

Physiopathology of bipolar disorders: what has changed in the last 10 years?

Fisiopatologia do transtorno afetivo bipolar: o que mudou nos últimos 10 anos?

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Abstract

Despite recent efforts to understand the neurobiology of Bipolar Disorder (BD), the exact pathophysiology remains undetermined. Due to the effects of various psychopharmacological agents, initial research focused on the study of biogenic amines. Recent evidence has shown that dysfunction in intracellular signaling systems and gene expression may be associated with BD. These alterations may cause interruptions in mood regulating circuits such as the limbic system, striatum and prefrontal cortex, and the neuroprotective effects of mood stabilizers may reverse this pathological process. This study aims to update the recent findings relative to the neurochemistry of BD.

Keywords: Bipolar disorder/physiopathology; Depression; Neurobiology; Neurochemistry

Resumo

Apesar dos crescentes esforços para o entendimento da neurobiologia do transtorno afetivo bipolar (TAB), sua exata fisiopatologia permanece indeterminada. Inicialmente, a pesquisa estava voltada para o estudo das aminas biogênicas, devido aos efeitos dos diversos agentes psicofarmacológicos. Mais recentemente, evidências apontam que disfunções nos sistemas de sinalização intracelular e de expressão gênica podem estar associadas ao TAB. Estas alterações podem estar associadas a interrupções nos circuitos reguladores do humor, como sistema límbico, estriado e córtex pré-frontal, sendo que os efeitos neuroprotetores do uso crônico dos estabilizadores de humor podem reverter este processo patológico. Este artigo tem como objetivo trazer uma atualização dos achados recentes sobre a neuroquímica do TAB.

Descritores: Transtorno bipolar/fisiopatologia; Depressão; Neurobiologia; Neuroquímica

Introduction

Bipolar Disorder (BD) is a chronic illness that affects approximately 1.6% of the population¹ and represents one of the main causes of incapacitation worldwide.² In the last 10 years, BD has been shown to be a heterogeneous disorder, with wide variations in symptomatology and course.³ Despite the advances in research methods used in biological psychiatry and the current knowledge of the mechanisms of mood stabilizer action, BD pathophysiology is still far from being completely understood.

The initial theories regarding BD pathophysiology focused specifically on the system of neurotransmission of biogenic amines.⁴ The behavioral and physiological manifestations of BD are complex and undoubtedly mediated by a chain of interconnected neural circuits. Therefore, it is not surprising that the brain systems which received greater attention in neurobiological studies of mood disorders were the monoaminergic systems, since these are extensively distributed in the limbic-striatal circuits of the prefrontal cortex, regions which control the behavioral manifestations of mood disorders.⁵ Initially, it was hypothesized that depression and mania would result from decreased transmitter transport in the presynaptic neuron or synaptic vesicles. The synaptic vesicles, acting as "buffer" systems, would not be able to fully perform their function, and, as a consequence, neurotransmitter deficit and overflow would not be satisfactorily counterbalanced. The

resulting greater transmitter fluctuation in the synaptic cleft could therefore be responsible for mood swings.¹ However, BD models focused on a single neurotransmitter or neuromodulator system cannot fully explain the diverse clinical presentations of this disorder.

It has been demonstrated that mood regulation involves the interaction of multiple systems and that most effective drugs probably modulate the functional balance between the various interactive systems rather than acting on a specific, isolated neurotransmission system.⁶ Complex interactions between semi-independent neural systems, working in harmony, are necessary for maintaining appetite and sleep patterns, as well as for stabilizing body weight and libido, all of which are neurovegetative functions that are typically altered in mood disorders.⁷ In fact, postmortem studies have shown a significant decrease in glial cells in the prefrontal cortex and limbic system, as well as fewer neuronal cells in the prefrontal cortex and hippocampus, of individuals with BD,⁸ supporting findings regarding anatomical and functional changes observed in neuroimaging studies.⁹ Furthermore, pharmacological studies have confirmed the neuroprotective activity of mood stabilizers in a series of neurotoxicity models.¹⁰ Recent research has shown that the therapeutic action of these drugs involves the regulation of various intracellular signaling systems, second messengers and gene expression.¹¹

