# The role of purinergic signaling in depressive disorders

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The purinergic signaling system consists of transporters, enzymes and receptors responsible for the synthesis, release, action and extracellular inactivation of adenosine 5'-triphosphate (ATP) and its extracellular breakdown product adenosine. The actions of ATP are mediated ionotropic P2X and metabotropic P2Y receptor subfamilies, whilst the actions of adenosine are mediated by P1 adenosine receptors. Purinergic signaling pathways are widely expressed in the central nervous system (CNS) and participate in its normal and pathological functions. Among P2X receptors, the P2X7 receptor (P2rx7) has received considerable interest in both basic and clinical neuropsychiatric research because of its profound effects in animal CNS pathology and its potential involvement as a susceptibility gene in mood disorders. Although genetic findings were not always consistently replicated, several studies demonstrated that single nucleotide polymorphisms (SNPs) in the human P2X7 gene (*P2RX7*) show significant association with major depressive disorder and bipolar disorder. Animal studies revealed that the genetic knock-down or pharmacological antagonism leads to reduced depressive-like behavior, attenuated response in mania-model and alterations in stress reactivity. A potential mechanism of P2rx7 activation on mood related behavior is increased glutamate release, activation of extrasynaptic NMDA receptors and subsequent enduring changes in neuroplasticity. In addition, dysregulation of monoaminergic transmission and HPA axis reactivity could also contribute to the observed changes in behavior. Besides P2rx7, the inhibition of adenosine $A_1$ and $A_{2A}$ receptors also mediate antidepressant-like effects in animal experiments. In conclusion, despite contradictions between existing data, these findings point to the therapeutic potential of the purinergic signaling system in mood disorders.

*(Neuropsychopharmacol Hung 2012; 14(4): 231-238; doi: 10.5706/nph201212003)*

**Keywords**: ATP, adenosine, purinergic receptors, P2X7 receptor, depressive disorder, bipolar disorder

## THE PURINERGIC SIGNALING SYSTEM

The purinergic signaling system, now also called as "Purinome", is a ubiquitous extracellular communication channel mediated by ATP and its extracellular breakdown product adenosine. It consists of transporters, enzymes and receptors responsible for the synthesis, release, action and extracellular inactivation of purines (Figure 1).

ATP is well-known as the universal "energy currency" of living cells. The first observation suggesting that it is also an important extracellular signaling molecule stems from Drury and Szent-Györgyi who reported in 1929 that adenylyl compounds have profound effect on heart rate and cardiovascular function (Drury, 1929). This idea was rediscovered by Geoffrey Burnstock in the early seventies, who proposed the "purinergic nerve hypothesis", suggesting that ATP acts as a specific neurotransmitter in the nervous system (Burnstock, 1972). In the past decades this concept has gained solid experimental proof in the central and peripheral nervous system. Moreover it also turned out that extracellular ATP has far more versatile functions in the neuronal information processing than a classical neurotransmitter, participating in pre- and post-synaptic neuromodulation, glia-neuron and glia-glia interactions. Importantly, purinergic signaling also plays a prominent role in the pathological brain and offers a number of target sites for therapeutic intervention in diseases of the

