Review: The auspicious role of the 5-HT3 receptor in depression: a probable neuronal target?

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Abstract

The serotonergic mechanisms have been successfully utilized by the majority of antidepressant drug discovery programmes, while the search for newer targets remains persistent. The present review focused on the serotonin type-3 receptor, the only ion channel subtype in the serotonin family. Behavioural, neurochemical, electrophysiological and molecular analyses, including the results from our laboratory, provided substantial evidence that rationalizes the correlation between serotonin type-3 receptor modulation and rodent depressive-like behaviour. Nevertheless, the reports on polymorphism of serotonin type-3 receptor genes and data from clinical studies (on serotonin type-3 receptor antagonists) were insufficient to corroborate the involvement of this receptor in the neurobiology of depression. The preclinical and clinical studies that have contradicted the antidepressant-like effects of serotonin type-3 receptor antagonists and the reasons underlying such disagreement were discussed. Finally, this critical review commended the serotonin type-3 receptor as a candidate neuronal antidepressant drug target.

Keywords

serotonin type-3 receptor, depression, antagonist, postsynaptic, behaviour

Introduction

The serotonin or 5-hydroxytryptamine (5-HT) neurotransmission system constituted by its 14 (groups 5-$HT_{1–7}$) receptors (Hoyer et al., 2002) and their downstream targets has been the platform for many drug discovery programmes targeting various neuropsychiatric conditions, especially depression. Proclaimed as the 'phylogenetically oldest receptor', the 5-HT_3 receptor is the only ligand-gated ion channel (LGIC) subtype among the serotonin receptor family which inherently influences membrane depolarization and neuronal excitation. This receptor was first identified in the guinea pig ileum as the 'M receptor', named after the antagonist morphine, which blocked the 5-HT-induced contractions (Gaddum and Picarelli, 1957). In 1986, a framework was proposed to resolve the controversy regarding the classification and nomenclature of functional receptors for 5-HT in the central nervous system (CNS). As a consequence, the M receptor was renamed as the 5-HT_3 receptor (Bradley et al., 1986). However, up to that point, radioligand-binding studies specifically targeting the 5-HT_3 receptor in brain tissue had not been published. The activation of the 5-HT_3 receptor facilitates influx of sodium/potassium/calcium ions due to the channel opening (Brown et al., 1998; Jackson and Yakel, 1995; Livesey et al., 2008; Rammes et al., 2004), followed by a characteristic and rapid desensitization (Hoyer, 1990; Jackson and Yakel, 1995). The subcellular localization of 5-HT_3 receptors dictate their function; presynaptic and somatodendritic 5-HT_3 receptors control neurotransmitter release, while the postsynaptic subtype mediates rapid ionotropic neurotransmission (Barnes and Sharp, 1999; Peters and Lambert, 1989; Peters et al., 1992).

The abundance of 5-HT_3 receptors in the chemoreceptor triggering zone (CTZ) has qualified them as primary targets for antinauseants/antiemetics (Haus et al., 2004; Mahesh et al., 2005). Selective 5-HT_3 receptor antagonists, for example, ondansetron, tropisetron and zatosetron are now recognized as drugs of choice in managing cancer chemotherapy-induced and postoperative nausea and vomiting. The encouraging results from preliminary behavioural tests on 5-HT_3 receptor antagonists, their excellent safety profile and the complementary effectual regional distribution of 5-HT_3 receptors in the CNS have urged further research to establish their potential usage in a range of CNS disorders (for reviews, see Bloom and Morales, 1998; Costall and Naylor, 2004; Färber et al., 2004; Greenshaw, 1993; Thompson and Lummis, 2007; Wilde and Markham, 1996; Wolf, 2000). The research so far suggests: (i) the localization of 5-HT_3 receptors in limbic regions of the rodent and human brain; (ii) the antidepressant-like effects of some of the 5-HT_3 receptor antagonists in rodent behavioural assays and pilot human trials; (iii) the 5-HT_3 receptor antagonistic property of antidepressants; and

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(iv) the genetic association of the 5-HT_3 receptor with bipolar disorder. This sparked a compilation of the first comprehensive review, aimed at revealing the association of 5-HT_3 receptor modulation with depression.

The 5-HT_3 receptor

Structure

The 5-HT_3 receptor defines an excitatory, fast activating, LGIC channel and shares a similar structure with the cys-loop family of receptors, along with gamma aminobutyric acid (GABA), glycine and nicotinic acetylcholine receptor (nAChR). The protein structure and signal transduction mechanisms resemble (by rule) the nAChR (Maricq et al., 1991). This receptor has a pentameric quaternary structure (Boess et al., 1995) and its ligand-binding site is formed by the convergence of β-sheets (Thompson et al., 2005; Yan et al., 1999). The receptor occurs in both homo (3A) and hetero (3A and 3B) forms. The 5-HT_{3A} subunit by itself functions as a homooligomeric receptor when expressed in cell cultures (Belelli et al., 1995; Gilon and Yakel, 1995; Green et al., 1995), resembling the native 5-HT_3 receptor in its pharmacological and electrophysiological properties (Maricq et al., 1991). In rodents, two alternatively spliced isoforms of the 5-HT_{3A} receptor are expressed, namely the long 5-HT_3-A_L variant and the short 5-HT_3-A_S variant (Hope et al., 1993). The latter, prevalent in the CNS (Doucet et al., 2000; Miquel et al., 1995), is deficient in an extra stretch of 5–6 amino acids (five amino acids in rats and guinea pigs and six amino acids in mice) in the intracellular loop domain of the long 5-HT_3-A_L variant (Isenberg et al., 1993; Lankiewicz et al., 1998; Miquel et al., 1995; Werner et al., 1994). Analogously, truncated (h5-HT_{3AT}, 238 amino acids) and long (h5-HT_{3AL}, 510 amino acids) splice variants are expressed in humans (Brüss et al., 1998, 2000). In cell lines, the heteromeric assemblies of both the 5-HT_{3AT} and 5-HT_{3AL} combine individually with the h5-HT_{3A} subunit (coexpressed in the amygdala and hippocampus), to display higher and lower 5-HT-induced cation fluxes, respectively, as compared with homomeric 5-HT_{3A} receptors (Brüss et al., 2000). Hence the splice variants, although not functional as homomeric units, contribute to the functional diversity of 5-HT_3 receptors (Brüss et al., 2000). The low single channel conductance of the homomeric 5-HT_{3A} receptor in comparison with the native form (Fletcher and Barnes, 1998), has led to the identification of the 5-HT_{3B} subunit, which is not functional as a homomeric unit (Davies et al., 1999; Dubin et al., 1999). Coexpressed with 5-HT_{3A}, the 5-HT_{3B} subunit forms a heteromeric complex (Davies et al., 1999; Dubin et al., 1999; Miyake et al., 1995) as identified in the human hippocampus (Brady et al., 2007). Reports indicate significant expression of the 5-HT_{3B} subunit in the human brain (Davies et al., 1999; Dubin et al., 1999; Niesler et al., 2003; Tzvetkov et al., 2007), while it is meagre/absent in the rodent brain (Morales and Wang, 2002; Sudweeks et al., 2002), underlining the interspecies heterogeneity of 5-HT_3 receptor distribution. Furthermore, two brain-specific transcripts (unofficially named BT-1 and BT-2) of the 5-HT_{3B} subunit have been identified (Tzvetkov et al., 2007). The translated proteins from these transcripts have not been characterized in the brain making their (patho)physiological roles unpredictable. The cloning of the 5-HT_{3B} subunit, one of the determinants of receptor function, provides greater scope for drug development (Davies et al., 1999; Jensen et al., 2008). The newer subunits namely 5-$HT_{3C, 3D, 3E}$ have been characterized recently, however, their function (*in vivo*) has yet to be resolved (Barnes et al., 2009; Jensen et al., 2008; Niesler et al., 2003, 2007).

