The Role of GB1 Subunit in $GABA_BR$ Heterodimer and GB1-GB1 Homodimer*

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ABSTRACT: $GABA_BR$ belongs to the Class C G protein-coupled receptor, and it is important inhibitory neurotransmitter receptors in central nervous system. $GABA_BR$ is encoding by two genes, GB1 and GB2, and researchers have confirmed that $GABA_BR$ is heterodimer formed by GB1 and GB2 since 1998, but recent studies have shown that GB1 could form GB1-GB1 homodimer in the absence of GB2 and exercise functions in vivo. In present systematically review the different splice variants of GB1, and its expression in the presence or absence of GB2, and its role in the activation process of $GABA_BR$ heterodimer and GB1-GB1 homodimer as well as its physiologic effect in vivo; and also prospect the significance of the above studies in basic research and pharmacology.

Key words: $GABA_BR$; GB1; GB2; GB1-GB1 homodimer; Activation mechanism

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γ -Amino butyric acid (GABA) is the chief inhibitory neurotransmitter in the mammalian central nervous system. It plays a role in regulating neuronal excitability throughout the nervous system. In humans, GABA is also directly responsible for the regulation of muscle tone [1]. The $GABA_BR$ belongs to the class C of G-protein coupled receptors (GPCRs). $GABA_BR$ is a member of that superfamily by activating second messenger cascades and modulating ion channel activity, control neurotransmitter release and postsynaptic silencing of excitatory neurotransmission [2]. Among class C GPCRs, the $GABA_BR$ was the first identified as being composed of two distinct subunits, GB1 and GB2 [3-6]. Each of these receptors is composed of an extracellular domain called the Venus flytrap domain (VFT), to which agonists bind, and a heptahelical domain (HD), which is responsible for the recognition and activation of heterotrimeric G proteins (Fig.1). Indeed, although GB1 bind all known GABAB ligands, GB2 is required for the normal trafficking of GB1 to the cell surface [7-10], as well as for G-protein activation. Another role identified for GB2 is to increase agonist (but not antagonist) affinity in GB1[6,11].

1 The different splice variants of GB1

As one of the GABABR encoding gene, GB1 is existed in different splice forms. The cloning of rat and human GB1 showed that it could exist as two splice variants, GB1a and GB1b(Fig.2) [3]. These differ at the N terminus, with the initial 147 amino acids of this region of GB1a being replaced with a different, shorter sequence of 18 amino acids in GB1b leading to the absence of a pair of conserved protein binding motifs, the sushi domains (SDs) in this splice variant. More recently other GB1 splice variants have been emerged (Fig.2). Two variants based on rat GB1b were reported: a 31 amino acid insertion, which produces a variation between the fifth transmembrane domain (TMD) and the second extracellular loop GB1c, and a 566 base-pair insertion causing a divergent C terminus with a 25 amino acid insertion GB1d [12]. More recently, a GB1e variant has been reported, in which exon 11 is spliced out of GB1a in both rat. More recently GB1j has also been described as a secreted GB1 subunit isoform. GB1j contains the sushi domains (SDs) domain present in GB1a in addition to the 870-bp extension of exon 4 at its 3' end (exon 4')[13].

