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G Protein-Coupled Receptors in Major Psychiatric Disorders

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Abstract

Although the molecular mechanisms underlying psychiatric illnesses such as depression, bipolar disorder and schizophrenia remain incompletely understood, there is increasing clinical, pharmacologic, and genetic evidence that G protein-coupled receptors (GPCRs) play critical roles in these disorders and their treatments. This perspectives paper reviews and synthesizes the available data. Dysfunction of multiple neurotransmitter and neuropeptide GPCRs in frontal cortex and limbic-related regions, such as the hippocampus, hypothalamus and brainstem, likely underlies the complex clinical picture that includes cognitive, perceptual, affective and motoric symptoms. The future development of novel agents targeting GPCR signaling cascades remains an exciting prospect for patients refractory to existing therapeutics.

Keywords

G protein-coupled receptors (GPCRs); depression; bipolar disorder; schizophrenia; serotonin; dopamine; glutamate

1. Introduction

Although major psychiatric diseases such as mood disorders and schizophrenia are among the most common and destructive of all human illnesses, the molecular and cellular mechanisms underlying their complex pathophysiology remains to be fully elucidated. Attempts to comprehend the biochemical underpinnings of major psychiatric disorders began in earnest as clinically effective mood-altering drugs began to appear in the late 1950s and early 1960s. Studies were, by and large, designed to detect relative excess or deficiency of individual neurotransmitters associated with pathological states; not surprisingly, progress in unraveling the neurobiology of these complex disorders was slow using such strategies in isolation. Psychiatry, like much of the rest of medicine, has entered a new and exciting age demarcated by current rapid advances and the future promises of genetics, molecular and cellular biology, and improving imaging technologies. Recent years have witnessed a more wide-ranging understanding of the neural circuits and the various mechanisms of synaptic transmission, a further elucidation of the molecular mechanisms of receptor and postreceptor signaling, a finer understanding of the process by which genes code for specific functional proteins, and the identification of causative genes in many neurological disorders that *in toto* reduce the

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complexity in gene to behavior pathways [1]. In other areas of medicine, the recent molecular medicine revolution has already had an immediate impact; unfortunately, clinical translation of these findings to psychiatric disorders has not been as rapid. In addition to the sheer complexity of the CNS, unraveling the etiology/pathophysiology of complex psychiatric disorders is hampered by numerous additional obstacles, including lack of a defined pathology, no direct tissue accessibility, and the daunting fact that the complexity of behavior is not simply the sum of its parts [1]. Nevertheless, major advances in our understanding of the role of G protein-coupled receptors (GPCRs) in the pathophysiology and treatment of major psychiatric disorders have indeed been made. In this perspectives article, we review and synthesize the available data, and discuss their implications for the strategic development of improved therapeutics. Due to space considerations, we have narrowed the scope of this review to the major psychiatric disorders, and the major families of GPCRs implicated, and have cited reviews in place of primary papers as often as possible.

2. Clinical Overview

It is beyond the scope of this article to discuss the role of GPCRs in all psychiatric disorders; here we limit ourselves to a discussion the most severe disorders – Schizophrenia and Mood Disorders. Since the readership of the journal may be less familiar with the clinical facets of these disorders, we first provide a brief clinical overview, prior to embarking on a discussion of GPCRs.

Mood disorders, such as major depression (MD) and bipolar disorder (BPD, previously referred to as manic-depressive illness), and schizophrenia are common, severe, and chronic illnesses. The Global Burden of Disease Study has identified major mood disorders among the leading causes of disability worldwide [2], and the World Health Organization estimates that mental illness accounts for 40 percent of disability funding in the U.S. [3].

2.1 Mood Disorders

MD has a lifetime incidence of about 15% [4], and affects twice as many women as men. There is a significant genetic component to the disorder; studies report an approximately three-fold increased risk of MD in first-degree relatives of probands with the disorder compared to the general population [4,5]. The course of MD is characterized by episodes of depressed mood, suicidal ideation, anhedonia, impaired sleep, changes in psychomotor activity, and impaired memory and concentration. Suicide is the cause of death in up to 15% of individuals with this disorder [6]. There are several classes of antidepressant medications used to treat MD, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and others that affect reuptake of monoamines such as norepinephrine, dopamine and serotonin.

BPD has an approximate lifetime incidence of 1% [8] and is characterized by two seemingly opposite mood states: mania and depression. It is equally prevalent in men and women [6]. The manic stages of BPD are characterized by a hyperaroused state (either euphoric or dysphoric), increases in motor activity, racing thoughts, impaired judgment, and an apparent decreased need for sleep [6,8]. The depressive phases of the illness present with similar symptomatology as those seen in MD. As with MD, suicide is the cause of death in up to 15% of individuals with BPD [6]. BPD is typically treated with the class of medications known as mood stabilizers (reviewed in [8]). Although other types of medications, including atypical antipsychotics, are also used to treat BPD, most studies have focused on mood stabilizers such as lithium, valproic acid and carbamazepine as the standard of treatment for this disorder.

3.2 Schizophrenia

Schizophrenia has a lifetime prevalence of approximately 1% [3] and affects men and women equally. Family prevalence, twin, and adoption studies have all demonstrated that there is a genetic component to this disorder; individuals with a first degree relative with schizophrenia are ten times more likely to be affected than an individual in the general population. Schizophrenia is a psychotic disorder characterized by delusions, hallucinations and/or thought disorganization ("positive symptoms") and flattened affect, poverty of thought and/or avolition ("negative symptoms"). The cognitive impairments in schizophrenia (sometimes quite profound) are increasingly being recognized as playing a major role in the long-term disability observed in this devastating illness. Not surprisingly, much of the new medication strategies have focused on improving the cognitive deficits (*vide infra*). The suicide rate among schizophrenic individuals is twice that of the general population [3]. Like mood disorders, schizophrenia is associated with a significant increase in medical comorbidities [3], a difficulty compounded by the increasingly recognized fact that newer antipsychotic medications can cause medical complications such as obesity and diabetes. The economic cost of managing a patient with schizophrenia is estimated to be six times that of a patient with a myocardial infarction [3]. Schizophrenia is generally treated with antipsychotic medications. The use of first generation, or typical, antipsychotics, has largely given way to the use of newer, second generation, or atypical, antipsychotics which have equivalent efficacy, but different and arguably more favorable side effect profiles.