Regional distribution

The behavioural effects of selective 5-HT_3 receptor antagonists (Peroutka, 1988a; Richardson and Engel, 1986; Richardson et al., 1985) in rodents and primates (Costall et al., 1987a, b; Hagan et al., 1987) have inspired several studies to establish the distribution of 5-HT_3 receptors in the brain. Given that the distribution of both peripheral and central 5-HT_3 receptors in rodents and humans is so well characterized (Boess and Martin, 1994; Morales et al., 1998; Tecott et al., 1993), the precise localization of the receptor can aid in the understanding of 5-HT_3 ligand-induced behaviour. This section gives a synopsis of pertinent reports on the distribution of 5-HT_3 receptors in certain species of prime interest. In rats, the preliminary radioligand-binding studies of [^{3}H]GR65630 (a potent 5-HT_3 receptor antagonist) demonstrated high densities of 5-HT_3 receptors in cortical and limbic regions (Kilpatrick et al., 1987). Furthermore, quantitative autoradiographic studies utilizing selective 5-HT_3 receptor agonists such as [^{3}H]quipazine and antagonists such as [^{3}H]LY278584 and [^{125}I]iodo-zacopride, reveal the abundance of 5-HT_3 receptors in the nucleus of the solitary tract (NTS), dorsal motor nucleus of the vagus and area postrema (Laporte et al., 1992), limbic regions (i.e. amygdala, hippocampus, frontal and entorhinal cortex), raphe nucleus (Gehlert et al., 1991; Laporte et al., 1992; Perry, 1990), and the olfactory bulb (Gehlert et al., 1991). The presence of the 5-HT_3 receptor in the raphe nucleus was also demonstrated by mRNA analysis (Fonseca et al., 2001). Edwards and coworkers showed that the pharmacological properties of 5-HT_3-like receptors in the rat medial prefrontal cortex are different from those found in peripheral tissues and cell lines (Edwards et al., 1996). In mice, 5-HT_3 receptors are abundant in the nucleus of the solitary tract, trigeminal nerve as well as the dorsal nucleus of the vagus nerve, and to a lesser extent in the amygdala, hippocampus and entorhinal cortex (Waeber et al., 1988). In humans, [^{3}H]granisetron labelling reveals the highest levels of 5-HT_3 receptors in the hippocampus, caudate nucleus, putamen, nucleus accumbens and amygdala (Bufton et al., 1993). Reverse transcriptase-polymerase chain reaction studies show colocalization of 5-HT_{3B} and 5-HT_{3A} populations in the amygdala, telencephalon and entorhinal cortex (Dubin et al., 1999; Niesler et al., 2003). At this juncture, it is crucial to highlight the difference in 5-HT_3 receptor expression in the forebrain of various species. In rats, higher levels of expression are seen in the cortex, hippocampus and amygdala (Kilpatrick et al., 1987), whereas in mice a relatively lower expression is observed in the hippocampus and amygdala (Waeber et al., 1988). In humans, the 5-HT_3 receptor expression is relatively low in the cortex but high in the hippocampus and amygdala

(Bufton et al., 1993; Parker et al., 1996), and is expressed contrariwise in the porcine brain (Fletcher and Barnes, 1996, 1999).

Subcellular distribution

In general, the 5-HT_3 receptors are located in the presynaptic regions of rats and guinea pigs (Blier and Bouchard, 1993; Blier et al., 1993; Galzin et al., 1990; Kidd et al., 1993; Martin et al., 1992a) and play a facilitatory role in 5-HT release that is typically revealed by experiments in the rat hippocampus (Martin et al., 1992a; Bagdy et al., 1998). Later studies suggest that the 5-HT_3 receptors in somatodendritic regions of the raphe nuclei and hippocampus of rat provide a feedback stimulation on 5-HT release (Badgy et al., 1998; Miquel et al., 2002). In addition, immunohistochemical techniques reveal the presence of 5-HT_3 receptors in the cell bodies, axon terminals and processes of specific neuronal structures of rat (for further details on specific neuronal structures, see Doucet et al. (2000), van Hooft and Vijverberg (2000), Miquel et al. (2002), Geurts et al. (2002), Mascagni and McDonald (2007)). In the rat NTS, 5-HT_3 receptors are observed in axonal (membranes of synaptic vesicles and extrasynaptic plasma membranes), somatodendritic (plasma membranes and golgi lamellae) and glial regions (plasma membrane) (Huang et al., 2004). In essence, we deduced two striking characteristics about 5-HT_3 receptor localization: (i) they have varying degrees of expression in several brain regions; and (ii) they occupy different domains within a single neuron. The intricacy with respect to their distribution is expected to divulge interesting psychopharmacological implications. The expression of 5-HT_3 receptors in putative neural correlates of depression in many species is the harbinger to study its modulation in relation to depressive states. Thus, the interspecies divergence in the regional and subcellular expression of the 5-HT_3 receptor necessitates prudence when the behavioural effects of their ligands are assessed. The forthcoming sections provide a comprehensive account (in chronological order) of the neuro-psychopharmacological research on 5-HT_3 receptor ligands which support the antidepressant potential of 5-HT_3 receptor antagonists.

