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The role of Regulatory G proteins signaling (RGS) proteins in brain excitability

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Authors

Simin Namvar Aghdash *

Department of biology, faculty of basic sciences, azarbaijan shahid madani university

***Corresponding author:**

Simin Namvar Aghdash,

Department of biology, faculty of basic sciences, azarbaijan shahid madani university

Email: Siminnamvar2@gmail.com

Tel: 09141764103

ABSTRACT

Heterotrimeric G proteins involved in many transmembrane signaling in the nervous system. Regulation of the signaling speed of G proteins is done by different types of proteins. One of the most important types of these proteins are called, Regulatory of G proteins signaling Proteins (RGS), that increase the GTPase activity of Ga subunit of G proteins. These proteins have more than 30 members and are characterized by the existence of a region of 120 amino acids, which is called the RGS region Today, it has been determined in addition to increase GTPase activity, RGS proteins can also act as antagonists of effectors by competing with effector molecules to bind to active Gα Another is RGS proteins specifically and selectively regulate the function of receptors coupled to G proteins and ion channels and other signaling events. The RGS protein family has essential roles in GPCR signaling in the nervous system. At neuronal synapses, GPCRs, G proteins, and RGS proteins work with together to regulate key aspects of neurotransmitter release, synaptic transmission, and synaptic plasticity that are necessary for CNS physiology and behavior thereby affecting neuronal excitability in the central nervous system. Studies have shown that the levels of cAMP and protein kinase A in the brain of seizure patients are more different than those of healthy subjects that this mediated by G proteins signaling.

Key words; G proteins, RGS proteins, Seizure, Brain excitability

INTRODUCTION

Heterotrimeric G proteins involved in many transmembrane signaling in the nervous system. These types of G protein were first recognized, named and characterized by Rodbell, Gilman and others close to 40 years ago. Heterotrimeric G proteins consist of three different subunits, α, β and γ. These proteins couple the activation of various types of plasma membrane receptor to a diversity of intracellular processes. Indeed, many types of neurotransmitter and peptide hormone receptors, as well as many cytokine and chemokine receptors, belong to a superfamily of structurally related molecules called G protein-coupled receptors [1,2]. Heterotrimeric G protein in early studies, are divided into four families based on structural and functional similarity of α subunits. Gs that stimulate the receptors to adenylate cyclase and cause the activation of adenylate cyclase. Gi/o binds inhibitory to adenylate cyclase and finally leads to the activation of potassium channels and voltage-dependent calcium channels and Gt, termed transducin, was identified as the G protein that couples rhodopsin to regulation of the function of photoreceptor [1,2]. Since then, more than 35 heterotrimeric G protein subunits have been recognized by a combination of biochemical and molecular modeling techniques. In addition to

Gt, Gs, and Gi/o, other types of G proteins in the brain are called Ggust, Gz, Gq, and G11-16. Furthermore, for many of these G proteins, several subtypes show a unique distribution in the brain and peripheral tissues. [2].

All members of the Gα families have GTPase properties that can hydrolyze the bound GTP to GDP and thereby cause the termination of signaling, and following this phenomenon, heterotrimeric G proteins are re-formed, that is, Gα bound to Gβδ. It will be GTPase activity acts as a timer that determines the free time of GTP-Gα and Gβδ, that is, the time that these proteins can react with their effector molecules [3].

Following the activity of receptors coupled to G proteins, GTPase activity in Gα increases 10 times. Effector enzymes that bind to Gα also increase the GTPase activity of these proteins, but even with this increased activity, another factor must exist to ensure the rate at which signaling is terminated in vivo [3]. Regulation of the signaling speed of G proteins is done by different types of proteins. One of the most important types of these proteins are called ,Regulatory proteins of G proteins signaling Proteins (RGS), that regulate the signaling of G proteins.

Regulatory proteins of G proteins signaling

These proteins have more than 30 members and are characterized by the existence of a region of 120 amino acids, which is called the RGS region. These proteins have the ability to increase GTPase activity and are directly connected to the active G protein alpha subunit and have a negative regulatory effect on G protein signaling and inhibit the signaling pathways initiated by G proteins. RGS proteins are known as modifiers and recapitulators of G protein signaling, which themselves are highly regulated. The big family of RGS proteins is divided into 6 big sub-families. This division is based on the protein structure and their amino acid sequence [3]. These 6 groups include:

A/RZ (RGSZ), B/R4 (RGS4), C/R7 (RGS7), D/R12 (RGS12), E/RA (Axin), F/RL (RhoGEFs, AKAPs, GRKs and RGS/PX1). At least 10 types of RGS are expressed in the brain. Examining the location of RGS proteins in the brain shows that RGS 2, RGS4, RGS7, RGS8, RGS 9 and RGS10 are densely expressed in the brain, while other subtypes such as RGS3, RGS5, RGS6 and RGS11 is expressed with less density and in very limited areas [4].

