Heterotrimeric G Proteins: Insights into the Neurobiology of Mood Disorders

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Abstract: Mood disorders such as major depression and bipolar disorder are common, severe, chronic and often life-threatening illnesses. Suicide is estimated to be the cause of death in up to approximately 10-15% of individuals with mood disorders. Alterations in the signal transduction through G protein-coupled receptor (GPCR) pathways have been reported in the etiopathology of mood disorders and the suicidal behavior. In this regard, the implication of certain GPCR subtypes such as α_{2A} -adrenoceptor has been repeatedly described using different approaches. However, several discrepancies have been recently reported in density and functional status of the heterotrimeric G proteins both in major depression and bipolar disorder. A compilation of the most relevant research topics about the implication of heterotrimeric G proteins in the etiology of mood disorders (*i.e.*, animal models of mood disorders, studies in peripheral tissue of depressive patients, and studies in *postmortem* human brain of suicide victims with mood disorders) will provide a broad perspective of this potential therapeutic target field. Proposed causes of the discrepancies reported at the level of G proteins in *postmortem* human brain of suicide victims will be discussed.

Key Words: Mood disorders, major depression, bipolar disorder, suicide, heterotrimeric G proteins, G protein-coupled receptors (GPCR), α_2 -adrenoceptors.

INTRODUCTION

Neither the neurobiology of mood disorders nor the mechanisms of action of antidepressants are completely understood to date, even if knowledge is progressively accumulating [135]. The essential feature of this group of disorders is a disturbance of mood, accompanied by a manic or depressive syndrome. Mood disorders include major depression and bipolar disorder, which are distinguished by whether or not there has been a manic episode [1].

The diagnostic criteria for major depressive episode include a dysphoric mood or loss of interest or pleasure in all or almost all usual activities, insomnia or hypersomnia, psychomotor agitation or retardation, loss of interest or pleasure in usual activities, fatigue, feelings of worthlessness, and suicidal ideation among others. The manic episode is characterized by a predominantly elevated, expansive, or irritable mood. The elevated or irritable mood must be a prominent part of the illness and relatively persistent, although it may alternate with depressive mood.

Alterations in the signal transduction through G protein-coupled receptor (GPCR) pathways [151] [72] have been reported in the etiopathology of mood disorders [117,118, 173]. The implication of certain GPCR subtypes and, among them, α_{2A} -adrenoceptors [52,62,69,126], has been repeatedly described using different approaches. Therefore, understanding the possible alterations in the signaling pathways modulated by these GPCR subtypes may open a new therapeutic field. Heterotrimeric G proteins have been described as the main signaling pathway downstream

receptor activation (see below). In this context, several discrepancies have been recently reported in density and functional status of the heterotrimeric G proteins both in major depression and bipolar disorder [49,57,62,69,149, 186]. The primary focus of this review will be to summarize recent advances in the study of the molecular biology of heterotrimeric G proteins. The most relevant research topics about the implication of heterotrimeric G proteins in the neurobiology of mood disorders (*i.e.*, animal models of mood disorders, studies in peripheral tissue of depressive patients, and studies in *postmortem* human brain of suicide victims with mood disorders) will be discussed, providing a broad perspective of this potential therapeutic target field.

MAJOR DEPRESSION AND SUICIDE

Suicide is a leading cause of death [92]. According to recent figures from Centers for Disease Control and Prevention (CDC) in the United States in 2002, suicide was the eleventh most common cause of death (in 1998 it was the eighth most common cause) [110]. One of the first studies showing a clear relation between suicide and psychiatric diseases reported that 45% of the suicide victims suffered mood disorders and 23% alcoholism [154]. Thus, several researchers have demonstrated that depression, alcoholism, drugs of abuse, and schizophrenia are the psychiatric pathologies more commonly related to suicide [32,87,119,158].

Depression is itself the principal cause of suicide. In this regard, mood disorders seem to be present in at least 50% of all suicide victims [14,78,79]. Reciprocally, it has been estimated that 60-70% of depressed patients experience suicidal ideation, and that 10-15% of depressed patients commit suicide [130]. These data indicate that close monitoring for suicidal ideation is imperative in patients with mood disorders.