Preclinical investigations

The preliminary investigations (i.e. behavioural, neurochemical and electrophysiological) on 5-HT_3 receptor antagonists in the early 1990s marked the inception of research into the role of 5-HT_3 receptors in CNS disorders including depression (Table 1). Systemic administration of tropisetron prevented restraint stress-induced dopamine release in the nucleus accumbens and prefrontal cortex in rats, which indicate that 5-HT_3 receptors mediate stress-dependent activation of dopaminergic neurotransmission (Imperato et al., 1990). Acute administration of ondansetron, a selective 5-HT_3 receptor antagonist significantly reduces glucose utilization in the limbic regions of the rat brain, especially the median raphe nucleus, which is associated with depression (Mitchell and Prat, 1991). The reversal of escape failures in rat (in the learned helplessness paradigm) by chronic (twice a day for five days) pretreatment with zacopride, ondansetron, ICS 205 930 (later named tropisetron) provide the first clue on antidepressant potential of chemically dissimilar 5-HT_3 antagonists (Martin et al., 1992b). The release of cholecystokinin (an abundant neuropeptide) in the cortex and nucleus accumbens is inhibited by 5-HT_3 antagonists (Raiteri et al., 1993), and such an inhibition is considered to be beneficial in depression (Becker et al., 2008). Voltage patch-clamp studies in rat nodose ganglia show that fluoxetine (Fan, 1994a), imipramine, phenelzine and iproniazid inhibit the 5-HT current mediated by the 5-HT_3 receptor, suggesting a therapeutic site for antidepressants (Fan, 1994b). From studies in the mouse forced swim test (FST), an antidepressant assay, it is speculated that quinine-induced additive effects are mediated via the 5-HT_3 receptor (potassium channel blockade), and partly contribute to the antidepressant-like effects of fluoxetine, imipramine, dothiepin and iprindole (Bourin et al., 1996). Further, it has been observed that the antidepressant-like effects of selective serotonin reuptake inhibitors are related to potassium ion (K^+) channel-linked 5-HT_3 receptors (Bourin et al., 1996; Guo et al., 1996; Redrobe and Bourin, 1997; Redrobe et al., 1996).

In rat FST, tropisetron exhibits antidepressant-like effects and pretreatment with mCPBG, a potent high affinity 5-HT_3 agonist (Kilpatrick et al., 1990), attenuates the antidepressant-like effects of tropisetron, imipramine, desipramine and mianserin (Nakagawa et al., 1998). Pindolol exhibits an additive antidepressant effect when combined with a low dose of ondansetron indicating a link between 5-HT_{1B} and 5-HT_3 receptor function in the mouse FST (Bourin et al., 1998). The clinical antidepressant effects of *N*-methyl *D*-aspartate (NMDA) receptor antagonists are attributed to their non-competitive 5-HT_3 receptor antagonistic property (Rammes et al., 2001). An interesting electrophysiological study that utilized both human 5-HT_{3A} receptor (expressed in HEK 293 cells) and endogenous 5-HT_3 receptors (rat hippocampal neurons and N1E-115 neuroblastoma cells), provided evidence that structurally dissimilar antidepressants, namely the tricyclics, the serotonin reuptake inhibitors, the norepinephrine reuptake inhibitors, and the noradrenergic and specific serotonergic antidepressants are functional antagonists of the 5-HT_3 receptor (Eisensamer et al., 2003). Their enrichment in raft-like domains within the cell membrane is considered to be crucial for their 5-HT_3 receptor antagonistic actions (Eisensamer et al., 2005). Thus, inhibition of the 5-HT_3 receptor could be considered as a novel principle effect for antidepressants. The 5-HT_3 receptor knockout mice exhibit sex-dependent differences in depressive states (Bhatnagar et al., 2004), substantiating the role of 5-HT_3 receptors in rodent depressive-like behaviour.

It is well known that selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed pharmacological class of antidepressants. The patch-clamp studies (mentioned above) on fluoxetine, and the following literature, envisage that the antidepressant-like effects of SSRIs are partially mediated by 5-HT_3 receptor antagonism (Eisensamer et al., 2003; Fan, 1994a, b; Redrobe and Bourin, 1997). The 5-HT_3 receptor antagonists augment the antidepressant-like effect of the SSRIs (Cryan et al., 2005; Ramamoorthy et al., 2008; Redrobe and Bourin, 1997). Similarly, therapeutically

Table 1. Antidepressant-like effects of 5-HT_3 receptor antagonists demonstrated in various *in vivo* animal behavioural models

5-HT_3 antagonist	Dose (mg/kg/day)	Duration (days)	Test system	Model/method of Assessment	Reference
Ondansetron	0.01	1	Rats	Glucose utilization in limbic regions of brain	Mitchell and Prat (1991)
Ondansetron	0.5	5	Rats	Learned helplessness paradigm	Martin et al. (1992)
Ondansetron	0.00001	1	Mice	Potentiation of quinine FST	Bourin et al. (1996)
Ondansetron	0.00001	1	Mice	Potentiation of fluoxetine in FST	Redrobe and Bourin (1997)
Ondansetron	0.00001	1	Mice	Potentiation of pindolol FST	Bourin et al. (1998)
Ondansetron	0.0001	14	Mice	FST and TST	Ramamoorthy et al. (2008)
	0.01	14	Rats	Olfactory bulbectomy	
Tropisetron	2	1	Rats (female)	FST	Bravo and Maswood (2006)
Tropisetron	0.3 and 1	2	Rats	FST	Nakagawa et al. (1998)
Tropisetron	0.5	5	Rats	Learned helplessness paradigm	Martin et al. (1992)
Bemesetron	3	1	Mice	TST	Kos et al. (2006)
Zacopride	0.06–0.5	5	Rats	Learned helplessness paradigm	Martin et al. (1992b)

FST: forced swim test; TST: tail suspension test

relevant concentrations of fluoxetine and its active metabolite, norfluoxetine, block the 5-HT_3-mediated currents in a concentration-dependent and voltage-independent manner (Choi et al., 2003). Evaluation of 5-HT_3 receptor antagonists individually, or in combination with fluoxetine, in animal models is recommended to investigate further the 5-HT_3 receptor as an underlying substrate in the behavioural effects of antidepressants (Cryan et al., 2005).

