Pharmacology & Therapeutics 157 (2016) 125–162

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

New therapeutic opportunities for 5-HT_{2C} receptor ligands in neuropsychiatric disorders☆

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ARTICLE INFO

Available online 23 November 2015

Keywords:
5-HT receptors
mRNA editing
G protein coupled receptors
Receptor oligomers
Dopamine
GABA

ABSTRACT

The 5-HT_{2C} receptor (R) displays a widespread distribution in the CNS and is involved in the action of 5-HT in all brain areas. Knowledge of its functional role in the CNS pathophysiology has been impaired for many years due to the lack of drugs capable of discriminating among 5-HT_2R subtypes, and to a lesser extent to the 5-HT_{1B}, 5-HT_5, 5-HT_6 and 5-HT_7Rs. The situation has changed since the mid-90s due to the increased availability of new and selective synthesized compounds, the creation of 5-HT_{2C} knock out mice, and the progress made in molecular biology. Many pharmacological classes of drugs including antipsychotics, antidepressants and anxiolytics display affinities toward 5-HT_{2C}Rs and new 5-HT_{2C} ligands have been developed for various neuropsychiatric disorders. The 5-HT_{2C}R is presumed to mediate tonic/constitutive and phasic controls on the activity of different central neurobiological networks. Preclinical data illustrate this complexity to a point that pharmaceutical companies developed either agonists or antagonists for the same disease.

In order to better comprehend this complexity, this review will briefly describe the molecular pharmacology of 5-HT_{2C}Rs, as well as their cellular impacts in general, before addressing its central distribution in the mammalian brain. Thereafter, we review the preclinical efficacy of 5-HT_{2C} ligands in numerous behavioral tests modeling human diseases, highlighting the multiple and competing actions of the 5-HT_{2C}Rs in neurobiological networks and monoaminergic systems. Notably, we will focus this evidence in the context of the physiopathology of psychiatric and neurological disorders including Parkinson's disease, levodopa-induced dyskinesia, and epilepsy.

Contents

Abbreviations: 5-HT_{2C} receptor, serotonin2C receptor; DRN, dorsal raphe nucleus; MRN, medial raphe nucleus; DA, Dopamine; 6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; CNS, Central Nervous System; HFS, high frequency stimulation; NAcc, Nucleus Accumbens; STN, subthalamic nucleus; EPN, entopeduncular nucleus; GPCRs, G-protein coupled receptors; GPi, internal globus pallidus; GPe, external globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; *m*-CPP, metachlorophenylpiperazine; TFMPP, Trifluoromethylphenylpiperazine; 8-OH-DAT, 8-hydroxy-2-(di-n-propylamino)tetralin; DOI, 1-hili-2-aminopropane; GAD, glutamic acid decarboxylase; TH, tyrosine hydroxylase; Q-PCR, quantitative polymerase chain reaction; PLC, phospholipase C; PLA_2, phospholipase A_2; BOLD, blood oxygen dependent level; OCD, Obsessive Compulsive Disorders; ICD, impulse control disorders; 5-HT, 5-hydroxytryptamine (serotonin); EPS, extrapyramidal side effects.

☆ Conflict of interest: The authors declare that there are no conflicts of interest.

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http://dx.doi.org/10.1016/j.pharmthera.2015.11.009
0163-7258/

1. Introduction

Many pharmacological classes of drugs including antipsychotics, antidepressants andanxiolytics, may display affinities toward the serotonin (5-hydroxytryptamin, 5-HT) 2C receptors (5-HT_{2C}Rs) (Jenck et al., 1998; Millan, 2006; Richtand et al., 2008; Meltzer et al., 2010b). Knowledge of its functional role has been limited for many years due to the lack of drugs discriminating 5-HT_{2C}Rs from the 5-HT_{2A} and 5-HT_{2B}R subtypes as well as, to a lesser extent, the 5-HT_{1B}, 5-HT_5, 5-HT_6 and 5-HT_7R subtypes (Zifa & Fillion, 1992; Hoyer et al., 2002). The situation has changed since the mid-90s with the progressive availability of new and selective synthesized compounds. Concomitantly to the development of a selective pharmacology, knockout (KO) mice were also obtained in the middle of 90s (Tecott et al., 1995) and the editing of the mRNA in the Rs coding sequence, a fundamental molecular event modifying the function of the receptor, was demonstrated two years later (Burns et al., 1997). Thus, the understanding of the role of 5-HT_{2C} receptors has rapedely accelerated since then, more than 10 years after its discovery (Pazos et al., 1984a).

Among the numerous 5-HTRs that have been mentioned, the 5-HT_{2C}R is probably the one with the most widespread distribution in the CNS and is able to mediate the action of 5-HT in virtually all brain areas. It is suspected to mediate tonic/constitutive and phasic controls in the activity of central neurobiological networks (Tecott et al., 1995; Berg et al., 2005, 2008; Navailles et al., 2013a). Its molecular properties (Schmauss, 2005) and its functional organization in the brain (Millan, 2005) imply that the 5-HT_{2C}R might be a target of survey. Virtually any medicine, including drugs of abuse, which modify the function of neurobiological networks would change the activity of 5-HT_{2C}Rs, likely in a region-dependent manner. Changes of 5-HT_{2C}R function have been evidenced in numerous psychiatric diseases. Selective 5-HT_{2C} ligands have been synthesized for the treatment of anxiety, depression, food intake and schizophrenia, and could be valuable in treating other psychiatric (Higgins & Fletcher, 2003; Giorgetti & Tecott, 2004; Millan, 2005; Rosenzweig-Lipson et al., 2012; De Deurwaerdere et al., 2013; Higgins & Fletcher, 2015; Howell & Cunningham, 2015a) and neurological diseases (Di Giovanni et al., 2006; Di Matteo et al., 2008; De Deurwaerdere et al., 2013; Di Giovanni, 2013). It is intriguing that both agonists and antagonists at 5-HT_{2C}Rs are proposed in the treatment of anxiety/depression and can also be utilized in the treatment of schizophrenia. This apparent paradox could be related to the specificity of the animal models used, the lack of pharmacological distinction between antagonists and inverse agonists, and/or the concomitant, multiple, and competing actions of 5HT_{2C}Rs in the brain as well as the combinated action among 5-HTRs and neurotransmission systems.