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MONOAMINERGIC THEORY OF DEPRESSION

The molecular research about mood disorders have screened for a biological substrate [185]. Several hypotheses have linked the pathogenesis of depression to alterations in the neurotransmission systems in the central nervous system. During the last four decades, alterations in the serotonergic and/or noradrenergic neurotransmission have been related to mood disorders. This monoaminergic theory of depression was based on several reports [27,35,162]. Reserpine, an antihypertensive drug, induced depressive disorders related to catecholamine depletion; whereas iproniazide, a monoamine oxidase inhibitor, was associated with hypomanic episodes in some subjects. The first antidepressant drugs developed in the fifties were reported to inhibit either reuptake or degradation of catecholamines. In this regard, several studies using depletion of neurotransmitters have shown a relationship between alterations in serotonin and catecholamines and mood disorders [2,15,16,23,44,170].

The etiopathogenesis of mood disorders is not fully explained by the monoaminergic theory [109]. For instance, the temporal delay between the acute effect of antidepressants on the neurotransmitter levels and the clinical improvement is not understood, whereas several pharmacological approaches have been reported [5,6,20].

GPCRs are involved in cellular responses to the majority of hormones and neurotransmitters, and represent an enormously significant target for drug discovery. Alterations associated with depressive disorders of certain GPCR subtypes, such as α_{2A} -adrenoceptor [30,69,164], 5-HT_{1A} serotonin [4,17,82,160], μ -opioid [52,58,73] and CB₁ cannabinoid [85] receptor, both in terms of density and functionality, have been reported using different approaches. Heterotrimeric G proteins are described as the main signaling pathway downstream GPCR. In this regard, several scientific groups have screened for alterations in heterotrimeric G proteins among the possible molecular causes underlying depressive disorders.

HETEROTRIMERIC G PROTEIN SIGNALING

G Protein-Coupled Receptors

The signaling molecules that control and regulate cellular activity include hormones, neurotransmitters, small peptides and proteins, ions, and lipids, as well as sensory stimuli such as odorants, pheromones, and photons. These signaling molecules bind to receptors molecules inducing specific cellular responses. The cellular receptors have been classified according to their general effector mechanisms. This functional classification describes at least three general types of cell surface receptors: ion-channel receptors, enzyme-associated receptors, and G protein-coupled receptors (GPCRs) [89,136].

The name GPCR refers to diverse heptahelical proteins that mediate the cellular signaling *via* heterotrimeric G proteins [72,100,151,175]. The first GPCRs cloned in the mid 1980s were the visual pigment opsin [134], and the β -adrenergic receptor [45]. Since then, hundreds of pharmacologically distinct GPCRs have been described [56,71,81].

GPCRs have an extracellular amino terminus, seven α -helical transmembrane domains, which form the transmembrane core, three extracellular loops, three intracellular loops, and an intracellular carboxy terminus. Each of the seven transmembrane domains is formed by 20-27 amino acids. In different GPCRs, the amino terminus (7-595 amino acids), loops (5-230 amino acids), and carboxy terminus (12-359 amino acids) vary considerably in length [71,152,174,175]. The first crystal structure of any GPCR, the structure of bovine rhodopsin, has been recently solved at 2.8 Å resolution [150].

The most widely used classification of neurotransmitter/hormone receptors has been proposed by the International Union of Pharmacology (IUPHAR) [56,84]. The three major subclasses include the rhodopsin-like receptors (subclass I), the glucagon-related receptors (subclass II), and metabotropic glutamate-related receptors (subclass III) [63,88,89,184]. While many GPCRs have been found to also couple by G protein-independent mechanisms [26,101], the interaction with heterotrimeric G proteins is the major signaling machinery of these proteins [18,25,76].

Heterotrimeric G Proteins

Heterotrimeric G proteins were reported for the first time in the 1970s by Rodbell [111,155] and Gilman [114]. The "nucleotide binding protein necessary to reconstitute the stimulation of adenylate cyclase" was purified by Gilman's laboratory [139].

Monomeric G proteins (small G proteins) [113,172], and heterotrimeric G proteins [24,172] have been described as the two main families of signal transduction-related proteins that bind and hydrolyze guanine nucleotides. Heterotrimeric G proteins are formed by three subunits (α , β , and γ). The β and γ form a complex that do not dissociate under physiological conditions. Heterotrimeric G proteins are soluble intracellular proteins that are bound to the plasma membrane through covalent links to fatty acids [182]. G protein activation modulates classical downstream effectors, such as adenylate cyclases [77], phospholipases [90], and ionic channels [39] through well-characterized molecular mechanisms [65,138,166].

Heterotrimeric G proteins are classified according to the G_α subunits. Mammals have more than twenty different described G_α subunits, encoded in seventeen different genes [168]. They are classified in four families according to their homology in their primary structure: $G_{\alpha s}$, $G_{\alpha i}$, $G_{\alpha q}$, $G_{\alpha 12}$, each family with several subtypes. These G protein subtypes are extremely conserved in evolution.