The hypothesis of the antidepressant effects of 5-HT_3 receptor antagonists and the role of 5-HT_3 receptors in the neurobiology of depression is strengthened by recent preclinical reports. MDL 72222 (bemesetron), a selective 5-HT_3 receptor antagonist, has been shown to reduce the duration of immobility in the mouse tail suspension test (TST), and the antidepressant-like effects are augmented by ketamine (Kos et al., 2006). Similarly, female Fischer rats treated with tropisetron spent less time immobile in the FST (Bravo and Maswood, 2006).

In our laboratory, molecules which satisfied the pharmacophoric requirements (as 5-HT_3 receptor antagonists) were screened for their antidepressant potentials. Amongst them, 2-(4-methyl piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile (NA-2) has a pA_2 value comparable to ondansetron, an optimum log *p*-value (to cross the blood–brain barrier) and an insignificant influence on the locomotor status of the mice. This molecule exhibits antidepressant-like effects in a battery of behavioural assays, which included FST, TST and reversal of olfactory bulbectomy-induced hyperactivity in the modified open field exploration paradigm (Mahesh et al., 2007). Another behavioural investigation to screen ondansetron was conducted using the above mentioned models. Drug-interaction studies with fluoxetine, desipramine, venlafaxine and 8-hydroxyl dipropylaminotetralin (5-HT_{1A} receptor agonist) were carried out in mouse FST. A chronic regimen (14 days) of ondansetron (in lower dose levels) exhibited antidepressant-like effects in mice and reversed the olfactory bulbectomy-induced behaviour of rats as observed from the modified open field and elevated plus maze exploration paradigms. It is noteworthy that 5-HT_3 receptor antagonists reversed the olfactory bulbectomy-induced behaviour, which is a sensitive model of chronic agitated hyposerotonergic depression (Lumia et al., 1992). Moreover, ondansetron augmented the antidepressant-like effects of fluoxetine and venlafaxine (at doses which were reported to affect the serotonergic system). It is predicted that the antidepressant-like effect is mediated by the postsynaptic 5-HT_3 receptors (Ramamoorthy et al., 2008). To summarize, the preclinical data on 5-HT_3 receptor ligands, particularly those resulting from behavioural assays, advocate the antidepressant-like effect of 5-HT_3 receptor antagonists. Owing to the dependence of behavioural effects on interspecies heterogeneity, data from clinical trials are vital to testify the present notion.

Probable mechanism of action: based on preclinical investigations

The putative mechanism of antidepressant action of 5-HT_3 receptor antagonists is based on the behavioural and neuropharmacological investigations that have been conducted in rodents. To propose a mechanism of action, it is vital to conceptualize the effect of 5-HT_3 receptor antagonism on various neurotransmitter systems. In accordance with the monoamine hypothesis of depression, enhancement in serotonergic neurotransmission is deemed to be a requisite for a candidate antidepressant drug. The results from the rodent antidepressant assays indicate that the 5-HT_3 receptor antagonists: (i) decrease the duration of immobility in FST and TST; (ii) increase the swimming behaviour in FST (Mahesh et al., 2007; Ramamoorthy et al., 2008); (iii) potentiate antidepressant-like effects of serotonin and norepinephrine reuptake inhibitors and SSRIs in FST (Bravo and Maswood, 2006; Mahesh et al., 2007; Ramamoorthy et al., 2008; Redrobe and Bourin, 1997); (iv) reverse olfactory bulbectomy-induced hyperactivity (Ramamoorthy et al., 2008); (v) alleviate reserpine-induced hypothermia; and (vi) potentiate 5-hydroxytryptophan-induced head twitch responses (unpublished data). Furthermore, the serotonin syndrome in humans (disorder of hyperserotonergic transmission), which is a characteristic sideeffect of drugs that enhance synaptic 5-HT levels, has been associated with ondansetron treatment (Turkel et al., 2001). These findings reveal that the inhibition of 5-HT_3

