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Review

The emerging role of GPR50 receptor in brain

Muhammad zahid Khan[a,*], Ling He[b], Xuxu zhuang[b]

[a] Department of Pharmacology, China Pharmaceutical University, Nanjing 210009, China
[b] China Pharmaceutical University, Department of Pharmacology, No. 24 Tong Jia Xiang, Nanjing,Jiang Su Province 210009, China

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ABSTRACT

GPR50 receptor one of the member of G protein-coupled receptors (GPCRs) is extensively expressed in the pituitary, hypothalamus,cortex, midbrain, pons, amygdala, and in several brainstem nuclei. The exact function of this receptor in brain is remains unclear. This review presents current knowledge regarding the function of GPR50 receptor in brain, with a focus on role of this receptor in the hypothalamus–pituitary–adrenal (HPA) axis and the glucocorticoid receptor (GR) signaling, leptin signaling, adaptive thermogenesis, torpor, neurite outgrowth, and self-renewal and neuronal differentiation of neural progenitor cells NPCs. Although the results are encouraging, further research is needed to clarify GPR50 role in neurobiology of mood disorders, adaptive thermogenesis, torpor, and in the pathophysiology of neurological disorders.

Contents

1. Introduction

G protein-coupled receptors (GPCRs) are one of the largest superfamilies of proteins with over one thousand members identified in the human genome, which play a key role in cell signaling and have a wide range of physiological functions. GPCRs mediate 80% of transmembrane signal transduction in response to ligand binding, linking interactions between the cell and the environment [1]. GPCRs are thus currently considered as key targets for drug development [2]. GPCR 50 (GPR50) encodes an integral membrane protein located on the X-chromosome (Xq28) and found exclusively in mammals [3]. This receptor is closely related to melatonin receptors 1 and 2, sharing 45% sequence homology [4], and can bind both subtypes forming heterodimers. GPR50, however cannot bind melatonin and remains an orphan receptor with no known ligands. GPR50 is ubiquitously expressed in various regions of the human brain including the pars intermedia of the pituitary, hypothalamus and hippocampus [5]. More than 10 years later, the function of GPR50 is still poorly understood. Recent research studies provided first hints on potential functions in the brain. This review intends to summarize to date known function of GPR50 receptor in brain including GPR50 molecular structure, interaction with melatonin receptors

* Correspondence to: Department of Pharmacology, China Pharmaceutical University, No. 24 Tong Jia Xiang, Nanjing 210009, China.
E-mail address: mzahidk786@hotmail.com (M.z. Khan).

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and expression in brain. Furthermore, we have briefly discussed the role of GPR50 receptor in neuropsychiatric disorders, the hypothalamic–pituitary–adrenal axis (HPA or HTPA axis) and glucocorticoid receptor (GR) signaling, leptin signaling, neurite outgrowth, and role in self-renewal and neuronal differentiation of neural progenitor cells NPCs.

2. GPR50 molecular structure

The human GPR50 gene has been mapped to the X-chromosome (Xq28) [3]. The full length gene encodes a protein of 617 amino acids that is 45% identical overall to human melatonin receptors MT1 and MT2, with identity increasing to 55% when the transmembrane domains alone are compared [6]. GPR50 is composed of 617 amino acids with 7TM hydrophobic segments. The principal features of GPR50 include a long *C*-tail of over 300 amino acids and the absence of consensus sites for N-linked glycosylation in either the amino terminus or the predicted extracellular loops [5]. Three polymorphisms located in exon 2 of the human GPR50 gene have been documented in the literature for GPR50 [7–9]. 1: Δ502–505 corresponds to the insertion/deletion of the four amino acids Thr–Thr–Gly–His (TTGH) at position 502 (Δ502–505 variant); 2: $Thr^{532}Ala$ corresponds to the substitution of Thr (T) to Ala (A) at position 532; 3: $Val^{606}Ile$ corresponds to the substitution of Val (V) to Ile (I) at position 606. There are two naturally occurring forms of the *C*-terminal domain of GPR50 which primarily differ in the presence of four amino acids (TTGH, amino acid residues 502–505) of lengths 617 and 613 amino acids (referred to as TTGH and ΔTTGH, respectively). The ΔTTGH form is rarer, but is common, with an allele frequency of approximately 30% [6] Fig. 1.

3. GPR50 interaction with melatonin receptors

Melatonin receptors are members of the G protein-coupled receptor (GPCR) family. Three genes for melatonin receptors have been cloned. The MT1 (or Mel1a or MTNR1A) and MT2 (or Mel1b or MTNR1B) receptor subtypes are present in humans and other mammals, while an additional melatonin receptor subtype, Mel1c (or MTNR1C), has been identified in fish, amphibians and birds. Another melatonin related orphan receptor, GPR50 which does not bind melatonin, is found exclusively in mammals [10]. GPR50 has been shown to heterodimerize with both MT1 and MT2 receptors, but interferes only with MT1 signaling [11]. Engagement of GPR50 with MT_2 does not modify the agonist-binding properties of MT_2 [11,12]. Binding of GPR50 to MT_1 had other profound consequences on MT_1 function such as the inhibition of heterotrimeric G-protein coupling and β-arrestin binding [12].