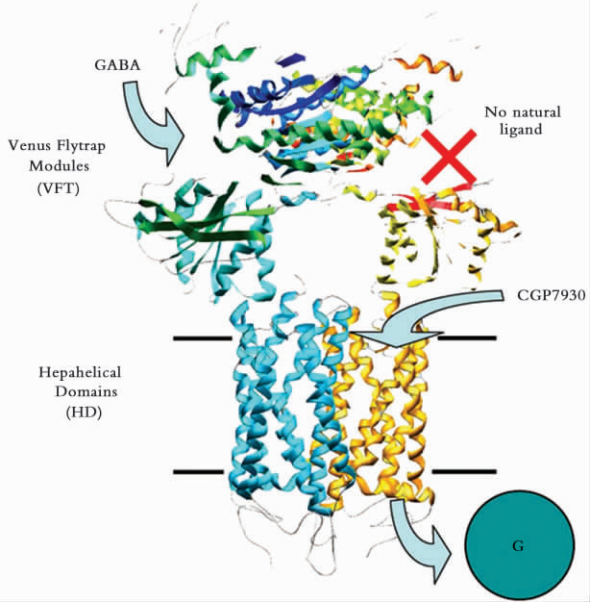

Fig.1 Structure of $GABA_BR$ heterodimer

2 Expression of GB1 subunit in vivo

2.1 The expression of GB1 in the presence of GB2

In the current model of $GABA_BR$ function, there is a require-

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ment for GB1/2 heterodimerisation for targeting to the cell surface. Expression of GB1 either in heterologous cells or in neurons [14] revealed that this does not lead to the formation of a functional GABABR, and that GB1 does not reach the cell surface. This suggests that the heteromer is formed in the endoplasmic reticulum (ER). The information necessary for retention is located in a seven amino acid segment between L 921 and P 928, in the vicinity of the LZ1 in the intracellular tails (Fig.3)[8].

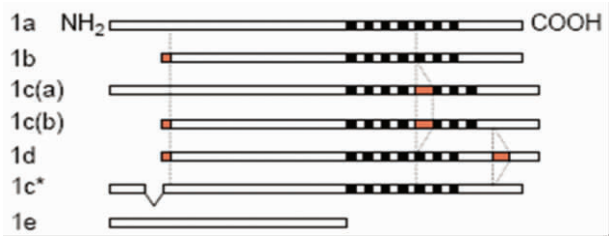

Fig.2 The diagram of the different GB1 splice variants

Fig.3 LRSRR is the ER-retention motif in GB1

It's has been demonstrated that both GB1a and GB1b can form heterodimer with GB2. The distribution of GABABR heterodimer component proteins, GB1 and GB2, is widespread throughout the rodent and human CNS [15,16], in agreement with receptor binding studies [17,18]. mRNAs encoding GB1 and GB2 colocalize in 95% of neurones in regions expressing both mRNA species [19]. GB1a and GB1b mRNAs are widely distributed in the majority of brain regions, although at varying levels [20]. In the cerebellum, GB1a mRNAis predominantly located in the granule cells, and GB1b mRNAis mainly located in the Purkinje cells. Localization of the rat GB1c variant is similar to that of GB1a and GB1b. GB1e mRNAis distributed predominantly in peripheral organs such as lung, kidney and intestine, with much lower levels of transcript found in the CNS [21].

2.2 The expression of GB1 in the absence of GB2

Different lines of evidence suggest that the GB1 subunit can form a functional receptor in the absence of GB2. GB1 expression has also been reported by Previous studies to be much higher than the GB2 in some brain regions, including the basal forebrain, striatum, nucleus accumbens, caudate putamen and hypothalamus [4,6,22], and cell types, such as glial cells [19,22]. The expression of the GB1 subunit also precedes that of GB2 in the developing brain [23]. Consisting with this hypothesis, atypical electrophysiological GABABR response has been detected in hippocamal slices of GB2-/- mice. These observations argue for the possible existence of functional GABABRs in the absence of GB2 subunits.

In supporting of this, co-immunoprecipitation and fluorescence resonance energy transfer experiments suggest that GB1 subunits can associate as stable homodimers in ER and ER-Golgi intermediate compartment. However, it remains controversial how ligands enter the cell to activate the intracellular receptors.