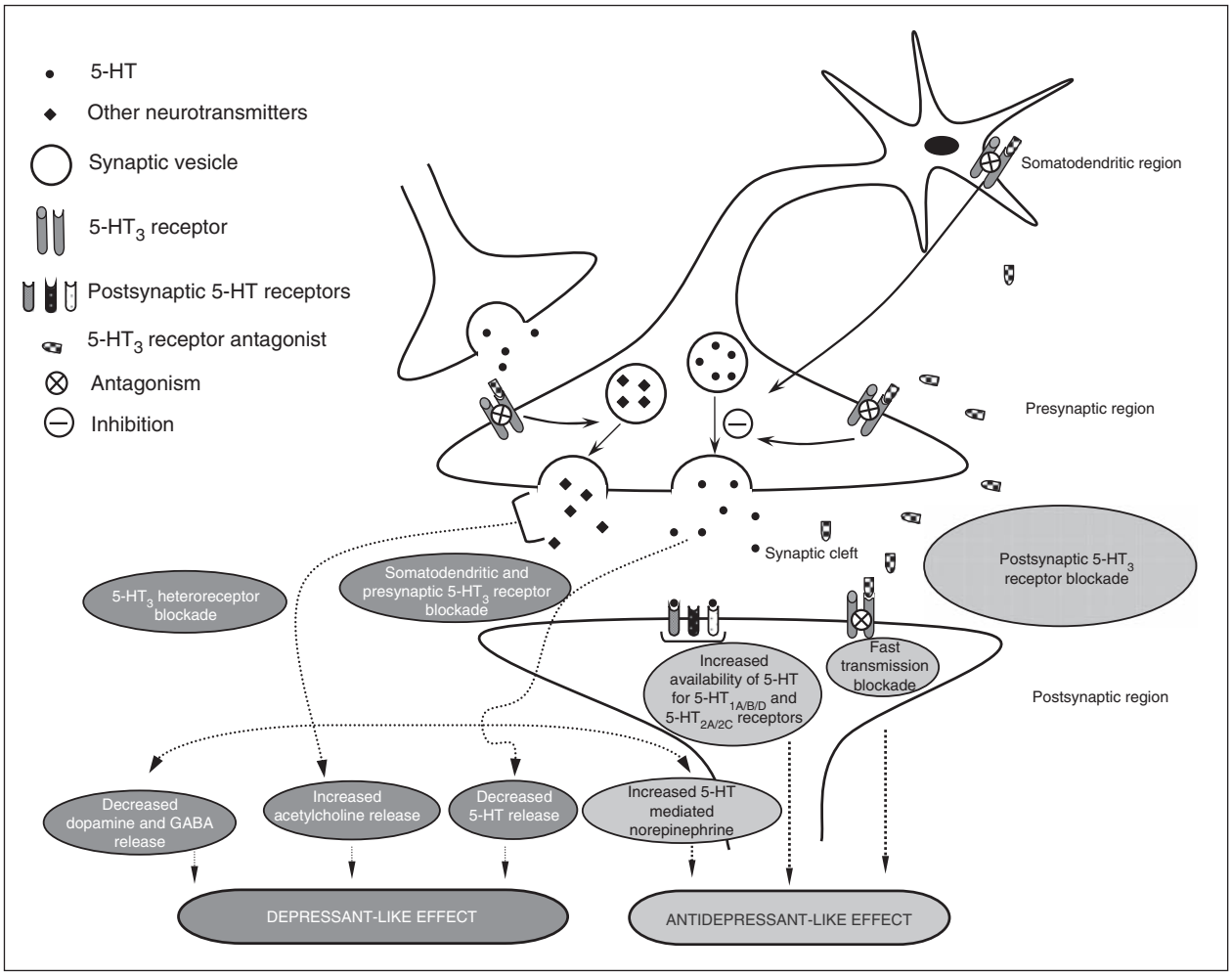

Figure 1. Schematic representation of the depression-related neuronal events (at the synapse) in response to 5-HT_3 receptor antagonism.

receptors facilitates 5-HT neurotransmission. Fluoxetine functions as an antagonist of 5-HT_3 receptors and blocks inhibitory neurotransmissions, thereby increasing the excitatory synaptic potential (Fan, 1994a,b,c). Hence blockade of presynaptic 5-HT_3 receptors in the inhibitory interneurons (Fan, 1994b,c) can partially contribute to the antidepressant effects. At low concentrations, 5-HT_3 receptor antagonists inhibit the postsynaptic 5-HT_3 receptors which mediate a fast excitatory potential in the limbic brain regions (Sugita et al., 1992). Although the cascade of events following the fast transmission blockade remains elusive, an overall antidepressant-like behaviour is conceivable. Postsynaptic 5-HT_3 receptor antagonism in serotonergic neurons can facilitate specific binding of 5-HT to other postsynaptic receptors such as 5-HT_{1B} (Bourin et al., 1998), 5-HT_{2A} and 5-HT_{2C}, thereby aiding in serotonergic transmission (Figure 1) as observed with the novel antidepressant, mirtazapine (Anttila and Leinonen, 2001; Berendsen and Broekkamp, 1997; Fawcett and Barkin, 1998; Sambunaris et al., 1997). At higher dose levels, the presynaptic and somatodendritic 5-HT_3 receptor blockade inhibits 5-HT release, eventually reducing the synaptic 5-HT levels that predispose to depression-like effects (Ramamoorthy et al., 2008).

Besides 5-HT, the 5-HT_3 (hetero) receptor located on nerve terminals, alters the release of other neurotransmitters, namely norepinephrine (NE), dopamine (DA), GABA and ACh. The accumulated evidence suggests that inhibition of this receptor has a variable impact on synaptic levels of these neurotransmitters, consequently affecting behaviour. For example, in the rat hippocampus, stimulation of 5-HT_3 receptors in the neuron terminal field facilitates 5-HT release (Martin et al., 1992a) and mediates the inhibitory effect of 5-HT on potassium-evoked NE release (Matsumoto et al., 1995). In rat hypothalamus, tropisetron has been shown to prevent the inhibitory effect of 5-HT on NE release (Blandina et al., 1991). Since increases in synaptic NE levels in the aforementioned regions has been related to antidepressant-like effects (Delgado and Moreno, 2000), the involvement of 5-HT_3 receptor is anticipated in such an effect.

However, there are reports on neurochemical effects of 5-HT_3 receptor antagonists that may be inconsistent with antidepressant effects. Several studies show that 5-HT_3 antagonists modulate evoked DA release in three separate dopaminergic pathways: the mesolimbic, mesocortical and nigrostriatal (De Deurwaerdere et al., 2005; Kankaanpaa et al., 2002; McNeish et al., 1993; Porras et al., 2003;

Wozniak et al., 1990). Nevertheless, the effect of 5-HT_3 receptor antagonism (acute and chronic treatment) on basal DA release remains controversial (Alex and Pehek, 2007; Invernizzi et al., 1995; Jacocks and Cox, 1992; Koulu et al., 1989; Rasmussen et al., 1991; Santiago et al., 1995). The antagonism of presynaptic 5-HT_3 receptors tends to suppress dopaminergic transmission (Benloucif et al., 1993; Blandina et al., 1989; Chen et al., 1991; Dremencov et al., 2006; Göthert, 1990), increasing the likelihood of depression-like effects. Similar to the effect on DA release, presynaptic 5-HT_3 receptor activation facilitates GABA release while this effect is inhibited by 5-HT_3 receptor blockers (Dorostkar and Boehm, 2007; Koyama et al., 2000; Turner et al., 2004). Hence, 5-HT_3 receptor antagonist treatment can result in a GABA-mediated, depression-like effect. The modulatory effect of 5-HT_3 receptors on the cholinergic system emerges from the colocalization of 5-HT_3 and nicotinic receptors in striatal nerve terminals of the rat brain (Nayak et al., 2000). Presynaptic 5-HT_3 receptor stimulation inhibits ACh release mainly in the cortex (Barnes et al., 1989; Crespi et al., 1997; Giovannini et al., 1998; Maura et al., 1992), and animal studies indicate that such an inhibition is beneficial in controlling depression (Chau et al., 2001; Dilsaver 1986; Overstreet et al., 1995). Although lacking tangible evidence, the 5-HT_3 receptor antagonists by their action on presynaptic receptors facilitate ACh release, which precipitates depression-like symptoms. Until now, no clinical study has reported depression-like symptoms associated with 5-HT_3 receptor antagonist treatment. This argues against the depression-like effect of 5-HT_3 receptor antagonists at higher doses.

