Review article

The P2X7 purinergic receptor as a molecular target in bipolar disorder

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Neuropsychiatria i Neuropsychologia 2013; 8, 1: 1–7

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Abstract

The purinergic system has been increasingly implicated in medical conditions, among them bipolar disorder (BD). This is based primarily on the role of extracellular adenosine triphosphate (ATP) and purinergic receptors in cytokine regulation and the pathological activation of glial cells, leading to neuroinflammation. In addition, adenosine metabolism is directly related to the pathophysiology of BD. Among purinergic receptors, P2X7 was associated with BD in several genetic studies. This particular receptor has a key role in the modulation of the inflammatory response, acting as a sensor of harm and responding to ATP released from injured or stressed cells in the central nervous system, ultimately driving microglial cells from their resting into the activated form. Of note, markers of excitotoxicity and neuroinflammation are significantly upregulated in frontal cortex from BD patients compared with controls, justifying the need for further research. The present review focuses on purinergic signaling in BD, with an emphasis on ATP and adenosine signaling, highlighting the potential role of P2X7R in modulating inflammation and microglia activation in bipolar patients. Due to its ability to act on microglia and modulate neuroinflammation, we believe that more detailed studies of the role of P2X7R in BD are warranted.

Key words: bipolar disorder, purinergic system, P2X7R, microglia, inflammation.

Introduction

The purinergic system includes nucleotides (most notably, adenosine triphosphate – ATP), nucleosides, as well as a large family of ectonucleotidases (Baroja-Mazo *et al*. 2013). There are two main purinoceptor classes: P1 receptors, which are activated by adenosine, and the P2 family, which is subdivided into P2Y and P2X, activated by different nucleotides and ATP, respectively (Baroja-Mazo *et al*. 2013). Purinergic signaling has been identified in virtually all cells and it is implicated in many neuronal and non-neuronal mechanisms, in physiological as well as pathological conditions, including secretion, immune responses, cell proliferation, cell death, pain and inflammation (Baroja-Mazo *et al*. 2013). Several purinergic receptor subtypes have been shown to be widely distributed throughout the CNS, in neurons and glia (Weisman *et al*. 2012).

Recently, purinergic pathophysiology has been emphasized in numerous medical conditions, especially neurodegenerative and psychiatric disorders, including bipolar disorder (BD)

(McQuillin *et al*. 2009; Lopes *et al*. 2011). This expanding area of research is based primarily on the role of extracellular ATP and purinergic receptors in cytokine regulation and pathological activation of glial cells, leading to neuroinflammation (Rao *et al*. 2010). Likewise, adenosine metabolism has been directly related to the pathophysiology of BD (Salvadore *et al*. 2010). Kraeplin proposed a long time ago an association between manic symptoms and purinergic system dysfunction when he related the former to hyperuricemia, uric acid excretion and gout (Kraeplin 1921). Current evidence points to purinergic system impairment in BD patients, mainly in adenosine P1 and P2X receptors. Recently, genetic studies demonstrated a potential role for purinergic system dysfunction in the pathophysiology of BD, primarily in the P2X7 receptor (P2X7R) (Backlund *et al*. 2011).

The present review focuses on purinergic signaling in BD, with an emphasis on ATP and adenosine signaling, highlighting the potential role of P2X7R in modulating inflammation and microglial activation in bipolar patients.

P1 receptors

Extracellular adenosine is present in organisms as an intermediate metabolite of ATP catabolism (Fredholm *et al*. 2001). It acts by regulating several physiological processes (Ferré 1997). Adenosine receptors are present in the CNS, among other tissues, and are divided into four types of receptors: A_1, A_{2A}, A_{2B} and A_3 (Fredholm *et al*. 2001). The A_1 receptor is responsible for many of the inhibitory effects of adenosine in the CNS, and has widespread distribution in different brain areas such as the cortex, hippocampus, cerebellum and thalamus, where it is found in higher concentrations (Ribeiro *et al*. 2002; Stone *et al*. 2009). Its activation causes a decrease in neuronal excitability, reduction of uric acid levels, and inhibition of Ca^{2+}-dependent excitatory neurotransmitter release, thus being responsible for the modulation of neurotransmitter release (Lopes *et al*. 2011).

