Adenosinergic-Dopaminergic Signaling in Mood Disorders: A Mini-Review

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Mood disorders are one of the biggest health problems, affecting the patients' emotional state, who experience depression or extreme euphoria or both of these. This review will focus on the participation of adenosinergic signaling in major depressive disorder and bipolar disorder (BPD) as well as in schizophrenia and schizoaffective disorder. Adenosine receptor activation may induce antidepressive actions in animal models, either by enhancing the A_1 receptor or decreasing the A_{2A} receptor activity. On the contrary, A_1 receptor activation can lead to manic-like behaviors in BPD models. Strong evidence points to adenosine modulation of the dopaminergic system, which has an important role in the pathophysiology of mood disorders. Most notable are the adenosine-dopamine receptor heteromers. Two of them, A_{2A} - D_2 and A_1 - D_1 receptor dimers, are well characterized, but A_{2A} - D_3 , A_{2A} - D_4 , and A_{2A} - D_2 - D_3 receptors heteromers have also been suggested. A_{2A} - D_2 heteromers are highly expressed in corticostriatal pathways, which, in turn, are linked to the pathophysiology of mood disorders. Thus, further research on the role of adenosine-dopamine receptor heteromers in mood control may lead to a better understanding of mood disorders' pathophysiology and novel therapeutic tools.

Keywords: major depressive disorder, bipolar disorder, schizophrenia, receptor heteromer, glutamate, GABA

Introduction

EXTREME HAPPINESS, SADNESS, or both for long periods characterize mood disorders, which are mental health problems affecting the individual's emotional state.¹ These disturbances cause big onus to society as they affect life quality and life span,¹ being the leading cause of disability worldwide.² Also considered affective disorders,³ mood disorders are classified by the World Health Organization (WHO) according to types of mood episodes, such as depressive, manic, mixed, or hypomanic episodes.⁴ Bipolar disorders (BPDs) and major depressive disorders (MDDs) are the most prevalent ones in the category.⁵ However, other disorders that fit in the mood spectrum, such as dysthymic disorder and cyclothymic disorder, are also part of the class.⁶ Prolonged phases of depressive episodes, the lower side of mood spectrum, characterize MDD, while BPD differs by alternating between depressive episodes and manic or hypo-

manic episodes, of elevated mood.^{7,8} On the contrary, schizoaffective disorder (SCA) is a chronic mental health condition with a debatable classification that involves symptoms of both MDD or BPD and schizophrenia (SCZ).⁹ We consider SCA as a mood disorder, given that around 50% of first hospitalizations reporting psychosis will be later diagnosed as SCA, and at least 25% of them were previously misdiagnosed as SCZ.¹⁰ SCZ will be also discussed, as it shares many pathophysiological features with SCA, which lack specific data on adenosinergic signaling. Since mood alterations might be influenced by external factors, the prevalence of mood disorders is widely different among cultures. Mean percentages of 5% and 1.2% were determined throughout cultures as MDD and BPD prevalence, respectively.^{1,11} Because of the overlapping symptoms among SCZ, MDD, and BPD, the prevalence of SCA is unknown, even though some studies suggest that it might be between 0.2% and 1.1%.¹²

The causes of mood disorders are still unclear although diverse research in the field points to genetic predisposition, neurotransmitters imbalance, abnormal neurocircuitry, circadian system disturbances, impaired neuroplasticity, oxidative and neuroinflammatory processes, and substance abuse as promoters of mood dysfunctions.^{13–17}

Adenosinergic System and Mood

The first observations of adenosine physiological properties were in 1929, but only in 2001, the receptors mediating adenosine signals were consensually classified based on their characterization.¹⁸ There are four adenosine receptor subtypes A₁, A_{2A}, A_{2B}, and A₃, differing by the type of G protein coupling. A₁ receptors are usually coupled to G_{i/o}, whereas A_{2A} receptors act through G_s. A_{2B} receptors activate phospholipase C via G_q or G₁₂ stimulation. A₃ receptors act mainly through G_i and G_q.¹⁹