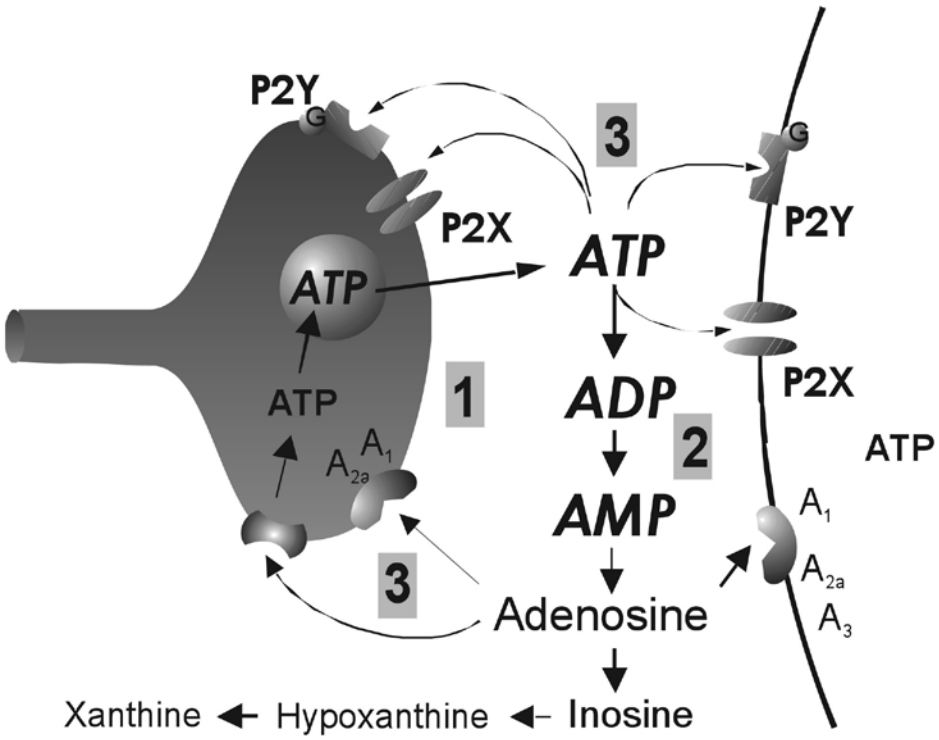


**Figure 1** Basic features of purinergic transmission. ATP is mainly synthesised through mitochondrial oxidative phosphorylation, however, it is taken up and stored in synaptic vesicles. Via physiological or pathological neuronal activity it is released into the extracellular space, where it is dephosphorylated by endonucleases yielding adenosine. Adenosine is then deaminated or is reuptaken into the nerve terminal where it is reincorporated into ATP stores. Effects of ATP are mediated by ionotropic P2X and metabotropic P2Y receptors, while effects of adenosine are mediated by metabotropic P1 receptors expressed both pre- and postsynaptically as well as non-synaptically.

nervous system, which potentially could be utilized for drug development (Burnstock et al., 2011).

The majority of ATP under normal metabolic conditions is synthesized in the mitochondria by oxidative phosphorylation and is stored in the cytoplasm of nerve terminals and glia in millimolar concentration (Figure 1). A part of the cytoplasmic ATP is taken up to synaptic vesicles by the vesicular nucleotide transporter (VNUT) and is stored there alone or together with other neurotransmitters. On the other hand, the basal intracellular adenosine concentration is less, in the low micromolar range, and the majority of adenosine, which is transported into cells is rapidly reincorporated into ATP stores. ATP is released into the extracellular space in response to physiological neuronal activity and pathological signals such as hypoxia/hypoglycemia/ischemia, inflammation, metabolic and osmotic stress, and cellular damage. The mechanism whereby it enters the extracellular space is also various, including (1) vesicular exocytosis, (2) carrier-mediated release, (3) release through channels and membrane pores, and (4) cytolytic release. However, the action of ATP in the extracellular space is rapidly terminated by the ectonucleotidases (ectoNTPDases, ectoNPPases, alkaline phosphatases and ecto-5'nucleotidases), a family of membrane bound enzymes, capable to dephosphorylate purine nucleotides and giving rise to the formation of adenosine. In addition, adenosine *per se* could also be released to the extracellular space. Finally, adenosine is taken up to the nerve terminal by specific equilibrative and concentrative nucleoside transporters (ENT and CNT), or deaminated extra-or intracellularly by the adenosine deaminase enzyme.

Although the synthesis, release and extracellular fate of ATP and adenosine is tightly coupled, they form separate signaling systems at the level of receptors. The actions of ATP are mediated by P2 nucleotide receptors, which could be subdivided into ionotropic

P2X and metabotropic P2Y receptor subfamilies. P2X receptors are ligand gated non-selective cation channels, forming various trimeric co-assemblies of seven individual subunits (P2X1, P2X2, P2X3, P2X4, P2X5, P2X6 and P2X7), whereas P2Y receptors belong to G protein coupled metabotropic receptors having eight subtypes ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$). The actions of adenosine are mediated by P1 adenosine receptors having four individual subtypes ($A_1$, $A_{2A}$, $A_{2B}$, $A_3$).

These receptors are widely expressed in the central nervous system (CNS) and convey a multiplicity of normal and pathological functions (Burnstock et al., 2011); among them, we will focus on those in this review, which have been implicated in mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BPD): the ionotropic P2X7 receptor and metabotropic $A_1$ and $A_{2A}$ receptors.

