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Review

# The roles of purinergic signaling in psychiatric disorders

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**Ecto-purines and ecto-pyrimidines are present in the extracellular space of the central nervous system (CNS). Together with P1 and P2 receptors and nucleotides metabolizing ecto-enzymes, they make signaling system involved in neurotransmission, the modulation of sensory signals, including pain stimuli conduction, and the induction of apoptosis and necrosis of the cells. Purines and pyrimidines have a dual effect: positive (neuroprotective) of nucleosides, and negative (pro-inflammatory and pro-apoptotic) of nucleotides. Adenosine-5′-triphosphate (ATP) in the CNS triggers the pro-inflammatory reactions, predominantly by activation of the P2X7 receptor, which results in production and release of pro-inflammatory cytokines. In contrast to ATP, adenosine acts generally as an anti-inflammatory agent and plays an important role in neuroprotection. Currently, it is believed that the initiation of CNS diseases, including mental disorders, is caused by any imbalance between the concentration of ATP and adenosine in the extracellular space. Genetic tests provide also the evidence for the participation of purinergic signaling in psychiatric disorders. It is believed that any action leading to the effective increase of adenosine concentration: activation of nucleotide metabolizing ecto-enzymes (mainly NTPDases — nucleoside triphosphate diphosphohydrolases), inhibition of adenosine deaminase and/or adenosine kinase activity as well as therapies using P1 receptor agonists (adenosine or its analogues) might be beneficial in therapy of psychiatric disorders.**

**Key words:** Ecto-purines, P receptors, central nervous system diseases, mental disorders, therapy of psychiatric disorders

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## PURINERGIC SIGNALING IN THE CENTRAL NERVOUS SYSTEM

Modern tendencies in scientific research aim at finding the specific biochemical markers for the pathophysiological conditions and diseases. It is commonly believed that finding such a marker may precede the diagnosis of the disease in the future or be of great importance in differential diagnosis, also in the case of psychiatric disorders. The experimental results indicate that elements of the purinergic signaling system: purines, purinoreceptors and purines metabolizing ecto-enzymes are involved in psychophysiological processes in health and disease conditions. Therefore, there are indications that purinergic compounds could potentially be markers of psychopathological processes.

Ecto-purines and ecto-pyrimidines are present in the extracellular space of the central nervous system (CNS), where they act as signaling molecules in many physiological and pathological processes. Ecto-nucleotides are involved in neurotransmission, the propagation of inflammatory processes, modulation of sensory signals, including the conduction of pain stimuli and neuroprotection (Burnstock, 2008; Burnstock *et al.,* 2011). In 1978, the purinoreceptors were divided into P1 metabotropic receptors activated exclusively by adenosine (Burnstock, 1978) and P2 receptors activated by adenine nucleotides — ATP, ADP and pyrimidine ones — UTP, UDP. P2 receptors are divided into ionotropic P2X and metabotropic P2Y receptors, what was corfirmed by cloning (Burnstock & Kennedy C, 1985; Ralevic & Burnstock, 1998) (Fig. 1).

ATP and ADP are released to the extracellular space mainly through exocytosis, also connexin and pannexin channels, or cell lysis (Lazarowski, 2012). The concentration of ecto-nucleotides, and thus nucleotide signaling, is controlled by ecto-nucleotidases and nucleotide kinases. ATP and ADP are hydrolysed by nucleoside triphosphate diphosphohydrolases (NTPDases) and ecto-5'-nucleotidase to adenosine — another potent signaling molecule — Fig. 1. Adenosine is released to the extracellular space directly from the neurons and astrocytes by nucleoside transporters, but its largest amount is produced through the ecto-nucleotidases-mediated degradation of ATP (Aliagas *et al.*, 2013). Adenosine outside the cell is phosphorylated to AMP by adenosine kinase or deaminated to inosine by adenosine deaminase (Wardas, 2008) – Fig. 1.

