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Review

The neuronal 5-HT_3 receptor network after 20 years of research — Evolving concepts in management of pain and inflammation ☆

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Abstract

The 5-HT_3 receptor is a pentameric ligand-gated cation channel which is found in the central and peripheral nervous system and on extraneuronal locations like lymphocytes, monocytes and fetal tissue. Five monomer subtypes, the 5-$HT_{3A–E}$ subunits, have been identified which show differences in the amino-terminal and the transmembrane region. The functional relevance of different receptor compositions is not yet clarified. 5-HT_3 receptors are located predominantly in CNS regions that are involved in the integration of the vomiting reflex, pain processing, the reward system and anxiety control. The preferential localization on nerve endings is consistent with a physiological role of 5-HT_3 receptors in the control of neurotransmitter release such as dopamine, cholecystokinin, glutamate, acetylcholine, GABA, substance P, or serotonin itself. 5-HT_3-receptor agonists cause unpleasant effects like nausea and anxiety, and no clinical use has been considered. In contrast, the introduction of 5-HT_3-receptor antagonists for chemotherapy-induced vomiting was extremely successful. After development of other gastrointestinal indications like postoperative vomiting and diarrhea-predominant irritable bowel syndrome recent research focuses on rheumatological indications such as fibromyalgia, rheumatoid arthritis and tendinopathies. Positive effects have also been observed for pain syndromes such as chronic neuropathic pain and migraine. These effects seem to be related to substance P-mediated inflammation and hyperalgesia. Furthermore, antiinflammatory and immunomodulatory properties have been observed for 5-HT_3-receptor antagonists which might explain promising findings in systemic sclerosis and other immunological conditions. For all of these innovative indications the optimal dosing schedule is a crucial issue, since a bell-shaped dose–response curve has been observed repeatedly for 5-HT_3-receptor antagonists, particularly in CNS effects.

Keywords: 5-HT_3 receptor; 5-HT_3-receptor antagonist; Tropisetron; Ondansetron; Pain; Immunomodulation

Contents

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1. Introduction

20 years after the first characterization of a so-called selective 5-HT_3-antagonist the time has come to re-examine the acknowledged concepts and rate critically new perspectives for this compound class.

In the early 1990s the introduction of 5-HT_3-receptor antagonists into the market was perceived as a tremendous step forward to combat chemotherapy-induced emesis. This great success transiently dampened the attention to other treatment areas like psychiatric diseases and pain management where clinical development of these compounds originally had started. During the last years researchers increasingly turned back to the beginnings, encouraged by promising results in challenging indications like fibromyalgia and irritable bowel syndrome.

This review focuses on recent investigations on the pharmacology of the 5-HT_3 receptor with its embedding in a complex neurotransmitter network and the recently emerging promising indications for 5-HT_3-receptor antagonists.

2. The 5-HT_3 receptor

2.1. Structure

Among the seven known classes of serotonin receptors the 5-HT_3 receptor occupies a special place: it is phylogenetically much older than the other serotonin receptors, all of which have developed from a single primordial 5-HT receptor and belong to the G-protein coupled receptors. In contrast, the 5-HT_3 receptor is a ligand-gated cation channel belonging to the nicotine/gamma-amino-butyrate (GABA) receptor super-family, and it shares structural and functional features with other members of this receptor group which are not observed for the other serotonin receptors.

The 5-HT_3 receptor is a pentamer consisting of five monomers which form a centrally permeable cylindrical body that can be readily penetrated by small cations (Fig. 1). Five monomer subtypes, the 5-$HT_{3A–E}$ subunits, have been identified which show differences in the amino-terminal and the transmembrane region. Functional homomeric 5-HT_{3A} receptors and heteromeric 5-$HT_{3A/B}$ receptors are expressed neuronally (Morales et al., 2001), which show a 40-fold difference between the single-channel conductances and different Hill coefficients for agonist action, possibly due to structural differences at the interfaces between the extracellular domains of the subunits (Barrera et al., 2005). 5-HT_{3B} and 5-HT_{3c} subunits alone are not able to assemble into complete receptors (Boyd et al., 2002). The recently identified D- and the E-subunits are not yet characterized with respect to their functional significance. According to preliminary results they are expressed only in the peripheral nervous system (Niesler et al., 2003). Picrotoxin may serve as a useful probe for differentiating homomeric vs. heteromeric 5-HT3 receptors due to different inhibitory effects in both receptor types. In whole-cell patch clamp recordings, the inhibitory effect of picrotoxin was reduced 100-fold in heteromeric mouse 5-$HT_{3A/3B}$ receptors, compared to homomeric 5-HT_{3A} receptors (Das and Dillon, 2003).

