Progress in Neuro-Psychopharmacology & Biological Psychiatry 66 (2016) 120–135

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

5-HT2C receptors in psychiatric disorders: A review

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ARTICLE INFO

Article history:
Received 10 November 2015
Received in revised form 25 December 2015
Accepted 26 December 2015
Available online 29 December 2015

Keywords:
5HT2C signaling
MRNA-editing
Gene polymorphism
Constitutive activity
Psychiatric disorders

ABSTRACT

5-HT2Rs have a different genomic organization from other 5-HT2Rs. 5HT2CR undergoes post-transcriptional pre-mRNA editing generating diversity among RNA transcripts. Selective post-transcriptional editing could be involved in the pathophysiology of psychiatric disorders through impairment in G-protein interactions. Moreover, it may influence the therapeutic response to agents such as atypical antipsychotic drugs. Additionally, 5-HT2CR exhibits alternative splicing.

Central serotonergic and dopaminergic systems interact to modulate normal and abnormal behaviors. Thus, 5HT2CR plays a crucial role in psychiatric disorders. 5HT2CR could be a relevant pharmacological target in the treatment of neuropsychiatric disorders. The development of drugs that specifically target 5-HT2C receptors will allow for better understanding of their involvement in the pathophysiology of psychiatric disorders including schizophrenia, anxiety, and depression.

Among therapeutic means currently available, most drugs used to treat highly morbid psychiatric diseases interact at least partly with 5-HT2CRs. Pharmacologically, 5HT2CRs, have the ability to generate differentially distinct response signal transduction pathways depending on the type of 5HT2CR agonist. Although this receptor property has been clearly demonstrated, in vitro, the eventual beneficial impact of this property opens new perspectives in the development of agonists that could activate signal transduction pathways leading to better therapeutic efficiency with fewer adverse effects.

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http://dx.doi.org/10.1016/j.pnpbp.2015.12.006
0278-5846/

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1. Introduction

Since serotonin (5-HT) was identified as a brain neurotransmitter (Bogdanski et al., 1956; Twarog and Page, 1953), it has been shown to modulate a number of functions within the central nervous system including impulsivity and mood regulation (Mohammad-Zadeh et al., 2008). Moreover, some effects of 5-HT are blocked by lysergic acid diethylamide (LSD), a psychotomimetic compound, which presents structural similarity with 5-HT, and has a high affinity for 5-HT receptors. It has been hypothesized that maintaining normal mental processes (Woolley and Shaw, 1954) and mood regulation in mental illness (Whitaker-Azmitia, 1999) may involve 5-HT. It is therefore not surprising that much research has been devoted to studying the role of 5-HT in several behavioral functions, including mood, sleep cycles, aggression, appetite, learning (Mohammad-Zadeh et al., 2008), and various pathophysiological processes including neuropsychiatric disorders (Fakhoury, 2015) schizophrenia, depression, and obesity (Hoyer et al., 2002). 5-HT2C receptor is widely expressed within the central and the peripheral nervous system and appears to play a prominent role in a multitude of behaviors. New approaches and especially in molecular biology and the genetic fields have provided important insights on functional status of the 5-HT2C receptor. Furthermore, both experimental and clinical investigations emphasize the importance of this receptor as a possible therapeutic target for the development of new pharmacologically active agents for a range of mental disorders including anxiety, depression and schizophrenia. For this purpose, a comprehensive bibliography of several sources (original articles, reviews) published and indexed in PubMed, between 1990 and 2015, were identified and surveyed for this review.

2. Serotoninergic system

According to the original Dahlstroem and Fuxe's classification, the B1–B9 areas which represent the distinct raphe nuclei of the brain stem contain the central serotoninergic neurons (Dahlstroem and Fuxe, 1964). The first precise anatomical mapping of serotonergic neurons in the mammalian central nervous system (CNS) was made using fluorescence microscopy studies and allowed separate cell groups to be shown. Fluorescence histochemistry studies determined that the 5-HT2 receptor system extends from the dorsal raphe of the midbrain, pons and medulla (Dahlstroem and Fuxe, 1964). Brain stem nuclei project 5-HT-containing neurons to the forebrain. 5-HT axons in the cortex may be subdivided into two distinct projections. The thin and abundant 5-HT fibers in the cortex, originate from the dorsal raphe nucleus, whereas the thick 5-HT fibers with large varicosities originate from the median raphe nucleus and are abundant in the hippocampus (Kosofsky and Molliver, 1987). Brain 5-HT is primarily released in the neurons of the raphe nuclei (Hannon and Hoyer, 2008).