The precise mechanism underlying the antidepressant-like effect of 5-HT_3 receptor antagonists cannot be deduced due to the characteristic subcellular and regional distribution pattern of this receptor in neuronal structures and its modulatory effects on other neurotransmitter systems. Therefore, we hightlight that a multitude of interlinked neurotransmitter mechanisms (Figure 1) determine the behavioural effects of 5-HT_3 receptor antagonists in the context of presynaptic receptors and it is reasonable to attribute the antidepressant-like effect to the postsynaptic receptor antagonism. The positive influence of 5-HT_3 receptor antagonism on the synaptic monoamine concentration for a resultant antidepressant-like effect is convincingly explained by the above mechanism.

Clinical investigations on 5-HT_3 receptor antagonists

The prevalence of depression as a comorbid illness with many other psychiatric conditions such as anxiety, psychosis and alcoholism has been extensively reported (Davis et al., 2008; Gum and Cheavens, 2008; Hettema, 2008). Clinical investigations (Table 2) have assessed the benefits of 5-HT_3 receptor antagonist treatment (mainly limited to ondansetron and tropisetron) in various psychiatric conditions, such as anxiety, depression and psychosis, which are comorbid with other diseases/disorders such as alcoholism, drug abuse, fibromyalgia, cancer, hepatitis and bulimia (for reviews, see Costall et al., 1990; Palfreyman et al., 1996; Wilde and Markham, 1996; Wolf, 2000; Wolters, 1999). The present section focuses on the published clinical data pertaining to 5-HT_3 receptor antagonist treatment in patients with various comorbid illnesses, with key emphasis on the association of 5-HT_3 receptor antagonism with improvement in depression-related symptoms.

A few clinical trials have indicated the effectiveness of 5-HT_3 receptor antagonist monotherapy or its combination with antipsychotics in patients with psychosis and schizophrenia. Ondansetron (4 mg/day) treatment has been shown to improve the mental state and social behaviour of a schizophrenic patient (White et al., 1991), and when treated at a higher dose (12 mg/day for 12 weeks), it alleviated the symptoms of tardive dyskinesia and psychosis in 20 schizophrenic patients (Sirota et al., 2000). Ondansetron treatment (12–24 mg/day for 4–8 weeks) in 16 patients with levodopa treatment-associated psychosis showed improvement in measures of visual hallucinations, paranoid delusions, confusion and associated global functional impairment (Zoldan et al., 1995). Six weeks of ondansetron treatment alleviated symptoms in 29 patients with Parkinsonian psychosis. More importantly, this trial validated the Parkinson's psychosis rating scale in comparison to the global functional impairment assessment scale (Friedberg et al., 1998). However, the high treatment cost of ondansetron has been a limiting factor which prevents further trials on psychosis in patients with Parkinson's disease (Fernandez et al., 2003). The double-blind, placebo-controlled randomized (DBPCR) study on ondansetron (8 mg/day for 12 weeks) in combination with haloperidol was shown to be effective in the control of negative and cognitive symptoms of treatment-resistant schizophrenia and a reduction in the severity of Parkinsonism, akathisia and behavioural hyperactivity (Zhang et al., 2006). Similar results were previously observed with mirtazapine (the 5-HT_2, 5-HT_3 and α_2 antagonist) treatment, which, however, failed to alter the depression scores in schizophrenic patients (Berk et al., 2001).

The following clinical studies refer to the positive outcomes of 5-HT_3 receptor antagonist treatment in anxiety, the most prevalent disorder comorbid with depression (Aina and Susman, 2006; Cameron, 2006; Dolnak, 2006; Nutt and Stein, 2006). A single dose of ondansetron (12 mg) abolished emotion-potentiated startle response in 12 healthy volunteers (Harmer et al., 2006). A DBPCR study of zatosetron in 43 patients noted an anxiolytic trend, although the results were not statistically significant (Smith et al., 1999). The results from trials with ondansetron against CCK agonist (pentagastrin and CCK-4)-induced panic disorder have been inconclusive. For instance, ondansetron (0.15 mg/kg) was reported to aggravate pentagastrin-induced, elevated adenocorticotrophic hormone (ACTH) levels and anxiety scores in 14 patients (McCann et al., 1997). In contrast, another study (in 36 patients) showed that administration of 2 mg/kg of ondansetron, acute and chronic (28 days), did not influence the CCK-4-induced increase in ACTH levels, but alleviated symptoms of anxiety in the visual analogue scale and increased the basal and CCK-4-induced release of neuropeptide Y (Dépôt et al., 1999). Ondansetron (3 mg/day for eight weeks) treatment has also been shown to reduce the anxiety and depression scores in the Yale-Brown obsessive compulsive scale and Hamilton

Table 2. Summary of clinical trials on 5-HT_3 receptor antagonists that focus on various neuropsychiatric conditions related to depression

5-HT_3 antagonist	Dose (mg/kg/day)	Duration (days)	Test population	Method of assessment	Outcome	Reference
Ondansetron	4	Not specified	1 schizophrenic patient	Routine examination	Improvement in social behaviour and mental state	White et al. (1991)
Ondansetron	12–24	28–56	16 patients with Parkinson's psychosis	Brief psychiatric rating scale, nurse observation scale for inpatients	Improvements in measures of visual hallucinations, paranoid delusions, confusion, and the associated global functional impairment	Zoldan et al. (1995)
Ondansetron	0.15	Single dose	10 healthy volunteers	National Institute of Mental Health self-rating scale and endocrine assessments	Reduction in amphetamine-induced euphoria/activation responses and prolactin levels	Grady et al. (1996)
Ondansetron	0.15	Single dose	14 patients (8 patients with panic disorder and 6 patients withsocial phobia) treated with pentagastrin (0.6 μg/kg)	Zung anxiety status inventory, Spielberger state anxiety, visual analogue scale and hormonal assessments	Aggravated pentagastrin-induced behavioural effects and increased adenocorticotrophic hormone levels	McCann et al. (1997)
Ondansetron	12	6	29 patients with Parkinson's psychosis	Parkinson psychosis rating scale and global functional impairment score	Parkinson psychosis rating scale is a relevant, reliable and valid instrument to assess the Parkinsonian psychosis	Friedberg et al., (1998)
Ondansetron	2	Single dose and 28	36 healthy volunteers	Hamilton anxiety scale, visual analogue scale and hormonal assessments	Alleviated symptoms of anxiety in visual analogue scale and increased neuropeptide Y levels	Dépôt et al. (1999)
Ondansetron	8–16	21	6 patients with Tourette's syndrome	Yale global tic severity scale, Yale-Brown obsessive-compulsive scale and Tourette's syndrome-clinical global impression scale.	Alleviation of the tics Component	Toren et al. (1999)
Ondansetron	12	84	20 schizophrenic patients	Abnormal involuntary movement scale, positive and negative syndrome scale and clinical global impression scale	Improvements in symptoms of tardive dyskinesia and psychosis	Sirota et al. (2000)
Ondansetron (with naltrexone 25 mg/bid)	0.008	56	10 early onset alcoholics	Number of drinks per day	The combination synergistically reduces drinking outcomes	Johnson (2000)
Ondansetron (with naltrexone 25 mg/bid)	0.008	56	10 early onset alcoholics	Obsessive compulsive drinking scale	Reduced craving behaviour	Ait-Daoud et al. (2001)
Ondansetron	0.008	84	253 alcoholics	Visual analogue scales	Treatment reduced the craving behaviour in early onset alcoholics	Johnson et al. (2002)
Ondansetron	0.032	77	321 early onset alcoholics	Profile of mood states	Reduced symptoms of overall mood disturbance, fatigue, vigour, confusion/bewilderment and depression	Johnson et al. (2003)