## THE P2X7 RECEPTOR (P2RX7)

P2X7 receptors (P2rx7) belong to the P2X receptors, which are ligand-gated non-selective cation channels having two transmembrane domains and a large extracellular loop and are sensitive to ATP and other purine nucleotides. The homo-oligomeric P2rx7 (Surprenant et al., 1996) has distinct structural, functional and pharmacological features within the P2X receptor family (Sperlagh et al., 2006): [1] its intracellular carboxyl-terminal domain is longer than those of other P2X receptor subunits, [2] it has several splice variants that display different functionality in wild-type (*P2rx7*+/+) and knockout (*P2rx7*-/-) mice lines (Nicke et al., 2009, Masin et al., 2012), [3] its persistent activation elicits the opening of a membrane pore permeable to high molecular weight substances, and [4] it needs high micromolar concentrations of ATP to be activated.

P2rx7s are widely distributed in different cells, including cells of hematopoietic origin, neurons, microglia and astrocytes. The primary role of P2rx7s in the brain is the modulation of neurotransmitter release (Sperlagh et al., 2006). The activation of P2rx7s elicits $Ca^{2+}$ influx followed by increased glutamate and subsequent GABA release (Sperlagh et al., 2002; 2006). Recent studies highlighted that P2X7 receptors play a regulatory role in a number of CNS-related functions, including learning and memory, sleep, fever and behavior. By regulating the activation and proliferation of microglia and the subsequent pathological process leading to neuronal death, P2rx7s might also act as a "danger signal" and contribute to neurodegenerative and neuroplasticity events underlying a variety of central nervous system (CNS) disorders from Alzheimer's disease to mood disorders (Burnstock, 2008; Skaper et al., 2010; Sperlagh et al., 2006). In the periphery, P2rx7s are involved in the regulation of different aspects of the inflammatory response and host defense reaction (Chen et al., 2006). A major immunomodulatory function of P2rx7 activation is that it acts as a necessary co-stimulus for the post-translational processing and subsequent release of the proinflammatory cytokine IL-1β in peripheral immune cells in response to bacterial endotoxin (Solle et al., 2001).

## THE ROLE OF P2RX7 IN MOOD DISORDERS: GENETIC STUDIES

According to the present knowledge, mood disorders, including MDD and BPD are caused by the complex interactions between genes, developmental and environmental factors. Linkage studies suggested that the chromosome 12q24.31 containing a candidate gene for P2X7 and P2X4 receptors may be an important genetic region for anxiety, bipolar and unipolar disorders (Erhardt et al., 2007). Gene polymorphism studies have revealed that non-synonymous single nucleotide polymorphisms (SNPs) in the human P2X7 gene (*P2RX7*) affect receptor function (Roger et al., 2010; Stokes et al., 2010) and are associated with BPD (Barden et al., 2006; Hejjas et al., 2009; McQuillin et al., 2009; Nagy et al., 2008) and MDD (Lucae et al., 2006; Soronen et al., 2011). In fact, a significant association of non-synonymous coding SNP rs2230912 (Glu460Arg) was associated with MDD (Lucae et al., 2006) which elicits a gain-of function effect on the recombinant receptor (Stokes et al., 2009). These mutations have been proposed to underlie the susceptibility to genetically-related mood disorders (Harvey et al., 2007; Sluyter et al., 2010). However, other studies failed to confirm the association of this or other SNPs of P2RX7 with mood disorders (Green et al., 2009; Grigoroiu-Serbanescu et al., 2010; Lavebratt et al., 2010; Viikki et al., 2011). More recent data have again reaffirmed the link between mutations of P2RX7 and mood disorders (Backlund et al., 2011, Soronen et al., 2011). The potentially relevant SNPs were introduced in the human P2X7 receptor and resultant mutants were expressed in human embryonic kidney cells and functionally characterized by electrophysiology (Roger et al., 2010). These studies suggested that the SNP mutational effects may result from changes in subunit interaction, agonist binding

and/or channel gating. Individuals predisposed to mood disorders, such as bipolar disorder and major depressive disorder, are associated with risk alleles of the P2X7 receptor gene and a correlation was found with the clinical course of disorder (Soronen et al., 2011). Moreover, very recently it turned out that neuroticism appear to mediate the effect of P2rx7 on the clinical outcome of mood disorder (Mantere et al., 2012). Finally, a clinical study showed reduced mRNA expression of the peripheral P2X7 receptor in a set of patients suffering from depression and posttraumatic stress disorder (Zhang et al., 2011), which raises the possibility to utilize P2RX7 expression as a biomarker of mood disorders.