The presence of purinergic receptors as well as ecto-enzymes activity were identified in different brain areas, such as cortex, hippocampus, basal ganglia, mesencephalon, thalamus, cerebellum, and many others — Table 1. Studies have shown the presence of purinoreceptors (P2X2, P2X7 and P2Y2) in the ventricular system of the brain — on the cells of choroid plexus of the lateral ventricles and at the surface of neurons contacting with CSF (cerebrospinal fluid-contacting neurons, CFCN) (Stoeckel *et al.*, 2003; Czarnecka *et al.*, 2011). Neurons and astrocytes express all subtypes of P receptors, while microglial cells contain P2X4, P2X7, P2Y6 and P2Y12 receptors (Di Virgilio, 2007; Di Virgilio *et al.*, 2009) and adenosine receptors, excluding subtype A2B (Cieślak *et al.*, 2011).

ATP and adenosine through P2 and P1 receptors activation, act antagonistically and therefore regulate the CNS functions. Under physiological conditions processes initiated by ATP-mediated P2 receptor activation

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**Abbreviations**: ATP, adenosine-5′-triphosphate; CNS, central nervous system

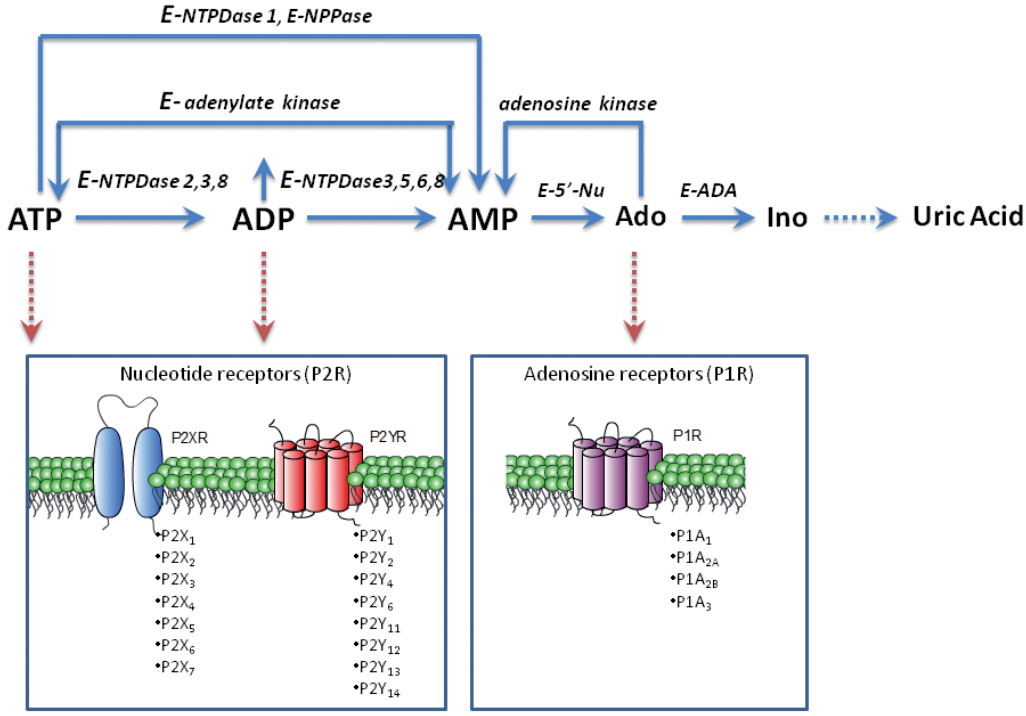


**Figure 1. Metabolism and receptors of extracellular adenosine derivatives.**
Extracellular ATP (agonist of P2 receptors) may be metabolised by hydrolases: ecto-NTPDases (E-NTPDases), ecto-NPPases (E-NPPases) and ecto-5′nucleotidase (E-5′NU) and by adenylate kinase to ADP (agonist of P2). Adenosine (agonist of P1 receptors) is phosphorylated by adenosine kinase to AMP or degraded by adenosine deaminase (E-ADA) and other enzymes to final product: uric acid.