The neurobiology of mood regulation

The process of generating complex affective states, namely the sentimental and behavioral response when confronting various stimuli (stressful events) involves: 1) identifying the emotional significance of the stimulus (stress); 2) producing a specific affective state in response to the stimulus; and 3) regulating the affective and behavioral responses, which involves modulating processes 1 and 2, thereby obtaining a contextually appropriate response.¹² In studies involving animals and humans, including patients with focal brain lesions, stimulation and functional neuroimaging studies have shown that the amygdala, the insular cortex and the caudate nucleus are involved in the process of identifying the emotional meaning of the stimulus (step 1). The same studies showed that, in step 2 (responding to the stimulus), the ventrolateral prefrontal cortex, orbitofrontal cortex, insular cortex, anterior cingulate gyrus, the amygdala and the striate all take part in the affective response. In contrast, regulation of the affective and behavioral responses (step 3) is carried out by the dorsolateral and dorsomedial prefrontal cortices, together with the hippocampus and dorsal anterior cingulate gyrus.^{7,12}

Studies evaluating the performance of bipolar patients in cognitive tasks have shown that such patients exhibit a deficit in tests of attention and working memory, as well as difficulty in recognizing the facial expressions of fear, sadness and joy. In addition, these studies have demonstrated that such patients have a tendency to perceive neutral stimuli as particularly negative.¹³ These findings are supported by postmortem studies, which have demonstrated a significant decrease in the number and density of neuron cells in the subgenual and dorsolateral prefrontal cortices, as well as in the hippocampus.⁸ Neurofunctional studies reporting alterations in the metabolisms of the insular, orbitofrontal and dorsal anterior cingulate cortices, as well as of the amygdala and caudate head, also provide supporting evidence.¹³ Together, these studies suggest that symptoms such as affective lability, depressive/manic cycles and distractibility, which are commonly associated with BD, may be associated with these alterations in the brain regions involved in processing emotions.

Neurotransmitters

1. Serotonergic System

Serotonin (5-HT) modulates various neuronal activities and, consequently, regulates several physiological and behavioral functions such as the control of impulses, aggressiveness and suicidal tendencies.¹⁴ Therefore, decreased 5-HT release and activity may be associated with a number of abnormalities, such as suicidal ideation, suicidal attempts, aggressiveness and sleep disorders, all of which are frequently seen in bipolar disorders.³ In the 1970s, Prange et al¹⁵ suggested that 5-HT participates in BD physiology and formulated the permissive hypothesis, in which a deficit in central 5-HT neurotransmission would allow the expression of both manic and depressive states. However, such states would differ in relation to central catecholamine (noradrenaline and dopamine) levels, which would be elevated in manic states and diminished in depressive states. Furthermore, it has been shown that levels of 5 hydroxyindolacetic acid (5-HIAA) levels, the principal serotonin metabolite, are lower in the cerebrospinal fluid of manic and depressed patients than in that of normal controls. This suggests that both mania and depression are associated with a reduction in central 5-HT function. A postmortem study of the brains of BD patients also showed significantly lower levels of 5-HIAA in the frontal and parietal cortices, compared to controls, providing additional evidence to support the hypothesis that central 5-HT activity is reduced in BD.¹⁶ Neuroendocrine challenge studies, as a whole, indicate that presynaptic 5-HT activity is reduced in the central nervous

system (CNS), whereas sensitivity of the post-synaptic receptors is increased in mania.¹⁴

2. Dopaminergic system

One of the most consistent findings regarding the role of dopamine in the neurobiology of BD is that direct and indirect dopaminergic agonists simulate mania and hypomania episodes in patients presenting, or predisposed to, subjacent bipolar disorder.^{1,5} Ackenheil³ suggested that, although the results have been inconsistent, greater dopaminergic activity induced by increased dopamine liberation, reduced synaptic vesicle buffering capacity or higher dopaminergic receptor sensitivity may be associated with the development of manic symptoms, whereas a reduction in dopaminergic activity would be correlated with depression.

3. Noradrenergic system

Studies have described a subfunction of this system in depressive states. In these states, lower noradrenaline deficits and lower α_2 receptor sensitivity have been reported, in contrast to a tendency toward higher noradrenaline activity in manic states.³ Following this logic, Baumann et al¹⁷ observed that individuals with BD present higher numbers of pigmented cells in the locus coeruleus than do unipolar patients. In addition, Shiah et al¹⁴ suggested that diminished central 5-HT function concomitant with increased noradrenergic function may be involved in the genesis of mania.

