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Review Article

The 5-HT$_{2C}$ receptor as a potential therapeutic target for the design of antiobesity and antiepileptic drugs

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CONTENTS

Introduction

5-Hydroxytryptamine (5-HT or serotonin), a key neurotransmitter of the peripheral and central nervous system (PNS and CNS), has been implicated in a variety of sensory, motor and behavioral processes. The diverse effects of this neurotransmitter are related to the extensive projections of serotonergic neurons throughout the brain and the large number of distinct serotonin receptor subtypes. At least 14 distinct serotonin receptor subtypes are expressed in the mammalian CNS, each of which is assigned to one of seven families, 5-HT$_1$ to 5-HT$_7$ (Fig. 1). This review highlights the developments in the knowledge of the mammalian 5-HT$_{2C}$ receptor subtype, specifically its structure, pharmacology, CNS distribution and actions at the molecular level. However, particular emphasis or focus will be on the therapeutic potential of this molecular target in the design of antiepileptic and antiobesity drugs.

5-HT$_{2C}$ receptor

The 5-HT$_2$ subfamily of serotonin receptors is composed of three subtypes, the 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors. All three receptors are G-protein-coupled to the activation of the phospholipase C (functionally linked to phosphatidyl inositol (PI) hydrolysis) and subsequent mobilization of intracellular calcium (1).

The 5-HT$_{2C}$ receptor was identified as a tritiated-5-HT binding site in the choroid plexus (tissue involved in production of cerebrospinal fluid, CSF) of various species that could also be labelled by tritiated mesulergine and tritiated lysergic acid diethylamide (LSD). Originally this site was seen as a new member of the 5-HT$_1$ receptor family, and termed 5-HT$_{1C}$, because of its high affinity for tritiated 5-HT (2). However, once the receptor was cloned and more information about its characteristics became available, a shift to the 5-HT$_2$ receptor family and reclassification as 5-HT$_{2C}$ receptor became unavoidable (3).

Structure

The partial cloning of the mouse 5-HT$_{2C}$ receptor (4) was shortly followed by the sequencing of the full length clone initially in the rat (5) and then the mouse (6) and human (7). A splice variant of the 5-HT$_{2C}$ receptor had been isolated and found to be present in brain tissue of the rat, mouse and human (8). The functional significance of this variant was, however, unclear since the protein product was a truncated 5-HT$_{2C}$ receptor without a 5-HT binding site. More recently, it has been reported that 5-HT$_{2C}$ mRNA undergoes post-transcriptional editing to yield multiple 5-HT$_{2C}$ receptor isoforms with different distributions in brain (9). In functional terms, this is potentially of great significance as the amino acid sequences predicted from the mRNA transcripts indicate that the isoforms (if expressed endogenously in significant amounts in brain tissue) may have different regulatory and pharmacological properties.

The 5-HT$_{2C}$ receptor is X-linked to the human chromosome, Xq24. The 5-HT$_{2C}$ receptor gene has three introns (rather than two as in the case of the 5-HT$_{2A}$ and 5-HT$_{2B}$) and may produce a protein product with eight rather than seven transmembrane regions, which, if proven, would be unusual for a G-protein-coupled receptor (6). There is high sequence homology (>80% in the transmembrane regions) between the mouse, rat and human 5-HT$_{2C}$ receptors. The mouse and rat 5-HT$_{2C}$ receptors possess six potential *N*-glycosylation sites, four of which are conserved in the human sequence. The rat 5-HT$_{2C}$ receptor has eight serine/threonine residues representing possible phosphorylation sites, all of which are conserved in the human sequence (1).

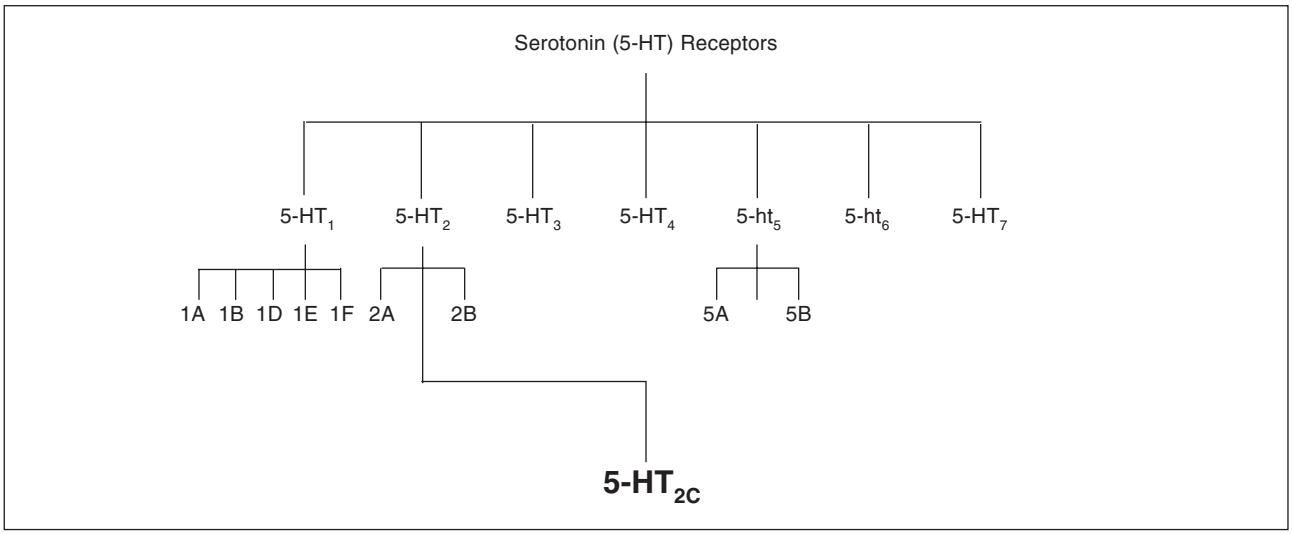

Fig. 1. A scheme showing the 14 serotonin receptor subtypes highlighting simplistically the subtype relationships.