3. GPCRs and Mood Disorders

Although most families of medications currently used to treat affective illnesses have been in use since the 1950s, our understanding of their mechanisms, and the etiology of the underlying diseases, is still incomplete. The "pharmacological bridge" approach to biomedical research refers to the development of etiologic theories of disease based on the known mechanism of effective pharmacologic treatments. In mood disorders, this approach first led to the monoamine theory. As discussed below, monoamines are still considered to be among the most important neurotransmitters in the pathophysiology of mood disorders. However, other neurotransmitter systems, most notably the glutamatergic, cholinergic and GABAergic systems, have also been implicated.

3.1 G protein-coupled noradrenergic receptors and mood disorders

The noradrenergic system was one of the first neurotransmitter systems to be suspected to play a role in affective disorders. Many initial studies indirectly addressed the question of noradrenergic receptor abnormalities in these disorders by investigating expression in peripheral cells. Further evidence has come from postmortem studies, pharmacologic challenge experiments, studies to elucidate the mechanism of action of effective medications, and genetic studies.

3.1.1 Peripheral blood cell studies—Due to the accessibility of platelets and lymphocytes, both alpha2 and beta2 adrenergic receptors have been extensively studied in mood disorders. It must be acknowledged at the outset that there may be several problems with the assumption that changes in adrenergic receptors on peripheral cells reflect similar alterations in the CNS. To begin with, receptors on blood cells are, by definition, noninnervated, exist in a markedly different environment, and may therefore poorly reflect central, innervated, adrenergic receptors. Another major problem when interpreting studies of dynamic receptor regulation in blood cells is that white blood cell counts and the relative proportions of subsets of lymphocytes may vary. Recruitment of cells with different characteristics into the circulation may frequently explain altered receptor function. Nevertheless, in some cases, similar findings have been found in postmortem brain studies and in certain CNS challenge studies as has been observed in peripheral cell studies.

Alpha2-adrenergic receptors: Studies of alpha2-adrenergic receptor (alpha2-AR) levels in platelets of depressed patients have yielded mixed results. A series of studies using yohimbine-alkaloid radioligands showed no differences in receptor numbers, while other studies using partial or full agonists have reported an increased maximal binding capacity in depressed patients relative to controls (reviewed in [7]). The findings of these latter studies have been called into question, however, because the ligands have been discovered to bind to nonadrenergic imidazoline sites [9-11], which are present on platelets [12]. Thus the alpha2 receptor hypersensitivity theory of depression, based on these initial findings, remains in question.

Few studies have addressed this question in bipolar disorder. One such study found a trend toward increased density of alpha2-ARs on platelets of patients with bipolar disorder [13].

Beta2-adrenergic receptors: Although studies investigating the levels of beta2-adrenergic receptors (beta2-ARs) in peripheral cells have yielded inconsistent results (reviewed in [7]), multiple studies have reported decreased beta-AR-stimulated adenylate cyclase (AC) activity in leukocytes of depressed patients [14-19]. This is hypothesized to be due to a disruption of the receptor/Gs/AC complex [20]. For both the alpha2 and beta2 findings in peripheral cells, it remains to be determined which abnormalities relate specifically to the pathogenesis of mood disorders, and which are related to nonspecific effects of stress, or homeostatic mechanisms [21].

3.1.2 Postmortem studies

Alpha-adrenergic receptors: Limited data suggests alpha2-AR levels are altered in the postmortem brains of depressed suicide victims (reviewed in [22]). These preliminary findings are limited by methodological considerations regarding the use of postmortem brains (e.g., postmortem delay, cause of death, drug history) and by the fact that some of the ligands used also bind imidazoline sites, as discussed above.

Beta-adrenergic receptors: Several studies have reported an increase in beta-AR density in the brains of suicide victims [23], including specifically in cortex [24], while at least one other study found no difference in cortex [25].

3.1.3 Pharmacologic challenge experiments

Alpha2-adrenergic receptors: Numerous studies have investigated the role of alpha2-ARs in mood disorders using pharmacologic challenge strategies. Multiple studies have compared the downstream effects of alpha2-AR agonists (such as clonidine) or antagonists (such as yohimbine) on plasma MHPG, blood pressure, sedation and cortisol in depressed patients compared to normal controls. While the findings have not been entirely consistent, most do not show significant differences (reviewed in [21]). However, multiple studies have consistently demonstrated a significant decrease in growth hormone (GH) response to the alpha2-AR agonist clonidine [26-32], supporting the hypothesis of postsynaptic alpha2-AR subsensitivity in depressed patients.

Far fewer studies have addressed the question of alpha2-AR sensitivity in bipolar disorder. Several such studies have demonstrated a blunted GH response in manic and/or bipolar depressed states (reviewed in [21]). Similar findings have been reported in panic disorder, general anxiety, and obsessive-compulsive disorder, suggesting that it may be a nonspecific response to stress and/or elevated norepinephrine [33-36].

3.1.4 Effects of antidepressants and mood stabilizers

Alpha-adrenergic receptors: Antidepressants have been shown to decrease alpha2-ARs and increase alpha1-ARs in animal studies (reviewed in [22]). Long-term lithium administration has been shown to attenuate alpha2-AR-mediated behavioral effects [37].