3. Distribution of 5-HT2C receptors

3.1. Localization

According to their molecular structure and pharmacological profiles, 5-HT receptors are classified into seven distinct families, 5-HT1 to 5-HT7 (Hoyer et al., 1994) (Table 1). 5-HT, interacts with at least 15 different receptor subtypes (Barnes and Sharp, 1999). 5-HT2C was originally designated as 5-HT1C because the 5-HT2C subtype has the same binding properties as 5-HT1A and 5-HT1B. The molecular cloning of the cDNA encoding this receptor showed that 5-HT2C belongs to the superfamily of seven transmembrane domain G-protein-coupled receptors (GPCR) (Werry et al., 2008). 5-HT receptor subtypes are expressed in all brain regions. Different areas of the brain as well as cell types show varying levels of 5-HT2C receptor (5-HT2CR) expression. 5-HT2CR messenger RNA (mRNA) investigation in human brain by in situ hybridization histochemistry, has shown the presence of 5-HT2CRs in the human cerebral cortex, cerebellum and substantia nigra (SN) (Pasqualetti et al., 1999). Through binding studies and distribution of 5-HT2CR mRNA it has been shown that 5-HT2CRs have a postsynaptic location; however, in some areas of the brain 5-HT2CRs may also be presynaptic (Becamel et al., 2004). 5-HT2CR is widely distributed throughout the CNS with high expression in choroid plexus epithelial cells (Herrick-Davis et al., 2015). Lower levels of expression are observed within the cingular cortex, basal ganglia (nucleus accumbens (NAc), ventral pallidum, caudate putamen and globus pallidus), amygdala, hippocampal formation (dentate gyrus subiculum), ventral tegmental area (VTA), olfactory system, epithalamus, thalamus, and subthalamus (Li et al., 2004). Using double-label fluorescence immunohistochemistry, 5-HT2CRs were detected at high levels on parvalbumin GABAergic neurons in the prelimbic prefrontal cortex (PFC) and to a lesser degree on pyramidal glutamatergic neurons (Alex and Pehek, 2007; Di Giovanni et al., 2000). Using anterograde and retrograde tract-tracing combined with GABA immunocytochemistry and electron microscopy in the rat, it has been shown that 5-HT2CRs are predominantly colocalized with γ-aminobutyric acid (GABA) but are expressed at lower levels on dopamine neurons within the ventral tegmental area (Carr and Sesack, 2000).

3.2. Genomic organization of 5-HT2CRs

5-HT2Rs consists of three subtypes: 5-HT2A, 5-HT2B and 5-HT2C (Leysen, 2004), which have a different genomic organization from the other members of 5-HT2Rs with three introns, which separate the coding sequence into four exons. 5-HT2CR gene is located on the human X chromosome at position q24 (Xq24), and on mouse X chromosome at region d-F4 (Milatovich et al., 1992). The existence of variants of 5-HT2CR is due to an alternatively spliced variant of the 5-HT2CR RNA that contains a deletion of the region that codes for the putative second intracellular loop and the fourth transmembrane domain of the 5-HT2CR, generating a truncated non-functional isoform of the 5-HT2CR, and termed 5-HT2C-tr (Canton et al., 1996; Xie et al., 1996). Additionally, 5-HT2CR exhibits other post-transcriptional modifications generating multiple functional receptor variants through a process known as mRNA editing (Werry et al., 2008) (see below).

3.3. Posttranscriptional modification of 5-HT2CRs

5-HT2C gene may be subject to changes that consist in post-transcriptional modification by mRNA editing processes or alternative mRNA splicing.