Distribution

In contrast to the 5-HT$_{2A}$ receptor (expressed in CNS and PNS tissues) and 5-HT$_{2B}$ receptor (expressed principally in the periphery and only sparsely in the CNS), the 5-HT$_{2C}$ receptor has been found primarily in CNS. Autoradiographic studies, using a variety of ligands including tritiated 5-HT, tritiated mesulergine and tritiated LSD, have provided a detailed map of the distribution of 5-HT$_{2C}$ binding sites in rat and many other species (10, 11). In addition to the very high levels detected in the choroid plexus, 5-HT$_{2C}$ binding sites are widely distributed and present in areas of cortex (olfactory nucleus, pyriform, cingulate and retrosplenial), limbic system (nucleus accumbens, hippocampus, amygdala) and the basal ganglia (caudate nucleus, substantia nigra). The presence of 5-HT$_{2C}$ binding sites in the pyriform cortex and substantia nigra is relevant to findings of 5-HT$_{2C}$ receptor-mediated electrophysiological response in these regions (12, 13).

Two studies have reported 5-HT$_{2C}$ receptor mRNA in the midbrain raphe nuclei (14, 15). In addition, both 5-HT$_{2C}$ receptor mRNA and immunoreactivity have been found in the central grey which is adjacent to the dorsal raphe nucleus (DRN). By and large there is a good concordance between the distribution of 5-HT$_{2C}$ receptor mRNA and 5-HT$_{2C}$ binding sites.

Furthermore, neurotoxic lesion experiments indicate that the 5-HT$_{2C}$ receptors are mostly postsynaptic but there is also evidence suggesting possible presynaptic localization on 5-HT nerve terminals. Thus, whilst the 5-HT$_{2C}$ receptor is clearly located postsynaptically, the possibility of a presynaptic location needs further study (16).

Pharmacology

The pharmacological profile of the 5-HT$_{2C}$ receptor is close to but distinguishable from other members of the 5-HT$_2$ receptor family (17). Most of the older more established 5-HT$_2$ ligands (*e.g.*, antagonists: ritanserin, LY-53857, mesulergine, mianserin; agonists: 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane DOI, m-chlorophenylpiperazine, mCPP (**1**), m-trifluoromethylphenylpiperazine, TFMPP (**2**), MK-212 (**3**)) do not discriminate sufficiently between the 5-HT$_2$ receptor subtypes. The contribution of these subtypes to the action of serotonin has been difficult to ascertain owing to the paucity of selective pharmacological agents.

The limited access to selective pharmacological tools amongst the 5-HT$_2$ subfamily of serotonin receptors has led to the use of gene targeting techniques to generate mouse lines that selectively lack functional receptor genes (18). This strategy has been applied to the study of 5-HT$_{2C}$ receptor function. Recently however, a number of novel more selective and nonselective 5-HT$_{2C}$ receptor agonists (Fig. 2) and antagonists (Fig. 3) have been developed and characterized. At present, it appears easier to discriminate the 5-HT$_2$ subtypes using antagonists. The highly selective 5-HT$_{2C}$ antagonists, SB-242084 (**17**) (K_i = 1 nM at the human cloned receptor) and RS-102221 (**18**) (K_i = 4 nM at the human cloned receptor), which are at least 2 orders of magnitude more selective for 5-HT$_{2C}$ *versus* 5-HT$_{2B}$, 5-HT$_{2A}$ and other binding sites, will prove useful in further defining the function of the 5-HT$_{2C}$ receptor subtype (19, 20). More recently, the 5-HT$_{2B/2C}$ receptors can be distinguished from the 5-HT$_{2A}$ receptor by their high affinity for SB-200646A (**19**) and SB-206553 (**20**), and their lower affinity for the antagonists MDL-100907, ketanserin and spiperone (21-23).

The novel arylhydronaphthazenalkanamine (**21**) (K_i = 2.5 nM at the human cloned receptor) which is a 5-HT$_{2C}$ antagonist (24), can also be used to study disorders associated with the 5-HT$_{2C}$ receptor. Other highly selective antagonists, which can be of value to unraveling 5-HT$_{2C}$ receptor function, include ligands **22**, **23** and **24** (25).