Beta-adrenergic receptors: Most studies have shown a consistent pattern of beta-AR downregulation in response to long-term treatment with antidepressants of all classes or electroconvulsive therapy (ECT) [22,38-42]. Long-term administration of desipramine, an antidepressant, results in uncoupling of beta-AR and Gs in cortex [43,44]. Both receptor downregulation and receptor-G protein uncoupling result in decreasing downstream cAMP signaling [43-45]. Desipramine also inhibits the breakdown of the beta-AR high affinity complex [46], which interferes with the downstream activation of adenylate cyclase [47].

Most studies addressing the effects of mood stabilizers have focused on lithium. Studies investigating the effects of lithium on adrenergic receptor binding in rat brain have been inconclusive (reviewed in [21]), but have consistently shown an inhibition in beta-AR-stimulated cAMP [48]. Lithium does not block antidepressant-induced beta-AR downregulation [49].

Fewer studies have investigated the effect of other mood stabilizers in this system. One in vitro study found that valproic acid caused decreased beta-AR density, as well as cAMP production and G-alpha-s levels [50], while other studies investigating beta-AR density in response to valproic acid have produced mixed findings. Carbamazepine has been shown to induce upregulation of beta-ARs, and, consistent with other mood stabilizers, carbamazepine decreases beta-AR-induced AC activity (reviewed in [21]).

3.1.5 Receptor polymorphisms—Studies examining alpha2-AR polymorphisms have not found an association with suicide or depression [51,52]. One study examining a beta1-AR polymorphism, G1165C, found a nonsignificant trend toward an association with an improved response to antidepressant treatment in depressed patients [53]. Most recently, a study investigated the effects of iv infusion of yohimbine on subjects carrying an-frame deletion of the alpha2C-adrenoreceptor subtype (alpha2CDel322-325) [54]. At rest, homozygotes for the alpha2CDel322-325 polymorphism had higher total body noradrenaline spillover than did heterozygotes; moreover, yohimbine produced larger, more sustained increments in noradrenaline spillover, heart rate, and anxiety in homozygotes than in the other groups. Since the pattern of catecholaminergic responses is similar to what has been observed in mood disorders [7], the role of this receptor polymorphism in these disorders is under investigation.

3.2 G protein-coupled serotonergic receptors and mood disorders

The efficacy of medications with serotonergic effects in the treatment of depression has been the primary impetus for proposing a role for serotonin in mood disorders. In addition to pharmacologic data, there is considerable evidence for serotonergic abnormalities in patients with depression, although the data for bipolar disorder is less clear. Some of the most compelling recent data that support a role for serotonin in mood disorders comes from the identification of receptor polymorphisms associated with disease susceptibility and/or treatment response.

3.2.1 Pharmacologic challenge, postmortem and imaging studies—Depressed patients have been shown to exhibit a blunted response of the serotonin system, as measured by fenfluramine-induced prolactin release [55], although other studies have not replicated this finding. This blunting was more pronounced in the subset of patients who made high lethality suicide attempts [56] and those with anger attacks [57].

5HT1A receptors: Several studies have shown blunted responses to 5HT1A receptor agonists and decreased 5HT1A receptor binding postmortem in depressed patients [58-59], although some studies have found an increase in the number of 5HT1 receptors in prefrontal cortex of suicide victims [60], or increased 5HT1A binding in depressed patients [61]. PET studies have demonstrated region-specific changes in 5HT1A receptor binding in depressed subjects compared to healthy controls [62,63]. It is speculated that the mechanism of decreased 5HT1A receptor binding is via increased cortisol secretion, which inhibits 5HT1A mRNA expression (reviewed in [21]).

5HT1B receptors: In a recent report, Svenningsson and colleagues [64] demonstrate that 5HT1B receptors are modulated by p11, which is decreased in an animal model of depression and in brain tissue from depressed patients, and is increased in rodent brains by antidepressants or ECT. The authors show that overexpression of p11 in mice increases 5HT1B receptor function and mimics certain behaviors seen in response to antidepressant treatment, while p11 knockout mice demonstrate a depression-like phenotype and have reduced responsiveness to 5HT1B receptor agonists. The intriguing findings from this study suggest a dynamic relationship between 5HT1B receptors and p11 that may be involved in the pathophysiology of depression.

5HT2 receptors: Postmortem studies have found an increase in the number of 5HT2A and 5HT2C receptors in the brains of patients with depression and in suicide victims (for example, see [65,66]), although other studies have found contradictory results (reviewed in [67,68]). Imaging studies [67,69], and studies investigating 5HT2A receptors on platelets [21] have similarly yielded mixed results.

3.2.2 Effects of antidepressants and mood stabilizers

5HT1A receptors: The postulated role of 5HT1A receptors in mood disorders is supported by evidence that chronic antidepressant treatment results in desensitization of somatodendritic 5HT1A autoreceptors in the dorsal raphe and subsequent enhancement serotonergic transmission in hippocampus [70,71]. Abnormalities in 5HT1A receptor binding in bipolar patients are normalized by chronic lithium administration [21]. Chronic antidepressant treatment has also been shown to increase 5HT1A receptor-G protein uncoupling [72].

5HT2 receptors: Antidepressants have been shown to downregulate 5HT2A receptor binding in cortex [73]. The evidence for the role of 5HT2A receptors in the mechanism of action of mood stabilizers is much less clear. Studies investigating 5HT2A receptor binding following chronic lithium administration have produced mixed results. Most suggest that lithium induces a decrease in 5HT2 receptor binding, with the strongest evidence in the hippocampus (reviewed in [21]), although studies in platelets have demonstrated a lithium-induced increase in 5HT2A receptor binding capacity in bipolar patients [74].

