Neuroscience and Biobehavioral Reviews 42 (2014) 208–223

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Controversies on the role of 5-HT_{2C} receptors in the mechanisms of action of antidepressant drugs

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ARTICLE INFO

Article history:
Received 3 October 2013
Received in revised form 22 January 2014
Accepted 2 March 2014

Keywords:
Depression
Anxiety
Serotonin$_{2C}$
Editing
Splicing
5-HTT
SSRI

ABSTRACT

Evidence from the various sources indicates alterations in 5-HT_{2C} receptor functions in anxiety, depression and suicide, and other stress-related disorders treated with antidepressant drugs. Although the notion of a 5-HT_{2C} receptor desensitization following antidepressant treatments is rather well anchored in the literature, this concept is mainly based on *in vitro* assays and/or behavioral assays (hypolocomotion, hyperthermia) that have poor relevance to anxio-depressive disorders. Our objective herein is to provide a comprehensive overview of the studies that have assessed the effects of antidepressant drugs on 5-HT_{2C} receptors. Relevant molecular (second messengers, editing), neurochemical (receptor binding and mRNA levels), physiological (5-HT_{2C} receptor-induced hyperthermia and hormone release), behavioral (5-HT_{2C} receptor-induced changes in feeding, anxiety, defense and motor activity) data are summarized and discussed. Setting the record straight about drug-induced changes in 5-HT_{2C} receptor function in specific brain regions should help to determine which pharmacotherapeutic strategy is best for affective and anxiety disorders.

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http://dx.doi.org/10.1016/j.neubiorev.2014.03.001
0149-7634/

1. Introduction

Growing evidence suggests an important involvement of 5-HT_{2C} receptors in both the etiology and the therapeutics of depression. Already in the mid 1980s, reduction of 5-HT_{1C} receptor binding had been observed following treatment with 5-HT receptor agonists or antidepressant drugs (ADs; Blackshear et al., 1986). The 5-HT_{1C} receptor was later renamed 5-HT_{2C} receptor (5-HT_{2C}R) based on homology with the 5-HT_2 receptor class (Loric et al., 1992). Like other receptors of this class, it activates phospholipase C (PLC) and phospholipase A2 (PLA2) and increases phosphatidyl-inositol (IP3) turnover and arachidonic acid release (Fig. 1; Masson et al., 2012). Because 5-HT_{2C}R-induced phosphatidylinositol turnover was observed mainly in the choroid plexus (Conn et al., 1986), a structure not traditionally involved in emotions, doubts were initially raised about relevance of this receptor in the therapeutics of depression. However, 5-HT_{2C}R are also present in other structures such as the septum, the hippocampus, the amygdala, the striatum, the frontal cortex (FCx), the periaqueductal gray (PAG) and the brainstem of primates and rodents (Sharma et al., 1997; Clemett et al., 2000; López-Giménz et al., 2001, 2002), *i.e.* structures all identified as being functionally important in brain mechanisms underlying emotions.

To date, there are three main sets of evidence supporting the implication of 5-HT_{2C}R in the mechanisms of action of ADs based on either 5-HT_{2C}R blockade, up-regulation of receptor function, and the activity of 5-HT_{2C}R ligands in screening behavior models of ADs action. First, as anticipated by Blackshear et al. (1986), mianserin and several classes of ADs act as antagonists with moderate to high affinity at these receptors (Jenck et al., 1993; Millan, 2005). This is notably the case of classical tricyclic ADs (TCA) such as amitriptyline, imipramine and clomipramine. In addition, ADs that selectively block noradrenaline reuptake (desipramine and maprotiline) and atypical ADs (mirtazapine, trazodone and nefazodone) also act as direct 5-HT_{2C}R antagonists. Even fluoxetine, a selective serotonin reuptake inhibitor (SSRI), exerts some antagonistic action at 5-HT_{2C}R (Ni and Miledi, 1997). Furthermore, the recently introduced AD agomelatine, initially developed as an agonist at MT_1 and MT_2 melatoninergic receptors, also blocks 5-HT_{2C}R (Millan et al., 2005, 2011), and extensive studies demonstrated that its antidepressant action requires the combined action at these two receptor types (Bertaina-Anglade et al., 2006). Although there are as yet no data concerning the effect of a selective 5-HT_{2C}R antagonist in depressed patients, a clear-cut antidepressant efficacy has been reported in a small-scale study with ritanserin, which is a potent 5-HT_{2C}R antagonist (Bakish et al., 1993).