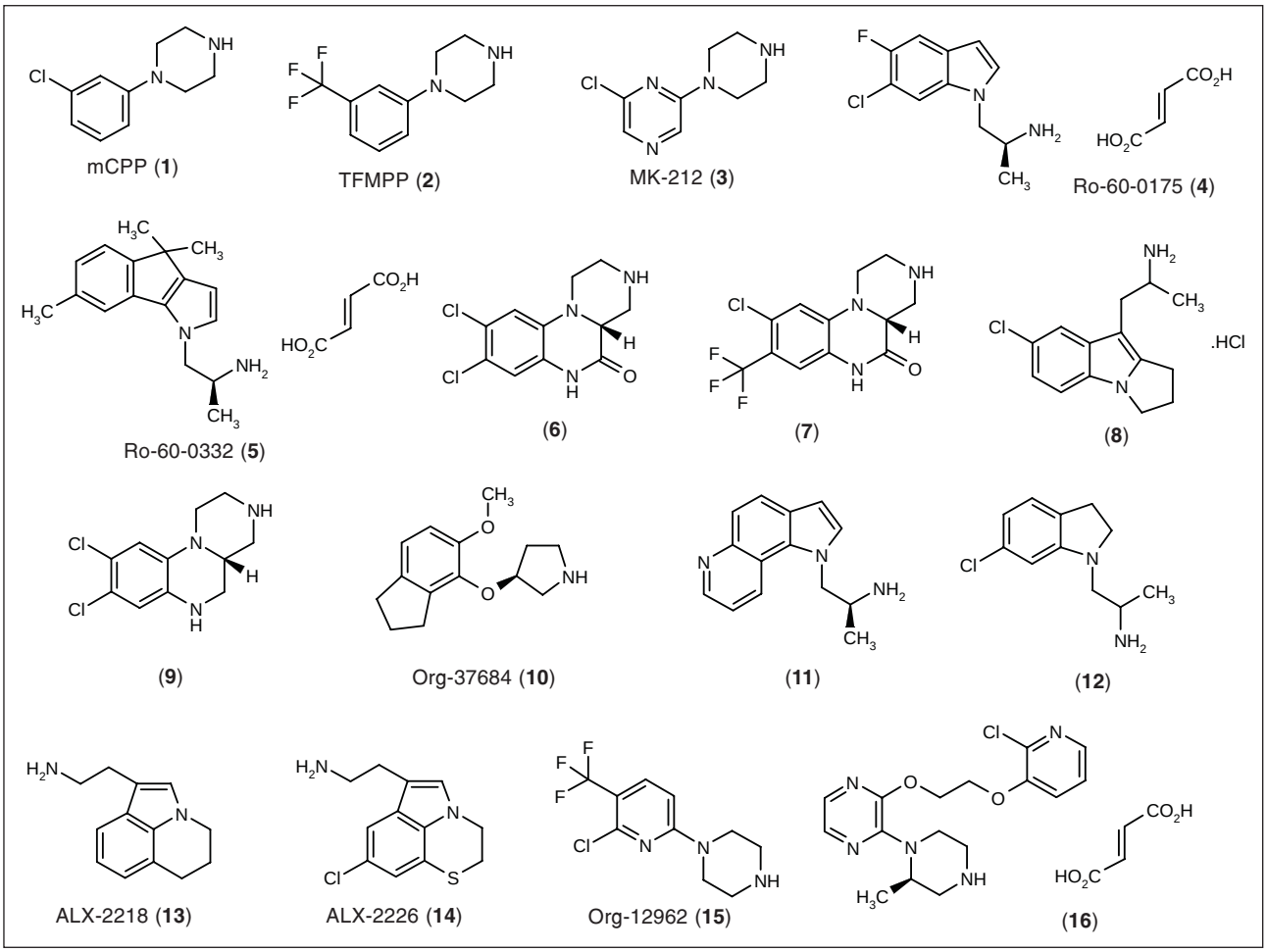

Fig. 2. 5-HT_{2C} agonists with potential antiobesity and antiepileptic properties.

A number of atypical and typical antipsychotic agents (including clozapine, loxapine and chlorpromazine), have a relatively high affinity for 5-HT_{2C} binding sites (5-HT_{2A} also) as do some conventional and atypical antidepressants (*e.g.*, tricyclics, doxepin, mianserin and trazodone) (26-28).

An issue, which may have an impact on the development of future therapeutic agents and the classification of 5-HT_2 receptor ligands, is that of constitutive activity of certain receptors in the family. Each of the 5-HT_2 receptors display a unique degree of constitutive activity with a rank order of 5-HT_{2C} >> 5-HT_{2A} > 5-HT_{2B}. RNA editing of the 5-HT_{2C} receptor yields a spectrum of constitutive activity for the different isoforms generated (29). In this regard, it has been reported that ligands such as mesulergine and mianserin act as inverse agonists and cause a reduction in the basal activity at 5-HT_{2C} receptors expressed in NIH-3T3 cells. More recently, atypical antipsychotic drugs (*e.g.*, clozapine, olanzapine, ziprasidone, risperidone, zotepine) displayed potent inverse agonist activity at the rat and human 5-HT_{2C} receptors (30). Deramciclane (**25**) is a putative anxiolytic drug, which is a serotonin 5-HT_{2C} receptor inverse agonist (31).

Signal transduction

The binding of the agonists to the 5-HT_{2C} receptor, activate phospholipase C through the intermediacy of a G-protein (Gq11). Phospholipase C catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate to inositol 1,4,5-triphosphate and diacylglycerol. The water soluble inositol 1,4,5-triphosphate, acting as a second messenger, diffuses through the cell cytoplasm and stimulates the release of calcium sequestered in the endoplasmic reticulum which in turn activates numerous cellular processes through the intermediacy of calmodulin and its homologs. The diacylglycerol remains associated with the plasma membrane where it activates protein kinase C to phosphorylate and thereby modulate the activities of a number of cellular proteins. In choroid plexus preparations, the nonselective 5-HT_2 receptor agonists, mCPP, TFMPP and MK-212 behave as agonists but only the latter compound had an efficacy equal to 5-HT. It has been suggested that 5-HT_{2C} receptors in choroid plexus may regulate CSF formation as a result of their ability to mediate cyclic guanosine monophosphate (cGMP) formation (32-35).