3.2.3 Receptor polymorphisms

5HT1A and 5HT1B receptors: Data from several studies support a role for the 5HT1A receptor in depression and treatment outcome. Lemonde and colleagues [75,76] report an association of the C-1019G 5HT1A promoter polymorphism with major depression and suicide, and with response to flibanserin, a 5HT1A agonist antidepressant. Other studies have similarly reported an association between antidepressant response and both this polymorphism [61,77] and Gly272Asp [78]. Arias and colleagues [79] found that a combined genetic effect of the HTR1A gene, which encodes the 5HT1A receptor, and the SLC6A4 gene, which encodes the serotonin transporter, influenced clinical outcome of depressed patients treated with the antidepressant citalopram. The G861C locus of the 5HTR1B gene has been shown to be associated major depression, but not bipolar disorder [80], although another study did not find such an association [81].

5HT2A receptors: A promoter polymorphism in the 5HTR2A gene, A-1438G, has been shown to be associated with major depression [82]. Many studies have attempted to identify an association between 5HT2A receptor polymorphisms and bipolar disorder, but these studies have yielded few demonstrated associations. The most widely studied polymorphism, T102C, has repeatedly not been found to have an association with bipolar disorder [83-85]. However, several studies have shown positive associations between other 5HT2A receptor polymorphisms (C516T, C1354T and A-1438G) and bipolar disorder [86-88].

Choi and colleagues [89] found an association between the A-1438G polymorphism of the 5HT2A receptor and treatment response to the antidepressant citalopram, although another group reported finding no such association using the antidepressant fluvoxamine [90]. Some of the most compelling evidence for a role for the 5HT2A receptor in the treatment of mood disorders comes from the Sequenced Treatment Alternatives for Depression (STAR*D) study. A significant association was found between treatment outcome and a marker in HTR2A, which encodes the 5HT2A receptor [91]. This study searched for genetic predictors of treatment outcome in 1,953 patients with major depression, and detected a significant and reproducible association between treatment outcome and an intronic marker in the 5HT2A receptor gene. Moreover, the A allele (associated with poorer response) was over six times more frequent in white than in black participants, and treatment was less effective among black participants [91]. Taken together with prior neurobiological findings, these new genetic data make a compelling case for a key role of HTR2A in the mechanism of antidepressant action; furthermore, the polymorphisms in this receptor may also contribute to racial differences in outcomes of antidepressant treatment.

5HT2C receptors: Lerer and colleagues [92] demonstrated an association between a 5HT2C receptor polymorphism and both major depression and bipolar disorder in a population derived from nine different European countries. Gutierrez and colleagues have investigated this same 5HT2C receptor polymorphism in bipolar disorder and have demonstrated a weak association in female bipolar patients that was not seen in a mixed gender sample [93,94]. Another group similarly found a trend toward an association between a 5HT2C polymorphism and female, but not mixed gender, bipolar patients [95].

3.3 G protein-coupled dopaminergic receptors and mood disorders

Although dopamine has been at the center of schizophrenia research for decades, it has been relatively under-examined with respect to its role in mood disorders. Nevertheless, there are several lines of evidence pointing to dopamine's role in these illnesses. The midbrain dopamine system regulates motor activity, motivation and reward pathways, and the mesolimbic dopamine system plays a critical role in goal-directed behavior. All of these functions are significantly disrupted in depression and mania. Multiple pharmacologic agents that act on dopamine receptors have effects on mood symptoms, further supporting the role of G protein-coupled dopamine receptors in mood disorders.

3.3.1 Imaging and pharmacologic studies—SPECT studies have demonstrated increased D2/D3 receptor availability in the striata of depressed patients with bipolar disorder (reviewed in [21]). Two such studies correlated increased receptor binding with psychomotor retardation [96,97].

Antipsychotics that block dopamine receptors are effective against acute mania. Multiple dopamine receptor agonists, including bromocriptine and pramipexole, have significant antidepressant properties, both in bipolar and unipolar depressed states [98]. Pramipexole has been found to be effective alone [99] and as an adjunct to selective serotonin reuptake inhibitor (SSRI) antidepressants [100] or mood stabilizers [101].

Dopamine receptor binding studies comparing lithium to placebo have been inconclusive. However, lithium has been shown to inhibit haloperidol-stimulated dopamine receptor upregulation and agonist-induced supersensitivity [21].

3.3.2 Receptor polymorphisms

D1 receptor: Although several studies have failed to find mutations in the D1 receptor gene in bipolar disorder [102,103], the results of two studies suggest an association between the D1 receptor A48G polymorphism and bipolar disorder [104,105].

D2 receptor: Numerous studies have attempted to identify an association between D2 receptor polymorphism and bipolar disorder and have failed to find such an association. Two studies, however, have reported positive findings. In a large European multicenter study, Massat and colleagues [106] found a significant association between the D2 receptor and bipolar disorder. In a smaller study of Han Chinese patients with bipolar disorder, Li and colleagues [107] found an association with a D2 receptor polymorphism which was not replicated when studied in a Caucasian population, suggesting a possible race-specific risk factor.

D3 receptor: One small study has found an association between a D3 receptor polymorphism and unipolar depression [108]. Multiple studies have failed to show clear evidence for the involvement of the D3 receptor locus in bipolar disorder.

D4 receptor: Several studies have investigated a possible role for the D4 receptor in depression. Lopez Leon and colleagues [109] performed a meta-analysis of these studies and found a significant association between the D4 receptor gene 48 base pair repeat polymorphism and unipolar depression but not bipolar disorder.

3.4 G protein-coupled cholinergic receptors and mood disorder

There has been a long-standing interest in the potential involvement of the cholinergic system in bipolar disorder, based primarily on studies indicating the prominent mood and behavioral effects of cholinergic agonists and antagonists. (reviewed in [21]). Most studies documenting cholinergic receptor sensitivity in mood disorders have been quite indirect. For example, REM occurs during discreet periods of sleep, but its onset can be induced earlier in normal volunteers by cholinergic agents. Several research groups have reported a faster induction of REM sleep with arecoline (a cholinergic agonist) in medication-free mood disorder patients (primarily bipolar disorder) (reviewed in [21]).

