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RNA editing of the serotonin $5HT_{2C}$ receptor and its effects on cell signalling, pharmacology and brain function

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ABSTRACT

The process of RNA editing involves the modification of mRNA at specific sites by *a*denosine *d*eaminases that *a*ct on *R*NA (ADAR) enzymes. By catalyzing the conversion of adenosine to inosine, these enzymes alter the way in which the mRNA is translated, and consequently alter the primary structure of the resultant proteins. The serotonin (5HT) 2C receptor ($5HT_{2C}R$) is currently the only known member of the superfamily of seven transmembrane domain receptors (7TMRs) to undergo this modification, and provides a fascinating case study in the effects of such changes. Here we review the current state of knowledge surrounding the editing of the $5HT_{2C}R$, the stark differences in signalling arising due to this process, and the potential for (and difficulties in) exploiting the phenomenon for improved therapeutic intervention in various neurological disorders.

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1. Introduction

The revision, or editing, of written work is a concept familiar to most research scientists (and the bane of many). The aim of editing in this instance is to simplify or clarify the content for unambiguous interpretation. Similarly, certain cellular components are also subject to editing but, in the molecular setting, these changes actually promote diversity and ambiguity in transcribed genomic information that can translate into a protein product with often dramatically altered structure and function. This review focuses on one particular edited protein, the serotonin (5HT) 2C receptor ($5HT_{2C}R$).

The $5HT_{2C}R$ is a member of the superfamily of seven transmembrane domain receptors (7TMRs) that signal to the internal cellular environment via heterotrimeric guanine nucleotide-binding proteins (G proteins) in response to stimulation of the extracellular surface of the receptor by hormones, neurotransmitters and pharmacological ligands. The overall homology of the $5HT_{2C}R$ with other members of the 5HT 7TMR family is broad, ranging from a 28% amino acid similarity with $5HT_7$ receptors to a 57% amino acid similarity with $5HT_{2A}$ receptors (Hoyer et al., 2002). While the $5HT_{2C}R$ was one of the first of the 5HT receptor family to be cloned, knowledge of its distribution and physiological functions has not progressed with equivalent pace to some of its cousins. This is, in part, because efforts to add depth to our understanding of this receptor have been hampered by a lack of truly selective $5HT_{2C}R$ ligands, and the burgeoning number of functional forms of the receptor produced by alternative splicing and RNA editing (see below). Despite this, however, through dedication and ingenuity, many of these problems have been circumvented and a large body of evidence now exists in support of roles for the $5HT_{2C}R$ in many physiological and pathophysiological roles.

1.1. $5HT_{2C}R$ distribution

The examination of the anatomical localisation of the $5HT_{2C}R$ has enabled us to speculate on the role of the receptor in complex behaviours. Various techniques have been used to identify and quantify $5HT_{2C}R$ expression in tissues, including measuring mRNA expression, ^{3}H-mesulergine autoradiography, and immunohistochemistry. These techniques have shown the $5HT_{2C}R$ to be almost entirely localised to the central nervous system (CNS), with little evidence to suggest that the receptor is expressed in high abundance in the periphery. Within the CNS, the distribution of $5HT_{2C}R$ is arguably more extensive than that of the $5HT_{2A}$ (Cornea-Hébert et al., 1999; Pompeiano et al., 1994) and $5HT_{2B}$ (Duxon et al., 1997) receptors, with particularly high levels within the epithelial cells of the choroid plexus (Sanders-Bush & Breeding, 1988). Lower levels of expression are observed within limbic areas (prefrontal cortex, anterior olfactory nucleus and the lateral habenular nucleus), hippocampal and associated regions (the pyramidal cells of the CA3 region of the hippocampus, the subiculum and entorhinal cortex, and lateral septal nucleus), amygdala, portions of the basal ganglia (caudate and substantia nigra pars compacta), portions of the mesocortical/mesolimbic pathways (nucleus accumbens and ventral tegmental area), and in the hypothalamus (arcuate, periventricular and ventromedial nuclei) (Clemett et al., 2000; Eberle-Wang et al., 1997; López-Giménez et al., 2001; Marazziti et al., 1999; Mengod et al., 1996; Pasqualetti et al., 1999; Pompeiano et al., 1994; Wright et al., 1995). Little expression has been noted in the cerebellum.

