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Review

# Orphan G protein-coupled receptors: The role in CNS disorders

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ABSTRACT

There are various types of receptors in the central nervous system (CNS). G protein-coupled receptors (GPCRs) have the highest expression with a wide range of physiological functions. A newer sub group of these receptors namely orphan GPCRs have been discovered. GPR3, GPR6, GPR17, GPR26, GPR37, GPR39, GPR40, GPR50, GPR52, GPR54, GPR55, GPR85, GPR88, GPR103, and GPR139 are the selected orphan GPCRs for this article. Their roles in the central nervous system have not been understood well so far. However, recent studies show that they may have very important functions in the CNS. Hence, in the present study, we reviewed most recent findings regarding the physiological roles of the selected orphan GPCRs in the CNS. After a brief presentation of each receptor, considering the results from genetic and pharmacological manipulation of the receptors, their roles in the pathophysiology of different diseases and disorders including anxiety, depression, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, and substance abuse will be discussed. At present, our knowledge regarding the role of GPCRs in the brain is very limited. However, previous limited studies show that orphan GPCRs have an important place in psychopharmacology and these receptors are potential new targets for the treatment of major CNS diseases.

## 1. Introduction

G protein-coupled receptors (GPCRs) constitute a large family of seven trans-membrane-spanning proteins that activate internal signal transduction pathways by binding to different ligands such as neurotransmitters, peptides, and lipids [1]. GPCRs are metabotropic receptors that bind to their ligands and cause slow synaptic transmission [2]. The rhodopsin or class A family of GPCRs has been recognized as the largest source of therapeutic targets [1]. However, a large number of the rhodopsin-like receptors are named "orphans" and mostly have no known ligand(s). They may be the answer for some known drug effects or adverse drug reactions with unidentified mechanisms of action. For example, it would be interesting to know that lorazepam is an allosteric ligand for GPR65 [3]. They may even be targets for finding newer and better therapeutics [4]. Although a large body of investigations has been devoted to understanding the functions of orphan GPCRs in the central nervous system (CNS), their effects have not been reviewed so far. So, in the present article, we will review selected orphan GPCRs that have been reported to have effects in the treatment of various central nervous system disorders. At first, there is a short overview on each orphan receptor. Then, their roles in different CNS disorders are discussed.

**GPR3**: GPR3 receptor is expressed highly in habenula region, which is actively involved in the modulation of stress-related behaviors. It is expressed in the hippocampus, amygdala and the cerebral cortex as well [5]. GPR3 promotes cAMP production through activation of the $G_s$ subunit of the G proteins and eventually activation of adenylate cyclase (AC) [6]. Lysophospholipid sphingosine 1-phosphate (S1P) has been suggested as the endogenous ligand for GPR3 in rats [7]. GPR3 has been reported to have a role in a variety of neurological diseases such as Alzheimer's disease [8] and emotional-like responses [9].

**GPR6:** GPR6 is an orphan GPCR that is coupled to $G_S$ and increases cAMP levels [7]. Primary studies showed that S1P is also an endogenous ligand for GPR6 [10]. However, further studies did not confirm this finding [11,12]. It is expressed in the brain, especially, in the striatopallidal neurons. Overexpression of GPR6 in an in vitro preparation increased neurite outgrowth in primary cerebellar granule neurons of rats [6]. Researchers showed GPR6 is an important regulator of dopaminergic signaling with neuroprotective effects in Parkinson's disease [13]. In addition, in the GPR6 knockout mice, the level of

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phosphorylated DARPP-32 (dopamine and cAMP-regulated phosphoprotein of 32 kDa) at Thr34 was higher in the striatum. DARPP-32 has been reported as an important regulator of D1 and D2 receptors [14]. In accordance, It was demonstrated that haloperidol raised DARPP-32 phosphorylation at Thr34 in the striatopallidal neurons. Therefore, GPR6 was suggested as an important target in the treatment of schizophrenia [15].