Homomeric and heteromeric 5-HT_3 receptors show clearly differing biophysical and pharmacological properties. Co-expression of the 5-HT_{3B} subunit alters receptor desensitization and deactivation and reduces the sensitivity for serotonin (Hapfelmeier et al., 2003). Heteromeric 5-$HT3_{AB}$ complexes are characterized by a large single-channel conductance of 16 pS (5-HT_{3A} monomers: <1 pS), a low permeability to calcium ions and a distinctive current–voltage relationship which resembles the one of characterized neuronal channels. The functional relevance of these differences is not yet clarified.

2.2. Localization and function

5-HT_3 receptors have been detected on mononuclear cells, lymphocytes and intestinal enterochromaffine cells and are

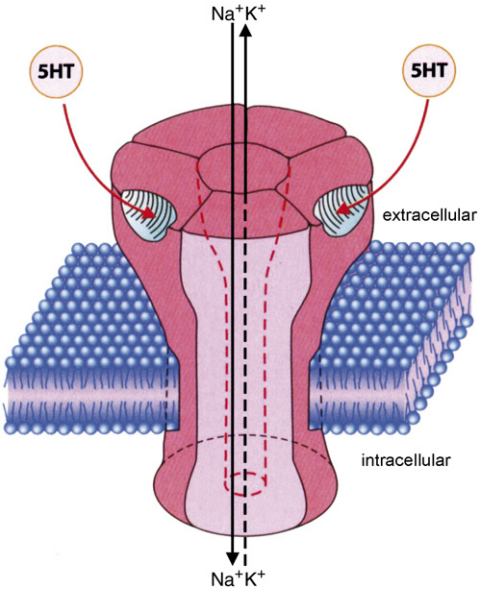

Fig. 1. The pentameric structure of the 5-HT_3 receptor (Teitler and Herrick-Davis, 1994).

present on peripheral and central neurons. In the periphery 5-HT_3 receptors have been detected on pre- and postganglionic autonomic neurons and on neurons of the sensory and enteric nervous system (myenteric and submucosal plexus). A high density of 5-HT_3 receptors (although still low compared to other serotonin receptors) has been found at the following central nervous system (CNS) localizations (mostly on GABAergic neurons): area postrema, nucleus tractus solitarii, nucleus dorsalis nervi vagi, nucleus caudatus, nucleus accumbens, amygdala, hippocampus, entorhinal cortex, frontal cortex, cingulate cortex, and dorsal horn ganglia (Kranzler et al., 2003; Tecott et al., 1993). The receptors are thus concentrated in regions that are involved, among other processes, in integration of the vomiting reflex, pain processing, the reward system and anxiety control. Peripheral receptors play a role in the regulation of autonomic functions and sensory transmission.

5-HT_3 receptors are found in the brain predominantly in presynaptic regions associated with axons and nerve terminals (70–80%) except in the hippocampus, where they are mostly postsynaptic receptors located on somatodendritic regions (Miquel et al., 2002). The preferential localization on nerve endings is consistent with a physiological role of 5-HT_3 receptors in the control of neurotransmitter release. On the molecular level activation of presynaptic 5-HT_3 receptors followed by rapid depolarization of the peripheral or central neuron causes a rapid rise in cytosolic Ca^{2+} concentration by inducing calcium influx and mobilization of intracellular calcium stores, as well as modulating the release of various neurotransmitters and neuropeptides such as dopamine, cholecystokinin, glutamate, acetylcholine, GABA, substance P or serotonin itself (Greenshaw and Silverstone, 1997; Funahashi et al., 2004). Postsynaptic activation leads to depolarization by Na^+- and K^+-influx (Ronde and Nichols, 1998).