With the exception of heterotrimeric G proteins expressed in sensory organs ($G_{\alpha t}$, $G_{\alpha gust}$ and $G_{\alpha olf}$), and certain subtypes found in hematopoietic ($G_{\alpha 16}$) or nervous ($G_{\alpha o}$) cells, most α -subunits are ubiquitous. In this regard, each cellular subtype expresses at least four or five G_α subtypes. In certain tissues, heterotrimeric G proteins are expressed at high concentrations. Thus, $G_{\alpha o}$ may represent 1-2% of the membrane protein in brain [80].

Six different G_β subunits have been described in mammals, expressed in six different genes [33]. These G_β

subunits present a 53-90% homology. Twelve different G_γ subunits, which are encoded on twelve different genes, show a high heterogeneity [28]. Although all the possible combinations of G_β and G_γ subunits could form up to seventy two $G_{\beta\gamma}$ dimers, not all the combinations are expressed *in vivo*. The functional significance of the diversity in the $G_{\beta\gamma}$ dimers is not yet understood. In this regard, most $G_{\beta\gamma}$ dimers (except for $\beta_1\gamma_1$ expressed in the retina) present similar functional properties.

Molecular Mechanism of Receptor-G Protein Coupling

The diversity of ligands activating GPCRs, as different as a photon of light and a 40 kDa protein, is reflected in the variety of mechanisms of ligand binding, such as the simplest mechanism for a ligand to activate a receptor binding the transmembrane core (norepinephrine, serotonin), or the protease ligand thrombin that cleaves the amino terminus of the receptor [21,91].

The most accepted molecular pharmacological model to describe GPCR activation is the ternary complex model (*i.e.*, agonist-receptor-G protein) [40]. The ternary complex model proposes that the receptor exists in an equilibrium between two conformational states: the functionally inactive (R) and the functionally active (R^*) state. This model assumes the classic pharmacological models, in which, in the absence of agonist, there are not detectable signal transduction pathways downstream the receptor. However, it has been demonstrated that, under certain conditions, the R^* state (and the G protein activation) may be detected in the absence of agonist [178]. Therefore, the pharmacological model has been extended describing the receptor-G protein coupling in the absence of agonist activation, and the basal functional activity of the signal transduction pathways [99,159]. According to this pharmacological model, the so-called inverse agonists, which are able to decrease the basal activity of the receptors, have been identified [133]. Thus, full and partial agonists bind R^* with higher affinity than R, shifting the equilibrium to the activated state, whereas inverse agonists bind R with higher affinity, shifting the equilibrium to the inactive state. This equilibrium is not shifted by the antagonists because they present equivalent affinity for the inactive R and the active R^* functional states of the receptor. Several reviews of the inverse agonism have appeared [19,31,41,128,176].

HETEROTRIMERIC G PROTEINS AND MOOD DISORDERS

Several groups have suggested that the heterotrimeric G proteins might be altered in mood disorders. This possibility was first raised in a study where GTP binding to brain membranes was performed in rat chronically treated with lithium [7]. Several works have been published showing alterations in heterotrimeric G proteins in both psychiatric [10,51,83,115], and neurodegenerative [22,36-38,55,70,108, 180] disorders. In this regard, the possible role of heterotrimeric G proteins in the pathophysiology of mood disorders, as well as the G protein signaling cascade as a molecular target for antidepressant therapy, has been mainly studied in three research lines: effects of antidepressant treatments in animal models, studies in peripheral tissue of depressive patients, and studies in *postmortem* human brain of suicide victims with mood disorders.

Effect of Antidepressant Treatment in Animal Models

Drug discovery in depression has been limited by the lack of a universally accepted animal model that can be used to screen for antidepressant effects. Although there are several animal models that reproduce some features of depression, their relevancy to the specifically human disorder major depression has been debated [185].

Several works have reported that the antidepressant drugs modulate the density of different heterotrimeric G proteins [103,105], as well as their functional response [127,143,44, 179] (Table 1). Experimental evidences have shown that lithium attenuates the GPCR-induced modulation of the second messengers, even in the absence of changes in the density of the receptor [117]. It has been consistently reported that chronic lithium affects G protein function [7,34,48,104,106,107,124,181]. The Mg^{2+} binding site in the G_α subunits has been proposed as one of the possible molecular targets for lithium [9,93,94].