Increased levels of uric acid have been implicated in the pathophysiology of BD (Salvadore *et al*. 2010). Uric acid is the nitrogenous end product of purine metabolism and is generated by the enzyme xanthine oxidase from xanthine and hypoxanthine (for review, see Moriwaki *et al*. 1999). Studies suggest that the purinergic modulator allopurinol acts by inhibiting the enzyme xanthine oxidase, reducing uric acid levels as a consequence. Patients in their first manic episode showed elevated plasma levels of uric acid compared to controls, indicating that a purinergic system dysfunction could be present early in the course of the disorder (Salvadore *et al*. 2010).

A randomized, double blind, placebo-controlled trial in patients with moderate to severe mania found that the use of allopurinol with lithium and haloperidol for 8 weeks compared to haloperidol lithium and placebo resulted in reduction of agitation and manic symptoms, as assessed by the Young Mania Rating Scale (YMRS) (Akhondzadeh *et al*. 2006). Based on this evidence, allopurinol has been proposed as an adjunctive drug to lithium for the treatment of manic episodes in patients with BD.

Since refractoriness rates among bipolar patients are still very high and a significant number of manic patients are not responsive to conventional mood stabilizers, often requiring different combinations of drugs, the purinergic pathways may provide future therapeutic targets for BD.

P2 receptors

Most of the evidence pointing to an association between BD and purinergic signaling relies on the P2 family of receptors, which are preferentially activated by extracellular ATP (Abbracchio and Burnstock 1998). These receptors are divided into two distinct families: the P2X ligand-gated ionotropic channel receptors, and the P2Y, metabotropic G-protein coupled receptors. Because they act as ion channels, P2X receptors respond more rapidly than P2Y and are mainly involved in rapid excitatory neurotransmission (Burnstock and Williams 2000). These receptors act as ion channels with high calcium permeability that open upon binding of extracellular ATP (North 2002). Of note, the activation of P2X7R, which presents a very low affinity for ATP, requires near millimolar concentrations of ATP (Skaper *et al*. 2009). Massive ATP release into the extracellular milieu can take place after acute cell injury or death, and also under inflammatory conditions and in response to tissue trauma (Skaper *et al*. 2009). Once activated by high ATP levels, P2X7R can act as a nonselective ion pore; however, continuous stimulation results in the formation of a larger pore, which facilitates the uptake of cationic molecules up to 900 Da, possibly triggering the activation of apoptosis or cell lysis (Skaper *et al*. 2009).

P2X7R mediates cellular processes such as apoptosis, as well as cell proliferation and pro-

inflammatory cytokine release (Apolloni *et al*. 2009). It acts on neurotransmission (supposedly influencing dopamine release), neuromodulation and neurotrophic mechanisms (Backlund *et al*. 2011). The expression of P2X7R is not restricted to immune-related cells, but is also present in microglia and astrocytes in the brain (Chakfe *et al*. 2002; Walter *et al*. 2004). In the CNS, it is found in the cerebral cortex, hippocampus, brainstem, nucleus accumbens, and spinal cord (Weisman *et al*. 2012).

The role of P2X7R in BD has been suggested mainly by linkage and association genetic studies. The P2X7R gene is located in the 12q23-24 chromosome region, which has been described as a susceptible locus for BD (Abkevich *et al*. 2003). Further studies have reported an association between the P2X7R gene and BD, especially with the non-synonymous single nucleotide polymorphism (SNP) rs2230912, Gln460Arg (McQuillin *et al*. 2009). In addition, other polymorphisms in this gene, such as the SNPs rs1718119 and rs1621388, have also been associated with BD manic symptoms (Backlund *et al*. 2011). This association may be mediated by the role of P2X7R in pro-inflammatory cytokine release, given that mania has been associated with increased cytokine levels (Stertz *et al*. 2013). Of note, some manic symptoms may be particularly vulnerable to such pro-inflammatory action (Backlund *et al*. 2011). In addition, it has been proposed that neuroticism, a personality trait reflecting individual differences in emotional stability and vulnerability to stress and anxiety, mediates the effect of another P2X7R polymorphism (rs208294) on medium-term outcome in major depressive disorder and BD (Mantere *et al*. 2012). This same SNP, together with rs2230912, was also associated with increased risk for a familial mood disorder in three independent cohorts, in which carriers of the risk alleles were ill for longer periods of time (Soronen *et al*. 2011).