(Continued)

Table 2. Continued

5-HT_3 antagonist	Dose (mg/kg/day)	Duration (days)	Test population	Method of assessment	Outcome	Reference
Ondansetron	1 mg/kg/day for 7 days followed by 3 mg/kg/day for 49 days		8 obsessive compulsive disorder patients	Yale-Brown obsessive compulsive scale, Hamilton anxiety scores and Hamilton depression scores	Improvement in anxiety and depression scores	Hewlett et al. (2003)
Ondansetron	8–24	21	30 patients with Tourette's syndrome	Tourette's syndrome global scale, the Yale global tic severity scale and the Yale-Brown obsessive compulsive scale	Alleviation of the tic component	Toren et al. (2005)
Ondansetron	0.008	56	12 alcohol-dependent adolescents	Children's interview for psychiatric syndromes, adolescent diagnostic interview and timeline follow-back	Improvement in all drinking outcomes	Dawes et al. (2005a)
Ondansetron	0.008	56	12 alcohol-dependent adolescents	Adolescent obsessive compulsive drinking scale	Reduction in the drinking scores	Dawes et al. (2005b)
Ondansetron	8	30	36 patients with chronic hepatitis C	Fatigue impact scale and Beck depression inventory	Significant reduction in fatigue and depression scores	Piche et al. (2005)
Ondansetron	24	28	17 patients with bulimia nervosa	Beck depression index and positron emission tomography	Reduction in vagally mediated depression	Faris et al. (2006)
Ondansetron	8	84	58 schizophrenic patients	Positive and negative syndrome scale and clinical global impression-severity scales	Effective (as adjunct to haloperidol) in treatment-resistant schizophrenia and effective in controlling negative and cognitive symptoms	Zhang et al. (2006)
Ondansetron	12	Single dose	12 healthy volunteers	Affective modulation of the startle reflex, emotional categorization (and memory) and facial expression recognition were assessed	Abolished emotion-potentiated startle, indicting anxiolytic prospect	Harmer et al. (2006)
Ondansetron	8	70	63 cocaine-dependent patients	Self assessment questionnaires and benzoylecgonine levels in urine	Reduction in cocaine use	Johnson et al. (2006)
Tropisetron	0.5, 5 and 25	21	91 generalized anxiety disorder patients	Hopkins symptom check list score, global impression scale and Hamilton anxiety scale	Dose-dependent effects on all anxiety-related outcomes	Lecrubier et al. (1993)
Tropisetron	5	28	418 patients with fibromyalgia	Beck depression index	Significant improvement in anxiety and depression states	Haus et al. (2000)
Zatosetron	0.2–5	28	43 patients with anxiety	Hamilton anxiety scale, Montgomery-Asberg depression rating scale, and clinical global impressions scale	The dose levels were safe, although no statistical significance, a trend towards anxiolytic effects	Smith et al. (1999)

rating scale in a small pilot trial conducted in patients with obsessive compulsive disorder (Hewlett et al., 2003). Ondansetron treatment has been shown to alleviate the tics component (i.e. sudden involuntary, repetitive, intermittent brief movements/sounds) of Tourette's syndrome (TS) (Singer, 2001), a disorder due to basal ganglia dysfunction (Kenney et al., 2008). The convincing results obtained from a pilot trial with ondansetron (8–16 mg/day for 21 days) in six patients with TS resistant to haloperidol treatment (Toren et al., 1999) prompted a broader trial involving 30 patients and an increased dose range (8–24 mg/day for 21 days). These trials have indicated an improvement in haloperidol-resistant TS patients when assessed with the Tourette's syndrome global scale (Toren et al., 2005).

5-HT_3 receptor antagonism also reduces the rewarding effects of drugs of abuse and alcohol by decreasing dopamine neurotransmission (Barnes and Sharp, 1999; Bradbury et al., 1985; Hagan et al., 1990; Johnson, 2004; Johnson and Cowen, 1993; McBride et al., 2004). In a trial with 10 healthy human volunteers, ondansetron (0.15 mg/kg) pretreatment attenuated both amphetamine (0.5 mg/kg)-induced activation/euphoria responses (National Institute of Mental Health self-rating scale) and increased prolactin levels (Grady et al., 1996). A DBPCR trial in 63 cocaine-dependent patients indicated that ondansetron treatment (8 mg/kg/day for 10 weeks) was effective in reducing cocaine intake as reported from self-assessment questionnaires and urine analysis (Johnson et al., 2006). However, a number of trials demonstrated that ondansetron was ineffective in drug dependence, such as clinical trials targeting opiate addiction (Sell et al., 1995), smoking cessation (West and Hajek, 1996), benzodiazepine withdrawal (Romach et al., 1998) and methamphetamine dependence (Johnson et al., 2008). In early onset alcoholism (EOA), a combination of naltrexone (50 mg/kg/day) with ondansetron (8 μg/kg/day) for 8 weeks, significantly reduced the craving behaviour (observed from the obsessive compulsive drinking scale) and improved drinking outcomes (Ait-Daoud et al., 2001; Johnson, 2000). A DBPCR trial in 253 patients with EOA indicated that ondansetron (8 μg/kg/day for 12 weeks) was effective in controlling subjective (craving), behavioural (self-reported drinking) and objective laboratory components (serum carbohydrate deficient transferrin) of alcoholism. The above human trials highlighted that ondansetron benefited early onset alcoholics, but not the late onset alcoholics. Ondansetron treatment (32 μg/kg/day for 11 weeks) decreased behavioural scores (assessed using the profile of mood states subscale) in 321 EOA patients, which showed the use of ondansetron in the alleviation of depression that manifests as one of the subsyndromal mood disturbances (Johnson et al., 2003). An open-label study of ondansetron (8 μg/kg/day for eight weeks) in 12 adolescent alcoholic patients indicated a treatment-related improvement in drinking outcomes as measured with the children's interview for psychiatric syndromes, adolescent diagnostic interview and timeline follow-back (Dawes et al., 2005a). The notable feature of the above study is that the alcoholic patients suffered from psychiatric comorbidities, namely disruptive behavioural disorder (eight out of 12), dysthymia or mild major depression (three out of 12). A similar trial conducted at the same dose level and duration showed a reduction in craving behaviour as observed from the adolescent obsessive compulsive drinking scale (Dawes et al., 2005b).