**GPR17:** GPR17 or purinergic P2Y-like receptor is a deorphanized receptor for both nucleotide sugars and cysteinyl leukotrienes such as UDP-glucose and leukotriene D4 [16]. GPR17 exists on neurons and some parenchymal quiescent oligodendrocyte precursor cells. GPR17 has been reported to be one of the key proteins expressed in human adult neuroprogenitor cells and probably has a role in neuronal repair [17]. In addition, it is expressed in organs that undergo ischemic injury including brain, kidney and heart. GPR17 participates in the traumatic spinal cord and ischemic brain injuries [18].

**GPR26:** GPR26 was discovered in 2000 for the first time [19]. It is expressed in many regions of the mouse brain, especially, in the olfactory area, amygdala, hippocampus, and cerebral cortex [20]. It also has expression in brain regions related to appetite control [21]. GPR26 is coupled to $G_s$ and increases cAMP levels in target cells [20]. No endogenous ligand has been discovered for GPR26 so far [22]. Some researchers believe that GPR26 is related to melatonin and sphingolipid receptors [23]. These receptors are involved in the regulation of anxiety and depression [24].

**GPR37:** GPR37 is also recognized as a parkin-associated endothelin-like receptor (Pael-R) as it is one of the parkin substrates [25]. Parkin is an E3 ubiquitin ligase that plays a role in neuronal death during Parkinson's disease [26]. GPR37 and GPR37L1 are orphan GPCR that are expressed mainly in the corpus callosum, cerebellum, caudate nucleus, putamen, substantia nigra, and hippocampus [27,28]. GPR37 has been proposed to play a role in certain diseases such as autism [29], depression, and bipolar disorder [30]. It has a special role in the modulation of dopaminergic system and in the pathophysiology of Parkinson's disease (PD) [31,32].

**GPR39:** GPR39 is a $G_q/G_{11}$ protein-coupled receptor of the ghrelin receptor family [33]. It is a metabotropic receptor that has two splice variants, GPR39-1a and GPR39-1b. GPR39-1a is expressed selectively throughout the gastrointestinal tract, whereas GPR39-1b has a broader expression pattern including different regions of the central nervous system such as the amygdala and hippocampus [34,35]. Obestatin has been identified as a GPR39 ligand [36]. Moreover, researchers believe that zinc is a natural ligand for GPR39 and activates this receptor in brain areas that have roles in mood disorders. It is a potential new target for neurological diseases [37].

**GPR40:** GPR40 is coupled to $G_q$ and activates phospholipase C. It belongs to GPR41 and GPR43 subfamily [38]. This receptor has been reported to be expressed in different human brain regions including midbrain, hippocampus, hypothalamus, cerebral cortex, olfactory bulb, medulla oblongata, cerebellum, and the spinal cord [39]. It is expressed in the pancreas as well and has an important role in the regulation of insulin secretion [40]. Various medium and long chain, saturated and unsaturated fatty acids have been recognized as ligands for the GPR40 receptor [41]. Therefore, it is believed that this receptor is important for normal development of the nervous system. Moreover, it participates in the modulation of pain [42] and emotions [43].

**GPR50:** The melatonin-related receptor or GPR50 is found almost exclusively in mammals [44]. This X-linked receptor is connected to melatonin receptors 1 and 2 [45]. It binds to both subtypes and forms heterodimers. Melatonin does not bind to this receptor, and it remains an orphan receptor with no known endogenous ligand. GPR50 has high expression levels in the hypothalamus, pituitary, and locus coeruleus, which have crucial roles in the regulation of stress and anxiety-related disorders [23,45,46]. In women, GPR50 has been introduced as a genetic risk factor for major depression and bipolar disorder [47].