Most recently, Cannon and associates [110] used positron emission tomography and [18F]FP-TZTP (fluorodopa F 18 [3-(3-[3-fluoroproply]thio)-1,2,5-thiadiazol-4-yl]-1,2,5,6-tetrahydro-1-methylpyridine), a selective M2 receptor radioligand, to assess the binding potential of muscarinic2 receptors in vivo. They found significantly lower M2 binding in anterior cingulate in BPD compared with both MD and control groups.

Many antidepressants, including tricyclics and serotonin reuptake inhibitors, have anticholinergic properties, although the relevance to their antidepressant action is not clear. Studies have produced conflicting reports regarding the effect of lithium on muscarinic receptor binding. Lithium has been shown to block muscarinic receptor supersensitivity without affecting the number of receptor binding sites, suggesting it acts at a post-receptor site [111].

One study has shown an increased frequency of homozygosity at the A1890T polymorphism in the cholinergic muscarinic receptor 2 (CHRM2) gene among women, but not men, with major depression [112].

3.5 G protein-coupled GABAergic receptors and mood disorders

There is some evidence that G protein-coupled GABA-B receptors play a role in mood disorders. Baclofen, a GABA-B receptor agonist, has been shown in a small number of patients to induce a reversible depression that remits following discontinuation of the agent [113]. Chronic administration of mood stabilizers such as lithium, valproic acid and carbamazepine increases GABA-B receptors in hippocampus [114,115], although the relevance of this finding to their pharmacologic effect is not known.

3.6 G protein-coupled glutamatergic receptors and mood disorders

It is surprising that the glutamatergic system has only recently undergone extensive investigation with regard to its possible involvement in the pathophysiology of mood disorders, since it is the major excitatory neurotransmitter in the CNS, known to play a role in regulating the threshold for excitation of most other neurotransmitter systems. There is now mounting evidence for a role of the glutamatergic system in the pathophysiology and treatment of mood disorders [116-118]. However, to date, most of the available evidence implicates ionotropic receptors -- both NMDA [118] and AMPA [119] -- in the treatment of mood disorders. In view of our focus on GPCRs, these will not be discussed here; interested readers are referred to recent reviews dealing with a broader discussion of the role of the glutamatergic system in mood disorders [116-118].

3.7 G protein-coupled neuropeptide receptors and mood disorders

Neuropeptides are short-chain amino acids that act as neurotransmitters in numerous brain circuits; indeed, the contribution of altered endocrine function to pathological mood states was among the earliest themes in biological psychiatry. The actions of a single neurohormone peptide on a wide range of brain receptors characteristically span a much longer time period than the actions of monoamines. The influence of neurohormones on neurons may have been elaborated for teleological reasons. The possibility that one substance effectively commands and organizes multiple coordinated physiological and behavioral responses is consistent with the importance of certain peptides in the long-term phasic changes typical of mood disorders [21]. The voluminous data implicating abnormalities of various neurohormones and neuropeptides is reviewed extensively elsewhere ([21] and other textbooks); here, we limit ourselves to those neuropeptide GPCRs that are being extensively investigated in the treatment of mood disorders.

3.7.1 Corticotropin-releasing factor (CRF) Receptors—CRF has become one of the most extensively studied of all the neuropeptides in relation to its potential role in mood disorders, due to demonstrations of abnormalities in patients and in animal models (reviewed in [21,120,121]). Preclinical studies using animal behavior models have indicated that CRF receptor antagonists, specifically of the CRF receptor-1 subtype, have anxiolytic and antidepressant activity [122]. These results led to the testing of a CRF receptor-1 antagonist, R121919, in an open trial in 24 patients with depression [123]. Initial results were encouraging, and further clinical studies are anticipated. However, at least two genetic linkage and association studies have failed to support the linkage of CRF polymorphisms to bipolar illness [124,125].

3.7.2 Neurokinin1 (NK1) receptors—Preclinical behavioral studies involving pharmacological or genetic inactivation of the neurokinin$_1$ receptor [126] suggested a promising target for antidepressant and/or anxiolytic drug discovery. Importantly, genetic or pharmacologic blockade of NK1 receptors were also observed to induce some of the same long-term neural effects as standard antidepressants on cell signaling molecules such as BDNF and hippocampal neurogenesis [127]. However, despite the promising preclinical data, a recent pooled analysis of five 8-week randomized, double-blind placebo-controlled multicenter studies of the substance P antagonist aprepitant in major depression found lack of efficacy [128].

3.7.3 Neuropeptide Y (NPY)—NPY, the most abundant peptide in mammalian brain, is a 36-amino acid polypeptide, rich in tyrosine residues, with a molecular weight of 4272 Daltons. There are 6 recognized NPY receptor subtypes (Y1-Y5) present in the brain and other tissues. In the brain, major sites of NPY production are the cerebral cortex, locus coeruleus, hippocampus, brainstem, and hypothalamus, where the highest concentrations are present. In fact, NPY is the most potent physiological stimulant of feeding behavior yet described [129]. A recent report found decreased CSF concentrations of NPY in patients with treatment resistant unipolar major depression [130]. The upregulation of amygdala NPY mRNA levels after chronic stress suggests potential involvement in the adaptive responses to stress exposure [131].

4. GPCRs and Schizophrenia

4.1 G protein-coupled dopaminergic receptors and schizophrenia

The dopamine hypothesis of schizophrenia remains the primary explanatory hypothesis for the florid psychotic symptoms of the disease (notably hallucinations and delusions), although it is clear that the true pathophysiology is much more complex. The hypothesis that schizophrenia is caused by hyperactivity of limbic dopaminergic transmission arose from the fact that all effective antipsychotic agents block dopamine D2 receptors, and amphetamine, which facilitates dopamine release, induces schizophrenia-like psychotic symptoms. The majority of data supporting the dopamine theory continues to come from studies of antipsychotic medications (see below).