It has been published that the level of expression of mRNA coding for certain G_α subunits is affected by antidepressants, however, this effect of chronic antidepressant treatment has generated some discrepancies [50]. The Electroconvulsive shock attenuates β -adrenoceptor and muscarinic cholinergic receptor coupling to G proteins [8], and augments heterotrimeric G protein-coupling to adenylate cyclase [147]. A modulation of the expression level of different G_α subunits by the Electroconvulsive shock has also been reported [124]. However, although chronic antidepressant treatment alters the expression and functional activity of heterotrimeric G proteins, they are unlikely a direct molecular target of antidepressant drugs.

Studies in Peripheral Tissue of Depressive Patients

The screening for peripheral markers of depression has been performed in order to facilitate the ease and accuracy of the diagnosis, as well as to improve the knowledge of its etiology. Markers reflecting the psychiatric state of the patient (such as the degree of severity or the response to medication) are termed state markers, whereas those present irrespective of the change in the psychological state are termed trait markers. Therefore, the detection of state markers would provide clinical information about the severity and treatment responsiveness, whereas the presence of a trait marker could be an index of the vulnerability to depression. Several reviews of the peripheral markers have appeared [102,132].

Certain discrepancies have been reported in the quantification of the densities and the functional status of the heterotrimeric G proteins in peripheral tissues of patients with mood disorders (Table 2). However, most of these studies (contrary to the studies performed in *postmortem* human brain, see below) have been performed in patients with a defined psychiatric diagnosis.

In platelets of patients with major depression, a higher density of $G_{\alpha 1/2}$, and a lower density of $G_{\alpha 3}$ subunit have been reported [61]. In mononuclear leukocytes, both decreased immunoreactive and functional levels of $G_{\alpha s}$ and

Table 1. Summary of Studies of the Effect of Antidepressant Treatment on Heterotrimeric G Proteins in Animal Models

Chronic antidepressant	Brain region	Finding in animal model	Citation
TCA (imi, clo, dsp) and clg	FCx, HT, HC, Str, DR and LC	↓ $G_{\alpha s}$ and $G_{\alpha i}$ with TCA and clorgyline	[103]
TCA (imi, dsp) and ECS	Limbic areas	↓ cAMP synthesis <i>in vitro</i>	[179]
TCA (amtp, dsp, imi, iprl) and ECS	Cx and HT	↑ cAMP synthesis activating G proteins	[127]
dsp	Cx	↓ β -adrenoceptor-mediated cAMP synthesis	[143]
dsp	Cx	↓ cAMP synthesis activating G proteins and AC	[144]
TCA (imi, clo, dsp), flx and clg	FCx, HT, HC, Str, DR, LC and ME	G protein density: ↓ $G_{\alpha s}$ with imi in HC, with TCA and clg in Str and LC. ↓ $G_{\alpha i/2}$ with dsp in FCx, with clg in Str, with imi and clg in HT, with imi in HC. ↑ $G_{\alpha o}$ with TCA and clg. G protein mRNA: ↑ $G_{\alpha 2}$ in FCx, $G_{\alpha q}$ in Str, and ↓ $G_{\alpha s}$ with flx in ME	[105]
amtp, dsp, trn	FCx	G protein density: ↔ $G_{\alpha s}$, $G_{\alpha i2}$, $G_{\beta 35}$, $G_{\beta 36}$ G protein mRNA: ↔ $G_{\alpha s}$, $G_{\alpha i2}$, $G_{\beta 1}$, $G_{\beta 2}$	[50]
ECS	FCx	↓ muscarinic and β -adrenergic-stimulated [3 H]GTP binding	[8]
ECS	FCx	↑ cAMP synthesis activating G proteins and AC	[147]
ECS	HC	↓ $G_{\alpha s}$, $G_{\alpha i2}$, and ↑ $G_{\alpha o}$ mRNA	[124]
Lithium	HC	↑ $G_{\alpha s}$, $G_{\alpha i2}$, $G_{\alpha o}$ mRNA	
Lithium	Cx	↓ muscarinic and β -adrenergic-stimulated [3 H]GTP binding	[7]
Lithium	Cx	↓ $G_{\alpha i1}$, $G_{\alpha i2}$ mRNA ↔ $G_{\alpha o}$, $G_{\alpha s}$, G_{β} mRNA	[34]
Lithium	FCx, HT, HC, Str, DR, LC	↑ $G_{\alpha i}$ in HT and HC ↔ $G_{\alpha o}$, $G_{\alpha s}$	[104]
Lithium	Cx	↓ $G_{\alpha s}$, $G_{\alpha i2}$, $G_{\alpha i2}$ mRNA	[106]
Lithium	Cx	↓ $G_{\alpha s}$, $G_{\alpha i2}$, $G_{\alpha i2}$ mRNA ↔ $G_{\alpha o}$, $G_{\beta 1}$, $G_{\beta 2}$, $G_{\beta 3}$ mRNA	[107]
Lithium	Cx	↓ 5-HT-stimulated $G_{\alpha s}$, $G_{\alpha i}$, $G_{\alpha o}$, $G_{\alpha q}$ ↔ $G_{\alpha s}$, $G_{\alpha i}$, $G_{\alpha o}$, $G_{\alpha q}$ densities	[181]