Given the emerging notion on the limited impact of individual SNPs to affect the pathology of mood disorders and the contradictions in the genetic results it is premature to draw a final conclusion on the precise role of gene polymorphisms encoding P2RX7 in either MDD or BPD. Nevertheless, increasing number of animal studies indicates that an alteration in the expression and/or function of P2rx7 do affect stress reactivity and emotional behavior and might play a role in its pathological alterations.

## THE ROLE OF P2RX7 IN MOOD DISORDERS: ANIMAL STUDIES

Mice genetically deficient in P2rx7 have been generated for the first time more than a decade ago (Sikora et al., 1999, Solle et al., 2001) and have been widely used to decipher biological functions mediated by P2rx7. In general, two different P2rx7 knockout (P2rx7-/-) mouse models are used:, whereas the "Glaxo" type has a LacZ gene and neomycin cassette (Neo) inserted into exon 1 (Sikora et al., 1999), the Pfizer type which has a Neo insertion in exon 13 resulting the invalidation of P2rx7 closed to the carboxy terminal domain of the receptor (Solle et al., 2001).

However, more recent investigations revealed that there are a number of splice variants of P2rx7 and certain variants are escaped from inactivation in the "Glaxo" and "Pfizer" type knockouts, respectively (Nicke et al., 2011; Masin et al., 2012). Therefore these models are cannot be regarded as fully deficient in functional P2rx7-like receptors, especially in the in the brain, where these splice variants are strongly expressed.

An alternative tool to study receptor function is to use receptor selective antagonists. Indeed, due to the immense interest of medicinal chemistry on this area, several potent and selective antagonists are available to inhibit P2rx7 receptors, such as Brilliant Blue G, A-438079 and AZ-10606120 (Friedle et al., 2010).

Using the Porsolt's forced swim test (FST) and the tail suspension test (TST) and Pfizer-type knockout mice, Basso et al reported an antidepressant phenotype and increased food intake in the absence of P2rx7, whereas no change in the basal locomotor activity and the anxiety was detected (Basso et al., 2009). In another study, Boucher et al. found that whereas the basal immobility time was not different in the two genotypes, a decreased immobility time was detected in repeated trials of FST (Boucher et al., 2011). These data were then confirmed an extended by our group showing that P2rx7 deficient mice display not only antidepressant, but a mood stabilizing phenotype showing decreased stress reactivity and attenuated response in the amphetamine induced hyperactivity test (AH), the latter represents an animal model of the manic pole of bipolar disorder (Csölle et al., 2012a). In this study we found that P2rx7-/- mice displayed a decreased immobility response in the repeated FST and single TST tests, and reduced amphetamine induced hyperlocomotion. Importantly, these changes could be reproduced in P2rx7+/+ mice by subacute administration of the selective P2rx7 antagonist Brilliant Blue G (BBG). In addition, P2rx7-/- mice responded with decreased elevation of plasma ACTH and corticosterone in response to restraint stress indicating the decreased reactivity of the HPA axis in the absence of P2rx7. Finally, in addition to FST and TST, which examines active coping with behavioral stress both genetic deletion and pharmacological antagonism of P2rx7 leads to decreased sucrose consumption in the sucrose preference test (SPT); an animal model reflecting anhedonia, another core symptom of depression (Csölle et al., 2012b). Most recently humanized mouse mutants reproducing the SNP rs2230912 (Glu460Arg) were also generated using a knock-in approach based on homologous recombination in embryonic stem cells (Deussing et al., 2012). The resultant mutants not only reproduced the disease-related alteration of receptor function, i.e. the increased IL-1β secretion in macrophages in response to bacterial endotoxin, but showed a compromised response to chronic social defeat stress and displayed reduced sleep quality. A further intriguing observation is that a mouse strain termed Madison (MSN), naturally exhibiting manic phenotype, reproduced dysregulation of the expression of genes associated with human BPD, including P2rx7 (Saul et al., 2012).