Adenosine concentration in the brain increases along the day and controls together with melatonin the sleep-wake cycle.²⁰ Nevertheless, changes in the levels of adenosine in different moments and regions of the brain can be harmful and involved in neuroinflammation.²¹ The response to different levels of adenosine depends on the expression profiles of adenosine receptor subtypes and their respective binding affinities. For instance, A_{2A} receptors have higher affinity to adenosine than A_{2B} receptors.²²

The role of the adenosinergic system in psychiatric diseases has drawn recent attention of scientists.²³ Experimental evidence pointing to A₁ receptor in MDD date back to 2013 by Hines *et al.*,²⁴ when they observed that the activation of the A₁ receptor led to sustained antidepressant behavior. Corroborating these data, Serchov, in 2012 and 2015,^{25,26} induced overexpression of the A₁ receptor in forebrain neurons, eliciting antidepressant behavior, while A₁ knockout mice presented depressive-like behavior.²⁷

The A_{2A} receptor has also been described in MDD, mainly by its participation in inhibiting the A₁ receptor activity.^{28,29} In agreement, extensive work by other groups showed that antagonism of A_{2A} receptor activity with caffeine or other pharmacological tools has an antidepressant effect,^{30–36} as reviewed by López-Cruz *et al.*³⁷ Furthermore, different animal models of MDD presented augmented expression levels of the A_{2A} receptor in the forebrain and striatum.^{38–41}

Although mechanisms underlying A₁ and A_{2A} adenosine signaling in MDD have been extensively reviewed, their participation in other mood disorders is still under investigation.^{23,42,43} In a meta-analysis performed by Hirota and Kishi, adenosinergic modulators in clinical trials showed efficacy as adjuvant treatment for both BPD and SCZ, especially manic episodes and positive symptoms, respectively.⁴⁴ The hypothesis of adenosinergic participation in SCZ is based mostly on alterations of

A_{2A} receptor expression and activity and its modulatory effect on dopaminergic and glutamatergic systems, as reviewed by Boison *et al.*⁴⁵ As further support for this hypothesis, postmortem brains of SCZ patients showed an increased density of striatal A_{2A} receptor,⁴⁶ although it is not clear whether this outcome is a secondary effect of antipsychotic treatments.⁴⁷ When it comes to the A₁ receptor, Brunstein *et al.* proposed that the efficacy of dipyridamole adjunctive treatment for SCZ is most likely to occur via adenosine A₁ receptor.⁴⁸

The hypothesis of adenosinergic role in BPD relates to the excretion of uric acid, the final metabolite of adenosine degradation, in manic patients.^{41,49,50} In fact, adenosine and uric acid have been lately considered as biomarker candidates for manic and depressive episodes in BPD patients.⁵¹ Moreover, application of the xanthine oxidase inhibitor allopurinol increases adenosine levels and has positive effects in acute mania patients when used in combination with the mood stabilizers lithium^{52,53} or valproate.⁵⁴ Peripheral adenosine levels are also reduced in euthymic BPD patients and this event was negatively correlated to depressive scores, indicating that depressive symptoms and impaired functioning might be associated to low levels of adenosine.⁵⁵

Concerning adenosine receptors, A₁ receptor activation may be antidepressant, while it may trigger symptoms of mania or hypomania in BPD patients.⁵⁶ Following this line, the treatment of acute and dysphoric mania with carbamazepine, an anticonvulsant and mood-stabilizing drug, is based on A₁ receptor antagonism.⁵⁷ A_{2A} receptor expression levels were otherwise found upregulated in platelets of bipolar patients after administration of typical, but not atypical, antipsychotics.⁵⁸ A_{2A} receptors might be involved in impulsive and depressive features associated to suicidal behavior⁵⁹ through downregulation of the adenosine A₁ receptor expression and upregulation of the glutamate N-methyl-D-aspartate (NMDA) receptor expression.⁶⁰