(for example glutamate secretion or inflammatory processes propagation (Cotrina *et al.*, 2000)) are inhibited by adenosine formed due to its degradation and activating adenosine P1 receptors (Frau *et al.*, 2011). However, the problem of this antagonism is more complex. Adenosine may in turn stimulate the release of glutamate from astrocytes *via* A2A receptors (Nishizaki, 2004). For synaptic transmission, activation of A1 receptors (ADORA1) exerts an inhibitory effect, whereas adenosine *via* 2A receptor subtype (ADORA2A), coupled to a stimulatory G protein, enhances excitatory neurotransmitter release. Moreover, the genetic variation of the ADORA2A gene results in changing the balance of the nucleotide/nucleoside signaling system (Shinohara 2013). Haplotype A causes high expression of the ADORA2A mRNA and ADORA2A protein, as well as high production of cAMP in response to adenosine, in an additive manner (diplotype AA>AB>BB). Thus, the adenosine activation of inhibitory ADORA1 will not compensate the stimulatory effect of ADORA2A activation and the equilibrium is shifted towards the stimulatory action (Saitoch, 2014). Generally, there must be a balance between the processes of the nervous system stimulation and quenching, and any disturbance leads to different disturbances disorders and diseases of the nervous system.

Co-localization of different types of purinergic receptors with ecto-nucleotidases activity on the cell membranes in the adjacent areas of CNS enables the precise regulation of nucleotide/nucleoside concentration, signaling and intercellular cross-talking.

Distribution of ecto-nucleotidases in the brain is well recognized in rats, less is known about the localization of these enzymes in humans (Langer *et al.*, 2008). The presence of different types of NTPDase, 5'-nucleotidase or ecto-adenosine deaminase was confirmed for most cell types throughout the CNS. Studies have shown the presence of NTPDase activity (mainly NTPDase1), on nerve endings membranes and on the surface of microglia cells (Robson *et al.*, 2006; Sperlagh& Illes, 2007). Expression of ecto-5'-nucleotidase was shown on astrocytes, oligodendrocytes and microglia (Sperlagh& Illes, 2007; Cieslak *et al.*, 2011).

It was also shown that enzymes activity is different in distinct areas of the brain: the neuronal cell membranes of the cerebral cortex and hippocampus present the high activity of NTPDase1 and NTPDase2, while the activity of these enzymes in the cerebellum and spinal cord (medulla oblongata) is minor (Kukulski *et al.*, 2004).

It is assumed that purinergic signaling may be important in some psychophysiological and psychopatophysiological states, such as fear and anxiety, and behaviors such as: memory and learning, sleep and wakefulness, movement, food intake, mood and anxiety, agression and motivation (Krügel *et al.*, 2001; Burnstock, 2008). Also in the case of psychophysiological processes it is important to maintain a balance between the ATP-mediated excitation and adenosine-mediated excitation or quenching. The results of recent studies on the purinergic signaling have already been used in the treatment of certain neurological diseases (e.g. Parkinson's disease and ischemic stroke), and may be used in the therapy of multiple sclerosis, epilepsy and migraine headache (Cieślak *et al.*, 2008; Burnstock, 2008; Cieślak *et al.*, 2015). The authors speculate that purinergic signaling may also participate in the pathophysiology of certain mental disorders.

## BIPOLAR AFFECTIVE DISORDERS

Mood disorders include depression and manic episodes. The involvement of genetic background in bipo-

**Table 1. Purinergic receptors and their distribution in the nervous system (compiled from Burnstock, 2007; Burnstock, 2008; Kovács *et al*., 2013; Del Puerto *et al*., 2013).**

| | |
|---|---|
| P1 receptors | |
| A1 | widely distributed – high expression levels in cerebellum, hippocampus, cortex, thalamus |
| A2A | brain neurons, astrocytes, high levels in dopamine-rich regions, low levels in hippocampus |
| A2B | widely distributed but low expression levels |
| A3 | neurons of cerebellum and hippocampus, astrocytes, low expression level |
| P2X receptors | |
| P2X1 | cerebellum, dorsal horn spinal neurons, astrocytes |
| P2X2 | CNS neurons, autonomic and sensory ganglia, astrocytes |
| P2X3 | sensory neurons, nucleus tractus solarius neurons, sympathetic neurons, astrocytes |
| P2X4 | CNS neurons, astrocytes, microglia |
| P2X5 | spinal cord, astrocytes |
| P2X6 | CNS neurons, motor neurons in spinal cord |
| P2X7 | neurons, astrocytes, microglia, apoptotic cells |
| P2Y receptors | |
| P2Y1 | neurons and glial cells |
| P2Y2 | Astrocytes |
| P2Y4 | brain neurons and glial cells |
| P2Y6 | activated microglia |
| P2Y11 | brain neurons and oligodendrocytes |
| P2Y12 | glial cells, spinal cord |
| P2Y13 | brain neurons and oligodendrocytes |
| P2Y14 | discrete brain regions |

