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The Potential Biofunctions of the Orphan Receptor GPR50: A Mini Review

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Abstract: GPR50 is an orphan seven-transmembrane receptor known as related to the melatonin receptor subfamily which comprised of MT1, MT2 and Mel1c receptors. Previous studies implicate that GPR50 might be involved in hypothalamic control of energy expenditure and feeding behavior. GPR50 expression in brain is highly responsive to energy status as being decreased in both fasting and high fat diet feeding circumstances. GPR50$^{-/-}$ mice present elevated metabolic rate, reduced fat accumulation, and partial resistance to diet-induced obesity. In human, GPR50 polymorphisms have been linked to elevated circulating triglycerides and cholesterol level, as well as psychiatric affective disorders. This review presents current knowledge regarding to the functions and associated diseases of GPR50. However, GPR50 may have more functions that remain to be discovered. To reveal the signaling pathway(s) of GPR50 and its functions well, it is crucial to do more works to identify the ligand(s) of GPR50 and the possibility of ligand-dependent signaling.

Keywords: GPR50, GPCR, energy metabolism, orphan receptor

I. INTRODUTION

Melatonin is a hormone secreted primarily by the pineal gland with highest levels occurring during the dark period of a circadian cycle and functions in the regulation of neural and endocrine processes, including readjusting the circadian pacemaker, the suprachiasmatic nucleus of the hypothalamus (SCN), and the photo-period signals [1]. Melatonin, acting through melatonin receptors, is involved in numerous physiological processes including blood pressure-reducing [2], anti-tumor, retinal physiology [3, 4], circadian entrainment [5], ovarian physiology [6], seasonal reproduction [7], osteoblast differentiation [8] and so on.

G protein-coupled receptors (GPCRs) as one of the largest superfamilies of protein receptors have a wide range of physiological functions. GPCRs are known to support a diversity of pharmacological profiles, which are thus considered as key targets for drug development [9, 10]. Melatonin receptors are members of the GPCRs family. Three genes for melatonin receptors have been cloned. The MT1 (also called Mel1a or MTNR1A) and MT2 (Mel1b or MTNR1B) subtype receptors are present in humans and other mammals, while another melatonin receptor subtype, Mel1c (or MTNR1C), has been identified in fish, birds and amphibians only [11-13].

G protein-coupled receptor 50 (GPR50) is a melatonin receptor related orphan receptor, also known as H9 or melatonin-related receptor. GPR50 gene is located on the X chromosome (Xq28) and encodes a protein of 617 amino acids (AAs) that has 45% identity with MT1 and MT2 receptors, and with 55% identity when comparing the transmembrane domains alone. The principal features of GPR50 include a long C-tail of over 300 AAs and the absence of consensus sites for N-linked glycosylation in either the N-terminus or the predicted extracellular loops [14]. The GPR50$^{-/-}$ mice show hyperactivity, higher metabolic rates, and resistance to obesity when fed on a high energy diet [15]. So far, previous studies have proved that GPR50 participates in lipid metabolism [16], energy homeostasis [15], neural

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development [17], neurotransmitter signaling [18], and neuropsychiatric disorders [19]. But, the exact mechanisms of GPR50 remain unclear.

II. ORIGINAL DISCOVERING OF GPR50

By using degenerated PCR primers which based on conserved regions of the MT1 and MT2 melatonin receptors, GPR50 was originally cloned from a human pituitary cDNA library [20]. Phylogenetic analysis further confirmed that GPR50 belongs to the melatonin receptor subfamily. Since GPR50 does not bind melatonin or any other known endogenous or synthetic ligands, it is classified as an orphan receptor. Evolutionary studies have provided evidences that the GPR50 evolved under different selective pressure than the orthologous group members MT1, MT2, and Mel1c [21]. GPR50 is an outgroup member to all other melatonin receptors and may have separated from an ancestor melatonin receptor before the split between Mel1c and the MT1/2 ancestor [1].

III. EXPRESSION PATTERN OF GPR50

GPR50 expression in brain regions controlling the HPA axis has been reported previously, Batailler *et al*. discovered an enlarged distribution of GPR50 protein [14, 22-24]. They used a specific antibody against the ovine GPR50 to analyze the neuroanatomical distribution of the GPR50 in sheep, rat and mouse whole brain. They showed that GPR50-positive cells widely distributed in various regions of the three species, including the pars tuberalis of the pituitary and the hypothalamus. GPR50 expressing cells were vast in the dorsomedial nucleus of the hypothalamus, the periventricular nucleus and the median eminence. In rodents, immunohistochemical studies indicated a broader distribution pattern for the GPR50 protein. GPR50 immunoreactivity was found 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, including the medial nuclei of amygdala. In mice, moderate to high numbers of GPR50-positive cells were also found in the subfornical organ. In addition, GPR50 protein was localised in the CA1 pyramidal cell layer of the dorsal hippocampus in the rat brain.