Mechanisms of action of RGS proteins

Today, it has been determined that the mechanism by which RGS proteins can affect G protein signaling is their ability to increase GTPase activity. that this ability exists in their RGS region. For example, for the first time, Berman noticed that RGS4 selectively enhances GTPase activity in Gαi, Gαi3, Gαi2, and Gαi1, but has no effect on Gαs [6]. Most RGS proteins usually do not react with Gα stimulatory subunits and do not have a specific regulatory effect on signaling mediated by Gas. But there are exceptions in this case. It has been shown that RGS-Px1 and RGS2 proteins selectively react with Gαs, but these findings are still not conclusive [6]. RGS2 is highly expressed in the brain. This protein inhibits adenylate cyclase and keeps the level of cAMP low inside the cell. In addition, it is likely to increase the GTpase activity of Gαs protein. RGS2 protein is expressed in a large amount in the hippocampus [6,7]. RGS4, which acts as an activator of the GTPase activity of several members of the Gαi subunits and prevents the inhibition of adenylate cyclase, is also expressed in a large amount in the hippocampus. [8]. RGS10 is densely expressed in the granule cells of the dentate gyrus. The activity of these proteins also increases the activity of GTpase Gαi/o and ultimately keeps the level of cAMP high [9].

RGS proteins can also act as antagonists of effectors by competing with effector molecules to bind to active Gα. Some of the RGS proteins, despite the fact that they have the property of increasing GTPase activity, can perform their inhibitory effects by competing with the effector alone (such as RGS3 and RGS2). Therefore, being an effector antagonist is an important inhibitory mechanism. [5, 3]. Another is RGS proteins specifically and selectively regulate the function of receptors coupled to G proteins and ion channels and other signaling events. The necessary condition for an RGS protein to specifically regulate its target protein is their simultaneous expression. RGS protein should be

expressed with its target proteins at a suitable time and place so that selective interaction takes place [6]. In the gene analysis, it has been determined that the genes of some RGS proteins are located near the genes related to G proteins such as Gα, Gß and G protein receptor kinase, and some of the genes of RGS proteins are also related to receptor genes. Certain genes are connected, which causes their simultaneous expression (Co-Expression) [6].

The role of RGS proteins in brain

The RGS protein family has essential roles in GPCR signaling in the nervous system. At neuronal synapses, GPCRs, G proteins, and RGS proteins work with together to regulate key aspects of neurotransmitter release, synaptic transmission, and synaptic plasticity that are necessary for CNS physiology and behavior, which is shown in figure one. Ample evidence has demonstrated key roles for specific RGS proteins in multiple signaling pathways at neuronal synapses, regulating both pre- and postsynaptic signaling events and synaptic plasticity. As potential therapeutic targets, various RGS proteins have been implicated in multiple neurologic disorders. RGS2 is involved in panic and post-traumatic stress disorder, and RGS4 is involved in schizophrenia. The elucidated role of some RGS proteins in synaptic plasticity, supported by the findings of RGS-insensitive Ga, allows new insights into how these proteins are regulated, as well as the myriad ways in which G protein signaling can affect synaptic connections. Future studies should not only elucidate the role of RGS proteins in neuronal signaling, but also work toward the use of novel RGS inhibitors as therapeutics in the central nervous system. [10]

