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New therapeutic opportunities for 5-HT$_2$ receptor ligands

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ABSTRACT

Serotonergic dysfunction is mainly associated with neuropsychiatric and cardiovascular disorders but has also been linked with many other pathological conditions. Serotonin (5-hydroxytryptamine, 5-HT) mediates numerous physiological functions in the brain and the periphery by activating a variety of receptors. 5-HT receptors are divided into four classes, three of which belong to the G protein-coupled receptor family. This review provides an overview of the recent pharmacological developments involving the Gq-coupled 5-HT$_2$ receptor subfamily as well as the pathological implications of this receptor subfamily with regard to fibrosis, the central nervous system, cardiovascular disorders, and cancer. The final section highlights new therapeutic opportunities and emerging research revealing unexplored medical opportunities for this class of 5-HT receptors. The development of biased 5-HT$_2$ receptor ligands appears to be an interesting topic in various areas. In light of recent discoveries, the need for the development of new and safer drugs should take into account the risk of cardiovascular side effects such as pulmonary hypertension and heart valve disease.

Contents

1. Introduction

This review focuses on three serotonin (5-hydroxytryptamine, 5-HT) receptors belonging to the 5-HT$_2$ receptor subfamily: the 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ subtypes. Although the work by Julius et al. (1988) was the first to report the cloning of a full-length functional serotonin receptor from rat (the 5-HT$_{1c}$ receptor), this publication was shortly followed by considerable efforts from several groups that cloned other unidentified 5-HT receptors. The classical 5-HT$_2$ receptor described by Peroutka et al. (1981) was cloned from rats slightly later in 1988 (Pritchett et al., 1988) followed by human analogue (Branchek et al., 1990; Saltzman et al., 1991) and was renamed 5-HT$_{2A}$. The 5-HT$_{1c}$ receptor was renamed 5-HT$_{2C}$ because of its structural similarity to the other 5-HT$_2$ receptor, identical second messenger pathways, and similar pharmacological properties. Pharmacological studies attempting to characterize the contractile serotonergic receptor in the rat stomach fundus initially documented its similarity to the 5-HT$_{2C}$ receptor. Despite the absence of detectable 5-HT$_{2C}$ receptor mRNA in the rat

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stomach fundus, only homology cloning permitted the identification of a new receptor in 1992 in rat and mouse that was named 5-HT_{2B} (Foguet et al., 1992a, 1992b; Kursar et al., 1992; Loric et al., 1992; Wainscott et al., 1993) and in 1994 in humans (Choi et al., 1994; Kursar et al., 1994; Schmuck et al., 1994; Wainscott et al., 1996).

The investigation of the contribution of these three 5-HT_2 receptors in mammalian physiology has led to a large number of reports in nearly all functions and organs. Some selective compounds stimulating or blocking these receptors provided an opportunity to explore various areas of human diseases. In this review, we will emphasize some important aspects of the cellular and molecular biology of these receptors and highlight some clinical situations in which these receptors appear as pathophysiological cornerstones.

2. 5-HT_2 receptors: structure, coupling, oligomerization, selective ligands, allosteric modulators, biased agonists

The closely related 5-HT_2 receptors are members of the rhodopsin family of G protein-coupled receptors (GPCRs) that activate multiple intracellular signalling networks. The classical signal transduction pathway for this subfamily is the Gq/11-coupled activation of phospholipase C (PLC), although these 5-HT_2 receptors can also activate phospholipase D and phospholipase A2 by interacting with additional pathways. These 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors are post-transcriptionally modified by alternative RNA splicing, a common mechanism for achieving protein diversity. RNA editing, on the other hand, is a less common process for generating molecular diversity. In fact, the 5-HT_{2C} receptor is one of the few GPCRs known to be edited. RNA editing of the 5-HT_{2C} receptor generates functionally distinct protein variants by altering the genetic code at the mRNA level.

2.1. Structure

5-HT_2 receptors are 7 transmembrane domain receptors with fairly long extracellular N-terminal loops ranging from 55 amino acids for the human 5-HT_{2B} and 5-HT_{2C} receptors to 75 amino acids for the human 5-HT_{2A} receptor and an intracellular C-terminus ranging from 85 amino acids for the human 5-HT_{2B} receptor to 75 amino acids for the human 5-HT_{2A} and 5-HT_{2C} receptors. A new and unanticipated role of the 5-HT_{2B} receptor N-terminus as a negative modulator affecting both constitutive and agonist-stimulated activity of the receptor has been shown (Belmer et al., 2014). The recently published crystal structure of the 5-HT_{2B} receptor bound to ergotamine showed that this receptor exhibits conformational characteristics in both the active and inactive states: an active-like state in the helix VII conformation of the 5-HT_{2B} receptor but only partial changes in helix VI. The differential signalling patterns were also mirrored in the crystal structures, which showed features of a β-arrestin-biased activation state for the 5-HT_{2B} receptor (Wacker et al., 2013; Wang et al., 2013). A likely structural explanation for the distinct conformational features and biased pharmacology of ergotamine for 5-HT_{2B} receptors can be found in the region of the extracellular loop 2 (ECL2) junction with helix V (E212-R213-F214), which forms an additional helical turn stabilized by a structured water molecule at the extracellular tip of helix V. The segment of ECL2 connecting helices III and V via the conserved disulphide bond is shortened in the 5-HT_{2B} receptor and creates a conformational constraint on the position of the extracellular tip of helix V (Martí-Solano et al., 2014). However, this structured water molecule involved in the ECL2 junction with helix V has been challenged since differential interactions of ergotamine with the top of helices V and VI could determine the rotational freedom of helix VI (Liu et al., 2013). No crystal structures have reported yet for the 5-HT_{2A} or 5-HT_{2C} receptors.