A few animal studies have strengthened the association between P2X7R and BD. The data are still inconclusive, showing that P2X7R knockout mice demonstrated an antidepressant-like phenotype and when treated with imipramine, a tricyclic antidepressant, had an augmented response compared with wild type (Basso *et al*. 2009). However, other authors described an impaired adaptive coping response to repeated stress, as well as greater anxiety behavior (Boucher *et al*. 2011). In addition, a recent study employing a novel animal model of mania found that P2X7R expression is downregulated in the hippocampus, possibly contributing to the manic-like behaviors reported for the mice (Saul *et al*. 2012). This discrepancy may account for a different role of the receptor in manic and depressive episodes. Interestingly, acute (*in vitro*) and chronic (*in vivo*) treatment with known mood stabilizers (lithium and valproate) prevented ATP-induced cell death (Wilot *et al*. 2007). Moreover, chronic treatment of rats with lithium induced an increase in ATP and AMP hydrolysis in hippocampal synaptosomes (Wilot *et al*. 2004), suggesting that mood stabilizers may act by modulating ectonucleotidases and interfering with the purinergic system. Altogether, these studies strongly support the hypothesis that P2 receptors, mostly P2X7R, play a role in the pathophysiology of BD and thus deserve further studies.

Role of P2X7 receptor in inflammation

The involvement of the purinergic system with BD may be related to its potential role in modulating inflammation and microglial activation. Microglia are immunocompetent cells of the CNS (Pessac *et al*. 2001), producing either a neuroprotective or an inflammatory response (Stertz *et al*. 2013). Under normal conditions microglia exhibit a resting state, producing and releasing anti-inflammatory cytokines and neurotrophic factors, removing cellular debris and neutralizing pathogens (Ekdahl 2012; Nimmerjahn *et al*. 2005; Monif *et al*. 2010). In pathological conditions, including response to tissue injury, trauma or toxins, microglia become activated and assume markedly different biochemical and morphological states (Monif *et al*. 2010). Microglial activation leads to the synthesis of proinflammatory mediators, triggering tissue impairment (Weitz and Town 2012). Excessive activity of microglia exposes the CNS to proinflammatory cytokines, including interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α), chemokines, reactive oxygen species, and proteases, all of which could have severe deleterious consequences in excessive amounts (Monif *et al*. 2010; Suzuki *et al*. 2004). This condition promotes neuroinflammation and contributes to a variety of pathological conditions, mainly neurodegenerative diseases like Alzheimer's (Weitz and Town 2012) and mental illnesses, such as depression, schizophrenia and BD (Rao *et al*. 2010; Bayer *et al*. 1999, Morgan *et al*. 2010).

Several studies have shown a significant relation between increased morbidity and heightened inflammatory levels in cardiovascular and metabolic syndromes and the same was observed in BD patients (Leboyer *et al*. 2012). These findings suggest the involvement of a proinflammatory state in the pathophysiology of BD (Berk *et al*. 2011). Multiple lines of evidence indicate that BD is a "multi-systemic inflammatory disease", with biochemical alterations occurring in and beyond the CNS (Munkholm *et al*. 2013). Progressive impairment of cognitive functions and brain atrophy have been consistently described in BD and suggest that the disease is progressive with important components of excitotoxicity and neuroinflammation (Lewandowski *et al*. 2011; Rao *et al*. 2010).