Antidepressant abbreviations: amtp, amitriptyline; clg, clorgyline; clo, clomipramine; dsp, desipramine; ECS, electroconvulsive shock; flx, fluoxetine; imi, imipramine; iprl, iprindole; TCA, tricyclic antidepressants; trn, tranylcypromine. *Brain region abbreviations:* Cx, cortex; DR, dorsal raphe; FCx, frontal cortex; HC, hippocampus; HT, hypothalamus; LC, locus coeruleus; ME, mesencephalus; Str, striatum.

$G_{\alpha i}$ [13], and not altered $G_{\alpha s}$ and $G_{\alpha i}$ densities [188] have been found. In patients with bipolar disorder, elevated levels of the two isoforms of $G_{\alpha s}$, both in platelets and in mononuclear leukocytes [116,129,188], without alterations in $G_{\alpha q/11}$, $G_{\alpha z}$, G_{β} , or in the different subtypes of $G_{\alpha i}$ [116,129], have been described. On the contrary, increased levels of $G_{\alpha i}$ have been found in mononuclear leukocytes of patients with bipolar disorder [188]. In platelets of patients with mood disorders (both major depression and bipolar disorder), decreased densities of 45 kDa $G_{\alpha s}$ [11], and unaltered levels of $G_{\alpha i/o}$ have been reported [140].

Regarding the identification of state markers of mood disorders, an increased [3 H]GppNHp (GTP analog) binding stimulated by β -adrenoceptor and cholinergic muscarinic receptor agonists has been reported in mononuclear leukocytes in the manic episodes in patients with bipolar disorder [163]. In the same context, the β -adrenoceptor and cholinergic muscarinic stimulated binding of [3 H]GppNHp was found elevated in the manic episodes, but decreased in depressive episodes [12]. State markers correlating with the severity of the bipolar disorder have been described according to the increased levels obtained in the density of

Table 2. Summary of Studies of Heterotrimeric G Proteins in Peripheral Tissue of Patients with Mood Disorders

Psychiatric diagnosis	Patients/Controls	Peripheral tissue	Finding in peripheral tissue	Citation
Major Depression	22 non-treated depressed patients 22 controls	platelet	$\uparrow G_{\alpha 1/2}$ $\downarrow G_{\alpha 3}$	[61]
Major Depression	37 non-treated depressed patients 31 controls	mononuclear leukocyte	$\downarrow G_{\alpha s}, G_{\alpha i}$ density and functionality	[13]
Major Depression and Bipolar Disorder	14 non-treated depressed patients 8 non-treated bipolar patients 17 controls	mononuclear leukocyte	$\leftrightarrow G_{\alpha s}, G_{\alpha i}$ in MD $\uparrow G_{\alpha s}, G_{\alpha i}$ in BD	[188]
Bipolar Disorder	14 non-treated bipolar patients 20 euthymic bipolar patients treated with lithium 11 controls	platelet and mononuclear leukocyte	$\uparrow G_{\alpha s}$ in BD $\leftrightarrow G_{\alpha 1/2}, G_{\alpha q/11}$ in BD Lithium $\downarrow G_{\alpha q/11}$ Lithium $\uparrow$ PTX labeling	[116]
Bipolar Disorder	44 treated euthymic bipolar patients 27 controls	platelet	$\uparrow G_{\alpha s}$ $\leftrightarrow G_{\alpha 1/2}, G_{\alpha q/11}$	[129]
Bipolar Disorder	10 non-treated manic bipolar patients 10 non-treated euthymic patients 10 controls	mononuclear leukocyte	$\uparrow$ G protein function in BD $\leftrightarrow$ in euthymic patients	[163]
Bipolar Disorder	20 manic bipolar patients 11 depressed bipolar patients 30 controls	mononuclear leukocyte	Manic BD: $\uparrow$ G protein function, and $\uparrow G_{\alpha i}, G_{\alpha s}$ Depressive BD: $\leftrightarrow$ G protein function, and $\leftrightarrow G_{\alpha i}, G_{\alpha s}$	[12]
Mood Disorder	3 bipolar patients 10 depressed patients 18 controls	platelet	$\leftrightarrow G_{\alpha i/o}$	[140]
Mood Disorder	18 depressed patients 8 depressed bipolar patients 10 controls	mononuclear leukocyte	$\downarrow G_{\alpha s}$ density and functionality	[11]
Mood Disorder	16-22 depressed patients 11-16 bipolar patients 14-23 controls	granulocyte	$\uparrow G_{\alpha s}, G_{\alpha 2}$, and $\leftrightarrow G_{\alpha q}$ mRNA in BD $\leftrightarrow G_{\alpha s}, G_{\alpha 2}, G_{\alpha q}$ mRNA in MD	[171]