lar affective disorders is estimated to be approximately 79–93% (McGuffin *et al*., 2003). The chromosome region 12q24.31 is extremely important for bipolar disorders, unipolar disorders and anxiety (Barden *et al*., 2006; Green *et al*., 2007; Erhardt *et al*., 2007). Few studies have suggested that it also may contain genes for receptors P2X7 and P2X4, that indicates the purinergic signaling involvement in the pathology of bipolar disorders.

The P2X7 receptor gene is highly polymorphic, present in various brain areas on the surface of neurons, astrocytes and microglia (Fuller *et al*., 2009). Its high expression was found in brain structures such as subthalamic nucleus, hypothalamus and substantia nigra, the functions of which are probably related to the occurrence of bipolar disorders (Backlund *et al*., 2012). Studies on polymorphism of the region 12q24.31 in humans have shown that non-synonymous single nucleotide polymorphisms (SNPs) within the P2X7 receptor gene affects the activity of the receptor, and is accompanied by major depressive disorders (MDD) and borderline personality disorder (BPD) (Hejjas et al., 2009; Soronen *et al*., 2011). Mutations within the P2X7 receptor gene predisposed to mood disorders consistently in three independent clinical cohorts. Moreover, the same risk alleles resulted in clinically significant differences in outcome of patients with major depressive and bipolar disorder (Soronen *et al*., 2011). The results of these genetic studies have raised a lot of controversy because other experiments proved that Gln460Arg (rs2230912) and His155Tyr (rs208294) P2X7 receptor gene polymorphisms are not associated with depressive disorders (Viikki *et al*., 2011).

In mice lacking the P2X7 receptor ($P2rx7^{-/-}$) in the brain, significant decline in depressive-like behavior and reduced locomotor hyperactivity after the administration of amphetamine were observed (Csölle *et al*., 2013). According to Backlund and co-authors P2X7 receptor gene expression is associated with bipolar disorders, especially in the form of a rapid cycling (rapid cycling bipolar disorder, RCBD), when 4 or more periods of depression or mania occur in a year (Backlund *et al*., 2012). These authors have found that sleep deprivation causes an increase in receptor gene expression in healthy subjects, and that in type 1 of bipolar disorders functional polymorphism of P2X7 receptor gene accompanies the occurence of the rapid cycling form (Backlund *et al*., 2012). Furthermore, expression of this receptor is associated not only with depression, but also with anxiety disorders and cognitive symptoms observed in mania (Erhardt *et al*., 2007; Hejjas *et al*., 2009; Backlund *et al*., 2011; Backlund *et al*., 2012). Thus, genetic studies clearly suggest a role of P2X7 receptor in the behavior disorders. It is unclear, however, how the activation of the receptor may interfere with the etiopathogenesis of depression and bipolar disorders.

One of the considered mechanisms is the increased release of glutamate following P2X7 receptor activation by ATP, which according to some authors, secondarily leads to the symptoms of depression (Malarkey & Parpura, 2008). In the CNS glutamate is the major excitatory neurotransmitter which affects the activity of neurons (Wardas, 2008). The glutamate receptors are involved in various processes in the brain, such as memory, the development of synaptic plasticity and locomotor activity (Collingridge, 1994; Collingridge & Bliss, 1995; Bannerman *et al*., 1995; Watkins & Collingridge, 1995).

Inflammation could also play a role in etiology of depression and bipolar disorders (Raison & Miller, 2013; Martinez *et al*., 2012). This pro-inflammatory effect of ATP is realized mostly by P2X7 receptor activation, as well as P2Y6 and P2Y11 receptors (Cieślak *et al*., 2011). The prolonged inflammation underlying the nervous system disorders is widely described in the literature. However, the involvement of inflammatory processes in the pathogenesis of psychiatric disorders is unclear.

It is suggested that in depression and bipolar disorders the A1- and A2AR-mediated modulation of concentration of such neurotransmitters as serotonin, corticotrophin, cortisol, corticosteron and glutamate may play an important role (Gomes *et al*., 2011; Machado-Vieira *et al*., 2002).