Dopaminergic System and Mood

Despite its classical association to motor function control, dopamine is an important neurotransmitter also involved in behavior and cognition. Dopamine receptors were first described in 1972 when it was proposed that dopamine stimulates adenylate cyclase activity.^{61,62} Later, it was shown that dopaminergic signaling is mediated by two different families of G protein-coupled receptors. D₁-like receptors are positively coupled to adenylate cyclase and include D₁ and D₅ dopamine receptors. They stimulate the production of cyclic adenosine monophosphate (cAMP) through G_{s/olf} coupling and are mostly associated to the regulation of the reward system, locomotor activity, memory, and learning. D₂-like receptors are otherwise independent of adenylate cyclase activation and include D₂, D₃, and D₄ dopamine

receptors.⁶³ They couple to $G_{i/o}$ and inhibit both adenylyl cyclase activity and cAMP production, also being the main target of neuroleptic and antipsychotic drugs.^{64,65} An extend review on dopamine receptors was published by Beaulieu *et al.*⁶⁶

The efficacy of drugs that act on the dopaminergic system to control mood and behavior both in human patients and in animal models of these diseases does not allow any doubts regarding the importance of dopaminergic signaling in mood disorders. An example is the antipsychotic drug cariprazine, which is a partial agonist of dopamine D_2 and D_3 receptors and the serotonin 5-HT_{1A} receptor, with a higher affinity for the D_3 receptor compared to the further cited ones. Clinical trials have shown encouraging results for the treatment of MDD, BPD, and SCZ with cariprazine.^{67–69} The antianhedonic effect of this drug, which can be linked to its antidepressant effect in humans, is not present in D_3 receptor knockout mice, corroborating that this receptor is at least partially involved in mood responses.⁶⁹

Studies in animals indicate that the D_1 receptor may be involved in depression. Levo-stepholidine had an antidepressant-like effect in Sprague-Dawley rats acting as a D_1 receptor agonist.⁷⁰ Its mechanism depended on the PKA/mTOR downstream signaling pathway, resulting in the strengthening of synapses in the medial prefrontal cortex.⁷⁰ Furthermore, overexpression of D_1 receptor in the rat prefrontal cortex increased hedonic-like behaviors while inhibiting depressive-like behaviors.⁷¹ Reversion of overexpression abolished these effects, leading to depressive-like symptoms associated with BPD and suggesting a possible role of cycling D_1 receptor expression in the pathophysiology of the disease.⁷¹

When it comes to animal mimicking of mood symptoms, the expression or activity modulation of dopaminergic system has been an important tool for the understanding of behavior, pathophysiology, and pharmacological responses. Notably, hyperdopaminergia has been used as a model of manic-like behavior through the selective inhibition of dopamine transporter (DAT) by GBR12909 administration⁷² or through the still unclear DAT/vesicular monoamine transporter mechanism underlying amphetamine administration in rodents.⁷³ A comparative study in knockout mice showed that DAT blockade is more likely to result in antidepressant effects when compared to norepinephrine or serotonin transporter blockade.⁷⁴

Another line of evidence for the participation of the dopaminergic system in mood disorders comes from receptor expression studies. Increases in D_1 receptor mRNA transcription levels in the CA2 region of the hippocampus⁷⁵ and dorsolateral prefrontal cortex,⁷⁶ and D_2 receptors in the prefrontal cortex were observed in BPD patients.⁷⁷ Differential splicing of the D_2 receptor gene in the dorsolateral cortex changed with lower expression of the shorter and higher expression of the longer variant.⁷⁶ In samples of peripheral lymphocytes, D_3 receptor gene expression

declined, which increased slowly following 3 weeks of treatment with antipsychotic drugs.⁷⁸ In patients with MDD, gene expression of D_4 receptors was significantly enhanced in the basal nuclei of the amygdala, whereas D_1 and D_2 receptor expression levels were not altered.⁷⁹