Fibromyalgia is a condition in which a high incidence of psychiatric disturbances including depression are observed (Epstein et al., 1997; Offenbaecher et al., 1998; Fietta and Manganelli, 2007; Buskila and Cohen, 2007; Arnold, 2008). Incidentally, tropisetron treatment (5 mg/kg/day for 28 days) showed significant improvement in depression and anxiety scores in patients with fibromyalgia (Haus et al., 2000). When examining the anti-fatigue effects of ondansetron (8 mg/kg/day for 30 days) in 36 chronic hepatitis C-infected patients, a considerable reduction in depression was noted on the Beck depression inventory (BDI) (Piche et al., 2005). Major depressive disorder was reported to be comorbid with bulimia nervosa, a disorder with increased appetite and a resultant metabolic imbalance (Braun et al., 1994; Casper, 1998; Herzog et al., 1992). Ondansetron (24 mg/kg/day for 28 days) was effective in controlling depression (assessed by BDI) associated with bulimia nervosa (Faris et al., 2006). This effect was attributed to the blockade of vagal activity by ondansetron (Faris et al., 2000, 2006).

The aforementioned studies confirmed that 5-HT_3 receptor antagonists have a notable neuropsychopharmacological profile and are well tolerated in patients. So far, clinical trials with an 'intention to treat' design have not been conducted, resulting in the lack of direct evidence to prove the antidepressant efficacy of 5-HT_3 receptor antagonists. The reduction in depression scores associated with 5-HT_3 receptor antagonist treatment in patients with comorbid conditions (Faris et al., 2006; Haus et al., 2000; Hewlett et al., 2003; Johnson et al., 2003; Piche et al., 2005) support our hypothesis and warrants further evaluation of 5-HT_3 receptor antagonists as antidepressants.

Perspective

There is certainly a dearth of direct evidence for preclinical and clinical antidepressant-like effects of other 5-HT_3 receptor antagonists, with the exception of ondansetron and tropisetron. Few earlier reports challenged the role of 5-HT_3 receptors in depression and the possible therapeutic value of 5-HT_3 receptor antagonism (Berendsen, 1995; Borsini, 1995; Borsini et al., 1991; De Vry et al., 1997; Hoyer et al., 1989; Luscombe et al., 1993). Recently a protein expression study showed that ondansetron (2 mg/kg) blocked the facilitatory effects of fluoxetine on neuronal plasticity in the rat medial prefrontal cortex (Varea et al., 2007) suggesting that 5-HT_3 receptor antagonists can mediate depression-like effects. Other issues that discourage the use of 5-HT_3 receptor antagonists as antidepressants are: (i) the inverted U-shaped dose response curves obtained in preclinical and clinical studies with 5-HT_3 receptor antagonists, especially ondansetron (Adrien et al., 1992; Costall et al., 1987a,b; Johnson et al., 2002, 2006; Jones et al., 1988; Martin et al., 1992b; Ramamoorthy et al., 2008); (ii) the antidepressant-like action at a lower dose range (1–8 mg/day) observed in the clinical trials (Faris et al., 2006; Haus et al., 2000; Hewlett et al., 2003; Piche et al., 2005), the reason for which remains unknown; and (iii) the lack of a direct correlation between the active doses used in animals and humans (Tables 1 and 2).

The reason for disagreement amongst various reports might be due to the variation in experimental protocols (and treatment schedule). The possible explanations for the dose-related issues available in literature are: (i) interspecies heterogeneity of this receptor (Newberry et al., 1991; Peroutka, 1988b; Peters et al., 1992) leading to pharmacological diversity (Brady et al., 2007; Fletcher and Barnes, 1998) and difference in the regional distribution of 5-HT_3 receptors across species, as discussed in earlier sections; (ii) mutual steric hindrance that is probable at high concentrations of the molecules at the receptor site; (iii) additional behavioural effects due to low affinity binding of 5-HT_3 receptor antagonists to other receptor types; and (iv) differences in 5-HT_3 receptor densities that exist in various neuronal structures (Wolf, 2000). One other reason for the observed discrepancy is the antagonistic effects at presynaptic and somatodendritic 5-HT_3 receptors that are likely to cause depressant effects mediated by hypercholinergic and hyposerotonergic, -dopaminergic and -GABAergic neurotransmission. The apparent influence on various neurotransmitter systems also explains the inverted U-shaped dose response curve often observed with 5-HT_3 receptor antagonists. The antidepressant efficacy in females (Bhatnagar et al., 2004, Bravo and Maswood, 2006, Yamada et al., 2006) is another intriguing aspect that remains unexplained.

It is considered worthwhile to mention that the systematic genomic analysis in Caucasians and the Japanese population have revealed the association of 5-HT_{3A} (Niesler et al., 2001) and 5-HT_{3B} (Frank et al., 2004; Yamada et al., 2006) genes with bipolar disorder, providing evidence to incorporate 5-HT_3 receptors into the neurobiology of depression. In conclusion, this commentary recommends the neuronal 5-HT_3 receptor as a candidate antidepressant drug target. Molecules which selectively target postsynaptic 5-HT_3 receptors could provide a pivotal solution and clinical trials (post-pilot dose response studies) of the 5-HT_3 receptor antagonists in patients with various subtypes of depressive disorder are advocated. However, in order to classify the 5-HT_3 receptor antagonists as a novel pharmacological class of antidepressants, it is mandatory to await results from human behavioural studies.

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