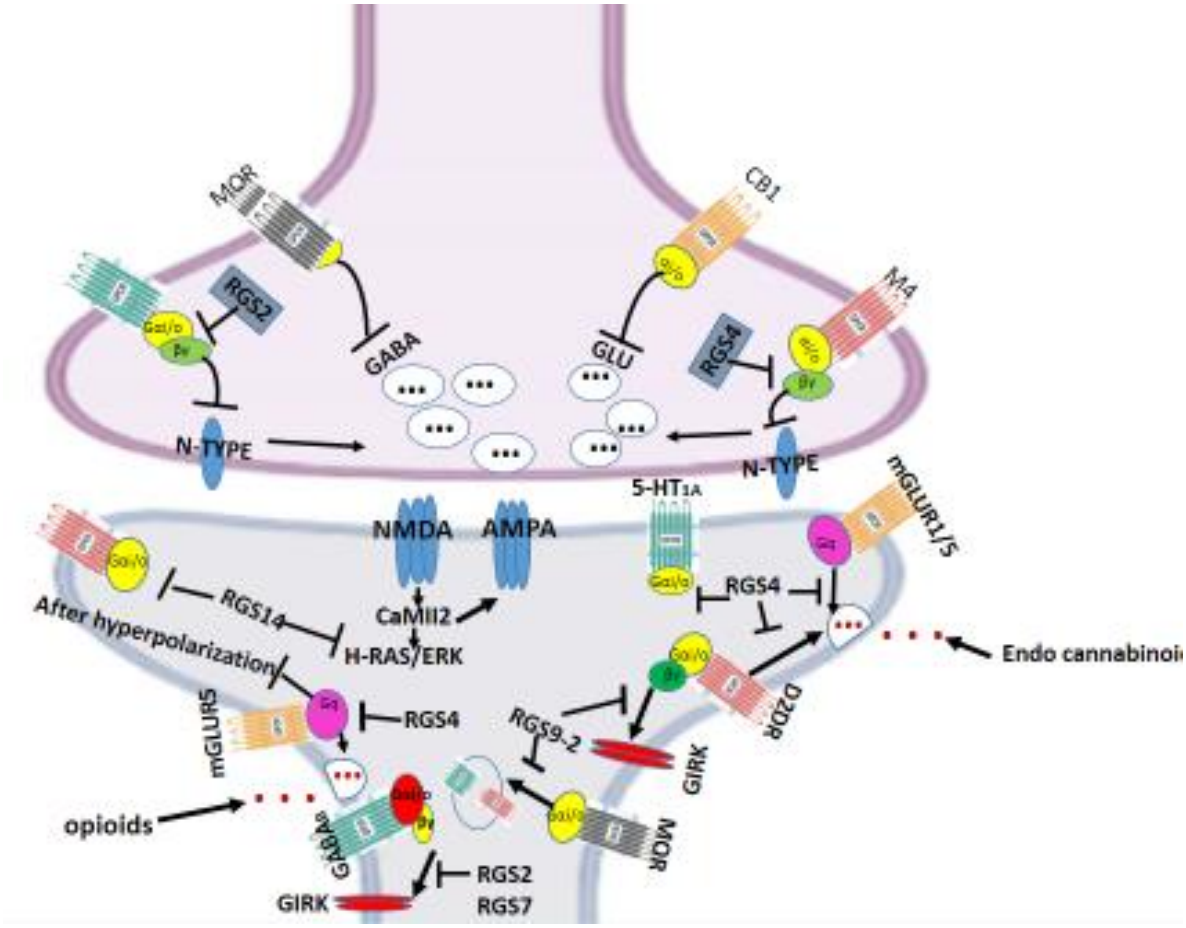

Figure1. The role of RGS proteins in neurotransmitter release, synaptic transmission, and synaptic plasticity.

In order to evaluate the regulation of mRNA expression of these proteins, the effect of acute seizures on the expression of RGS7, RGS8 and RGS10 in the hippocampus was investigated. Among them, the change in the levels of RGS10 was very obvious and decreased by approximately 40% [9]. It has also been shown that following kindling, the expression of RGS4 in the hippocampus increases [11]. This indicates the dynamic regulation of the RGS protein by epigenetic, transcriptional and post-translational mechanisms [12]. On the other hand, other studies have shown the role of these proteins in changing synaptic activity. They have also observed that RGS proteins regulate intracellular signaling pathways with G proteins. They are located presynaptically, they play an essential role in presynaptic inhibition, and in this way, they inhibit the release of a wide range of neurotransmitters, including adenosine, GABA, glutamate, and peptides. In this way, it can be said is particularly important that RGS proteins regulate activity of central nervous system [13]. In this regard, previous studies have shown that the RGS4 protein causes the termination of the intracellular pathways of glutamate receptors type 1 and 5, thereby affecting neuronal excitability in the central nervous system. [14].