Many studies investigating the role of dopamine in MDD used binding techniques to evaluate possible alterations in its signaling patterns in the brain. While one of them showed no significant alterations,⁸⁰ many others found significant changes in the binding of D_2 and D_3 receptors in the temporal cortex,⁸¹ amygdala,⁸² and in different subsections of the striatum.^{83–85} The use of classical serotonin reuptake inhibitor antidepressants can also reduce the binding of D_2 and D_3 as suggested by Montgomery *et al.*⁸⁶ These alterations may undermine the transference of information between different regions of the brain, as the increase of D_2 and D_3 receptor-binding sites in the striatum decreased connectivity in the corticostriatal-pallido-thalamic circuit.⁸⁷

In vivo binding to striatal D_1 receptors in MDD patients is also affected in a strongly lateralized pattern, with left to right binding ratio being correlated inversely with illness duration.⁸⁸ In postmortem brain, binding to DAT in the amygdala was reduced, while D_2 and D_3 receptor binding was increased, indicating that a reduced mesolimbic activity is also associated with MDD as previously hypothesized for rats.⁸²

Another important line of evidence is the relationship between different genotypes and the susceptibility to mood disorders and the age of onset. A meta-analysis has shown that the G/G genotype on the rs4532 locus of the DRD1 gene was associated with an increased risk for BPD.⁸⁹ The same genotype has also been linked to an age of disease onset later than 18 years old.⁹⁰ A few studies reported no genetic association of D_2 receptors to MDD, BPD, or SCA.^{91,92} Other works, however, found an association between the A1 allele of the polymorphism Taq1A on the DRD2 gene^{93,94} and the allele 5 and genotype 5–5 of the intron 2 DRD2 microsatellite and the susceptibility to type II BPD.⁹⁵ The GG genotype of the Taq1A polymorphism has also been linked to the early onset of BPD.⁹⁶

Polymorphisms in the DRD2 gene are also connected to MDD. The A1 allele of the Taq1A polymorphism is associated with a lower binding of dopamine in the middle caudate and the ventral striatum, which in turn is associated with the susceptibility to depression.⁹⁷ Another polymorphism, at the locus rs4460839 of the same gene, may play a role not only in the susceptibility to depression, but also in the onset-time of antidepressant response.⁹⁸ Polymorphisms in the DRD3 and DRD4 genes have been also linked to BPD. The Ser⁹Gly polymorphism of the DRD3 gene was associated with the development of type I, but not type II BPD.^{99,100} Two different polymorphisms in the DRD4 gene have been associated with BPD: the rs3758653, which has been linked to the development of type I BPD,¹⁰¹ and the

DRD4-7R, which is associated with an early onset of BPD despite gender, and late-onset of SCZ in females.¹⁰²

Adenosinergic-Dopaminergic Interactions: Receptor Heteromers and Implications in Classical Mood Control Pathways

The influence of caffeine and other adenosine modulators on dopamine receptor sensitivity and responsiveness has been proposed since the early 70's.¹⁰³ However, only in 1991, it was shown that the direct stimulation of the A_{2A} receptor reduces the affinity of D₂ receptor agonist-binding sites in striatal neurons. This suggests strong interactions between those receptors and may explain why adenosine receptor antagonists, such as caffeine, increases locomotor activity, while adenosine receptor agonists have an antipsychotic-like effect.¹⁰⁴ Ever since, numerous works have explored pre- and postsynaptic direct interactions between the two systems, reinforcing an antagonistic association of adenosine and dopamine stimulation.