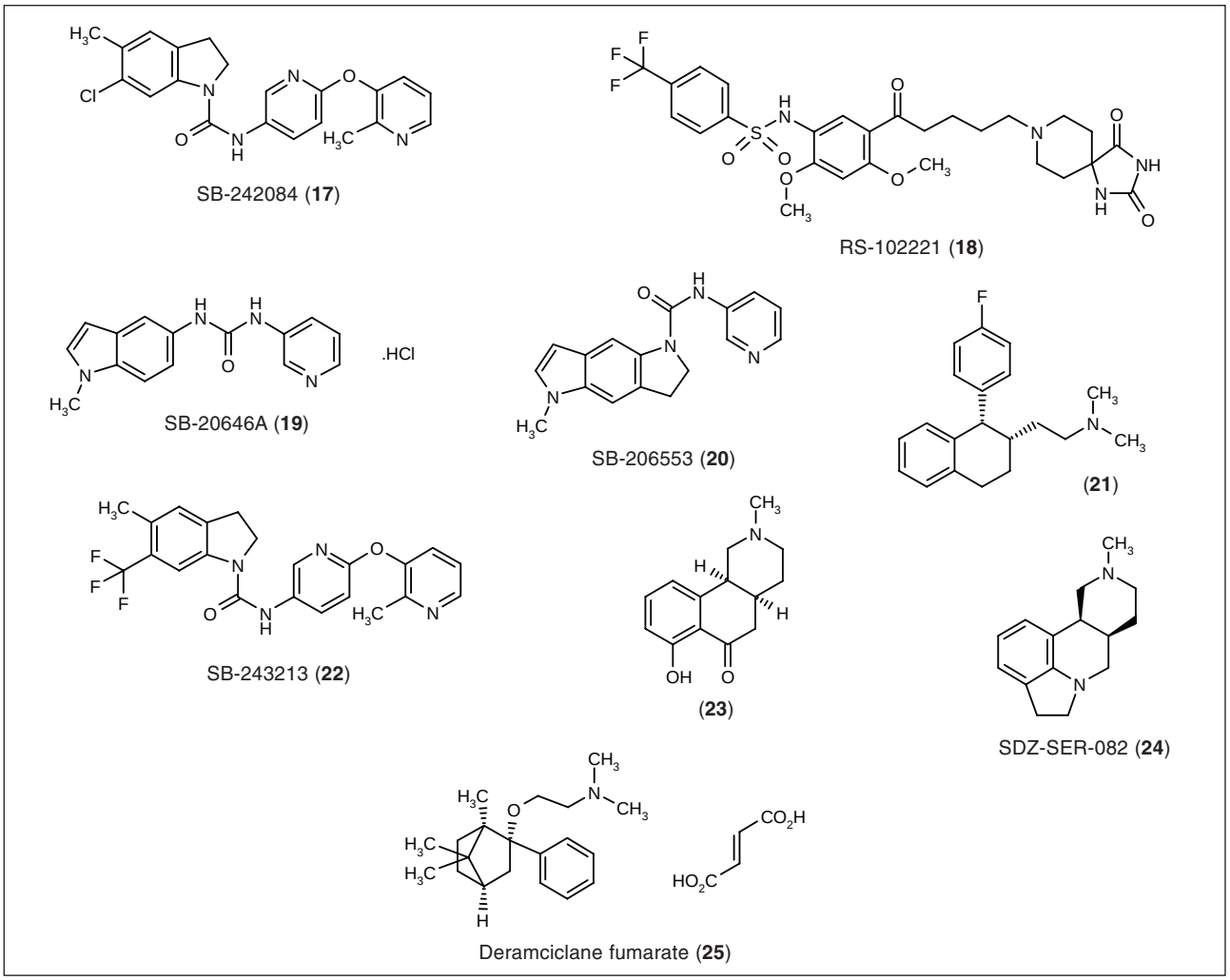

Fig. 3. 5-HT$_{2C}$ receptor antagonists and inverse agonist.

To further determine the intracellular mechanism of the 5-HT$_{2C}$ receptor endogenously expressed in the choroid plexus epithelial cells, an elegant strategy of targeted disruption of protein-protein interactions was recently employed (36). The strategy entails the delivery of conjugated membrane-permeable peptides that disrupts domain interaction at specific steps in the signaling cascade. For example, peptides targeted against receptor Gα q-protein interaction domain were found to disrupt the 5-HT$_{2C}$ receptor-mediated phosphatidylinositide hydrolysis. In contrast, peptides that bind to and sequester free Gβγ subunits were ineffective at blocking 5-HT$_{2C}$ receptor-mediated phosphatidyl inositol turnover. These results provide the first direct demonstration that active Gα q subunits mediate 5-HT$_{2C}$ receptor activation of phospholipase C β and that the Gβγ subunits released from Gα q heterotrimeric proteins are not involved.

The different 5-HT$_{2C}$ receptor isoforms generated from RNA editing have demonstrated altered dynamics of agonist-induced calcium release. These distinctions in agonist-induced calcium release imply that edited 5-HT$_{2C}$ receptors may produce distinct physiological responses within the CNS (37).

5-HT$_{2C}$ receptors, in common with 5-HT$_{2A}$ receptors, also downregulate in response to chronic exposure to both agonists and antagonists, which could in part relate to apparent inverse agonist properties (38, 39).

Behavioral and other physiological responses

There are several behavioral responses that have been associated with activation of central 5-HT$_{2C}$ receptors. These include hypolocomotion, hypophagia, anxiety, penile erections and hyperthermia (40, 41). To a large extent these associations are based on the behavioral effects in rats of nonselective 5-HT$_2$ receptor agonists such as mCPP, TFMPP and MK-212, and their antagonism by nonselective 5-HT$_2$ receptor antagonists, such as ritanserin and mianserin. Nevertheless, evidence for the

involvement of the 5-HT_{2C} receptor in many of these *in vivo* responses is now compelling.

Importantly, the 5-$HT_{2C/2B}$ receptor antagonists SB-200646A or SB-206553 (42) antagonize mCPP-induced hypophagia, hypolocomotion and anxiety. The selective 5-HT_{2C} receptor antagonist SB-242084 also potently antagonizes mCPP-induced hypolocomotion and hypophagia. Somewhat surprisingly, RS-102221 does not antagonize the hypolocomotor response, possibly due to a restricted brain penetration (43).