In animal models it has been demonstrated that both excitotoxicity and neuroinflammation are associated with increased brain levels of reactive oxygen species, nitric oxide and, most notably, proinflammatory cytokines (Chang *et al*. 2008). In a model of excitotoxicity, the chronic administration of subconvulsive doses of N-methyl-D-aspartate (NMDA) upregulated rat brain protein and mRNA levels of neuroinflammatory markers IL-1β, glial fibrillary acidic protein (GFAP), inducible nitric oxide synthase (iNOS) and TNF-β (Chang *et al*. 2008). A recent postmortem study demonstrated that markers of excitotoxicity and neuroinflammation are significantly upregulated in frontal cortex from BD patients compared with controls (Rao *et al*. 2010). Increased levels of c-Fos and iNOS mRNA have also been described in the same samples (Rao *et al*. 2010), as well as increased protein and mRNA levels of IL-1β, IL-1 receptor (IL-1R), and transcription factor nuclear factor-kappa B (NF-κB) subunits (p50 and p65), ultimately contributing to upregulation of proinflammatory gene products (Weisman *et al*. 2012). Likewise, there was a significant increase in GFAP expression and in the levels of CD11b mRNA (a marker of astrocyte and microglial activation) (Rao *et al*. 2010). These results indicate an important role of the cascade activation of the IL-1R on microglial activation. The authors suggest that this upregulation might result in cell death with subsequent brain atrophy and cognitive impairment that have been reported in BD patients (Rao *et al*. 2010).

Other studies have shown significantly higher levels of IL-1β in cerebrospinal fluid of patients with one or more recent manic/hypomanic episodes compared with patients without recent episodes. These findings indicate a relationship between the presence of acute episodes and activation of the IL-1R cascade (Söderlund *et al*. 2011). Furthermore, a recent review discussed the relevance of microglial activation on BD (Stertz *et al*. 2013). Researchers have suggested activation of microglia by damage-associated molecules in the first acute episode and a state of constant activation after several episodes, resulting in excessive production of proinflammatory cytokines, mainly IL-1β and TNF-α (Weitz and Town 2012). This condition leads to inhibition of neurogenesis, damage and neuronal death, potentially perpetuating systemic toxicity (Stertz *et al*. 2013).

An important damage-associated molecule candidate that would trigger microglial activation could be ATP by means of P2X7R. ATP has already been included in the limited family of those factors that signal danger to the immune system (i.e. damage-associated molecular patterns [DAMPs]) (Di Virgilio *et al*. 2009). The same authors suggest that P2X7R acts as a "sensor of danger", responding to the so-called "danger signal" ATP, which is released from injured or stressed cells in the CNS and drives resting microglial cells into their activated form (Weisman *et al*. 2012). There are several studies showing microglia activation induced by P2X7R stimulation (Suzuki *et al*. 2004; Monif *et al*. 2010), suggesting P2X7R as a key component of neuroinflammation (Monif *et al*. 2010). Moreover, P2X7R has been put forward as an essential component for the induction of microglial activation (Monif *et al*. 2010). When the P2X7R nucleotide binding site was blocked with oxidized ATP (oxATP), microglial activation was significantly attenuated, indicating that receptor occupancy is essential for microglial activation (Monif *et al*. 2010). In this same line of thought, P2X7R activation promotes neuroinflammation by inducing the release of proinflammatory cytokines, such as IL-1β and TNF-α (Di Virgilio 2007; Tschopp and Schroder 2010), and activation of NF-κB, resulting in upregulation of proinflammatory gene products (Skaper *et al*. 2010). Indeed, mice deficient in P2X7R demonstrated decreased inflammatory responses (Lucattelli *et al*. 2011), confirming the relationship between neuroinflammation and P2X7R.

Considering that the pathophysiology of BD includes a proinflammatory state, with a potential key role of microglia activation and neuroinflammation, our current understanding is