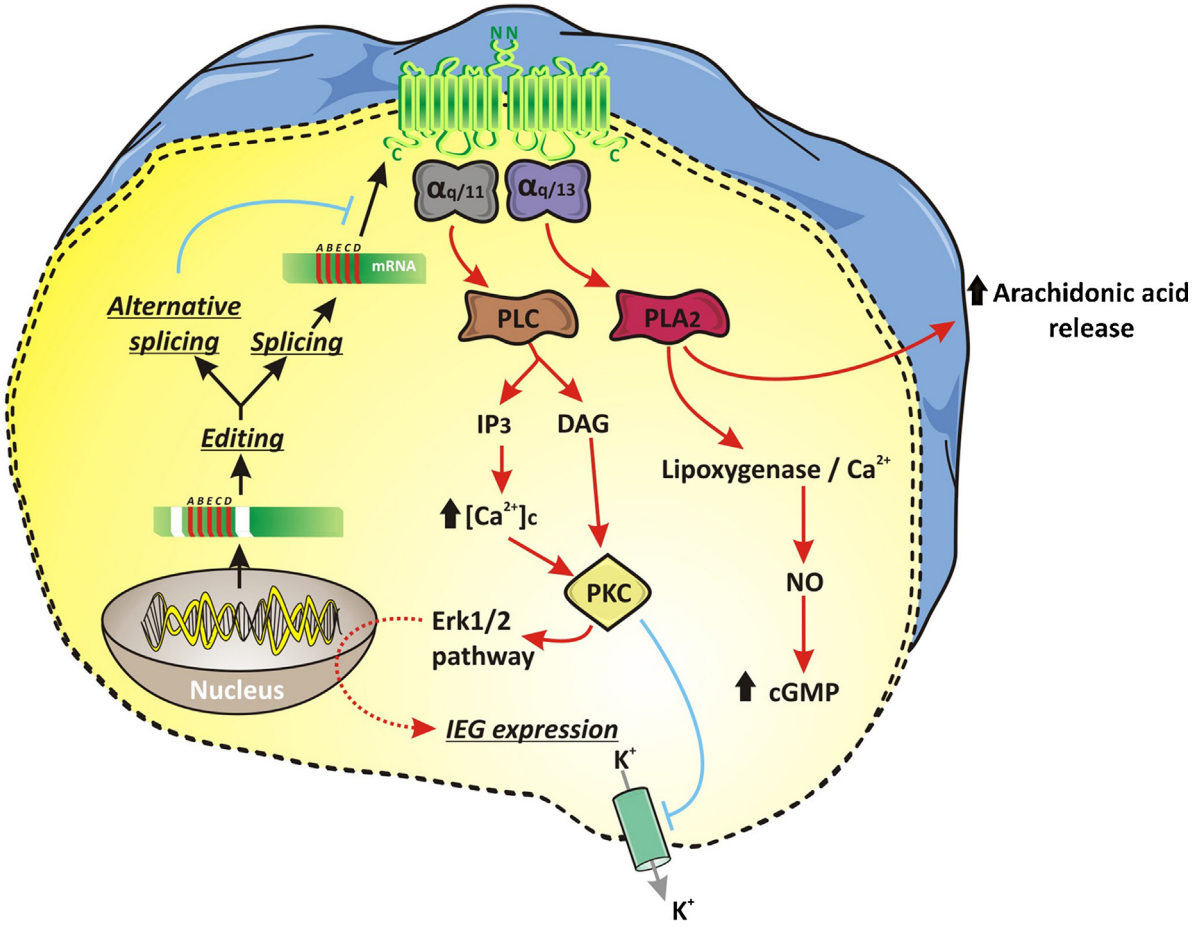

Fig. 1. Cellular mechanisms related to 5-HT_{2C} receptor functions. The 5-HT_{2C} receptor (5-HT_{2C}R) gene generates a pre-mRNA, which gets edited, or not, by adenosine deaminases (ADARs) involving the conversion of adenosine to inosine at 5 sites (A, B, C, C′, or E, D) located in the sequence corresponding to the second intracellular loop of the receptor. This process can generate 24 measurable isoforms of the receptor (for a review see Werry et al., 2008). The pre-mRNA then goes to maturation processes including splicing, leading to the functional form of the receptor and a truncated form that can retain, through heterodimerization, the functional receptor in the endoplasmic reticulum (see Martin et al., 2013). The functional 5-HT_{2C}R is coupled to phospholipases C (PLC) and A2 (PLA2), *via* respectively G-proteins $\alpha_{q/11}$ and $\alpha_{q/13}$. Activation of PLC leads to IP_3 accumulation triggering an increase in cytoplasmic calcium ($[Ca^{2+}]c$), and an activation of the protein kinase C (PKC), which stimulates the ERK1/2 pathway and inhibits K^+ conductance. Activation of the PLA2 pathway induces the release of arachidonic acid, activates lipoxygenase and triggers the mobilization of cytoplasmic Ca^{2+}. The latter leads to nitric oxide (NO) and cGMP productions (for a review see Masson et al., 2012).