When administered alone, 5-HT_{2C} receptor antagonists are anxiolytic in various animal models. Available evidence suggests that animals treated with these drugs do not overeat or have a propensity for epileptic convulsions, even though both of these features are characteristic of 5-HT_{2C} knockout mice. Thus, the abnormalities in the knockout mice may be developmental in nature and not due to the loss in the adult of 5-HT_{2C} receptor function (44).

There are recent reports that 5-HT_{2C} antagonists increase the release of noradrenaline and dopamine in microdialysis experiments. These data suggest that 5-HT_{2C} receptors exert a tonic inhibitory influence on mesocortical/mesolimbic dopaminergic and noradrenergic projections. In rat, corticosterone and ACTH responses to mCPP and similar agonists may be mediated via the 5-HT_{2C} receptor. There is evidence that in humans, mCPP-induced prolactin secretion also involves 5-HT_{2C} receptor activation. Finally, in humans, blockade of 5-HT_{2C} receptors is thought to increase slow wave sleep (45-49).

5-HT_{2C} and obesity

Obesity, the storage of excess fat, results from the ingestion of more food than is necessary for the body's energy needs. However, there is no clear definition of a "normal" amount of body fat and it is difficult to measure body fat content; thus, most clinical and epidemiological studies use "surrogate markers" of fatness such as body mass index (BMI) and waist circumference. The BMI is calculated as body weight in (kg) by height squared (m^2) and can be used to distinguish between healthy weight (18.1-25.0), underweight (<18), overweight (25.1-29.9) and obese (>30). Fat distribution can also be assessed by measuring the circumference of the waist and hip to obtain the waist:hip ratio (50).

During the development of obesity, several factors contribute to a state of positive energy balance (weight gain). For example, hypothalamic defects such as tumors can result in obesity. If the balance between the hunger and satiety centers in the hypothalamus is improper, the patients may have a constant prolonged urge to eat. In addition, emotional stress may also cause a hypothalamic imbalance, so that a person experiencing emotional stress may overeat. However, in most cases of obesity no specific cause can be detected (51).

Obesity can be considered to be of two types: hypertrophic and hyperplastic (51). In hypertrophic obesity (also called adult onset obesity) people who were thin or of average weight and quite active when young become less active as they become older. They begin to gain weight at age 20 to 40, and, although they no longer use as many calories, they still take the same amount of food as when they were younger. The unused calories are turned into fat. In this type of obesity, the amount of fat in each adipocyte (fat cells) increases, but the total number of adipocytes does not increase.

In hyperplastic obesity (occurring early in life) the total number of adipocytes increases. People with hyperplastic obesity are obese as children and become more obese with age. This type of obesity is a major health problem in school-aged children.

Being overweight or obese is a major risk factor in the development of type II diabetes in men and even more so in women. Obesity is also associated with increased risk of back pain and osteoarthritis; modest weight loss can bring substantial release from these symptoms (51). As a result of the prevalence and enhanced risk associated with this chronic disease, efforts to develop innovative and more effective antiobesity drugs have intensified.

At present, the most promising target for the development of novel antiobesity treatment appears to be the 5-HT_{2C} receptor subtype (52, 53). The role of this receptor in the control of feeding in animals has been established through the use of selective 5-HT_{2C} receptor agonists, antagonists and transgenic mouse models (54). Moreover, detailed behavioral analysis suggests that 5-HT_{2C} receptor agonists have a specific effect on feeding and probably reduce food intake by enhancement of satiety. It appears from both preclinical and clinical data that the 5-HT_{2C} receptor is largely responsible for the clinical efficacy of the antiobesity drug, dexfenfluramine (**26**) (55) (Fig. 4). Despite the efficacy of dexfenfluramine (a 5-HT-releasing agent) as an antiobesity drug, it ultimately failed as a treatment option because of side effects and toxicity. 5-HT_{2C} receptors are apparently absent in peripheral tissues and therefore activation of 5-HT_{2C} receptors is unlikely to be responsible for the cardiac valvular toxicity and primary pulmonary hypertension associated with dexfenfluramine. Direct activation of 5-HT_{2C} receptors by administration of a selective 5-HT_{2C} receptor agonist therefore represents a potential opportunity to develop a safe and effective antiobesity agent.

Sibutramine (**28**) (a 5-HT and noradrenaline reuptake inhibitor) and fluoxetine (**27**) (a selective serotonin reuptake inhibitor) increase extracellular levels of 5-HT and thereby nonselectively cause stimulation of all postsynaptic 5-HT receptor subtypes (Fig. 4). This nonselective postsynaptic stimulation can in turn activate 5-HT_{2C} receptors, which is thought to be involved in their clinical efficacy as antiobesity drugs (56, 57). Therefore, selective 5-HT_{2C} receptor agonists may represent a direct means to produce beneficial therapeutic effects.

There is increasing evidence for an important role of the 5-HT_{2C} receptor in the control of ingestive behavior.

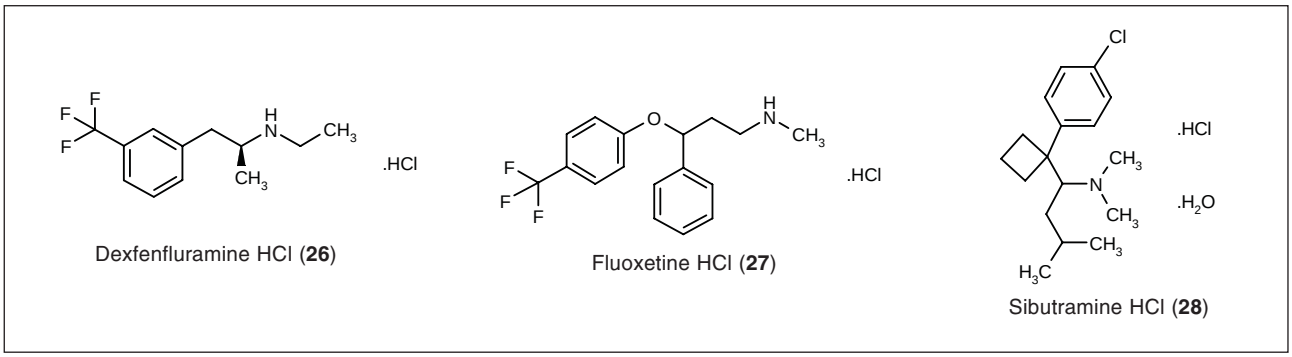

Fig. 4. Drugs that increase extracellular serotonin levels resulting in 5-HT$_{2C}$ activation.