The activation status of the 5-HT_3 receptor is influenced by multiple factors which are probably only in part identified at present. The activation of 5-HT_2 receptors can exert an enhancing effect on the function of coexistent 5-HT_3 receptors (Hu et al., 2004). As for other fast ligand-gated ion channels the 5-HT_3 receptor is a target for ethanol and volatile anesthetics which potentiate its activation (Lovinger et al., 2000; Suzuki et al., 2002). Furthermore, protein kinase C activation can enhance surface immunolabeling and surface expression of 5-HT_{3A} receptors in concordance with observations on PKC regulation of NMDA and $GABA_A$ receptor trafficking (Sun et al., 2003).

3. 5-HT_3-receptor ligands — is receptor selectivity of 'setrons' an outdated concept?

Application of 5-HT_3-receptor agonists like 2-methyl-5-hydroxytryptamine and meta-chlorophenylbiguanide (mCPBG) causes unfavourable effects like nausea and anxiety. No clinical use is targeted at present.

Six 5-HT_3-receptor antagonists are currently available on the market (further compounds are in the pipeline): tropisetron, ondansetron, granisetron, dolasetron, palonosetron and alosetron. All of these are highly potent compounds which can induce complete competitive blockade of peripheral and central 5-HT_3 receptors. Animal studies have produced evidence of species- and tissue-specific differences in the binding behaviour of the various 5-HT_3 receptor antagonists, such as a lack of binding of ondansetron to 5-HT_3 autoreceptors on enterochromaffine cells in contrast to tropisetron (Gebauer et al., 1993). It is uncertain whether these differences are clinically relevant.

At their introduction to the market the 5-HT_3-receptor antagonists were characterized as highly selective compounds with no relevant action on others than 5-HT_3 receptors. Indeed, at the beginning of the 90s this classification was correct with respect to the actually known pharmacological properties. Later molecular biological studies showed that 5-HT_3 receptors exhibit significant homologies to other ligand-gated pentameric ion channels. Tropisetron has been shown to act as partial agonist on α_7-nicotinic receptors while ondansetron had an antagonizing effect (Macor et al., 2001; Papke et al., 2005). On $\alpha_9\alpha_{10}$-nicotinic receptors the concentrations of the 5-HT_3-receptor antagonists tropisetron, ondansetron and MDL72222 needed for blocking ACh-induced currents were in the same order of magnitude as those observed for 5-HT_3 receptors (Rothlin et al., 2003). Especially the latter observation poses fundamentally into the question the formerly postulated "selective" mode of action of "5-HT_3"-receptor antagonists.

The clinical significance of these effects remains completely unclarified at present. Nevertheless, the possible involvement of other than 5-HT_3 receptors is underlined by the observation of Libert et al. (2004) that the acetaminophen-induced antinociceptive action involves a spinal tropisetron (not ondansetron and granisetron)-sensitive receptor that is not the 5-HT_3 receptor.

4. New perspectives in clinical use of 5-HT_3-receptor antagonists

Blockade of the 5-HT_3 receptors in animal models does not modify normal behavioural patterns, and the only changes observed in physiological functions in healthy volunteers are a certain prolongation of intestinal transit time and discrete, clinically insignificant changes in cardiac conduction, but no evidence of particular CNS effects.

In certain pathological conditions, however, central and/or peripheral 5-HT_3-receptor blockade has very pronounced effects. Significance of 5-HT_3-receptor stimulation in gastrointestinal motility and secretion and related effects of 5-HT_3-receptor antagonists in situations characterized by massive release of serotonin from the enterochromaffine cells, such as chemotherapy-induced emesis, have been reviewed extensively elsewhere and will be excluded from this overview which focuses on recent results for the use of 5-HT_3-receptor antagonists in inflammatory and CNS-related conditions.

4.1. Psychiatric indications

4.1.1. Anxiety

Serotonergic neurotransmission in prefrontal cortex plays a key role in regulating emotion and cognition under normal and pathological conditions.

Increased availability of 5-HT on 5-HT_2 and 5-HT_3 receptors increases anxiety (Bell and Gilmore, 2003) and is probably at least in part responsible for anxiogenic-like effects of antidepressants while 5-HT_3-receptor blockade has anxiolytic effects (Lecrubier et al., 1993). Both hippocampal and accumbens 5-HT_3 receptors seem to contribute to the anxiolytic-like effects of 5-HT_3-receptor antagonists. It also appears that this effect of 5-HT_3-receptor antagonists is related to their action on postsynaptic 5-HT_3 receptors within the nucleus accumbens, and depends on the functional state of the 5-HT innervation ascending from the raphe nuclei. The role of presynaptic 5-HT_3 receptors in this field is not yet clear. The 5-HT_3-receptor antagonist tropisetron was reported to reduce GABAergic synaptic transmission (Turner et al., 2004) while classical anxiolytics act as direct GABA agonists and/or as potentiators of GABA.