3 Function of GB1 subunit in $GABA_BR$ heterodimer and GB1−GB1 homodimer

3.1 Activation mechanism and function in the $GABA_BR$ heterodimer

GABA acts by stabilizing the closed state of GB1 VFT, allowing a specific conformation of the VFT dimer. According to the known structure of the mGlu1 VFT dimer, it is possible that the closure of the GB1 VFT stabilizes a new relative orientation of the GB1-GB2 VFTs, leading to a direct association of lobe-II. This new conformation of the GB1-GB2 VFT heterodimer is expected to stabilize the new conformation of the dimer of heptahelical domains, and especially the active conformation of the heptahelical domain of GB2 [24]. The Proposed activation mechanism of the heterodimeric $GABA_BR$, as based on the known structure of the mGlu1 VFT dimer solved in the absence and presence of bound agonist. In the absence of agonist, both VFTs are in an open form, and in such a relative orientation that maintain the dimer of HDs in an inactive relative position. Agonist binding in the GB1 VFT induces or stabilizes its closed state (step 1), and this is proposed to favors a new relative orientation of the VFTs (step2). In this orientation, the dimer of VFTs in turn favors a new relative position of the HDs, allowing GB2 HD to reach an active conformation leading to G-protein activation. It is actually not known whether the GB2 VFT is in an open or closed state in any of these different states of the $GABA_BR$ dimer (Fig.4A)[24].

Recently, a glycan wedge scanning approach was used to investigate how the $GABA_BR$ VFT dimer controls receptor activity [25]. First it has been identified the dimerization interface using a bioinformatics approach and then showed that introducing an N-glycan at this interface prevents the association of the two subunits and abolishes all activities of GB2, including agonist activation of the G protein. It has also been identified a second region in the VFT where insertion of an N-glycan does not prevent dimerization, but blocks agonist activation of the receptor. These data provide new insight into the function of this prototypical GPCR and demonstrate that a relative movement of the GABAB VFTs is required for receptor activation (Fig.4B)[25].

Several years ago, the hypothesis of possible direct transactivation between 7TMs was proposed, but never firmly demonstrated. More recently By using a novel orthogonallabelling approach compatible with time-resolved FRET and based on ACP- and SNAP-tag technologies to verify the heterodimerization of wild-type and mutated GABABR subunits, It was demonstrated the existence of a direct allosteric coupling between the 7TMs of GABABR heterodimers [26]. Indeed, a GABABR, in which the GB2 extracellular domain was deleted, was still capable of activating G proteins. This finding is the best evidence of direct transactivation between 7TMs in $GABA_BR$. Also synthetic ligand for the GB2 7TM could increase agonist affinity at the GB1 subunit in this mutated receptor [26]. How does the ligand-bound closed form of GB1 VFT activate the 7TM domain of GB2 in the absence of

GB2 VFT? One possibility is that the active, closed form of GB1 VFT directly interacts with and activates the 7TM domain of GB2. Such a process has been shown for the glycoprote in receptor, whereby the agonist bound to the extracellular domain of one protomer acts directly on the second protomer[27,29](Fig.4C).

The propose model of the mechanism of $GABA_BR$ activation show that closure of GB1 VFT results in a conformational change of GB1 7TM that is sufficient to activate the associated GB2 7TM. In support of this model, the insertion in the 7TM of GB1 of two cysteines expected to cross-link the extracellular part of TM2 and TM3 (GB1-DCRC mutant) prevented the activation of DVGB2 (absence of the VFT of GB2) by GB1, further indicating that a conformational change in the 7TM domain of GB1 is required to activate DVGB2[26](Fig.4C).