In summary, animal studies strongly indicate that decreased P2rx7 function leads to antidepressant

and mood stabilizing phenotype with altered stress reactivity and the opposite is observed in the case of the gain-of-function of P2rx7. In contrast, regarding anxiety, the available data are still controversial showing either no-change (Basso et al., 2008; Csölle et al., 2012a) or increased anxiety (Boucher et al., 2011) in the P2rx7 deficient animal model.

The question arises how the activity of P2X7 receptor leads to alterations in animal or human behavior. Although the answer is not complete yet, some details have already been uncovered. P2rx7s are widely expressed on hematopoietic cells and participate in the regulation of posttranslational processing of circulating cytokines, in particular IL-1β which are important mediators of depressive-like behavior (Dantzer et al., 2008). Therefore a reasonable possibility is that peripheral IL-1β could be a mediator of P2rx7 activation on mood-related changes. However, recently we have presented evidence that the deletion of P2rx7 in non-hematopoietic cells leads to the observed antidepressant phenotype. When bone marrow chimeras were generated that lacked the P2rx7 only in their hematopoietic compartment, no difference was found in TST and AH tests, indicating that the mood-stabilizing phenotype found in P2rx7-/- mice was not transferred to wild-type recipients with the engraftment of the P2rx7-/- bone marrow cells. Consequently, P2rx7s expressed on cells of hematopoietic origin, such as circulating immune cells, macrophages and microglia are not responsible for the detected alterations in mood in the absence of P2rx7 (Csölle et al., 2012a). Instead, P2rx7s expressed on other cell types, most likely on neurons or astrocytes, mediate the observed changes.

According to the current view, major depressive disorder and bipolar disorder are caused by plastic alterations of distributed networks involving a multiplicity of neurotransmitters and signaling pathways. Therefore in order to explore the impact of genetic deletion of P2rx7 on different signaling pathways on the level of gene expression we have performed a microarray analysis with Taq-man validation on amygdala samples collected from wild-type and P2rx7 deficient mice. The absence of P2X7 receptors lead to a widespread alteration of the gene expression in the limbic system, including the up- and downregulation of genes crucial for synaptic transmission and plasticity, such as various glutamatergic receptor subunits (Csölle et al., 2012). Consistent with these results, other studies have shown enhanced c-Fos expression in the amygdala and hippocampus of P2rx7-/- mice after repeated forced swim tests which indicates that the amygdala and the hippocampus are important target areas that mediate the effect of P2rx7 activation on emotional behavior (Boucher et al., 2011).

The marked gene expression changes affecting glutamatergic transmission detected in the absence of P2rx7 are consistent with previous results showing that the activation of P2rx7s in the brain leads to an increased glutamate release from nerve terminals and astrocytes. Therefore one possibility is that P2X7 receptor mediated glutamate release and subsequent activation of extrasynaptic NMDA receptors leads to changes in level of neurotrophic factors, such as BDNF and thereby causing enduring changes in neuronal plasticity, which might underlie pathological changes in behavior. The finding that we found an upregulation of NR2B subunits after genetic deletion of P2X7 receptors might reflect compensatory changes and points to this direction. This assumption is strengthened by numerous observations from animal and human studies indicating that excessive glutamate transmission might be involved in the pathophysiology of depressive disorders (Sanacora et al., 2008).

Other mechanisms, such as the alteration in extracellular levels of monoamines in the brain might also serve explanation for the role of P2rx7 in mood regulation. In our studies, changes in behavior were accompanied with corresponding alterations in brain monoamine levels in the hippocampus, amygdala and the striatum of *P2rx7*-/- mice (Csölle et al., 2012a). In line with the decreased behavioral despair in the FST and decreased immobility in the TST, an increase in basal norepinephrine level was found in the amygdala, which could be reproduced by P2rx7 antagonist treatment. As a neurochemical correlate of decreased hyperlocomotion, amphetamine induced elevation of dopamine content and release in the striatum were alleviated in *P2rx7* deficient mice. Finally, elevated 5-HT levels were detected in the hippocampus, which might underlie antidepressant-like behavior (Csölle et al., 2012b). Nevertheless, the causal relationship between the observed neurochemical and gene expression changes and behavioral alterations awaits further investigation.