As the concept of receptor heteromers became better understood and accepted, scientists have driven strong attention to characterize receptor heteromers' functions in health and disease.¹⁰⁵ Here, we assume the definition of receptor heteromer proposed by Ferré *et al.* as a "macromolecular complex composed of at least two (functional) receptor units with biochemical properties that are demonstrably different from those of its individual components"; it is also expected that heteromers have a direct physical interaction.¹⁰⁶ The main adenosine-dopamine functionally relevant heteromers characterized up to now are A_{2A}-D₂ and A₁-D₁ complexes, although there is also evidence of A_{2A}-D₃ and A_{2A}-D₄^{107,108} and more recently A_{2A}-D₂-D₃ receptor heteromers.^{107,108}

Anatomically, A_{2A} receptors are largely found in the basal ganglia, more specifically in striatopallidal GABAergic neurons from the dorsal striatum,^{109–111} where they co-exist with D₂ receptors.¹¹² In fact, the striatum has emerged in the past years as a brain region encompassing mood control circuitry. Hyperactivation of the corticostriatal pathway has been associated with BPD, while its hypoactivation might be involved in MDD.¹¹³ While glutamate and GABA are well-known corticostriatal neurotransmission mediators of information processing, A_{2A}-D₂ heteromers in this circuitry might also interplay to control neuropsychiatric behaviors, with an emerging role for adenylate cyclase 5 and antipsychotic effects of A_{2A} receptor agonism/D₂ receptor antagonism.^{114–116}

Despite the scenario reinforces the idea of the A_{2A}-D₂ receptors heteromer playing an essential role in SCZ pathophysiology,^{117,118} data supporting the role of A_{2A}-D₂ in BPD are still scarce and in need of further research. Only a few data identifying A_{2A}-D₂ heteromers and increased levels of A_{2A} in platelets of BPD patients under typical antipsychotic treatment have proposed such hy-

pothesis.⁵⁸ A_{2A}-D₂ heteromeric receptor participation in MDD pathophysiology also needs further studies. Nevertheless, strong evidence for such correlation exists, since the administration of haloperidol, a classical antipsychotic with D₂ antagonism mechanism, successfully prevented the antidepressant-like effect of the selective A_{2A} antagonist SCH 58261 in the forced swim test.³¹ In view of that, adenosine-dopamine interactions in the prefrontal cortex are a promising target for antidepressants.

A_{2A} receptors are also abundant in glutamatergic terminals in the hippocampus,⁴² a region where the number of dopaminergic active neurons is enhanced by NMDA-glutamate receptor activation and GABAergic inhibition,^{119,120} and this effect has been associated to MDD and SCZ.^{121,122} Abnormalities in both glutamatergic and GABAergic signaling have been observed in mood disorders.¹²³ Elevated glutamate signaling has been strongly associated with BPD and SCZ, in contrast to reduced signaling in MDD; however, magnitudes of these alterations differ among the brain regions.^{124,125}

Although alterations in GABAergic signaling have been observed in BPD patients, GABA modulators' therapeutic efficacy is controversially discussed.¹²⁶ GABA levels and signaling are significantly decreased in plasma, cerebrospinal fluid, and brain samples from MDD patients, and some of these observations have also remained after disease remission, suggesting that GABA is involved in the disease pathophysiology, but is not a good biomarker.¹²⁶ Nevertheless, drugs that enhance GABAergic neurotransmission are promising for treating mood alterations, but are not notably specific only for mood disorders.¹²⁷ These data suggest that a deeper investigation in the regulatory mechanisms of glutamate/GABA balance is of interest,^{123,126} and adenosine-dopamine signaling might play an important role,¹²⁵ especially considering the glutamate-GABA modulatory effect of both A_{2A} and D₂ receptors individually.^{128,129}

The aforementioned findings regarding the A_{2A} receptor and the D₂ receptor in GABAergic neurons were the first evidence of a possible role of adenosine-dopamine receptors integrated functional control of neuropsychiatric symptoms; however, there is emerging evidence of other heteromers' participation. As the role of the D₃ receptor in mood disorders is being investigated,^{69,78,130} the antagonistic modulation of A_{2A}-D₃ heteromer is proposed as a possible antischizophrenic approach.¹³¹ Further research regarding its effect, as well as A_{2A}-D₂-D₃ receptors in MDD and BPD could bring new insights for the treatment of mood symptoms. Despite the strong evidence of A₁-D₁ heteromer presence in basal ganglia circuits,¹³² no relevant inputs of its role in mood responses have been proposed yet.