PTX, pertussis toxin

$G_{\alpha s}$ [188]. On the contrary, a possible trait marker was proposed when increased levels of $G_{\alpha s}$ were found without a correlation with the pharmacological treatment of the patient [129]. Similar results have been reported in granulocytes for the mRNA levels codifying for $G_{\alpha s}$ [171].

Unfortunately, little progress has been made in the research of peripheral markers for depression. A number of hypotheses have been proposed, none of which satisfactorily explains all the discordant results that have been reported [132].

Studies in Postmortem Human Brain of Depressed Subjects

According to the indirect evidence for abnormalities at GPCR signaling described above, and to the molecular

mechanism of action of certain classes of antidepressants [86,98,120,121,165,173], several independent laboratories have examined heterotrimeric G proteins in brain of patients with mood disorders [46,64,115,117,177]. These studies have been focused on the density and functionality of these proteins in *postmortem* human brain of suicide victims with or without a diagnosis of mood disorders, both major depression and bipolar disorder (Table 3).

Several discrepancies have been reported. Thus, in prefrontal cortex of subjects with major depression, both increased immunoreactive levels of $G_{\alpha 1/2}$ [62], and decreased $G_{\alpha 2}$ without alterations in $G_{\alpha 1}$ [149] have been described. The densities of 45 kDa $G_{\alpha s}$ have been reported to be increased in prefrontal cortex of suicide victims with major depression [36,149]. A significant decrease in both

Table 3. Summary of Studies of Heterotrimeric G Proteins in *Postmortem* Human Brain in Suicide and Mood Disorders

Psychiatric diagnosis	Suicide/depressed/controls	Brain region	Finding in suicide or depression	Citation
Suicide victims	43 suicides 38 control	PFCx	mRNA and protein: ↓ $G_{\alpha i2}$, $G_{\alpha o}$ ↑ 45 kDa $G_{\alpha s}$	[49]
Suicide victims with major depression	13 depressed 13 control	PFCx	↓ $G_{\alpha i2}$ ↑ 45 kDa $G_{\alpha s}$ ↔ 52 kDa $G_{\alpha s}$, $G_{\alpha i1}$, $G_{\alpha o}$, $G_{\alpha q/11}$	[149]
Suicide victims with major depression	7 depressed 11 unknown diagnosis 22 control	FCx	↑ 45 kDa $G_{\alpha s}$ in depressed subjects ↔ 45 and 52 kDa $G_{\alpha s}$ in suicide victims	[36]
Major depression	4-6 depressed 1-4 dysthymic 7 control	PCx, TCx	↔ 45 and 52 kDa $G_{\alpha s}$, G_{α} , $G_{\alpha q}$, G_{β} ↑ GTP analog binding to $G_{\alpha i/o}$ in depressed subjects	[148]
Bipolar disorder	7 bipolar 7 control	TCx, OCx, CB	↑ 45 and 52 kDa $G_{\alpha s}$ ↔ $G_{\alpha i1/2}$, G_{α} , G_{β}	[186]
Bipolar disorder	10 bipolar 10 control	PFCx, TCx, OCx, Thal	↑ 45 and 52 kDa $G_{\alpha s}$ in PCx, TCx, OCx ↔ $G_{\alpha i1/2}$, G_{α} , G_{β}	[187]
Bipolar disorder	5 bipolar 5 control	PFCx	↑ 45 and 52 kDa $G_{\alpha s}$ ↔ $G_{\alpha i}$, G_{α} , $G_{\alpha o}$, $G_{\alpha q/11}$, G_{β}	[57]
Bipolar disorder	10 bipolar 10 control	FCx, TCx, OCx	↑ $G_{\alpha q/11}$ in OCx ↔ $G_{\beta 1}$, $G_{\beta 2}$	[122]
Bipolar disorder	10 bipolar 10 control	FCx, TCx, OCx	↔ 45 and 52 kDa $G_{\alpha s}$ mRNA	[189]
Major depression and bipolar disorder	15 depressed 15 bipolar 15 control	TCx, OCx	↔ 45 and 52 kDa $G_{\alpha s}$, $G_{\alpha i1/2}$	[47]
Suicide victims with mood disorder	13 depressed 3 bipolar 8 other diagnosis 9 unknown diagnosis 20 control	PFCx	↑ $G_{\alpha i1/2}$ in non-treated suicide victims with mood disorder ↔ $G_{\alpha i1/2}$ in treated suicide victims with mood disorder ↔ $G_{\alpha i1/2}$ in suicide victims without diagnosis ↔ $G_{\alpha q/11}$ in treated suicide victims	[62]
Suicide victims with mood disorder	21 depressed 6 bipolar 1 dysthymic 28 control	PFCx	↔ 45 and 52 kDa $G_{\alpha s}$, $G_{\alpha i1/2}$, $G_{\alpha i3}$, $G_{\alpha o}$	[69]