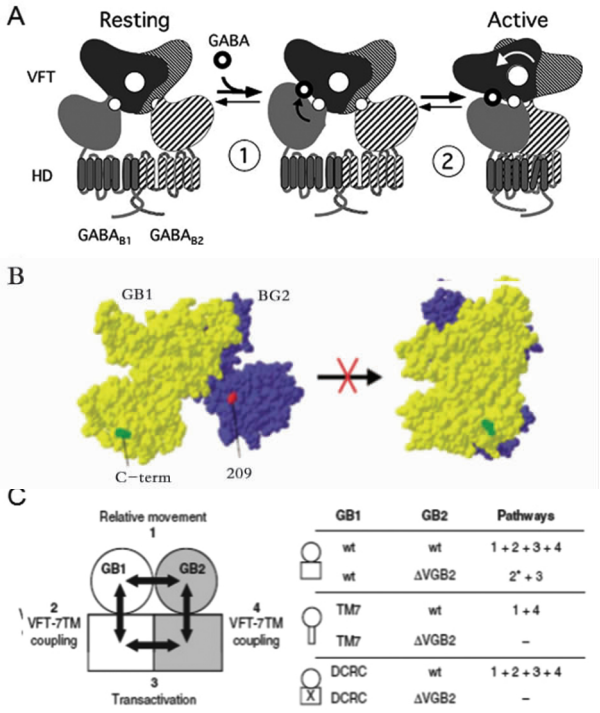

Fig.4 A, the diagram of the activation process of $GABA_BR$ heterodimer upon ligand binding, ligand is binding in GB1-VFT as described in the picture; B, the activation of $GABA_BR$ heterodimer need the relative rotation of GB1-LB2 and GB2-LB2 revealed by glycan wedge scanning; C, GB1 employed multi- interaction between GB1 and GB2 to participate activation process of $GABA_BR$ heterodimer

3.2 Activation mechanism and function in the GB1−GB1 homodimer

Since 2000, it was demonstrated that it was unclear whether both subunits of $GABA_BRs$ are important in determining G protein coupling and specificity [30]. A Schematic representation of $GABA_BR$ system and its downstream signaling pathways was proposed with G protein binding both GB1 and GB2 subunits, suggestion a possible activation of G protein signaling by these two subunits from the cell surface [30]. This suggestion has been confirmed by further studies in which GB1 subunit is expressed in the absence of GB2.

It has been demonstrated that GB1 homodimers might form and remain trapped inside the cell, presumably because of their ER retention sequences [9]. This hypothesis is an agreement with a recent study in which it has indicated that homodimeric GB1 receptors can form and are retained in the ER [31]. Furthermore studies have done investigating the potential role of GB1 homodimers in cells.

3.2.1 Activation of GB1 subunit in DI−TNC1 glials cells line and Human Embryonic Kidney cells (HEK cells)

In this study the formation of GB1 homodimeric receptors was proved by using both co-immunoprecipitation and BRET approaches. The DI-TNC1 cell line, which resulted from the transfection of diencephalic type I astrocytes from neonatal rat with a DNA construct containing the oncogenic early region of SV40 under the transcriptional control of the human GFAP promoter [32], was chosen following reports demonstrating the lack of GB2 expression in native glial cells [19]. It has been shown that these cells Expresses endogenous GB1 receptors in Absence of GB2 transfected. The same conclusion has been observed in Human Embryonic Kidney cells (HEK cells) transfected with GB1 subunit alone [33]. It has also been shown that activation of ERK1/2 by endogenous GB1a Receptor Dependent on Gi/o and MEK1/2 in HEK293 Cells. ERK1/2 stimulation in nontransfected was shown to be ineffective [33].

These results suggest that surface-targetted GB1/2 receptors may not be the only functional form of the $GABA_BR$. Other recent studies have indicated that the cell surface may not be the only site where 7TM-Rs are functionallytargetted. For example, a number of these receptors are functional on the nuclear membrane [34], and GPR30, an Erlocalised 7TM-R, has been demonstrated to act as a receptor for estrogen[35].

3.2.2 Expression of GB1 subunit into adipocytes and also in GB2−deficient mice

In order to demonstrate the functional expression of GABAergic signaling machineries by adipocytes, it has been shown that GB1 subunit mRNA and protein were constitutively expressed by adipocytes to primarily regulate leptin expression at the transcriptional level through a mechanism not relevant to the heterodimeric assembly to functional $GABA_BR$ with GB2 subunit. This is the first direct demonstration of constitutive and functional expression of GB1 subunit by adipocytes [36]. It has also been demonstrated that in GB2-deficient mice, but not in GB1- deficient mice, however, atypical electrophysiological $GABA_BR$ responses are still seen, suggesting that GB1 subunit plays a functional role even in the absence of the dimerization partner, GB2 subunit [37]. In addition to a crucial role as a dimerization partner for the negative autocrine regulation [38], GB1 subunit would be also involved in the expression of endocrine molecule leptin by adipocytes with the critical importance as a regulator of energy homeostasis in mammals.