4.1.2. Drug addiction

5-HT_3-receptor antagonists influence the 'reward pathway': they have been shown to attenuate drug (e.g. high-dose morphine, cocaine) induced increases in mesolimbic dopamine, locomotor activation, aggression-stimulating effects and self-administration of drugs like ethanol and cocaine in rats (Ricci et al., 2005). Basal dopamine release and basal aggression levels seem not to be affected. On the other hand, ondansetron potentiated the methamphetamine-induced hyperactivity in rats (Ginawi et al., 2004). In humans, ondansetron has been shown to reduce alcohol intake and alcohol related problems in early onset alcoholism (Ait-Daoud and Johnson, 2002).

4.1.3. Cognitive functions

5-HT_3-receptor antagonists inhibit serotonergically stimulated release of acetylcholine in the cortex and the dorsal hippocampus, while basal acetylcholine release remains unaffected. Both the cortex and hippocampus are important structures for memory function, and ondansetron in dosages of 0.25 and 1 mg/d was indeed found to improve memory performance in elderly patients >50 years in a placebo-controlled study (Preston, 1994).

4.1.4. Schizophrenia

The role of 5-HT_3-receptor antagonists in schizophrenia is not yet finally clear. Serotonin modulates the activity of mesolimbic and nigrostriatal dopaminergic pathways via 5-HT_3 receptors, and 5-HT_3-receptor antagonists are known to decrease hyperactivity of dopaminergic neurons. However, this effect underlies a bell-shaped dose–response curve, as was demonstrated in rats (Ashby et al., 1994). Although results of clinical trials with 5-HT_3-receptor antagonists in schizophrenia were not favourable (Meltzer, 1991), it cannot be excluded that wrong doses were chosen for this indication. Interestingly, several neuroleptics and antidepressants have been shown to block the 5-HT_3 receptor in a non-competitive manner, possibly via interaction with the receptor–lipid interface (Eisensamer et al., 2003, 2005; Rammes et al., 2004). Since these effects were observed in tissue concentrations achievable in vivo they might contribute to the clinical effects of those compounds.

4.1.5. Satiety control

Preclinical data point to an important role of 5-HT_3 receptors in regulation of food intake. Within-meal anorectic signals include gastric distension, intraintestinal nutrients, and release of gut peptides including cholecystokinin and serotonin. It has been shown that the suppression of food intake by peripheral serotonin release is mediated via 5-HT_3 receptors. Cholecystokinin (CCK) and peripheral serotonin suppress food intake synergistically, and blockade of 5-HT_3 receptors attenuates the effect of CCK on food intake in combination with gastric distension (Hayes and Covasa, 2006). Methamphetamine-induced anorexia in mice is antagonized by 5-HT_3-receptor blockade (Ginawi et al., 2005). Moreover, central 5-HT_3 receptors are involved in the regulation of blood glucose levels (Carvalho et al., 2005). The relevance of these pharmacological effects for the use of 5-HT_3-receptor antagonists in humans has not yet been elucidated.

4.2. Pain syndromes

Peripheral and central 5-HT_3 receptors located on primary nociceptive afferences in the dorsal horn as well as in the monoaminergic descending inhibitory system, in certain brain regions involved in pain modulation, and on peripheral nerve endings and autonomic afferences play an essential role in spinal pain transmission and endogenous pain suppression. Their function in this context has still not been satisfactorily explained, and studies have yielded partly contradictory results.