Brain region abbreviations: CB, cerebellum; FCx, frontal cortex; OCx, occipital cortex; PCx, parietal cortex; PFCx, prefrontal cortex; TCx, temporal cortex; Thal, thalamus

mRNA and protein levels of $G_{\alpha i2}$ and $G_{\alpha o}$, and a significant increase in levels of 45 kDa $G_{\alpha s}$ have been observed in prefrontal cortex of suicide subjects. These alterations were reported to be independent of the retrospective psychiatric diagnosis [49]. On the contrary, several publications have not found alterations in the densities of the different subunits of the heterotrimeric G proteins, both G_{α} [47,69] and G_{β} [148]. The G proteins can be directly activated *in vitro* in an experimental receptor-independent manner with the peptide mastoparan [141,142]. In *postmortem* prefrontal cortex,

mastoparan displayed concentration-response curves with similar pharmacological profiles in suicide victims with mood disorders and in control subjects [69], suggesting that the functional availability of the heterotrimeric G proteins to be activated by GPCR is not altered in depression. Recently, certain polymorphisms in the olfactory $G_{\alpha f}$ have been reported in major depression [190].

In suicide victims with bipolar disorder, increased levels of the two isoforms of $G_{\alpha s}$ [57,186] and of $G_{\alpha q/11}$ [122] have

been reported. More recently, the immunoreactive levels of these heterotrimeric G proteins have not shown significant changes in suicide victims with bipolar disorder when compared with control subjects [47,69]. No changes in the level of expression of the mRNA sequences encoding the 45 and 52 kDa $G_{\alpha s}$ [189], or abnormalities in the gene encoding for these α -subunits [153] have been reported.

The possible alterations in the level of expression and in the functional activity of the heterotrimeric G proteins in *postmortem* human brain of suicide victims with mood disorders have generated numerous publications with several discrepancies (see above, and Table 3), even within the same scientific group. This disappointing result does not come as surprise because clearcut methodological flaws have been repeated in many studies. Such methodological deficits may have influenced the obtained results in several ways. The presence of small sample sizes [57], heterogeneous groups (suicide victims without a medical diagnosis) [36,62,75], or the establishment of retrospective (*postmortem*) diagnosis of mood disorders in suicide victims [36,57,122,186,187] may be the basis of certain scientific discrepancies. Thus, it has been recently reported that, opposite to schizophrenia, reaching an accurate diagnosis for mood disorders is difficult to determine using retrospective diagnosis [43].

It has been demonstrated that several of the studied pharmacologic and biochemical parameters are affected by the intrinsic variables of *postmortem* human brain, such as gender, age, *postmortem* delay, and freezing storage period of the sample [70,123,156,161]. In this regard, experimental designs testing more suicide victims than control subjects [62], or the absence of matched pairs of subjects (suicides and their respective controls) according to these intrinsic variables [36,47,62,148,149] might be, as discussed somewhere else [69,70], some of the causes of the above reported discrepancies. The impact of these methodological shortcomings must be accounted for.

In summary, the evidence for an association between heterotrimeric G proteins and mood disorders is not as strong as believed [47,69].

G PROTEIN-COUPLED RECEPTORS IN DEPRESSED SUICIDE BRAIN: FUNCTIONAL SUPERSENSITIVITY OF α_{2A} -ADRENOCEPTORS

The possible alterations in the different subtypes of neurotransmitter GPCRs in *postmortem* human brain of suicide victims have been reviewed [74,96,98,173]. Several reports have described altered levels of the presynaptic α_2 -adrenoceptor in *postmortem* human brain of suicide victims [30,42,52,62,66,125,126]. It has been demonstrated that the chronic treatment with antidepressant drugs, as well as with lithium, induces desensitization and down-regulation (a loss in the total receptor number) of the α_2 -adrenoceptors both in rat brain [97,121,131,169], and in platelets of depressed patients [59,60]. In *postmortem* human brain of suicide victims with major depression, a down-regulation of the α_2 -adrenoceptor promoted by chronic treatment with antidepressants has been reported by antagonist radioligand binding techniques [42]. This selective effect of the antidepressants in suicide victims was not described quantifying the immunoreactive densities of the α_2 -adrenoceptors [62].

