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PERSPECTIVE

Role of G-Proteins and GPCR-Mediated Signalling in Neuropathophysiology

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Abstract: G-protein-coupled receptors (GPCRs) are activated by manifold neurotransmitters, and their activation, in turn, evokes slow synaptic transmission. They are profoundly related to numerous psychiatric and neurological disorders such as schizophrenia and Parkinson's disease. The significant malady indications for GPCR modulators demonstrate a change towards obesity, diabetes, and Alzheimer's disease, while other central nervous system disorders persist highly represented. GPR52, GPR6, and GPR8 are recognised as orphan GPCRs, co-exist either with both the dopamine D2 and D1 receptors in neurons of the basal ganglia or with the dopamine D2 receptor alone, and recommend that between these orphan receptors, GPR52 has the maximum potential of being a therapeutic psychiatric receptor. Genetically modified creature models and molecular biological investigations have suggested that these improved GPCRs could be potential therapeutic psychiatric receptors. In this perspective, the role of molecular targets in GPCR-mediated signalling has been discussed that would be novel drug design and discovery options for a scientist to elaborate previous knowledge with modern techniques.

Keywords: Alzheimer's disease, G protein-coupled receptors, neuropathophysiology, psychiatric receptors, neurotransmitters, neurological disorders.

1. INTRODUCTION

A few traditional metabolites fill in extracellular flagging atoms that actuate cell-surface G-protein-coupled receptors (GPCRs), like chemicals and synapses, notwithstanding their bioenergetic intracellular job. 'Signaling metabolites' are delineated in the lamina propria of the intestinal mucosa and liver by supplements or by intestinal microbiota focusing on mostly enteroendocrine, neuronal, and sound cells, and the remainder of the body by techniques for these problems [1]. Notwithstanding the law of a few cell steps, conformational changes in GPCRs are accomplished by their endogenous ligands' conformational changes conducted by clear G-protein pathways and G protein-coupled receptor kinase (GRK) pathways alongside noncanonical β-arrestin. G protein pathways are shown by subunits of Gα, Gβ, and Gγ; GPCRs want to get together with intracellular heterotrimeric G proteins. The G alpha subunits can gather into four fundamental families (G α, G α/o, G α/11, and G α12/13), all of which manage rule effectors and incite the hour of second couriers, for example, Inositol 1,4,5-triphosphate (IP3), cAMP, and Ca^{2+} (Fig. **1**) [2]. This way, these subsequent dispatches initiate arranged hailing falls. Several undeniable GPCRs can couple with a practically identical G α protein, and with more than one G α protein, a relative receptor can correspondingly couple. Both the administrative and hail segments of Gβγ subunits serve either as kinase frameworks, for example, protein kinase D (PKD) and phosphatidylinositol 3-kinase (PI3K), or as atom channel modulators [3, 4]. GPCRs like dopamine, acetylcholine, and glutamate are associated with neuropathology and neurophysiology, potentially affecting neurological disorders. G-protein coupled receptor kinase phosphorylates the receptor and activates the GPCRs pathway by G-proteinsignaling. In that case, dopamine acts on GPCRs to activate G-protein. Generally, several types of complexity have been shown in patients with psychiatric disorders and chronic medical diseases [5].

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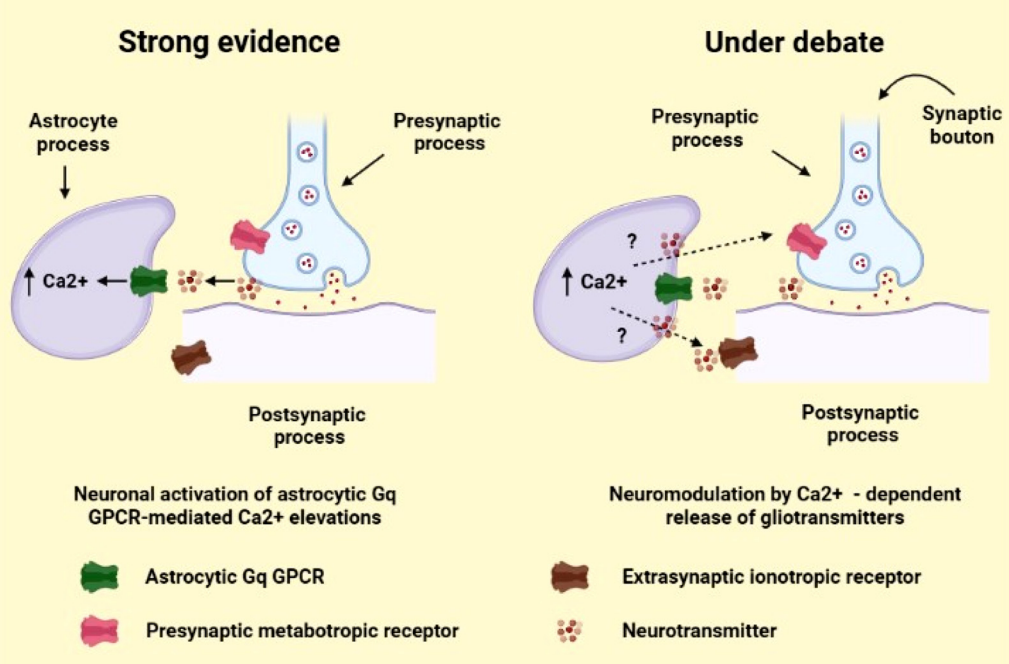