4.1.1 Postmortem and imaging studies—Many studies have looked for evidence of dopamine receptor dysregulation in schizophrenic patients, with mixed results. In contrast with some early findings, recent studies have generally been consistent in showing no abnormalities in D2 receptor density in schizophrenia (reviewed in [132,133]). With regard to other dopamine receptor subtypes, one intriguing study demonstrated decreased D1 receptor density in prefrontal cortex by PET and correlated this finding with the severity of negative symptoms and impairment in prefrontal cognitive performance [134]. One report demonstrated an increase in D3 receptor in the nucleus accumbens [135], while another showed decreased D3 receptor levels in parietal and motor cortex [136]. Studies have shown decreased D3 and D4 mRNA in orbitofrontal cortex [137] and increased D4 receptor levels in putamen in schizophrenia [138].

4.1.2 Effects of antipsychotic medications—The hyperactive dopamine theory was initially developed in light of the high D2 affinity of typical antipsychotics and the tight correlation between receptor affinity and clinical response [139]. PET and SPECT studies confirm the relationship between D2 receptor occupancy and therapeutic effect: typical antipsychotic efficacy appears to be optimized at 65-70% D2 receptor occupancy, and greater than 80% occupancy significantly increases the risk of extrapyramidal symptoms (EPS), a known side effect [140].

Several lines of evidence suggest that D2 receptor binding is insufficient to fully account for the pathophysiology of schizophrenia. First, not all patients with schizophrenia improve on typical antipsychotics, despite 70% or greater receptor occupancy [140]. Second, typical antipsychotics effectively treat only about 70% of positive symptoms [133] and are relatively ineffective with respect to negative and cognitive symptoms. Third, the timecourse of receptor blockade, which occurs in a matter of hours, does not correlate with the timecourse of clinical effect, which occurs over days or weeks [133,140]. It is hypothesized that downstream or longer-term changes mediate the clinical effect; for example, long-term administration of typical antipsychotics have been shown to upregulate D2 receptors [140]. Finally, atypical antipsychotics have overall lower D2 receptor binding affinity than typical antipsychotics but are not less effective. The atypical antipsychotics clozapine and quetiapine, for example, exert therapeutic effects at less than 70% occupancy [140].

Together these data suggest that although some level of D2 blockade is necessary for antipsychotic effects, it is not sufficient. Atypical antipsychotics act on other dopaminergic receptors subtypes as well as non-dopaminergic receptors. Compared to typical antipsychotics, atypicals have a much stronger binding affinity for D4 receptors as well as multiple other GPCRs, including D1, D3, 5HT1A, 5HT2A, 5HT2C, and muscarinic receptors. Typical antipsychotics have been shown to induce increased expression of D1 receptors [141].

Clinically, typical antipsychotics are effective only against positive symptoms, presumably via D2 receptor antagonism, while atypical antipsychotics are additionally effective with regard to negative and cognitive symptoms. D2 antagonists can block stimulant-induced psychosis in healthy individuals [142]. Dopamine agonists have been shown to improve negative symptoms and prefrontal cognitive performance [143], and these symptoms, when induced by amphetamine treatment, are not blocked by D2 antagonists [144]. Taken together these data lend support to a newer and more complex hypothesis of schizophrenia in which hypoactive D1 receptors in the mesocortical pathway correlate with negative symptoms and hyperactive D2 receptors are associated with positive symptoms [145].

4.1.3 Receptor polymorphisms

D2 receptors: Given the above findings, numerous researchers have investigated the role of D2 receptor polymorphisms in schizophrenia. Although controversial, multiple reports, both primary studies and meta-analyses, have demonstrated a positive association between the D2 receptor Ser311Cys polymorphism and schizophrenia [146-149]. Other studies, however, have found no association [150,151]. One study did find an association between Ser311Cys and symptom severity, although not diagnosis [152]. A second polymorphism from the D2 receptor promoter region, -141C Ins/Del, has also been shown by several groups to be associated with schizophrenia [153-156]. Other reports have implicated other D2 receptor polymorphisms such as C957T [157], His313 [158], and the Taq1A locus [159]. Several studies have shown an association of -141C Ins/Del with timing or degree of response to antipsychotic medications, with a more favorable response associated with the -141C Ins allele [160-162], although other studies have not supported these findings [163,164]. Multiple studies have similarly shown an association between treatment response and the Taq1A locus [162,163,165-166], the Ser311Cys polymorphism [167] and the His452Tyr polymorphism [168].

Other dopamine receptor subtypes: The D3 receptor polymorphism, Ser9Gly, is the most widely studied for the D3 receptor, but results correlating it with susceptibility to schizophrenia have been inconclusive [169-173]. Multiple studies have demonstrated an association between this polymorphism and response to antipsychotics [174-177]. There is some discrepancy among these studies regarding which subset of symptoms primarily correlates with this polymorphism, and one published study failed to find any correlation [173]. A pattern of association is seen between the Ser9 allele and response to typical antipsychotics, and between the Gly9 allele and response to atypical antipsychotics (reviewed in [162]).

Other D3 receptor variants that have shown association with schizophrenia include G-205A [169,171], G-7685C [169], and G-712C [171]. Mixed results have been reported regarding the BalI [178-184] and MscI [185,186] restriction sites in exon 1.

In the D4 receptor, a 48 base pair repeat in exon 3 has been the subject of much research; however studies have failed to show a significant association with schizophrenia [187-190]. Although one study reports an association between this polymorphism and response to the atypical antipsychotic clozapine [191], two other studies showed no such correlation [192, 193].

4.2 G protein-coupled serotonergic receptors and schizophrenia

Although evidence for changes in serotonin receptors in schizophrenia has been controversial, pharmacologic data, such as the serotonergic effects of pro-psychotic drugs of abuse and of atypical antipsychotic medications, suggest a role for serotonin in this disease.