1.2. $5HT_{2C}R$ physiological roles and signalling

The distribution pattern of the $5HT_{2C}R$ in the brain is suggestive of specific roles in normal physiology and also, when dysregulated, in the development of certain disease states such as obesity, anxiety, epilepsy, sleep disorders and motor dysfunction. Many of these predictions are supported by data acquired through the use of knock-out mouse models that lack the $5HT_{2C}R$, and are summarised in Table 1. A significant body of pharmacological data has also been accumulated that confirms findings from the knock-out models and also reveals additional roles for the receptor that were not phenotypically evident in the genetically modified mice; this is summarised in Table 2. Examples of ligands from this group suggest that selectively targeting the $5HT_{2C}R$ is viable for certain diseases. For instance, APD356 (lorcaserin) is a $5HT_{2C}R$ agonist in phase IIb clinical trials for the treatment of obesity (Halford et al., 2007). Selective $5HT_{2C}R$ antagonists alone have been shown to produce pronounced inhibition of anxiety-like behaviours (Harada et al., 2006; Kennett et al., 1997). Ro 60-0175 (an agonist at $5HT_{2C}R$) has been shown to reduce cocaine-induced locomotor activity and self-administration (Fletcher et al., 2004) and also to block some of the addiction-related behaviours associated with Δ^9-THC and nicotine (Ji et al., 2006; Zaniewska et al., 2007). This is perhaps through its ability to inhibit the firing rate of dopaminergic neurons in the ventral tegmental area (VTA) (Di Giovanni et al., 2000; Pozzi et al., 2002; Prisco et al., 1994). It is to be hoped that more $5HT_{2C}R$-targeting ligands will be discovered that will improve the available pharmacotherapy of these disorders, and a better knowledge of the receptor and its idiosyncrasies may assist in this search.

On a cellular level, the $5HT_{2C}R$ stimulates intracellular responses via $G\alpha_{q/11}$, $G\alpha_{12/13}$ and $G\alpha_i$ G proteins, and by doing so can regulate the levels of second messengers such as inositol trisphosphate ($Ins(1,4,5)P_3$), calcium (Ca^{2+}), cyclic AMP, arachadonic acid (Berg et al., 1994; Berg et al., 1998), cyclic GMP (Kaufman et al., 1995) and the activity of extracellular signal-regulated kinases 1 and 2 (ERK1/2) (Werry et al., 2005) and

Table 1
Effects of $5HT_{2C}R$ gene knock-out (KO) in the mouse

Physiological role or disease state	Manifestation in KO mouse	Refs
Metabolic regulation	Hyperphagia ⇧ body weight ⇧ adipose tissue deposition	(Nonogaki et al., 2002; Tecott et al., 1995; Vickers et al., 1999)
Epilepsy	⇧ sensitivity to audiogenic seizure ⇩ seizure threshold ⇧ seizure propagation	(Applegate & Tecott, 1998; Brennan et al., 1997; Tecott et al., 1995)
Motor function	Hyperactivity ⇧ responsiveness to locomotor effects of cocaine	(Heisler & Tecott, 2000; Rocha et al., 2002)
Sleep	⇧ wakefulness Abnormalities in REM sleep patterns	(Frank et al., 2002)
Drug dependence	⇧ cocaine self-administration	(Rocha et al., 2002)
Anxiety	⇧ responsiveness to repeated stress Altered responsiveness to anxiety stimuli	(Chou-Green et al., 2003b; Heisler et al., 2007)
Obsessive compulsion	Highly organised behaviour	(Chou-Green et al., 2003a)

Table shows the diverse effects observed in a genetically modified mouse model lacking the $5HT_{2C}R$ gene.