Perspectives

Neuropsychiatric diseases, especially mood disorders, are known by their multifaceted and complex neurobiology.

Although many different hypotheses have emerged to explain the pathophysiology of MDD, BPD, and SCZ/SCA, the whole picture associated with mood control remains unclear. Mood, cognition, and behavior have been traditionally linked to dopaminergic and glutamatergic pathways, but strong evidence during the past decades has supported a possible role of adenosine in these processes, including the idea of an integrated signaling mechanism within adenosinergic and dopaminergic systems in a more specific way.

In this study, we revisited these two systems and discussed how they are individually involved in mood disorders' biology, symptomatology, and response to treatments, reinforcing a possible role of the direct interaction of adenosine and dopamine receptors through heteromer formation, as summarized in Figure 1. The role of these interactions in classical glutamatergic and GABAergic neurotransmission mechanisms associated

with mood control should also be taken into consideration for further investigations. Despite the most common evidence of A_{2A} - D_2 receptor interactions in the central nervous system in mood control circuitries, A_{2A} - D_3 , A_{2A} - D_4 , and possibly A_{2A} - D_2 - D_3 receptors might be also of interest regarding mood symptoms, as well as their interaction with glutamate receptors, such as the mGlu5 subtype.^{133,134}

The data here reviewed greatly suggest that identification, functional characterization, and specific modulation of adenosine-dopamine heteromers in specific brain regions and classical dopaminergic pathways, such as the mesocortical and mesolimbic ones, might be of interest for new therapeutic tools for mood disorders. Such understanding might help to better elucidate the different mechanisms underlying MDD, BPD, and SCA/SZC pathophysiology, promoting the development of new specific therapeutic strategies for mood disorders.

FIG. 1. Adenosinergic and dopaminergic control of mood symptoms. **(A)** Mood disorders, such as bipolar disorder and major depressive disorder, are neuropsychiatric conditions characterized by altered mood states. Modulation of adenosine A_1 and A_{2A} receptors expression and activity is associated to elevated mood and depressive-like symptoms, respectively, especially in striatopallidal neurons. **(B)** Adenosine receptors are G protein-coupled complexes activated by adenosine. While activation of the A_1 receptor is associated with manic/hypomanic episodes and with the antidepressant effects of some drugs, activation of the A_{2A} receptor is associated with depressive-like symptoms, which can be reversed to a normal state when receptor activity is antagonized, for example, by caffeine. **(C)** While psychosis can be a feature of mood disorders, mood alterations can occur as well in schizophrenia, characterizing the schizoaffective disorder. The antipsychotic effects of drugs widely used to treat schizophrenia and schizoaffective disorder, such as, haloperidol, result from the antagonistic association of A_{2A} and dopamine D_2 receptors to form A_{2A} - D_2 receptor heteromers. The binding of haloperidol to the adenosine A_{2A} receptor in the heteromer complex reduces the sensitivity of dopamine D_2 receptor-binding sites to dopamine, which has an antipsychotic effect.

Authors' Contributions

M.C.B.G. conceived and drafted the work, contributed to adenosine and mood control, dopamine and mood control, adenosine-dopamine interactions and implications in mood control and perspectives sections, as well as overall article organization; T.G. contributed to introduction and adenosine in mood control section and figure design; S.L.B.O. contributed to abstract and dopamine in mood control sections; H.U. conceived the study, contributed with the expertise to knowledge input for the insights here proposed and revised the article critically for important intellectual content. All authors have reviewed and approved the final version of the article before submission.

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