Ellen Grünewald *et al*. [18] studied the developmental expression of GPR50 in mouse brain. In the study, they performed extensive expression analysis of GPR50 and three protein interactors (Nogo-A, Abca2, and Cdh8) using rt-PCR and immunohistochemistry in the developing and adult mouse brain. GPR50 was predominantly expressed by neurons, and was expressed at embryonic day 13, peaks at embryonic day 18. Additionally, they identified many novel regions of GPR50 expression, inculding brain stem nuclei involved in neurotransmitter signaling such as the locus coeruleus, substantia nigra, and raphe nuclei, as well as nuclei involved in metabolic homeostasis.

IV. GPR50 INTERACT WITH MELATONIN RECEPTORS

Despite GPR50 structural similarities with MT1 and MT2, but GPR50 is not melatonin's receptor and lack of identified ligands [22] has hindered the elucidation of the role of GPR50. By using biochemical and biophysical approaches in intact cells have identified that GPR50 has the ability to heterodimerize with MT1 or MT2 receptors. However, the interaction between GPR50 and MT receptors only interferes MT1 signaling, but not for MT2's functions [25]. Deletion of the large C-terminal tail of GPR50 suppressed the inhibitory effect of GPR50 on MT1 without affecting heterodimerization, indicating that the C-terminal tail controls the interaction of regulatory proteins to MT1 [26]. When engaged in heterodimeric interactions with MT1 subtypes, the MT1 agonist-binding properties are substantially altered. Binding to MT1 also induces the inhibition of heterotrimeric G protein coupling and β-arrestin binding through interaction with the long C-terminal tail of GPR50, indicating that GPR50 did not directly involve in the binding with melatonin, might be a key regulator of the message conveyed [27].

To receive and relay melatonin photo-periodic transmission codes to appropriate neural networks, MTI and MT2 must assemble into functional homodimer or heterodimer configurations within the bilayer lipid membrane to initiate second

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messenger cascades. For instance, endogenous GPR50/MT2 heterodimers are melatonin responsive, whereas MT1/GPR50 heterodimers are relatively silent to periodic depolarization pulses from pinealocytes [26]. The spatiotemporal diversity of these interactions highlights the wide range of GPR50-mediated responses to extracellular signaling events, which in turn converge on processes regulating gene transcription and the synthesis of proteins by local ribosomes [28]. These data indicate that MT1 or MT2 heterodimers with GPR50 may represent a new target for the treatment of melatonin receptor-associated diseases.

V. GPR50 AND LIPID METABOLISM

Existing studies have shown that GPR50 plays an important role in energy metabolism. GPR50$^{-/-}$ mice exhibited reduced body weight and showed a partial resistance to diet-induced weight gain when fed with calorific, high-fat diet [15]. At the fifth week of feeding, the weight of GPR50$^{-/-}$ mice was significantly lower than that of wild-type (WT) mice, mainly due to the decrease in fat content in GPR50$^{-/-}$ mice. GPR50$^{-/-}$ mice weight gain was attenuated although they consumed more food per gram of body mass. Again, GPR50$^{-/-}$ mice were more active than WT mice. Wheel-running activity records revealed that, the overall levels of activity were significantly increased over wild types in both nocturnal and diurnal phases. Coordinated with this basal metabolic rate, O_2 consumption, CO_2 production, and respiratory quotient were elevated in knockout mice. *In situ* hybridization studies on mouse, rat, and hamster brain sections have demonstrated an expression of the GPR50 receptor in several areas associated with energy metabolism namely the dorsomedial hypothalamic nucleus (DMN), lateral hypothalamus, and arcuate nucleus [23].

A recent study finished by Bhattacharyya *et al.* [16] investigated the sequence variations of GPR50 in an obese cohort of human. The authors' findings , include an insertion of four amino acid residues (TTGH) at position 501 (C-terminal tail) and several single-nucleotide polymorphisms that show significant associations with elevated circulating triglyceride and high-density lipoprotein levels, suggesting a role for this receptor in the regulation of lipid metabolism.