Pharmacological studies have shown that low frequency stimulation [LFS] as a therapeutic procedure on the experimental model of seizure, exerts its inhibitory effects in part by activating receptors that are coupled to Gi proteins. It has been shown that the activity of metabotropic glutamate receptors type II in CA2 of the hippocampus and the activity of metabotropic glutamate receptors type I and II in the prefrontal cortex are necessary for the development of long term depression in synapse (LTD) [15, 16]. It has also been shown that the activation of presynaptic metabotropic glutamate receptors is involved in synaptic weakening [17]. These receptors and D2 group dopamine receptors [18], the metabotropic receptors GABAB [19, 20], adenosine via A1 receptors [21], and galanin [22] all act by activating the alpha subunit of the Gi protein [17-22].

Following the activity of these receptors, the level of intracellular cAMP and protein kinase A decreases. By activating transcription factors, protein kinase A increases the expression of proteins involved in kindling and seizures. Studies have shown that the levels of cAMP and protein kinase A in the brain of seizure patients are more different than those of healthy subjects [23]. Therefore, it is possible that LFS may help suppress seizures by increasing Gi activity. Examining the expression level of Gi protein α subunit showed that there is no change in its expression after applying LFS. Of course, there is still a possibility that following the application of LFS, the amount of Gi protein activity increases [3].

The activity of Gi protein α subunit is regulated by a number of G protein signaling regulatory proteins including RGS4 and RGS10. These proteins cause the termination of its signaling by increasing the GTPase activity of the α subunit of Gi protein [3]. The studies showed that following LFS, the expression of RGS4 and RGS10 decreases, which indicates the role of these proteins in the anticonvulsant effects of LFS [25].

The results of studies demonstrated that expression of RGS10 and RGS4 proteins, in acute seizures model in the hippocampus has been investigated. The change in the expression level of RGS10 is obvious and almost 40% decrease in its expression has been seen [9]. RGS4 expression in the hippocampus has also been observed to increase following kindling [11]. These results indicate the dynamic regulation of RGS4 and RGS10 proteins.

On the other hand, other studies have shown the role of RGS proteins in changing synaptic activity [12]. It has also been shown that RGS proteins play an essential role in presynaptic inhibition through the regulation of intracellular signaling pathways of receptors coupled to Gi protein that are located presynaptically, thereby inhibiting the release of a wide range of neurotransmitters, including Adenosine, GABA, glutamate and peptides [13]. In addition, previous studies have shown that the RGS4 protein causes the termination of the intracellular pathways of metabotropic glutamate receptors type 5, thereby increasing neuronal excitability in the central nervous system. affects [14]. In this way, it can be said that RGS proteins are particularly important in regulating the activity

of the central nervous system [15]. The finding of one investigation showed, following the application of LFS and the reduction of RGS4 and RGS10 proteins, the duration of the effect of the inhibitory neurotransmitters that are coupled to the Gi protein increases, and these factors can also exert an inhibitory effect on the kindling process [24].

RGS proteins are mostly coupled to inhibitory subunits of the alpha subunit of G proteins. But there is an exception in this case, it has been reported that the RGS2 protein couples to the Gs alpha subunit and causes the negative regulation of the signaling pathway of this protein [6]. The role of RGS2 protein in synaptic plasticity has been investigated so far only in relation to the relationship of this protein with Gi and Gq proteins. Because RGS2, in addition to the alpha subunit of Gs protein, also regulates the activity of the alpha subunit of Gi and Gq proteins [24].

Studies have shown that in the hippocampus, RGS2 increases the release of presynaptic vesicles through the downregulation of Gi-mediated inhibition of calcium channels, thereby affecting synaptic activity. It has also been shown that stimulations that cause synaptic plasticity induce RGS2 protein in the hippocampus and cerebral cortex, which ultimately reduce the inhibitory effects of this protein on synaptic activity by inhibiting the Gi protein signaling pathway [24].

Many neurotransmitters in the brain are coupled to the Gs alpha subunit and affect synaptic activity by activating adenylate cyclase and increasing cAMP. The studies showed that the expression of RGS2, as a negative regulator of Gs alpha subunit, did not change after applying LFS, but it decreased in the Kindle group. The decrease in GRS2 expression in Kindle group increases the duration of activity of intracellular signaling pathways related to Gs, such as cAMP and protein kinase A. Following the activity of protein kinase A (PKA) the expression of proteins involved in kindling increases. However, following the application of LFS, the decrease in RGS2 protein expression is prevented, and as a result, the duration of Gs protein activity is shortened. This process causes the increase of cAMP and the activation of protein kinase A to be reduced, thus exerting the anticonvulsant effect of LFS [25].

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