4. GABAergic system

Clinical data indicate that decreased GABAergic function accompanies manic and depressive states, and that GABA agonists possess both antidepressant and antimanic properties.¹⁸ Low GABA levels have been found in the plasma of bipolar patients, during depression as well as during mania.¹⁹

5. Glutamatergic system

The participation of this system in the etiology of BD has been confirmed through the action of mood stabilizers on glutamatergic neurotransmission. It is known that valproic acid increases glutamate concentration in cultures of the neurons and brains of animals, as well as stimulating the liberation of glutamate in the mouse cerebral cortex. Consequently, an increase in glutamate may chronically induce mechanisms that maintain glutamate balance in the synapse through negative feedback.¹¹ Valproic acid also modulates those physiological responses that are mediated by N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid and kainic acid (KA).²⁰ Carbamazepine, on the other hand, suppresses glutamate liberation and reduces depolarization produced by NMDA and KA. In addition, lithium causes a sharp increase in synaptic glutamate concentrations, resulting in chronic upregulation of transporter activity. It has been hypothesized that the chronic use of lithium will eventually cause excitatory neurotransmission to stabilize.¹¹ Furthermore, recent *in vivo* studies using the magnetic resonance spectroscopy (MRS) technique have shown that bipolar patients present a significant increase in glutamine/glutamate concentrations in the dorsolateral prefrontal cortex and cingulate gyrus.²¹⁻²²

Intracellular signaling

Despite the range of alterations observed in neurotransmitter levels and their interaction with the respective receptors, signaling pathway abnormalities have been shown to be directly related to a series of neurotransmission system alterations.²³⁻²⁴ In fact, highly complex brain functions such as behavior, mood and cognition are critically dependent on signal transduction processes for their appropriate performance. In addition, the biochemical effects of mood disorder treatment on neurotransmitters in the synaptic junction are seen immediately (within hours), whereas the

clinical response takes longer (days or weeks), underscoring the central importance of intracellular events involving modulation of gene expression and cellular plasticity in mood regulation.^{23,25}

The G proteins (GTP-binding proteins) are molecules which translate the signal emitted by the transmembrane receptors to which they are coupled and relay that signal to the second intracellular messengers. The specificity of the interaction between the receptor and a particular G protein determines the nature of the effector mechanism to which the activated receptor will be connected. The G proteins transduce the signals of more than 80% of the signaling extracellular molecules, including hormones, neurotransmitters and neuromodulators. Therefore, these are interesting candidates for abnormalities involving communication among multiple neural systems.²⁶

Two initial studies showed an increase in stimulatory G protein (G_s) levels in the frontal, temporal and occipital cortices of individuals with BD,²⁷⁻²⁸ whereas another study showed an increase in G_s activity when stimulated by an agonist.²⁹ In a more recent study, a significant increase in G_s was shown among patients not using lithium. However, there were no differences between the group of patients as a whole and a group of normal volunteers, suggesting a possible effect of lithium on G_s activity.³⁰ In addition, studies employing specific markers have also shown alterations in G_s levels in BD patients,³¹⁻³³ suggesting that alterations in this protein may be involved in BD pathophysiology.

Adenylate cyclase signaling pathway

Adenylate cyclase is an enzyme that converts ATP in the cyclic AMP (cAMP) second messenger. The G_s protein is involved in the stimulation of adenylate cyclase, whereas the G_i protein inhibits this enzyme, and most receptors that regulate cAMP action do so through the effect they have on one of these G proteins. A central effect of cAMP is the activation of protein kinase A (PKA), an enzyme that regulates ionic channels, cytoskeleton elements and transcription factors, therefore constituting a critical factor in lasting neurobiological changes. One of the transcription factors phosphorylated and modulated by PKA is the cAMP response element binding protein (CREB), which regulates a number of neuronal processes, including excitation, neuron development and apoptosis, as well as synaptic plasticity.³⁴

Postmortem studies and studies of peripheral cells have consistently shown an increase in adenylate cyclase, cAMP and PKA activity in patients with BD.³⁵⁻³⁶ In addition, pharmacological studies have shown that lithium, valproic acid and carbamazepine have a regulatory action in this signaling pathway.²⁰

Phosphatidylinositol signaling pathway

The activation of a receptor coupled to the phosphatidylinositol (PIP_2) cascade stimulates an effector protein known as phospholipase C, which induces the formation of two important second messengers: diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3). The DAG activates the protein kinase C (PKC), which is involved in cellular processes including secretion, exocytosis, gene expression, modulation of ionic conduction, cellular proliferation and downregulation of extracellular receptors. The IP3 regulates the release of intracellular reserves of calcium kept in the endoplasmic reticulum. The released calcium interacts with a number of cellular proteins, including a group of receptors known as calmodulins (CaMs), which are sensitive to intracellular calcium and activate calmodulin-dependent protein kinases (CaMKs), leading to the activation of ionic channels, signaling molecules, apoptosis, and transcription factors.²⁶