For example, the acute administration of the 5-HT$_{2C}$ receptor agonist, mCPP, induces hypophagia in rats. In addition, it has been shown that mutant mice lacking functional 5-HT$_{2C}$ receptors exhibit obesity corroborating the notion that the 5-HT$_{2C}$ receptor is involved in the regulation of food intake (58).

Furthermore, since the hypothalamus has been extensively implicated in the control of ingestive behavior, the effect of chronic drug administration on 5-HT$_{2C}$ receptor mRNA levels in the hypothalamus was assessed using mCPP. This chronic treatment with mCPP did not affect hypothalamic 5-HT$_{2C}$ receptor mRNA levels suggesting that 5-HT$_{2C}$ receptors were not downregulated by this treatment regime (59).

Receptor binding studies and functional models have demonstrated that mCPP has approximately 10-fold selectively for the 5-HT$_{2C}$ receptor over the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors where it acts as a partial agonist. In similar models, mCPP has 10-fold selectivity for the 5-HT$_{2C}$ over the 5-HT$_{2A}$ receptor where it may act as an antagonist. In a recent characterization study at cloned human receptors, mCPP was reported to be only 3-fold selective for the 5-HT$_{2C}$ receptor over the 5-HT$_{2A}$ receptor and approximately equipotent at the 5-HT$_{2C}$ and 5-HT$_{2B}$ receptor. However, the relative efficacy of mCPP at 5-HT$_{2A}$ and 5-HT$_{2B}$ receptor was considerably lower than that at the 5-HT$_{2C}$ receptor. With the exception of the 5-HT$_3$ receptor (96-fold selectivity), which has little documented role in rodent feeding, mCPP has greater than 100-fold selectively for other 5-HT receptors. The recent demonstration that mCPP (a nonselective 5-HT$_{2C}$ partial agonist) reduces appetite and body weight in obese humans has intensified discovery efforts to design novel selective 5-HT$_{2C}$ agonists for treating obesity (59).

Research efforts by Bos and coworkers at Hoffmann-La Roche (60) led to the synthesis of a novel series of indoles and 1,4-dihydroindeno[1,2-*b*]-pyrroles in which a 2-aminopropyl side chain is attached to the N atom of the heterocycle. In analogy to the phenyl-alkyl-amines, the alpha methyl group was incorporated in order to suppress metabolic side chain deamination and to increase the lipophilicity of the compound allowing better CNS penetration. Within these series, two key compounds, Ro-60-0175 (**4**) and Ro-60-0332 (**5**) were identified as agonists at the 5-HT$_{2C}$ receptor with good selectivity over the 5-HT$_{2A}$ receptor. Ro-60-0175 is a high efficacy agonist (K_i = 1.3 nM at human cloned 5-HT$_{2C}$ receptor with EC_{50} = 200 nM) and is claimed to be 100-fold selective over other 5-HT receptors with the exception of the 5-HT$_{2B}$ receptor at which it also has high affinity and efficacy. However, a recent study suggests that the compound may only be 14-fold selective for the human 5-HT$_{2C}$ receptor over the human 5-HT$_{2A}$ receptor where, unlike mCPP, it exhibits high efficacy. Ro-60-0175 (3 mg/kg) has been reported to significantly decrease rat food intake (*i.e.*, increased latency to first meal and reduced meal size) and to have a similar effect on the microstructure of feeding behavior to dexfenfluramine. When Ro-60-0175-induced hypophagia (3 mg/kg) was challenged by SB-242084 (1, 3 mg/kg), a significant attenuation in the decrease in feeding rate and increase in latency to feed was observed. Ro-60-0332 is also a high efficacy agonist (K_i = 3.2 nM at human cloned 5-HT$_{2C}$ receptor with EC_{50} = 200 nM) on feeding in a palatable food intake paradigm. Ro-60-0332 significantly reduced food intake at 30 mg/kg when administered orally (61, 62). These results demonstrate that Ro-60-0175 and Ro-60-0332 are useful probes for examining the importance of 5-HT$_{2C}$ receptor activation in the control of food intake, and that compounds from this chemical class may prove usefully effective drugs in the treatment of obesity.

The significant reduction in human body weight and appetite by mCPP led Welmaker and coworkers at Wyeth-Ayerst into performing a substructure search through their corporate data bank for phenylpiperazine-like agents. This search revealed a series of 2,3,4,4a-tetrahydro-1*H*-pyrazino[1,2-*a*] quinoxalin-5-(6*H*)ones originally evaluated as antihypertensive agents. Subsequent screening for 5-HT$_{2C}$ receptor binding and analog synthesis lead to a series of 2,3,4,4a-tetrahydro-1*H*-pyrazino[1,2-*a*] quinoxalin-5-(6*H*)ones and 2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*] quinoxalines with potent 5-HT$_{2C}$ receptor agonist activity *in vitro* and *in vivo* (63). In the quinoxalone series, the R-enantiomers **6** (K_i = 3 nM at human cloned 5-HT$_{2C}$ receptor with EC_{50} = 8 nM) and **7** (K_i = 25 nM at human cloned 5-HT$_{2C}$

receptor with EC_{50} = 19 nM) demonstrated potent activity and functioned as full agonists. In contrast, in the quinoxaline series **9** (K_i = 7 nM at human cloned 5-HT_{2C} receptor with EC_{50} = 49 nM) there was no significant difference in binding activity at the 5-HT_{2C} receptor between the two enantiomers; functionally however, only the R-enantiomer exhibited full agonism. Compound **6**, when administered to fasted rats (feeding model) produced a dose-dependent decrease in food intake with ED_{50} values of 2 mg/kg (intraperitoneal) and 10 mg/kg (oral). This again is glaring evidence that 5-HT_{2C} agonists can regulate feeding behavior.