More work is needed to precisely understand the structure and function of these receptors as well as their specific properties.

2.2. Selective agonists

There is virtually no highly selective agonist for a particular 5-HT_2 receptor:

- BW723C86: 1-methyl-2-[5-(2-thienylmethoxy)-1H-indole-3-yl] ethylamine hydrochloride has been reported to have 10-fold selectivity over the human 5-HT_{2C} and 100-fold selectivity over the 5-HT_{2A} receptors (Porter et al., 1999; Jerman et al., 2001; Knight et al., 2004; Cussac et al., 2008). Lorcaserin [(1*R*)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3 benzazepine] has approximately 10-fold higher affinity for 5-HT_{2C} receptor (Thomsen et al., 2008) over the 5-HT_{2A} and 5-HT_{2B} receptors.
- Nor-dexfenfluramine (a metabolite of dexfenfluramine), methylergonovine (a metabolite of methysergide), and Ro 60-0175: 2(*S*)-1-(6-chloro-5-fluoro-1H-indol-1-yl)-2-propanamine fumarate are all preferential 5-HT_{2B} agonists with approximately 10-fold selectivity over the 5-HT_{2C} receptor (Cussac et al., 2002).
- 2,5-dimethoxy-4-iodoamphetamine (DOI) is a non-selective nearly full agonist at 5-HT_2 receptors with similar affinity to the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors (Porter et al., 1999; Jerman et al., 2001; Knight et al., 2004; Cussac et al., 2008).
- Alpha-methyl-5-HT is a non-selective nearly full agonist at 5-HT_2 receptors with a similar affinity towards the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors (Porter et al., 1999; Jerman et al., 2001; Knight et al., 2004).

2.3. Selective antagonists

A few selective antagonists are available for the 5-HT_2 receptor subtypes:

- The first highly selective 5-HT_{2A} receptor antagonist reported was MDL100907 [(*R*)-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol] (Knight et al., 2004). Sarpogrelate [succinic acid mono-(1-dimethylaminomethyl-2-(2-[2-(3-methoxyphenyl) ethyl] phenoxy) ethyl) ester hydrochloride], SR46349B [4-((3Z)-3-(2-dimethylaminoethyl)oxyimino-3-(2-fluorophenyl)propen-1-yl)phenol hemifumarate], and ketanserin [3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]quinazoline-2,4(1*H*, 3*H*)-dione] are preferential 5-HT_{2A} receptor antagonists with a 10-fold higher affinity over the 5-HT_{2C} and/or 5-HT_{2B} sites.
- The first highly selective 5-HT_{2B} receptor antagonist reported was LY266097: 1-(2-chloro-3,4-dimethoxybenzyl)-6-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole hydrochloride, with a pKi of 9.7 for the human cloned 5-HT_{2B} receptor and a 100-fold greater selectivity over human 5-HT_{2C} and 5-HT_{2A} receptors (Audia et al., 1996). SB204741: *N*-(1-methyl-5-indolyl)-*N*′-(3-methyl-5-isothiazolyl) urea has been reported as a selective 5-HT_{2B} receptor antagonist with approximately 100-fold selectivity over the 5-HT_{2C} and 5-HT_{2A} receptors but with a low potency (Ki approximately 100 nM) (Bonhaus et al., 1995). The tetrahydro-β-carboline LY272015 [6-chloro-5-methyl-*N*-(5-quinolinyl)-2,3-dihydro-1H-indole-1-carboxamide] is also a fairly selective and highly potent antagonist (Cohen et al., 1996). RS127445 [2-amino-4-(4-fluoronaphth-1-yl)-6-isopropylpyrimidine] was found to have sub-nanomolar affinity for the 5-HT_{2B} receptor (pKi = 9.5) and 1000-fold selectivity for this receptor compared to numerous other receptor and ion channel binding sites and appears as the most selective, high-affinity 5-HT_{2B} receptor antagonist currently available (Bonhaus et al., 1999). SB215505 [6-chloro-5-methyl-*N*-(5-quinolinyl)-2,3-dihydro-1H-indole-1-carboxamide] behaves as a high-affinity and preferential inverse agonist at 5-HT_{2B} receptors (Reavill et al., 1999).
- SB242084 [6-chloro-5-methyl-1-[6-(2-methylpyridin-3-yloxy) pyridin-3-yl-carbamoyl]indoline] and RS-102221 [*N*-[5-[5-(2,5-dioxo-spiro[imidazolidine-4,4′-piperidin]-1′-yl)pentanoyl]-2,4-