Brown et al³⁷ observed increased levels of PIP_2 in the platelets of manic bipolar patients. This was also observed in the depressive

state, whereas treatment with lithium reduced PIP_2 levels during other states.³⁹⁻⁴⁰ Similarly, postmortem studies and studies of peripheral cells have shown that, in individuals with BD, PKC levels are increased⁴¹⁻⁴² and that lithium treatment reduces those levels.⁴³ In fact, two studies, both employing MRS, have demonstrated the action of lithium in this signaling pathway, showing that lithium significantly reduces myo-inositol levels, thus diminishing the activity of this signaling pathway.⁴⁴⁻⁴⁵ Using the MRS technique, our group recently showed that, during manic episodes, bipolar patients present significantly elevated levels of myo-inositol in the left dorsolateral prefrontal cortex in comparison with normal volunteers (Frey et al., submitted).

Gene expression regulation and neuroprotection

The regulation of several intracellular signaling cascades modulates gene transcription factors, which are proteins linked to specific genes in the DNA, inducing the formation of new proteins involved in cellular plasticity. Therefore, alterations at any level of the cascade may cause cell death through the formation of proapoptotic proteins or through a reduction of cellular protection factors and survival factors, such as neurotrophins and cytoskeletal anchoring proteins.

Pharmacological studies have consistently shown that lithium increases cell survival in a variety of neurotoxicity models.¹⁰ More specifically, lithium has been shown to promote a significant increase in the expression of bcl-2 and BDNF, proteins involved in neuroprotection,⁴⁶⁻⁴⁷ and to inhibit GSK3- β activity, a protein associated with apoptosis.⁴⁸ In addition, valproic acid and, more recently, lamotrigine, have also been shown to inhibit GSK3- β activity.⁴⁹

Furthermore, an essential factor in cellular response in stress situations is regulation of mRNA stability during the gene transcription phase and of new protein formation. Within this context, Chen et al⁵⁰ showed that lithium and valproic acid enhance the expression of AUH protein, one of the proteins that stabilizes mRNA during the transcription phase. Therefore, these drugs regulate the expression of multiple genes in the CNS, an effect that may play a central role in the treatment of complex illnesses such as BD.

Animal models

The lack of consistent animal models is one of the current limitations to the understanding the neurobiology of mood disorders.⁵¹ To date, there are no animal models appropriate for the study of BD, since the models currently available cannot mimic the cyclicity of the manic-depression states⁵². Animal models of mania have been induced through the use of psychostimulants (amphetamine and cocaine),⁵³⁻⁵⁴ sleep deprivation,⁵⁵ brain lesions⁵⁶ and electrical stimulation,⁵⁷ and also include genetic models.⁵⁸ Animal models of depression, on the other hand, included those created through the use of olfactory bulb ablation (hyposerotonergic hypothesis),⁵⁹ intracranial self-stimulation (desensitization of the reward system),⁶⁰ social isolation,⁶¹ forced swim,⁶² chronic mild stress,⁶⁴ learned helplessness⁶⁴ and genetic models.⁶⁵

Conclusion

Advances in molecular biology research techniques have demonstrated that BD is associated with alterations in intracellular substances involved in the regulation of neurotransmitters, synaptic plasticity, gene expression, neuronal survival and neuronal death. In addition, postmortem studies have shown a significant reduction in nerve cells in brain regions involved in mood regulation. Nevertheless, it is still impossible to determine the role that atrophy/death of neurons plays in the evolution of

the disease. Prospective studies involving individuals in their first episode and genetic studies of individuals at greater risk are interesting investigative strategies used in this area.

Notably, there is increasing evidence that the action of mood stabilizers in the regulation of intracellular signaling pathways is implicated in the processes of neuroplasticity and neuroprotection.^{20,43,46,49} In fact, the clinical effects of mood stabilizers require long-term treatment consistent with the time needed for the cascade of intracellular events and subsequent modulation of gene expression. The search for new medications that act on more specific signaling pathways is a promising area in the treatment of complex chronic illnesses such as BD.

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