Another class of 5-HT_{2C} agonist with potential antiobesity property is the pyrrolo[3,2,1-*ij*]quinoline derivatives, exemplified by ALX-2218 (**13**) and ALX-2226 (**14**), developed at NPS Allelix (64). Compound ALX-2218 (K_i = 41 nM at human cloned 5-HT_{2C} receptor with EC_{50} = 0.2 nM) and ALX-2226 (K_i = 47 nM at human cloned 5-HT_{2C} receptor with EC_{50} = 0.23 nM) were found to be full agonists at the 5-HT_{2C} receptor subtype with good functional selectivity over the 5-HT_{2A} receptor subtype. Efforts to determine the *in vivo* efficacy of these ligands in animal feeding models will provide further evidence for the role of the 5-HT_{2C} receptor in obesity.

Workers at Cerebrus Pharmaceuticals recently reported a series of indole, indazole, and indoline derivatives as antiobesity agents. Compound **8** showed K_i values of 110 nM, 229 nM and 457 nM against 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptor binding respectively. The quinoline-derived indole **11** possessed enhanced potency at all three receptor subtypes with K_i values of 9 nM, 12 nM and 45 nM against 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptor binding, respectively. The indoline series was exemplified by **12**, which showed K_i values of 55 nM, 138 nM and 252 nM against 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptor binding, respectively. In a functional activity assay using Chinese hamster ovary (CHO) cells, **12** showed higher relative efficacy in reducing response of the 5-HT_{2C} receptor (62%) compared to the 5-HT_{2A} receptor (49%) (65-68).

The piperazine derivative Org-12962 (**15**) and the pyrrolidinyloxyindane Org-37684 (**10**) are two 5-HT_{2C} receptor agonists developed by Organon. Org-12962 is a potent agonist at the 5-HT_{2C} receptor (K_i = 12 nM at human cloned 5-HT_{2C} receptor) with little selectivity over the 5-HT_{2A} receptor (K_i = 65 nM at human cloned 5-HT_{2A} receptor). Org-12962 is shown to be well tolerated in humans and would therefore be a potential drug candidate for the treatment of obesity. However, Org-37684 has a K_i value of 5 nM at human cloned 5-HT_{2C} receptor with good selectivity over the 5-HT_{2A} receptor (K_i = 320 nM). Org-37684, which was developed by optimizing Org-12962 for potency and selectivity, is yet another valuable addition to the selective 5-HT_{2C} receptor agonists as potential antiobesity agents (69).

The recent *in vitro* evaluation of novel piperazines, by researchers at Pharmacia, lead to the discovery of 1-(3-[2-(2-chloropyridin-3-yloxy)ethoxy]pyrazin-2-yl)-2-methylpiperazine (R-enantiomer) (**16**) as a very potent 5-HT_{2C} receptor agonist (K_i = 5 nM at the at human cloned 5-HT_{2C} receptor). Its use in the treatment of eating disorders was claimed, however no supporting evidence for this was provided. Nevertheless, this compound could provide further support for the hypothesis that the 5-HT_{2C} receptor is important in the regulation of food intake and hence obesity (70).

5-HT_{2C} and epilepsy

Epilepsy, a brain disorder manifested by recurrent seizures, refers to a complicated constellation of more than 40 distinct disorders. The seizure, a sudden massive neuronal discharge, can be either partial or complete, depending on the amount of brain involved or whether or not consciousness is impaired. Normally there is a balance between excitation and inhibition in the brain. When this balance is disrupted by increased excitation or decreased inhibition, a seizure may result. The neuronal discharges may stimulate muscles innervated by the nerves involved, resulting in involuntary muscle contractions, or convulsions (71).

What causes epilepsy? Epilepsy has been termed the sacred disease, caused by a misfiring of neurons in the brain. When the normal energy flow between neurons in the brain is disrupted in any way, the brain malfunctions. The effect is similar to an electrical storm, which can "short out" the power to an entire city. An epileptic seizure effectively short-circuits the brain so that it cannot interpret visual, auditory and sensory signals, nor can the brain control the muscles. Thus, an epileptic seizure can cause a person to fall down, convulse and lose consciousness.

Epilepsy can arise at any age. While the exact percentage of causal attributes is unknown, it is clear to clinicians that substantial portions of epileptic cases have strong genetic determinants. Another leading cause arises as a consequence of brain injury. These brain traumas most commonly include stroke or head injury following a motor vehicle accident. Progress in understanding the mechanisms of epilepsy during this decade of the brain has been astounding.

Researchers have found more than 40 genes that cause epilepsy in mice or humans. There is great diversity within these 40 genes and it is thought that a large portion of the human epilepsies comprises disorders in which the inheritance of two or three susceptibility genes in the same individual is required to produce epilepsy (71).