3.3 How GB1 subunit function autonomously in cells?

It is unclear whether homodimeric entities or heterodimeric

receptors composed of GB1 and as yet unidentified $GABA_BR$ subunits or chaperones can explain this autonomy. Two hypothesis to explain the ability of the GB1 subunit to function autonomously in cells appears. The first hypothesis is the possibility that GB1 subunit can directly bind G protein and suggest a possible activation of G protein signaling by the direct stimulation of GB1 subunit. This hypothesis appears interesting because it has previously been demonstrated that the coupling between GB1 VFT and GB1 7TM can result from GB1 VFT closure (which is likely to occur in the GB1-DVGB2 combination) and from the relative movement between VFTs. Accordingly, only one allosteric pathway leading to the activation of GB1 7TM remains in the GB1-DVGB2 combination (from GB1 VFT to GB1 7TM and finally to GB1 7TM) [26]. The activation of GB1 7TM by GB1 VFT can probably lead to a direct activation of G protein signaling. The second hypothesis is a possibility of heterodimer formation between GB1 subunit and another GPCR, which formation lead to GB1 expression in the absence of GB2. This hypothesis to explain the ability of GB1 subunit to function autonomously appears very interesting and suggests investigating the mechanism of dimer formation as an intense area of study. The requirement of multi-subunit complex assemblies for activation, maturation and ligand specificity is emerging as an important topic in the modulation of GPCR function.

4 Conclusion and perspectives

The basic aspects of $GABA_BR$ assembly and surface trafficking are now well understood and include the occlusion of an ER retention/retrieval signal in the GB1 subunit. Study of combinations of existing variants, and the possible discovery of additional proteins in this family, will provide more information about one of the more elusive targets in neuroscience, including its functional role and future therapeutic potential. It therefore will be interesting to address whether the production of the various secreted GB1 isoforms is regulated in response to physiological stimuli. Drug development in the $GABA_BR$ field was largely hampered because receptor subtypes cannot be dist inguished pharmacologically. For example, it would be desirable to selectively inhibit heteroreceptors to boost excitatory neurotransmission in patients with cognitive impairments [38]. Now it was directly showed that this is possible by targeting the SDs. The expression of GB1 in the absence of GB2 subunit shown in recent studies suggests that GB1 alone plays a functional role in signaling pathway. So it's appear that GB1 subunit is thus a potential target for the discovery and development of an innovative drug useful for the therapy and treatment of a variety of lifestyle related diseases with accumulated adipose in human beings [36]. In the other hand, the existence of GB1-GB1 homodimer bring huge shock to classic activation model of $GABA_BR$. The GB1 have been proved to have ability to couple G protein by the above studies, so it bring an interesting question that why the conformation change in VFT only choose GB2-HD to active in GABABR heterodimer, and the evolution of $GABA_BR$ heterodimer and GB1-GB1 homodimer is also a fascinating question to scientists.

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$GABA_BR$ 异二聚体和 GB1-GB1 同二聚体中的 GB1 亚基的作用 *

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摘要:$GABA_BR$ 属于 C 族 G 蛋白偶联受体,是中枢神经细胞重要的抑制性神经递质受体。在体内 $GABA_BR$ 由 GB1 和 GB2 两个基因编码,1998 年以来研究者证实 $GABA_BR$ 是由 GB1 和 GB2 形成的异二聚体,但近年来的研究表明,GB1 也可以单独形成 GB1-GB1 同二聚体并在体内行使功能。本文系统介绍了 GB1 亚基的分类,在 GB2 存在或不存在时的表达,以及在 $GABA_BR$ 异二聚体和 GB1-GB1 同二聚体激活过程中所扮演的角色和生理功能,同时也展望了这些研究成果对于基础研究和药学研究的意义。

关键词:$GABA_BR$;GB1;GB2;GB1-GB1 同二聚体;激活机制

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