VI. GPR50 ROLE In TORPOR

Torpor is a condition of decreased physiological activity in animal, which can invokes comprehensive physiological changes [29]. Torpor is a well-controlled thermoregulatory process. For example, a torpid mouse is no longer homeothermic, has lower metabolic rate than its basal metabolic rate, lower body temperature which just a few degrees above environment temperature, lower heart rate with 100 beats per minute, lower respirations as a few breaths per minute, and lower blood pressure [30]. A few candidate hormones have been suggested as mediators and/or synergists inducing a torpid state [31]. Leptin is an adipocyte-secreted hormone that helps to regulate the energy homeostasis [32]. Leptin has previously been found to block bouts of fasting-induced torpor in mice and other small mammals. Even during a fed state, leptin deficient mice (ob/ob mice) would be much more likely to enter bouts of torpor than WT mice [33].

Recently, Bechtold *et al.* [34] identified that GPR50$^{-/-}$ mice are much more likely to enter fasting-induced torpor, and are much more sensitive to the hypothermia-inducing agent 2-deoxyglucose than WT mice, revealing that GPR50 could be a novel component of adaptive thermogenesis in mammals. GPR50$^{-/-}$ mice have an elevated metabolic rate despite the lowered expression of UCP1 in brown fat, and this is likely a consequence of the increase in general cage activity. Contrary to expected elevated body temperature as a result of the elevated metabolic rate, these mice actually had a lowered body temperature. Multiple lines of evidence showed GPR50 activity downstream of leptin action. First, leptin administration has no impact on the depth, duration, or even likelihood of torpor bouts in GPR50$^{-/-}$ mice. Second, reduced expression of GPR50 is seen in both ob/ob mice and fasted mice, with the former being rescued by leptin treatment. Third, expression of GPR50 in cell culture modifies the expression of hundreds of leptin-sensitive genes [35]. All these information indicated that GPR50 plays an important role in regulating entry into torpor.

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VII. GPR50 AND TIP60

TIP60, HIV-1 *tat* interactive protein (gene name *Kat5*), is a transcriptional co-activator with histone acetyltransferase (HAT) activity, which has been implicated in the regulation of transcription, apoptosis and DNA repair [36, 37]. Among other interactions, TIP60 enhances the transcriptional activity of a range of transcription factors including nuclear hormone receptors (NHR) [38]. TIP60 has been implicated in glucose homeostasis [39] and adipogenesis [40]. Further, TIP60 can repress the activity of the downstream target of leptin signaling protein STAT3 [41, 42].

Bechtold *et al*. [19] revealed that GPR50 as a signaling partner and modulator of the TIP60. In the study, to identify potential binding partners for GPR50, the authors employed a yeast two-hybrid system to screen mouse testes cDNA library. When using the intracellular c-terminal domain of GPR50 as bait, they discovered the transcriptional co-activator, TIP60. The association between GPR50 and TIP60 was further confirmed by co-immunoprecipitation and co-localization in HEK293 cells. Co-expression of TIP60 with full length GPR50 increased perinuclear localization of both proteins, demonstrating a functional interaction of GPR50 and TIP60. They also demonstrated that GPR50 could enhance TIP60-coactiavtion of glucocorticoid receptor (GR) signaling in pituitary cells. The functional impact of GPR50 on GR signaling is supported by genetic knockdown in pituitary cells and *in vivo* studies using GPR50$^{-/-}$ mice. In summary, the current study reveals a novel role for GPR50 in GR signaling through TIP60.

VIII. GPR50 ROLE In NEURONAL DIFFERENTIATION

Wnt/β-catenin signaling promotes neuronal differentiation in the late embryonic stage [43] and self renewal [44, 45]. Notch signaling through Hes1 inhibits differentiation of neural progenitor cells while enhancing self renewal and play a vital role in modulating NPCs in developmental cortex [46]. An impairment of notch and wnt/β-catenin signaling was observed in GPR50^{-} knockdown NPCs.

Ma *et al*. [47] described that GPR50 was expressed by neural progenitor cells in the ventricular zone of embryonic 14 day mouse brain. Furthermore, GPR50 mRNA was detected in lysates of cultured NPCs as well as of E14 mouse cerebral cortex by RT-PCR analysis. Knockdown of GPR50 with small interference RNA (siRNA) decreased neuronal differentiation and self-renewal, but not glial differentiation of NPCs. Overexpressing of full-length GPR50 or truncated GPR50 without its intracellular domain demonstrates that the intracellular domain of GPR50 increases neuronal differentiation of NPCs. In addition, decreased levels of transcription factor 7-like 2 (TCF7L2) mRNA was observed in GPR50 siRNA-transfected NPCs, suggesting that knockdown of GPR50 impairs wnt/β-catenin signaling. Moreover, the mRNA levels of neurogenin (Ngn) 1, Ngn2 and cyclin D1, the target genes of notch and wnt/β-catenin signaling, in NPCs were reduced by knockdown of GPR50, too. Therefore, it is possible that GPR50 promotes self-renewal and neuronal differentiation of NPCs through regulating of notch and wnt/β-catenin signaling pathways.