An important aspect of the obtained results valuating the role the α_2 -adrenoceptors in *postmortem* human brain of suicide victims with mood disorders is the pharmacological characteristic of the radioligand utilized in the quantification. The quantification of the receptor density with α_2 -adrenoceptor agonists strongly suggests an increased level of this receptor subtype in several brain regions of suicide victims with mood disorders [66,125,126,146]. On the opposite, no significant differences have been reported quantifying the α_2 -adrenoceptor density with radioligand antagonists [30,126]. Increments in the density of α_2 -adrenoceptors were suggested in a manuscript using a radioligand antagonist in temporal cortex of suicide victims with a retrospective diagnosis of depression [42]. In *postmortem* human brain of suicide victims without a specific psychiatric diagnosis, both increased [145] and not altered densities [3] of α_2 -adrenoceptors have been reported.

The repeatedly reported increased densities of α_2 -adrenoceptors in *postmortem* human brain of suicide victims with mood disorders quantified with radioligand agonists suggest alterations in the functional activity of the receptor without alterations in its total density [30]. Antagonists present, by definition [95,183], comparable affinities to the different functional states of the receptor. According to the above discussed papers, the total density of the α_2 -adrenoceptors is not altered in *postmortem* human brain of suicide victims with mood disorders. Agonist chemicals are recognized by the active conformation of the receptor with a higher affinity than antagonists (see above) [40]. Thus, the described alterations in α_2 -adrenoceptors might be related to modifications in the functional receptor-G protein coupling.

A direct evaluation of the receptor-G protein coupling can be obtained by measuring the agonist stimulation of [35 S]GTP γ S binding (a radiolabeled GTP analog) [112,167,178]. This technique has been optimized in *postmortem* human brain allowing the quantification of receptor-G protein coupling in membrane preparations [67,68], and in tissue sections [157]. The altered functional state of the α_2 -adrenoceptors associated with mood disorders, suggested by the increased radioligand agonist binding (see above), has been recently supported quantifying agonist stimulation of [35 S]GTP γ S binding in *postmortem* human brain of suicide victims with *antemortem* medical diagnosis [69]. A higher potency (lower EC_{50}) of the α_2 -adrenoceptor agonist UK14304 promoting receptor-G protein coupling has been reported without alterations in the efficacy (E_{max}). This higher receptor-G protein coupling was demonstrated to be selective for the α_2 -adrenoceptors within the tested GPCRs (5-HT $_{1A}$ serotonin, μ -opioid, GABA $_B$, and cholinergic muscarinic receptors) [69]. One of the possible explanations for the selective increased α_2 -adrenoceptor-G protein coupling without alterations in the above discussed total receptor or heterotrimeric G protein densities maybe the presence of a higher proportion of constitutively active receptors. According to this proposal, the quantification of the α_{2A} -adrenoceptor density with a selective inverse agonist [29,133] (presenting higher affinity for the inactive conformational state of the receptor, see above) suggests decreased binding sites in *postmortem* human brain membranes of suicide victims with mood disorders [30].

Recently, a very promising preliminary study has been published suggesting a polymorphism associated with suicide victims in the third intracellular loop of the α_{2A} -adrenoceptor [164]. In this regard, detailed mutational analysis of different GPCRs has demonstrated the role of this intracellular loop 3 playing a key role in determining receptor-G protein coupling in conjunction with residues present in the intracellular loop 2 [25,137,184]. In the therapeutic context, the α_2 -adrenoceptor antagonist mirtazapine is prescribed for the treatment of patients with major depression with positive results [53,54].

CONCLUSIONS

Decades of research have not allowed us to understand the molecular basis of mood disorders. The cellular mechanisms of action of many antidepressants are still unknown, and many depressed patients do not respond to antidepressant therapy. By understanding the cellular and molecular alterations associated with depressive disorders, the design of more efficacious therapeutic chemicals could be achievable.

Several discrepancies have been reported in the literature according to the possible alterations in G proteins associated with mood disorders. The last published results suggest that there are no detectable alterations either in the density or in the intrinsic functionality of heterotrimeric G proteins in *postmortem* human brain of suicide victims with mood disorders.

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