**GPR52**: GPR52 is an orphan $G_s$-coupled receptor that is expressed especially in the striatum. It is involved in dopaminergic transmission at D1-expressing neurons in the medial prefrontal cortex and in D2-expressing medium spiny neurons (MSNs) in the striatum [48]. Recent findings revealed that GPR52 acts as a dopamine D1 receptor activator and as an inhibitor of dopamine D2 receptor [49]. It has been suggested that GPR52 agonists have the potential to improve positive and negative symptoms of schizophrenia [50].

**GPR54:** GPR54 has been found in the cortical and medial nucleus of the amygdala and dentate gyrus of the hippocampus which are involved in the learning and memory-related processes [51]. GPR54 alters excitatory postsynaptic currents by changing the AMPA receptor number or conductance. Neuropeptide kisspeptin is the endogenous ligand of GPR54 that plays roles in the regulation of the reproductive system, food intake, anxiety-related behaviors, and suppression of metastasis cancers [52].

**GPR55:** GPR55 has been recognized mainly in CNS-derived cells and tissues including the hippocampus [53]. The GPR55 gene has a widespread expression in the mouse brain including the hippocampus, frontal cortex, cerebellum, striatum, hypothalamus, and brain stem [54]. It is expressed in the liver, cancer cells, and osteoclasts and has roles in pain modulation and bone formation as well [48]. GPR55 signaling is mediated mainly through activation of $G_q$ and $G_{\alpha 12/13}$. Downstream signaling cascades of GPR55 include calcium release from intracellular stores, Rho and extracellular regulated kinase signaling, small GTPases, and a variety of transcription factors including nuclear factor of activated T-cells, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and cAMP response element binding (CREB). Despite its low sequence homology to CB1 and CB2 receptors, GPR55 has been introduced as a putative candidate of the cannabinoid receptor family [55]. GPR55 is a lysophosphatidylinositol (endogenous non-cannabinoid ligand)-sensitive receptor [56] and is activated by numerous cannabinoid ligands [57].

**GPR85:** GPR85 or SREB2 is highly expressed in the hippocampal formation, particularly in the dentate gyrus, an area with a recognized contribution in psychiatric disorders and cognition [58]. GPR85 is detected in the purkinje cells as well [59]. SREB family was found by a similarity to dopamine D4 receptor sequence but low sequence similarity to known GPCRs. No endogenous ligands and signal transduction modulators have been identified for this receptor yet [60,61].

**GPR88:** GPR88 is highly expressed in the GABAergic medium spiny projection neurons of the nucleus accumbens, olfactory tubercle, thalamus, cortex, and inferior olive [62–64]. GPR88 alters glutamatergic and GABA-dependent signaling. 2-PCCA is the synthetic agonist for GPR88. It inhibits intracellular cAMP accumulation and prevents calcium influx in GPR88 expressing cells, suggesting that GPR88 is coupled to $G_i$. Administration of antidepressants, lithium, and valproate alters GPR88 expression, which likely mediates some of the adverse effects of the mentioned drugs [65].

**GPR103:** GPR103 is a $G_{i/o}$ and $G_q$ protein-coupled receptor that has two isoforms in rodents, designated as GPR103A and GPR103B [66,67]. It is expressed in several brain regions of the rodents, such as paraventricular and magnocellular hypothalamic nuclei, bed nucleus of stria terminalis (BNST), lateral septum, medial supramammillary nucleus, olfactory bulb as well as in the brain stem [68,69]. The 26RFa (peptide P550) is synthetic agonist for GPR103 that exhibits anxiolytic-like effects [70,71].

**GPR139:** GPR139 is expressed exclusively in the lateral striatum and hypothalamus [72,73]. It is activated by the essential amino acids; l-tryptophan and l-phenylalanine. Overexpression of GPR139 promoted basal intracellular cAMP level which is suggesting that GPR139 is predominantly coupled to $G_s$ [74]. GPR139 has been reported to play a role in the regulation of food intake/metabolism and movement control [75]. Therefore, this receptor is a potential candidate for the treatment of Parkinson's disease.