In order to better apprehend this complexity, this review will briefly describe the molecular pharmacology of 5-HT_{2C}Rs and their central distribution. The efficacy of 5-HT_{2C} agonists, antagonists and inverse agonists has been presented in numerous preclinical studies on mood disorders, addiction, obsessional compulsive disorders, energy balance, and motor disturbances, to highlight the clinical interests of 5-HT_{2C} pharmacy and to emphasize the existence of multiple brain targets and neurobiological networks for a single receptor. Several preclinical tests have stressed a role for 5-HT_{2C}Rs on modulation of monoaminergic systems, notably dopamine (DA). Finally, we furthered these notions in the context of the physiopathology of schizophrenia, Parkinson's disease, spinal cord injury and epilepsy.

2. Molecular pharmacology of 5-HT_{2C} receptors

2.1. 5-HT_{2C} receptor pharmacology

The 5-HT_{2C}R was discovered in 1984 and was initially termed 5-HT_{1C}R (Pazos et al., 1984a; Yagaloff & Hartig, 1985). It corresponded to a 5-HTR with a nanomolar affinity for 5-HT (5-HT1 subtype) and to a distinct pharmacology and distribution compared to the other existing subtypes, 5-HT_{1A} and 5-HT_{1B}Rs (Pedigo et al., 1981). In terms of ligand affinity, the pharmacology of 5-HT_{2C}R was similar to the 5-HT_2R which was characterized by its low affinity for 5-HT. The 5-HT_2Rs form a closely-related subgroup of G-protein coupled receptors (GPCR) and depict the typical heptahelical structure of an integral membrane protein. The 5-HT_2Rs are currently classified as 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes (Humphrey et al., 1993; Hoyer et al., 1994). The amino acid sequences of the 5-HT_2Rs share a high degree (>70%) of identity within the transmembrane segments (Hannon & Hoyer, 2008). Consequently, it is not surprising that many compounds bind with high affinity to all these three receptor subtypes. The three receptors couple the Gq/11 protein and stimulate phospholipase C (PLC) (Boess & Martin, 1994; Barnes & Sharp, 1999; Hoyer et al., 2002; Hannon & Hoyer, 2008).

Table 1 illustrates the affinity of various ligands that are able to bind with 5-HT_{2C}Rs and emphasizes the selective antagonists or preferential agonists that have been synthesized since the mid 90s. The pharmacology remains similar between 5-HT_2R subtypes and even selective compounds such as SB 242084 (selective 5-HT_{2C} ligand) or SR 46349 (selective 5-HT_{2A} ligand), have to be used with caution if the purpose is to discriminate between 5-HT_{2C}Rs and the other subtypes in a biological response (Sotty et al., 2009; Scarlota et al., 2011). The 5-HT_2R subtypes are also interesting because in view of their ability to bind a variety of psychoactive drugs, including some antidepressants (Marek et al., 1989; Fontaine, 1993; Jenck et al., 1994; Palvimaki et al., 1996; Dremencov et al., 2005; Millan, 2005, 2006), anxiolytic/anxiogenic (Curzon & Kennett, 1990; Millan, 2005; Jensen et al., 2010), antipsychotic (Canton et al., 1990; Herrick-Davis et al., 2000; Rauser et al., 2001; Meltzer et al., 2003; Rosenzweig-Lipson et al., 2007), hallucinogenic (Leysen, 2004; Nichols, 2004) and anorexogenic (Higgins & Fletcher, 2015; Voigt & Fink, 2015) drugs. The involvement of 5-HT_{2C}Rs in various CNS pathologies and the identification of their function in numerous cerebral networks continue to stimulate the search for new ligands that are either selective, such as lorcaserin (Thomsen et al., 2008), (1R, 3S)-(−)-trans-PAT (Booth et al., 2009), vabicaserin (Dunlop et al., 2011), (+)-((1S,2S)-2-(2-(Allyloxy)-5-fluorophenyl)cyclopropyl)methanamine (Cheng et al., 2015) or multitarget compounds such as CP 809,101 (Siuciak et al., 2007), S32006 (Dekeyne et al., 2008), S32212 (Millan et al., 2012) or (−)-trans-(2S,4R)-4-(3′[meta]-bromophenyl)-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine ((−)-MBP) (Canal et al., 2014) (Table 1).

2.2. 5-HT_{2C} receptor coupling

Stimulation of the 5-HT_{2C}R usually excites neurons and cells that express the receptor in various tissues (Hoyer et al., 2002). Fig. 1 reports some intracellular pathways that could contribute to 5-HT_{2C}R-dependent transmission. Indeed, 5-HT_{2C}R agonists enhance phosphoinositol (IP) turnover via Gq protein coupling and the activation of PLC (Conn et al., 1986; Berg et al., 1998c; Chang et al., 2000),