## $A_1$ AND $A_{2A}$ ADENOSINE RECEPTORS IN DEPRESSION

Although the accumulating data is far less than in case of P2rx7, animal studies indicate that the adenosinergic signaling system is also involved in the regulation of mood related behavior. This is not surprising

as $A_1$ and $A_{2A}$ adenosine receptors are expressed in the limbic system and have profound pre- and post-synaptic modulatory actions on both glutamatergic and monoaminergic transmission (Burnstock et al., 2011). Whereas adenosine agonists and drugs, which increase adenosine bioavailability, such as adenosine deaminase inhibitors mimic depressive behavior (Woodson et al., 1998), adenosine antagonists, such as caffeine, the non-selective adenosine antagonist or SCH412348, the selective $A_{2A}$ receptor antagonist have clear antidepressant effect in behavioral paradigms, i.e. in the FST and TST (Hodgson et al., 2009, El Yacoubi et al., 2003). As far as the underlying receptor subtype is concerned, the involvement of both $A_1$ and $A_{2A}$ receptors seems likely (Kaster et al., 2007).

## CONCLUSION

In conclusion, rapidly emerging knowledge points to the regulatory role of purinergic signaling in mood related behavior, stress reactivity and their pathological alterations.

Whereas genetic research have not always resulted consistently replicable findings in favor of the involvement of P2rx7 mutations in the genetic susceptibility to mood disorders, animal studies clearly indicates that emotional behavior can be affected by targeting P2rx7. Nevertheless, further rapid progress is expected on this field in the next years, which might pave the pathway to the therapeutic utilization of P2rx7 or other promising purinergic receptors, enzymes and transporters in the neuropsychopharmacological therapy.

**Acknowledgments**. This study was supported by grants from the Hungarian Research and Development Fund (NN79957) and the Hungarian Medical Research Council (ETT 05-102).

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# A purinerg jelátviteli rendszer szerepe depressziós kórképekben

A purinerg jelátviteli rendszer az adenozin-5'-trifoszfát (ATP) és extracelluláris lebontási terméke, az adenozin szintéziséért, raktározásáért, felszabadulásáért és extracelluláris inaktivációjáért felelős enzim- és transzporter molekulákat, valamint a hatásaikat közvetítő purinreceptorokat foglalja magába. Az ATP hatásait ionotróp P2X valamint metabotróp P2Y receptorok közvetítik, az adenozin hatásaiért P1 adenozinreceptorok felelősek. A purinerg jelátviteli pályák széles körben kifejeződnek a központi idegrendszerben és részt vesznek a normál és patológiás neuronális funkciókban. A P2X receptorok közül a neuropszichiátriai alap- és klinikai kutatásokban különösen nagy figyelem övezi a P2X7 receptort (P2rx7), amely markáns hatásokat közvetít központi idegrendszeri betegségek állatmodelljeiben, és amelynek szerepe mint a genetikusan determinált hangulatbetegségek hajlamosító génje is felvetődött. Bár a genetikai kutatások eredményei a különböző mintákon nem mindig következetesen reprodukálódtak, több tanulmány is kimutatta a humán P2X7 gén (*P2RX7*) SNP variánsainak szignifikáns asszociációját major depresszióval és bipoláris betegséggel. Az állatkísérletes adatok tanúsága alapján a P2rx7 hiánya vagy farmakológiai blokádja antidepresszáns fenotípushoz vezet, csökkent válasz tapasztalható a mánia állatkísérletes paradigmáiban és megváltozik a stresszreaktivitás is. A P2rx7 hangulatra és magatartásra gyakorolt hatásainak magyarázataként szolgálhat, hogy a receptor aktivációja fokozott glutamát-felszabaduláshoz vezet, ez aktiválja az extraszinaptikus NMDA receptorokat és tartós változásokat okoz a neuroplaszticitásban. Emellett a monoaminerg rendszer és a HPA axis diszregulációja is szerepet játszhat a kialakult változásokban. A P2rx7-en kívül az adenozin $A_1$ és $A_{2A}$ receptor gátlása is közvetít antidepresszív hatást állatkísérletekben. Összefoglalva, bár néhány ellentmondásos adat is van az eddigi eredmények közt, a purinerg rendszer fontos új terápiás lehetőségeket rejt a hangulatzavarok kezelésében.

**Kulcsszavak**: ATP, adenozin, purinerg receptorok, P2X7 receptor, depresszió, bipoláris betegség