The identification of these genes, which cause the rarer forms of epilepsy, can provide powerful clues to novel antiseizure drug mechanisms and, thus, new forms of effective antiseizure drugs. In other words, the protein coded by the mutant gene can suggest new molecules to be targeted by the antiseizure drugs. These drugs might regulate the structure and function of the molecule to have antiseizure effects. Conversely, understanding the mechanism by which these drugs act may in turn provide a clue to decoding the epilepsy genes.

Even in individuals known to be at high risk for developing epilepsy, there is currently no effective method of preventing the development of the disease. In addition, once individuals become afflicted with epilepsy, doctors have no way of curing the disease. Rather, current therapies are entirely symptomatic, analogous to the treatment of diabetes with insulin. Like the diabetic, the epileptic can take drugs that inhibit the symptoms of the disease, in this case seizures, but these drugs cannot abolish the problem entirely.

There are currently several drugs in clinical use to inhibit seizures, which fall into three different categories in terms of their target (72). Most common are the drugs that affect the flow of sodium into the cell via voltage-gated sodium ion channels. A sodium ion channel is a structure in the cell membrane that is selectively permeable to sodium ions and is opened by changes in voltage across the cell membrane. Other drugs affect calcium ion channels. The third category of drugs affects some aspect of inhibitory synapses that are activated by the neurotransmitter γ-aminobutyric acid (GABA). Despite the availability of these drugs, a large proportion of patients continues to have seizures. Furthermore, among those in whom seizures are effectively inhibited, substantial numbers experienced persistent and undesirable effects from these drugs. In light of this, the current goal of researchers is to identify new classes of antiseizure drugs that act on novel molecular targets and by novel mechanisms that may permit effective treatment of large numbers of individuals unsatisfactorily treated at present. The recently cloned 5-HT$_{2C}$ receptor has revealed a novel molecular target that provides just this opportunity for the development of novel antiepileptic drugs.

Studies have shown that mice bearing a targeted disruption of the 5-HT$_{2C}$ receptor gene exhibit an epilepsy syndrome associated with sporadic spontaneous seizures that occasionally result in death. In all epileptic paradigms, mice lacking the 5-HT$_{2C}$ receptor were significantly more seizure susceptible than wild-type controls. Results indicate that mutants have lower focal seizure thresholds, increased focal seizure excitability, and facilitated propagation within the forebrain seizure system. Mutants also exhibit lower generalized seizure threshold for the expression of both generalized clonic and generalized tonic seizures. Importantly, the 5-HT receptor antagonist mesulergine (2 or 4 mg/kg), administered prior to electroshock testing, recapitulated the mutant phenotype in wild-type mice. Together, these data strongly implicate a role for serotonin and hence the 5-HT$_{2C}$ receptor in the modulation of neuronal network excitability and seizure propagation globally, throughout the CNS (73-75).

Fluoxetine (**27**), a selective serotonin reuptake inhibitor, has been documented to exert a protective action against convulsive seizures in animal models when administered systemically or focally into the substantia nigra (76). In addition to fluoxetine, the directly acting 5-HT$_{2C}$ receptor agonists mCPP and TFMPP, when microinjected bilaterally into the substantia nigra, protected rats from limbic motor seizures. This indicates that the 5-HT$_{2C}$ receptor subtype in the substantia nigra may contribute to seizure regulation (77, 78). Furthermore, among the clinically effective anticonvulsants such as carbamazepine, dose-related anticonvulsant effects correlate with increased extracellular serotonin further implicating the role of serotonin and hence the 5-HT$_{2C}$ receptor agonist in epileptic seizures. Nevertheless, cross talk between the 5-HT$_{2C}$ and GABA receptors in the mediation of the observed anticonvulsant activity should not be overlooked (79).

In additional studies, the 5-HT$_{2C/2B}$ receptor-preferring agonist mCPP weakly elevated seizure threshold in mice (but not in rats) electroshock test; however, appreciable protection against pentylenetetrazol-induced myoclonic and/or tonic seizures in mice and rats was observed. This protection against pentylenetetrazol-induced myoclonic and/or tonic seizures in mice and rats was inhibited by the 5-HT$_{2C/2B}$ receptor antagonist SB-206533. The fact that the 5-HT$_{2B}$ agonist BW-723C86 had no effect on animal seizure models further indicates that the 5-HT$_{2C}$ receptor mediated the mCPP induced anticonvulsant effects (80).

The selective 5-HT$_{2C}$ receptor antagonist SB-242084 does not induce proconvulsant effects in rats, which are characteristic of mutant mice lacking the 5-HT$_{2C}$ receptor. This failure to exhibit proconvulsant properties in rats in contrast to the reported characteristics of mutant mice lacking 5-HT$_{2C}$ receptors might be accounted for by species differences (81).

To further realize the growing potential of 5-HT$_{2C}$ agonists as useful antiepileptic drugs, a larger number of the more selective 5-HT$_{2C}$ agonist ligands (Fig. 2) recently identified need to be evaluated in preclinical and clinical epileptic paradigms.

Conclusions

The 5-HT$_{2C}$ receptor subtype appears to be a rational target for the development of novel antiobesity and antiepileptic drugs. The effects seen with 5-HT$_{2C}$ agonists are consistent with data on mutated 5-HT$_{2C}$ receptor deficient animals suggesting that the 5-HT$_{2C}$ receptor may mediate anorectic feeding behavior and tonic inhibition of neuronal network excitability. Polymorphism at the 5-HT$_{2C}$ receptor gene has been proposed for the association with a number of CNS disorders. However, the possible role of somatic mutations in the 5-HT$_{2C}$ receptor in the genetic predisposition to or pathophysiology of obesity and epilepsy cannot be excluded. Recent advances in the understanding of the biology and function of the 5-HT$_{2C}$ receptor, along with the design and development of novel, potent and selective agonist ligands, raises the exciting possibility of an entirely novel class of antiobesity and antiepileptic drugs in the future.

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