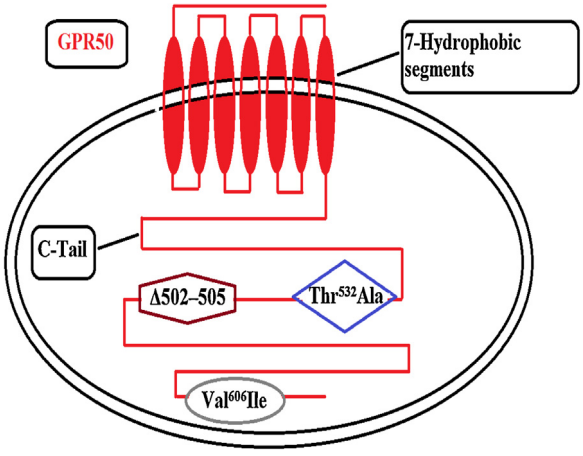

Fig. 1. The molecular structure of GPR50 receptor. GPR50 receptor consist of 7-hydrophobic segments and long C-tail. Localization of the three polymorphisms includes (Δ502–505, $Thr^{532}Ala$ and $Val^{606}Ile$). All three polymorphisms induce amino-acid changes in the C-tail of the human GPR50.

Deletion of the large *C*-terminal tail of GPR50 abolishes the inhibitory effect of GPR50 on MT1 without affecting heterodimerization, indicating that this domain interacts with MT1, but not MT2 [11,13]. More recent studies confirm that this deletion is associated with Bipolar affective disorder (BPAD) [14]. The potential significance of the inhibitory effect of GPR50 on MT_1 receptor function was shown in immortalized human endothelial cerebral hCMEC/D3 cells that express both proteins endogenously [11]. Whereas MT_1 activity was undetectable in cells expressing GPR50. MT_1 receptors became fully functional upon GPR50 silencing, demonstrating that endogenous GPR50 expression levels can indeed regulate MT_1 activity [15,16]. However, it should be noted that GPR50 has obviously additional functions not related to melatonin.

4. Expression of GPR50 in brain

GPR50 is highly expressed in the hypothalamus, pituitary, and the adrenal glands, in humans, rodents, and sheep [17–20]. Batailler et al., used specific GPR50 antibody to analyse the neuroanatomical distribution of the GPR50 in sheep, rat and mouse whole brain. They observed extensive GPR50-positive cells distribution in various regions including the hypothalamus and the pars tuberalis of the pituitary in all the three species studied. In rodents, immunohistochemical studies revealed a broader distribution pattern for the GPR50 protein. GPR50 immunoreactivity was observed in the medial preoptic area (MPA), the lateral septum, the lateral hypothalamic area, the bed nucleus of the stria terminalis, the vascular organ of the laminae terminalis and several regions of the amygdala. Additionally, in the rat brain, GPR50 protein was localised in the CA1 pyramidal cell layer of the dorsal hippocampus. In mice, moderate to high numbers of GPR50-positive cells were also found in the subfornical organ [20]. Recently Grünewald et al., studied the developmental expression of orphan GPR50 receptor in mouse brain. They performed extensive expression analysis of GPR50 and three protein interactors using rt-PCR and immunohistochemistry in the developing and adult mouse brain. GPR50 expression was observed at embryonic day 13 (E13), peaks at E18, and was predominantly expressed by neurons. Furthermore, they identified many novel sites of GPR50 expression in the adult and E18 mouse brain, in neurons in the cortex, midbrain, pons, amygdala, and in several brainstem nuclei [21]. A subcellular investigation of GPR50 expression has not been published previously. Further studies are required to explain GPR50 cellular expression and to confirm the type of neurons which express GPR50.

5. GPR50, the hypothalamic–pituitary–adrenal axis (HPA or HTPA axis) and glucocorticoid receptor (GR) signaling

The hypothalamus–pituitary–adrenal (HPA) axis and the glucocorticoid receptor (GR) are the two important biological factors of mood disorders. The hypothalamic–pituitary–adrenal axis (HPA or HTPA axis), is a complex set of direct influences and feedback interactions among three endocrine glands, the hypothalamus, the pituitary gland and the adrenal gland. The interactions among these organs constitute the HPA axis. The HPA axis is involved in the neurobiology of mood disorders including bipolar disorder, anxiety disorders, posttraumatic stress, insomnia, personality disorder, and major depressive disorder. Antidepressants which are usually prescribed for many of these illnesses serve to regulate HPA axis function [22].