmentation of serotonin activity was found to be anticonvulsant [56]. However, data regarding the role of 5-HT_3 receptor or effects of its selective antagonists on seizure susceptibility is limited. A few case reports have described a proconvulsive proclivity for ondansetron [57] although experimental findings are rather contradictory. In agreement with clinical reports, our group recently demonstrated that granisetron decreased the pentylenetetrazol (PTZ)-induced clonic seizure threshold and that nitric oxide system is somehow involved in the observed effect of granisetron on seizure propensity [58]. 5-HT_3 receptors are expressed in high density on cortical and hippocampal inhibitory interneurons and their activation may result in two opposite effects; one toward increased firing of interneurons and subsequent GABA release, which is anticonvulsant, and another toward increased nitric oxide synthase (NOS) activity, owing to elevation of $[Ca^{2+}]i$, and proconvulsive consequences [58]. Therefore, antagonism at 5-HT_3 receptor theoretically can either provoke or impede seizure development. Nonetheless, given the case reports addressing proconvulsive effect of ondansetron, caution should be exercised when administering these agents until future investigations exactly delineate whether this adverse effect occurs with all 5-HT_3 antagonists in humans and if so, whether it is dose-dependent.

Concluding remarks

A drug discovered to possess one property, when subjected to scrutiny, is often found to have another. 5-HT_3 receptor antagonists, first developed in the mid 1980s, have successfully fulfilled their mission as expeditious agents to offset chemotherapy-induced emesis. Nonetheless, other therapeutic potentials of this class were neglected for a while until recent investigations demonstrated that these compounds drastically improve symptoms associated with fibromyalgia, OA and RA. These promising findings prompted several *in vivo* and *in vitro* studies which, in turn, revealed an array of immunomodulatory and neuroprotective actions. Table 1 exemplifies evidence regarding anti-inflammatory

TABLE 1

Select evidence showing the anti-inflammatory properties of 5-HT_3 antagonists

Compound	Setting investigated	Effect	Refs
Tropisetron	INS-1 cell line	↑Insulin release	[8]
Granisetron	Experimental IBD	↓Colonic levels of TNF-α, IL-1β, IL-6 and MDA, ↓colonic MPO activity, ↓histologic and macroscopic damage score	[17]
Tropisetron	Experimental IBD	↓Colonic levels of TNF-α, IL-1β, IL-6 and MDA, ↓colonic MPO activity, ↓histologic and macroscopic damage score	[16]
Tropisetron, Ondansetron	SEB- or PMA + Io-stimulated human T cells	↓T cell activation	[20]
Tropisetron	SEB-stimulated human T cells	↓IL-2	
	PMA + Io-stimulated Jurkat T cell line	Inhibition of NFAT, AP-1and NF-κB transcriptional activity	[20]
Ondansetron, Tropisetron	Human airway	Blockade of 5-HT-induced contraction	[25]
Tropisetron	Cerebellar granule neurons	Inhibition of calcineurin activity	[27]
Tropisetron, Ondansetron	LPS-stimulated human monocytes	↓TNF-α and IL-1β release	[33]
Tropisetron	Serotonin-stimulated macrophage-like synovial cells	↓PGE_2	[28]
Tropisetron	Osteoarthritis, rheumatoid arthritis	↓Joint swelling and pain	[34]
Granisetron	TMJ arthritis	↓Movement pain	[32]
Tropisetron	Experimental embolic stroke	↓Brain edema and infarct volume, ↓cortical TNF-α and MPO	[51]
Tropisetron	Experimental sepsis	↓IL-6 and noradrenaline	[38]

Abbreviations: MPO, myeloperoxidase activity; TMJ, temporomandibular joint.

effects reported for 5-HT_3 receptor antagonists. The plausible mechanisms can be listed as follows:

(i) Agonism at α7nAChR; these receptors are widely expressed in various immune cells including T cells, B cells, neutrophils and macrophages and their activation triggers anti-inflammatory cascades within cells. Tropisetron is an established agonist of this subset of receptors.

(ii) Decrease in intracellular Ca^{2+} as a result of 5-HT_3 ion channel blockade. This mechanism contributes to the observed neuroprotective aspects of 5-HT_3 receptor antagonists against a variety of neurotoxic stimuli.

(iii) Inhibition of calcineurin phosphatase activity that can underlie the immunomodulatory properties observed with 5-HT_3 receptor antagonists.

(iv) Inhibition of neurogenic inflammation subsequent to 5-HT_3 receptor antagonism which might take part in peripheral and central antiphlogistic effects.

(v) In their structure, some 5-HT_3 receptor antagonists bear indoles and electron-rich aromatic rings, and thus serve as electron-donors, thereby reducing and quenching electrophilic radicals. This property enables them to combat oxidative stress in an inflammatory context.

Moreover, several neuroprotective agents like memantine [59], 17β estradiol and cannabinoids [60] bind the allosteric site and antagonize the 5-HT_3 receptor. It is conceivable that such interaction mediates some therapeutic features of these compounds.

Their low incidence of adverse reactions and a lack of considerable impact on physiological function over wide dose ranges make 5-HT_3 receptor antagonists suitable candidates for use in a variety of peripheral and central inflammatory conditions. They can also serve as a scaffold to develop new pharmacotherapeutics targeting inflammation and neurodegenerative events. The observed bell-shaped dose–response curve of these drugs [5], however, necessitates careful assessment of the doses in which the desired effect is optimal. To date, no immunosuppressive actions have been reported for 5-HT_3 receptor antagonists in humans. The lack of evidence for immnosuppresive effects of 5-HT_3 antagonists might be because the anti-emetic doses do not elicit such effect or that they are concurrently used with chemotherapeutics which *per se* possess immunosuppressive properties [20].

Conflicts of interest

Authors disclose no conflicts of interest.

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