The stimulation of spinal 5-HT_3 receptors in the dorsal horn has antinociceptive activity in acute pain models, probably via release of GABA and activation of the descending inhibitory system. This antinociceptive effect is abolished by administration of 5-HT_3-receptor antagonists. For example, pain reactions to thermal stimuli and to intrathecally administered substance P and *N*-methyl-D-aspartate were reduced by 5-HT_3-receptor agonists (Alhaider et al., 1991), and pain relief by electroacupuncture in animal models was blocked by 5-HT_3-receptor antagonists (Tagaki and Yonehara, 1998). The analgesic effect of paracetamol was also supposed to be associated with stimulation of 5-HT_3 receptors, since the antinociceptive effect of paracetamol was inhibited by intrathecal administration of tropisetron (Pelissier et al., 1995). However, recent studies revealed that this effect cannot be reproduced with other 'setrons' and accordingly cannot be attributed to 5-HT_3-receptor blockade (Libert et al., 2004).

On the other hand, contrasting results with increased responsiveness of dorsal horn neurons to noxious stimulation after injection of the 5-HT_3-receptor agonist mCPBG (0.02–0.2 nmol) and reduction of neuronal nociceptive reactions to thermal stimuli by 5-HT_3-receptor antagonists have been published (Ali et al., 1996).

Studies in 5-HT_{3A}-knock out mice lead the authors to the interpretation that 5-HT_3 receptors are not involved in acute pain. They observed a significant reduction of the second-phase behaviour in the formalin test intrathecal administration of a 5-HT_3-receptor antagonist. The antagonist did not alter nociceptive thresholds when it was administered alone, i.e., in the absence of ongoing injury. The authors concluded that, for involvement of 5-HT_3 receptors, spinal cord levels of serotonin

must be increased under conditions of injury and presumably of pain (Zeitz et al., 2002).

Pain-inhibiting effects of 5-HT_3-receptor antagonists seem to be related to substance P-mediated inflammation and hyperalgesia, especially in chronic pain. Substance P is known to have a dual effect on nociception (Oehme et al., 1980). Intracerebrovascular application of low doses causes analgesia, possibly by release of endogenous opioid peptides, while the application of higher doses stimulates the neural activity in nociceptive pathways. Indeed, tachykinin NK_1-receptor antagonists cause analgesia at high doses which also lead to muscle weakness. Elimination of tachykinin NK_1-receptors prevents the increase in the magnitude and duration of response to stimuli (wind-up) of spinal cord neuronal activity due to repetitive pain stimuli (Herrero et al., 2000).

Tachykinin NK_1-receptors are expressed in the same regions of the central and peripheral nervous system as 5-HT_3-receptors which points to a close functional relationship of the both transmitters, e.g. in the spinal horn (Conte et al., 2005). This concept is further underlined by the observation that 5-HT_3-receptor antagonists have been shown to inhibit the stimulated release of substance P, neurokinin A and calcitonin gene-related peptide from primary afferents (Saria et al., 1990) and to prevent unmasking of autonomous tachykinin NK_2-receptors (Moore et al., 2002).

Substance P-related pain modulation is supposed to be at least one of the mechanisms responsible for beneficial effects of 5-HT_3-receptor antagonists in fibromyalgia (Faerber et al., 2001; Mueller and Stratz, 2001). Treatment responders show higher substance P levels in blood than non-responders, and levels in responders decrease during treatment with 5-HT_3-receptor antagonists while in non-responders substance P remains unchanged (Stratz et al., 2004).

This concept is compatible also with positive outcomes in other pain syndromes, e.g. migraine (Loisy et al., 1985; Couturier et al., 1991). Chronic neuropathic pain is also improved with 5-HT_3-receptor antagonists (McCleane et al., 2003). The involvement of peripheral 5-HT_3-receptors on sensory nerve endings has been demonstrated by antagonism of pain and vasodilatation by intracutaneously injected serotonin or capsaicin and of experimentally induced inflammatory pain on topical as well as on systemic administration. Mueller and Stratz (2004) used tropisetron very successfully for local treatment of rheumatoid arthritis, tendinopathies, peri-arthropathies, and myofascial pain syndrome and found a long-lasting analgesic and an antiphlogistic effect. In double-blind studies in patients with tendinopathies the effect of tropisetron lasted much longer than with prilocain, and compared to local infiltration with dexamethason + lidocain it was comparably good. Although no significant antipruritic effect was found in a clinical experimental study in haemodialysis patients (Weisshaar et al., 2004), there are several reports on efficacy of systemic 5-HT_3-receptor antagonists in biliary, uremic and other forms of pruritus (Schumann and Hudcova, 2004). Since capsaicin, a substance P depletor, has also an antipruritic effect, the substance P-blockade must be taken into consideration in this observation, too.