4.2.1 Postmortem and imaging studies—Some postmortem studies show a decrease in 5HT2A receptors in schizophrenia, although others do not (reviewed in [194]). One PET study showed no difference between untreated schizophrenic patients and controls with respect to 5HT2A receptor expression in cortex [194], while another demonstrated an increase in both 5HT1 and 5HT2A receptors [195].

4.2.2 Pharmacologic studies—The strongest evidence for a role for serotonin in schizophrenia comes from pharmacologic studies. D-lysergic acid diethylamide (LSD) can cause psychotic symptoms in healthy individuals, and its structural similarity to serotonin prompted further investigation of this neurotransmitter system in psychosis [196]. It is now known that LSD exhibits effects on the serotonin system in the raphe nucleus via 5HT1A receptors, and most likely induces hallucinations via agonist action at the 5HT2A receptor (reviewed in [196,197]).

The discovery of atypical antipsychotics, which block the 5HT2A receptor in addition to dopamine receptors and others, prompted the development of the serotonindopamine antagonism theory. This theory states that the higher the ratio of 5HT2A receptor affinity to D2 receptor affinity, the more “atypical” the antipsychotic, i.e., the more effective and the less likely to produce EPS (reviewed in [140]). The atypicals clozapine, risperidone, olanzapine and ziprasidone demonstrate greater than 80% occupancy of cortical 5HT2A receptors at therapeutic doses [140]. It is hypothesized that 5HT2A receptor antagonism partially reverses D2 receptor blockade, resulting in less EPS [140,198]. The 5HT2A effects of these medications are not sufficient to mediate their antipsychotics effects, however, as 5HT2A receptor antagonist monotherapy with M-100907 is ineffective [199].

In addition to receptor blockade, atypical antipsychotics have also been found to induce subcellular redistribution of the 5HT2A receptor. Willins and colleagues [200] demonstrated that atypical antipsychotics with high affinity for the 5HT2A receptor (clozapine, olanzapine and risperidone) induce internalization of the 5HT2A receptor in fibroblasts in vitro. Consistent with this finding, they also report loss of 5HT2A receptor immunoreactivity on pyramidal neurons in response to clozapine and olanzapine [200].

Action at the 5HT1A receptor is thought to synergize with actions at the dopamine receptor and 5HT2A receptor in the treatment of schizophrenia. Some studies have demonstrated that 5HT1A agonists augment the effect of dopamine antagonists [201], and it is hypothesized that the partial 5HT1A agonism of clozapine [202] and aripiprazole [203] contribute to their therapeutic effects on negative and cognitive symptoms.

4.2.3 Receptor polymorphisms

5HT1A receptor: Multiple studies have investigated an association between the T102C polymorphism of the 5HT1A receptor and susceptibility for schizophrenia, with both primary studies and meta-analyses producing mixed results [204-217]. An association of genotype distribution and allele frequency of the 5-HTR1A C-1019G locus with schizophrenia has been reported [218].

5HT2A and 5HT2C receptors: Results from studies investigating an association between 5HT2A receptor polymorphisms and response to antipsychotic treatment have been variable and generally not significant. Some studies have shown an association between the T102C polymorphism and atypical antipsychotic response [219-221], while at least one other has not [222]. The results of two studies have shown a nonsignificant association between G-1438A polymorphism variants and response to the atypical antipsychotics olanzapine or clozapine [223,224]. Studies investigating the his452tyr polymorphism have yielded mixed results, and in those that found an association, it was not significant or not replicated with the same significance in subsequent reports [222,224-226].

Two 5HT2C polymorphisms have been shown to be associated with response of schizophrenic patients to antipsychotic treatment: the C-759T polymorphism in the promoter region [227] and Cys23Ser [228].

4.3 G protein-coupled noradrenergic receptors and schizophrenia

While a primary abnormality in the noradrenergic system has not been demonstrated in schizophrenia, norepinephrine plays a key role in regulating prefrontal cognitive function, which is impaired in patients with this disorder. In addition, several pharmacologic agents have effects on adrenergic receptors, suggesting a potential, indirect role for this system in the treatment of the disease.

4.3.1 Pharmacologic challenge studies—Recent studies have investigated the potential role of stress-induced noradrenergic dysfunction of prefrontal cortical function. The prefrontal cortex allows us to appropriately guide our behaviors, thoughts, and emotions by using representational knowledge [229]. Lesions of the prefrontal cortex produce symptoms of impulsivity, distractibility, and poor judgment; more extensive disruptions of prefrontal cortical function may also contribute to thought disorder and hallucinations -- among the hallmarks of schizophrenia. It is thus noteworthy that studies have shown that alpha1 adrenergic antagonists (or agents affecting its signaling cascades, such as protein kinase C) attenuate stress induced PFC-mediated cognitive deficits [229], and the alpha2-AR agonist clonidine improves prefrontal cognitive functioning in patients with schizophrenia [230]. Guanfacine, another alpha2A-AR agonist, was demonstrated to be safe and efficacious in treating cognitive impairment in schizophrenic patients when given as an adjunctive treatment with risperidone in a placebo-controlled, double-blind trial [231]. These findings raise the possibility that some of the beneficial cognitive effects of atypical antipsychotics like clozapine may be mediated by their effects on alpha1 adrenergic receptors, and is worthy of further study.

4.3.2 Effects of antipsychotic medications—Most atypical antipsychotics, as well as many typical antipsychotics including haloperidol, have high binding affinity for alpha1-AR (reviewed in [140]), although the clinical significance of this action is unclear. Some atypical antipsychotics, including clozapine and risperidone, act as potent antagonists at alpha2-ARs. It is hypothesized that this action contributes to their antipsychotic effect by enhancing dopaminergic transmission in the frontal cortex relative to subcortical pathways via the blockade of inhibitory alpha2-ARs on dopaminergic neuron terminals [232,233].