IX. GPR50 ROLE In NEURITE OUTGROWTH

NOGO-A is an inhibitor of neurite outgrowth *in vitro* and *in vivo* [48]. Ablation of neuronal NOGO-A in knockout mice causes neurite extension or branching of the major neurite. In neurons, overexpressing NOGO-A causes destabilization of inhibitory synapses *in vivo*. The subcellular distribution of neuronal NOGO-A matches with microtubules, indicating that NOGO-A may play a role in microtubule dynamics [49]. Neuronal NOGO-A accumulates in axonal growth cones which remains in the central region and does not enter the filopodial processes [50].

For understanding the function of orphan receptor GPR50 through identification of protein interactors, Grünewald *et al*. [17] identified neurite outgrowth inhibitor NOGO-A as an interacting partner of GPR50 by yeast two-hybrid study. They confirmed the interaction in mammalian cells and at the synapse found an enrichment of both GPR50 and neuronal NOGO-A. They also identified that overexpression of GPR50 resulted in an increase neurite length and filopodia-like and lamellipodia-like structures, in which GPR50 is present and co-localizes with actin. This difference in distribution may be related to the opposite effects on neurite outgrowth. Although the expression pattern needs to be confirmed in the

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developing brain, the enrichment of neuronal NOGO-A and GPR50 in the post synaptic density possibly indicates a role in spine development. More studies are necessary to elucidate the relationship between GPR50 and the important neurite outgrowth inhibitor NOGO-A.

X. GPR50 ROLE In AFFECTIVE DISORDERS

Bipolar disorder (BD) and the related affective illness, major depressive disorder (MDD), affect approximately 1% and 17% of the world's population, respectively. And, BD and MDD are 9th and 4th disease-related lifetime disability estimated by WHO, respectively. Studies show that genes and environment play a shared part in determining disorders risk [51, 52].

Candidate genes studies and more recently genome-wide association studies have identified that the GPR50 gene is located on Xq28, a region previously implicated in linkage studies for BD. To investigate the association between GPR50 and BD, studies have been performed. Up to now, these studies provide that GPR50 is a candidate gene playing a role in affective disorder, especially in female population. Alaeres *et al*. [53] suggested that GPR50 was lack of association of an insertion/deletion polymorphism with BD in a Northern Swedish population. However, Blackwood group [54] replicated the study in the Scottish population. They identified an association with BD in women with an intronic SNP, rs1202874 that withstood correction for multiple testing. This knowledge was the first association of rs1202874 with BD. M. Delavest et al. [55] also suggested that the intronic rs2072621 GPR50 polymorphism (allele A) variant was a gender-specific risk factor for Seasonal Affective Disorder (SAD). Importantly, the intronic rs2072621 variant is the only one expected to modify GPR50 expression levels by modifying GPR50 gene splicing.

XI. DISCUSSION

GPR50 is a putative genetic risk factor for diseases. So far, GPR50 as an orphan receptor, it is difficult to exclude the question of an endogenous ligand and the possibility of ligand-dependent signaling. GPR50 may have further functions that remain to be discovered and there are many problems needing to be solved. GPR50 heterodimerizes with MT2, however, the consequences of GPR50 on the MT2 function are currently unknown and warrant further attention; GPR50 interacts with TIP60 to modulate transcriptional activity and as a GR signaling. However, the possibility that proteolytic cleavage of the C-terminal tail of GPR50 produces functional signaling proteins is needed further investigation; Recent identification that GPR50 promotes self-renewal and neuronal differentiation of embryonic neural progenitor cells through regulation of notch and wnt/b-catenin signaling. But GPR50 may modulate other proteins/signaling which could not exclude the possibility now. Answers of these questions will be useful for determination of etiological mechanism and underlying biological pathways in MDD, BD, torpor and other diseases.

At present very limited studies exist which can highlight GPR50 role and much work remains to be done for identification of ligand for GPR50 and understanding of whole signaling pathway to clarify the role of receptor. All in all, identification of endogenous or synthetic ligand will open new pharmacological perspectives for GPR50.

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