Fig. (1). GPCR mediated Ca^{2+} signaling involvement at the synapse [2]. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Additionally, physicians may fall into trouble detecting psychiatric disorders with other medical conditions [6, 7]. The following treatments may interact with one another [8, 9]. They retrograde other disease conditions as well. According to recent research, a psychedelic compound, lysergic diethylamide (LSD), is similar to the endogenous neurotransmitter serotonin, which has the potential effect on molecular psychiatry, according to recent research [10-12]. Psilocybin-associated psychotherapies have given a more beneficial result than psychotherapy alone. Still, there has been an unclear demonstration in favour of psilocybin alone. Psilocybin should be further investigated if this novel approach is effective in psychiatric disorders with anxiety and depression [13]. Oxidative biology offers a new aspect for the investigation of psychiatric disorders, which correlates oxidative damage to the disease process [14].

Several oxidative stresses lie in the disease approach due to an imbalance of oxidants that will continue with cellular dysfunction with cell death. In that case, glutathione (GSH), a ubiquitous cellular antioxidant, can implicate oxidative stress in psychiatric disorders, which will be a novel treatment approach [15, 16]. ROS may cause damage to tissues and cells, resulting in oxidative stress. Resistance to oxidative stress is required to minimize free radical effects and repair damaged tissues, which are essential for survival and prevention of the development tendency of other diseases, including neurodegenerative disorders. Resistance to oxidative stress can be modified by G-protein coupled receptor kinase. In the case of animal studies, *Ce-GRK2* modifies the oxidative resistance of *C. elegans*. However, the animal becomes more resistant to oxidative stress without *Ce-GRK2*. Disease-related to oxidative stress and GRK2 inhibitor, protein kinase, is used as a biomarker. GRK2 inhibitors, as well as paroxetine, significantly increase the resistance to oxidative damage. In schizophrenia and bipolar disorder, alteration of mRNA mitochondrial complex proteins will occur. Indeed, altered gene expression metabolic activity has been shown in psychiatric disorders [17].

Moreover, the oxidative metabolism of dopamine has a significant role in oxidative stress [18], which will further interrupt an antioxidant pathway [19]. Glutathione can be induced by the oxidation of dopamine [20]. N-acetyl-cysteine is a derivative of cysteine, an antioxidant precursor of glutathione. It is available as a potent antioxidant for brain disorders and some psychiatric disorders [21, 22], schizophrenia, mood disorders, addicted conditions [23].

The most challenging issue for developing a novel treatment approach for a psychiatric disorder is a better diagnosis. These incidents mainly occur, resulting in a limited understanding of behaviour, cognition, and emotion [24]. It is not surprising that altered psychological function is associated with psychiatric conditions, sleep, anxiety, and stress. Consequently, GPCR receptors are highly potential for psychiatric disorders in developing novel treatment approaches. The following perspective will investigate the pharmacokinetics, pharmacodynamics, and the role of GPCRs in composing a novel treatment for psychiatric disorders.

CONCLUSION

Psychiatric disorders like SZ and major depressive disorder are correlated with the imbalance of neurotransmitters, and G-protein and GPCR mediated signaling pathways. Alteration of these can represent the dysfunction of the brain. A clear understanding of these phenomena may help develop a novel treatment strategy for psychiatric disorders. There is strong evidence that dysregulation of ROS, glutathione, and oxidative stress may alter psychological func-

tions. Several compounds along with RGS receptors, aripiprazole, quetiapine, and some kinds of receptors have been included that can be fruitful for managing the disorders.

Moreover, N-acetyl cysteine will provide an exciting output for novel treatments to handle mental illness. The way of targeting GPCR mediated signals by individual molecules has been included in our discussion. Nevertheless, further investigation is required before considering it as a standard treatment and monotherapy with a neuro potential effect. The current treatment process that works better or somehow cannot provide satisfactory performance should be investigated. Brain atrophy and dysregulation of neuronal plasticity are associated with the stress-related disorder, so as a positive consequence, it may aid in developing a novel treatment strategy. Such understanding will provide a new treatment approach to improve the current treatment method and technique.

LIST OF ABBREVIATIONS

GPCRs = G Protein-Coupled Receptors

RGS = Regulators of G-Protein Signaling

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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