4.3.3 Receptor polymorphisms—
Clark and colleagues [234] identified two single nucleotide polymorphisms (SNPs) in the promoter region of the alpha1A-adrenergic receptor gene that are associated with schizophrenia.

4.4 G protein-coupled cholinergic receptors and schizophrenia

4.4.1 Postmortem and pharmacologic studies—
M1 receptor expression has been shown to be decreased in the cortex of postmortem brains of schizophrenic patients [235]. Muscarinic agonists are effective in animal models of negative symptoms and cognitive dysfunction (reviewed in [236,237]), and the atypical antipsychotics clozapine and olanzapine act as partial agonists at cholinergic M1, M2 and M4 receptors [140], although the clinical significance of these actions is not known.

4.4.2 Receptor polymorphisms—
Liao and colleagues [238] demonstrated an association between the C267A polymorphism of the M1 cholinergic receptor and performance of schizophrenic patients on the Wisconsin Card Sorting Test, a measure of prefrontal cognitive function. This polymorphism was not associated with susceptibility to the disease or treatment response [238].

4.5 G protein-coupled glutamatergic receptors and schizophrenia

There is now compelling evidence for the involvement of the glutamatergic system in schizophrenia [239-241]. However, as is the case with mood disorders, the preponderance of the available data pertains to the role of ionotropic glutamatergic receptors, and is not discussed here. The interested reader is referred to several outstanding recent reviews on the topic [239-241].

4.5.1 Pharmacologic studies—
Growing interest in the glutamate system in schizophrenia is based primarily on pharmacologic studies. Studies have shown that Group I metabotropic glutamate receptor (mGluR1 and mGluR5) antagonists potentiate the schizophrenia-like behavioral effects induced by phencyclidine (PCP) and amphetamines (reviewed in [242]). Group I agonists inhibit amphetamine-induced sensorimotor gating deficits [242] and PCP-stimulated dopamine release in prefrontal cortex in rats [243]. Group II receptor (mGluR2/3) agonists block PCP-induced behavioral activation and working memory impairment [244, 245]. mGluR1 and mGluR5 knockout mice show disruptions in sensorimotor gating, which is disrupted in schizophrenia (reviewed in [242]).

4.5.2 Receptor polymorphisms—
Several studies have examined the metabotropic glutamate receptors for associations with schizophrenia. Fujii and colleagues [246] found a single nuclear polymorphism (SNP) in GRM3, the gene for mGluR3, to have a positive association with schizophrenia. A second study failed to replicate these results but identified another SNP in GRM3 associated with the disease [247]. One study by Takaki and colleagues [248] identified haplotypes of GRM8, the gene for mGluR8, associated with schizophrenia, suggesting a susceptibility locus in this gene.

5. Summary and Conclusions

Major depression, bipolar disorder, and schizophrenia are severe, chronic diseases that cause significant morbidity and mortality, as well as extraordinary economic costs to patients, their families, and society. Our limited but increasing understanding of the etiology of these diseases comes from the convergence of pharmacologic, postmortem, imaging and genetic research. There is a clear need to elucidate the molecular and cellular underpinnings of these disorders in order to develop improved therapeutics. As we have reviewed here, there is a considerable body of evidence both conceptually and experimentally that support abnormalities in the regulation of GPCRs as integral to the underlying neurobiology of schizophrenia and mood disorders. The pathophysiology of these illnesses must account for profound changes in cognition, mood, and motoric function, as well as a constellation of neurovegetative features derived from dysfunction in limbic-related regions, such as the hippocampus, hypothalamus and brainstem. The highly integrated monoamine and prominent neuropeptide pathways are known to originate and project heavily within these regions of the brain, and it is thus not surprising that abnormalities have been noted in their function across clinical studies. In fact, the contribution of these pathways to the pathophysiology of these illnesses must be reasonably robust, given the variability that might be expected in assessing such dynamic systems under the constraints in experimental design imposed upon such research.

Through functional brain imaging studies, circuits have been identified that mediate the behavioral, cognitive, and somatic manifestations of schizophrenia and mood disorders. Key areas of these circuits include the orbital and medial prefrontal cortex, anterior cingulate, amygdala and related limbic structures, medial thalamus, and related regions of the basal ganglia. Imbalance within these circuits, rather than an increase or decrease in any single neurotransmitter in a given region of the circuit, seems to predispose to and mediate the expression of the major psychiatric illnesses. Treatments that more directly restore balance to these circuits may prove more effective particularly in refractory cases.

It is also becoming increasingly clear that for many patients with refractory illnesses, new drugs simply mimicking the ‘traditional’ drugs that directly or indirectly alter neurotransmitter levels may be of limited benefit. This is clear because such strategies implicitly assume that the target receptor(s)—and downstream signal mediators—are functionally intact, and that altered synaptic activity will thus be transduced to modify the postsynaptic ‘throughput’ of the system. However, the possible existence of abnormalities in GPCRs (and potentially their signal transduction pathways) suggests that for patients refractory to conventional medications, improved therapeutics may only be obtained by the direct targeting of post-receptor sites. Recent discoveries concerning a variety of mechanisms involved in the formation and inactivation of second messengers offer the promise for the development of novel pharmacological agents designed to target signal transduction pathways (discussed in [249]).

Although clearly more complex than the development of receptor-specific drugs, it may be possible to design novel agents to selectively affect second messenger systems, because they are quite heterogeneous at the molecular and cellular level, are linked to receptors in a variety of ways, and are expressed in different stoichiometries in different cell types. Additionally, since signal transduction pathways display certain unique characteristics depending on their activity state, they offer built-in targets for relative specificity of action, depending on the ‘set-point’ of the substrate. These developments hold much promise for the advancement of novel therapeutics for the long-term treatment of these major psychiatric disorders. The challenge for the next era in neuropsychopharmacology is to transform the knowledge gained from advances in neurobiology, cellular physiology and molecular pharmacology into clinical use.

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