Not only somatic pain, but also visceral hypersensitivity in irritable bowel syndrome is positively influenced by 5-HT_3-receptor antagonists. In animal experiments, colonic distension leads to enhanced c-fos expression in diverse brain nuclei, among these the rostral ventrolateral medulla and the nucleus tractus solitarii. Pretreatment with granisetron significantly reduced the number of cells with c-fos activation in the nucleus tractus solitarii by 40% (Moennikes et al., 2003). In humans with irritable bowel syndrome, increased cerebral blood flow in amygdala, hippocampus and orbitofrontal cortex induced by painful colonic distension is reduced with 5-HT_3-antagonists (Mayer et al., 2002). Symptom improvement due to alosetron treatment is significantly correlated with regional blood flow decreases in the 5-HT_3-receptor-rich amygdala, ventral striatum, and dorsal pons (Berman et al., 2002). Gender-specific differences in response may be related to different central processing of visceral pain in males and females.

Chronic heart pain resulting from ischemia is probably transmitted via capsaicin sensitive C-fibers. Since capsaicin is known to induce a release of substance P and 5-HT_3-receptor antagonists inhibit this release, the use of 5-HT_3-receptor antagonists in chronic cardiac pain is discussed in view of the proven serotonin release from platelets in coronary arteries with endothelial damage (Miller et al., 1993; Feyer et al., 1998). In some patients with complex coronary artery lesions, the transcardiac serotonin concentration was permanently increased (Alon and Biro, 1996).

Overall, the experimental and clinical findings relating to the effect of stimulation or blockade of 5-HT_3 receptors on nociception lead to the impression that 5-HT_3-receptor antagonism is useful in situations linked to inflammatory stimuli and altered pain perception in chronic pain. Some discrepant observations are not surprising considering the general complexity of serotonin mediated reactions. In exploration and interpretation of isolated effects it must not be neglected that serotoninergic projections represent the most extensive neurotransmitter network at all. A study with ondansetron in bulimia patients, for example, demonstrated not only a normalization of the elevated pain threshold but also a reduction of binge/vomit episodes (Faris et al., 1998). The therapeutic effects in fibromyalgia include not only pain reduction but also an improvement of various autonomic/functional symptoms (Kohnen et al., 2004). 5-HT_3-receptor antagonists have also shown to be useful in chronic fatigue syndrome (Spaeth et al., 2000; Piche et al., 2005). Investigating the still unexplained mechanisms underlying these effects is a task for the future.

4.3. Immunomodulation

An important step into this direction may be the recent observation of antiinflammatory and immune modulatory properties of 5-HT_3-receptor antagonists which have been demonstrated in vitro and in vivo (Fiebich et al., 2004; Seidel et al., 2004; Schneider et al., 2004; De la Vega et al., 2005). Tropisetron was found to inhibit lipopolysaccharide-stimulated secretion of tumor necrosis factor-α and interleukin-1β in monocytes and serotonin-induced prostaglandin E_2 release from synovial cells, it inhibits calcineurin-induced T-cell activation and modulates Th_1 cytokines in patients with musculoskeletal diseases who responded to the treatment.

The relevance of these results is underlined by the exciting observation that two patients with systemic sclerosis who were treated with tropisetron for a secondary fibromyalgia syndrome showed a clear clinical improvement with respect to skin score, movability of joints and pain reduction (Stratz and Mueller, 2004). Furthermore, in osteoarthritis the effect of an intra-articular injection was similar for tropisetron and methylprednisolone (Samborski et al., 2004).