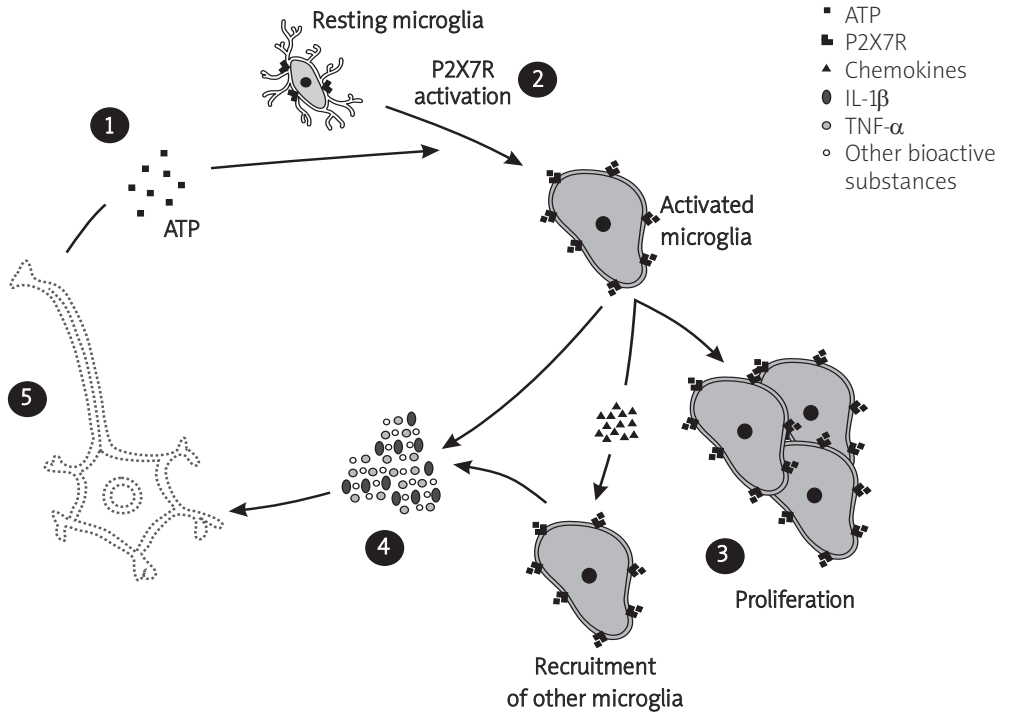

Fig. 1. The hypothetical role of P2X7R activation in the pathophysiology of bipolar disorder. 1) Acute episodes lead to neuronal injury that causes the release of damage-associated molecular patterns (DAMPs), such as ATP. 2) Released ATP may ultimately drive microglial cells from their resting state into their activated form through the activation of P2X7R. 3) Once activated by signaling cascades involving the activation of P2X7R, microglial cells induce proliferation and recruitment of other microglia through the release of chemokines. 4) Activated microglia release proinflammatory molecules (IL-1β, TNF-α) and other bioactive substances, such as reactive oxygen species and proteases, which can induce neuronal damage. 5) Therefore, in the continuous presence of ATP, microglial activation and excess of proinflammatory cytokines can form a self-perpetuating neuroinflammatory cycle.

reflected in a proposed scheme of the hypothetical role of P2X7R on microglial activation, which consists in elevated ATP release from injured or stressed cells, stimulating P2X7R and thus activating resting microglia as described in detail in Figure 1. Once activated, and by means of signaling cascades involving activation of P2X7R and upregulation of proinflammatory gene products, microglia release proinflammatory substances (IL-1β, TNF-α), which in turn are capable of promoting further microglial activation, in an autocrine manner. In the same way, the release of chemokines can also recruit other microglia. Therefore, in the continued presence of ATP, with increasing proinflammatory cytokines and other bioactive substances, a self-propagating cycle of neuroinflammation may be formed.

Conclusions

In summary, several lines of evidence suggest that the purinergic system is associated with the pathophysiology of BD, including the P1 adenosine receptors and P2 receptors. Specifically, genetic studies have been pointing to the P2X7R gene as a susceptibility gene for BD, and its role in the disorder has been increasingly acknowledged. Based on this scenario, a more detailed study of the role of P2X7R in BD is warranted, especially due to its ability to act on microglia and modulate neuroinflammation. A better understanding of the relevance of such alterations in the mechanisms of action of known mood stabilizers may further indicate the pathways through which the purinergic system, mainly the P2X7 receptor, is involved in BD pathophysiology.

Acknowledgments

This work was supported by grants from INCT Translational Medicine, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). CG and AR are recipients of scholarships from CNPq. GRF and BWA are recipi-

ents of scholarships from CAPES. The authors also thank Guilherme Gagliardi for his support in designing Figure 1.

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