4.4. An unresolved issue: the optimal dosing schedule

Although data have been collected in manyfold conditions as described above no efforts are made yet by pharmaceutical companies to apply for new indications. No results of large phase III trials proving hypotheses emerging from pilot studies in the new indications have been published. Registered indications for 5-HT_3-receptor antagonists still are restricted to chemotherapy-induced, radiation-induced or postoperative nausea and vomiting and diarrhea-predominant irritable bowel syndrome. Development was stopped in several indications, e.g. anxiety and migraine, because 5-HT_3-receptor antagonists as single therapy were assumed not to be able to compete with established therapeutic principles. It cannot be excluded that good opportunities may have been missed in this way. Bell-shaped dose–response curves have repeatedly been observed for central nervous effects of 5-HT_3-receptor antagonists both in preclinical and clinical studies, e.g. in treatment of anxiety, migraine, alcohol consumption and fibromyalgia. Evidence of this activity pattern is sometimes already observed in a very low dose range. Whether this is due to a group-specific characteristic or special pharmacological features of individual compounds is still obscure. For agonists at ion channels, a response of this type can be attributed to rapid receptor desensitization; e.g. for mCPBG a bell-shaped dose–response curve is observed at the 5-HT_3 receptor in vitro (Hapfelmeier et al., 2003). As regards the 5-HT_3-receptor antagonists, the underlying mechanism has not been defined. There are no hints for relevant differences in the affinity of 5-HT_3-receptor antagonists for peripheral and central nervous receptors (Pinkus et al., 1990; Ito et al., 1995) which might e.g. cause dose-dependent prevailing of central or peripheral effects.

Several causes contributing to a bell-shaped dose–response curve must be considered. A steric hindrance at the receptor binding site might occur at higher drug concentrations in the intercellular space. Antagonists might act differently at 5-HT_{3A} and 5-$HT3_{AB}$ receptors as it was observed for agonists which showed different desensitization patterns in homomeric 5-HT_{3A} and heteromeric 5-HT_{3AB} receptors (Hapfelmeier et al., 2003).

If 5-HT_3-receptor densities and/or composition differ in various neuronal systems, one type could be inhibited at low, and the others only at higher concentrations of 5-HT_3-receptor antagonists, resulting in different effects. Similar situations could apply for secondary neurotransmitters/peptides exhibiting different concentration-dependent effects as described for substance P. According to calculations by Yamada et al. (2004), which were based on pharmacokinetic and pharmacodynamic parameters, the receptor occupancy correlates to the applied dosage and varies considerably after oral application of standard doses of 5-HT_3-receptor antagonists. While for intravenous standard doses receptor occupancy was calculated as >85% in 3 of 4 tested compounds, they predicted for oral application values of 49.5% (ondansetron 4 mg/d) to 97% (azasetron 10 mg/d) receptor occupancy at steady state. For tropisetron 5 mg/d a relatively high receptor occupancy of 78% was calculated.

5-HT_3-receptor antagonists are usually administered in fixed doses. This proceeding is obviously adequate for those indications where peripheral effects dominate and a linear dose–effect curve is observed, e.g. in conditions caused by massive serotonin release. In chemotherapy-induced emesis no decline of efficacy has been observed with higher doses. Also the incidence and severity of obstipation as a clearly peripheral effect increases steadily with higher doses. It should be considered that the daily oral dose of 5 mg tropisetron, which was tested e.g. in fibromyalgia, may not represent the optimal choice in all cases.

Possibly, individual dose titrations instead of a fixed dose regimen might be a more appropriate strategy to achieve optimal results with 5-HT_3-receptor antagonists in central nervous system (CNS)-related indications.

Besides a different dose–response curve also the gradual onset of efficacy in CNS-related diseases contrasts with the experience in nausea and emesis. Intake over several weeks is necessary to achieve optimal results. Virtually no information exists on adaptive changes in neuronal functions caused by chronic 5-HT_3-receptor blockade as they have been described for antidepressives and neuroleptics. E.g. down-regulation of receptors on the cell surface, changes in receptor sensitivity and altered expression of gene products belong to the effects that must be considered in this context and should be explored.

5. Conclusion

The synthesis of 5-HT_3-receptor antagonists 20 years ago resulted in a milestone in supportive cancer therapy since chemotherapy-induced emesis was suppressed far more effectively than with any other drug. The dominating idea at that time was that of a highly selective compound class with mainly gastrointestinal effects. During the last two decades it has been replaced by a concept of drugs which interfere with complex central nervous processes, which show immunomodulatory functions and which exhibit unexpected pharmacodynamic properties. Preliminary results in musculoskeletal diseases possibly open the door to an innovative, unconventional approach in treatment of inflammatory and autoimmune diseases. Indeed, it seems that there are more open questions on 5-HT_3 receptors and their ligands than were 20 years ago. Future research should concentrate on further clarification of possible immunomodulatory and neuromodulatory effects, optimal dosing schedules in new indications and effects of innovative drug combinations.

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