The connection between purinergic signalling and manic episodes has been suggested by researchers who hypothesized that the appropriate balance between adenosine (as neuromodulator) and ATP (as neurotransmitter) regulates a variety of behaviors such as sleep, motor activity, cognitive processes, memory, aggressive behavior and social interaction (Burnstock, 2007; Burnstock, 2011; Wei *et al*., 2011).

The special role in the antidepressant-like action of adenosine is attributed to the activity of A1 adenosine receptor (Machado-Vieira *et al*., 2002). There are several pieces of evidence showing that adenosine A1 receptors are able to modulate responses via NMDA receptors. Activation of adenosine A1 receptor and inhibition of the L-arginine-nitric oxide-cGMP (L-arginine-NO-cGMP) metabolic pathway results in the inhibition of postsynaptic NMDA (N-methyl-D-aspartate) receptor (Cunha, 2005; Fredholm *et al*., 2005; Kaster *et al*., 2012). More-

over, activation of A1 receptors triggers the reduction in the release of the excitatory neurotransmitters, particularly glutamate, and therefore is able to regulate indirectly the presynaptic NMDA receptor (Cunha, 2005; Fredholm *et al.*, 2005). Besides the purine derivatives, such compounds as folic acid, ifenprodil, magnesium or lectins obtained from *Canavalia brasiliensis*, exhibit antidepressant-like action, mainly by inhibitory effect on the NMDA receptors, by lowering the concentration of nitric oxide (NO) and reduced synthesis of cGMP (Brocardo Pde *et al.*, 2008; Poleszak *et al.*, 2013; Pochwat *et al.*, 2014; Rieger *et al.*, 2014).

Preliminary evaluation of anti-depressant agents action is carried out mostly in mice. Based on the forced swimming test (FST) in mice it was proved that the concomitant use of adenosine (or antagonist of NMDA receptors — MK-801) and imipramine, tricyclic antidepressant, resulted in formation of an additive anti-depressive effect (Kaster *et al.*, 2012). Also chronic administration of antidepressants has reduced the reactivity of NMDA receptors (Palucha & Pilc, 2005). The similar results were obtained earlier by Maj and the collaborators. The authors of this study explained an additive effect of MK-801 and imipramine by blocking NMDA receptor and serotonin/noradrenaline reuptake inhibition (Maj *et al.*, 1992). In animal studies, it was found that adenosine analogues showed sedative, anticonvulsant, anti-aggressive and antipsychotic activity (Lara *et al.*, 2006).

Bettio and colleagues reported, that an antidepressant effect by interaction with the NMDA receptors and L-arginine-nitric oxide (NO)-cGMP and PI3K-mTOR pathways is also exerted by guanosine (Bettio, 2012). Additionally, guanosine acts as neuroprotective agent, increasing the uptake of glutamate by astrocytes (Lara *et al.*, 2001; Schmidt *et al.*, 2000; Schmidt *et al.*, 2008).

Immunohistochemical studies confirmed colocalization of A2A and D2 receptors and A1 and D1 receptors within the striatum and basal ganglia, which provides a balance between the action of adenosine and dopamine (Ferré, 1997; Azdad *et al.*, 2009). Analyses of co-localization of dopamine and adenosine receptors outside the striatum (on blood platelets) showed that in patients with bipolar disorders an increase in A2A receptor expression is followed by an increase in its affinity and reactivity (Martini *et al.*, 2006). It is suggested that these patients are more sensitive to adenosine, that is beneficial in therapy. However, this phenomenon may be explained as less effective compensative mechanism present on the cells beyond the CNS.

Despite the strong evidence indicating the involvement of purinergic receptors in the affective bipolar disorders or depression, the data concerning nucleosides and nucleotides concentration in blood and cerebrospinal fluid of patients is still lacking. Over the years, research results showed that there are changes in levels of uric acid — the end product of adenine nucleotides metabolism (Salvadore *et al.*, 2010). The first reports concerning the involvement of purinergic signaling in bipolar disorders can be found in the publication of Kraepelin, who described for the first time the relationship between the excretion of uric acid and symptoms of mania (Kraepelin, 1921). In 1968, Anumonye found that remission of manic symptoms is accompanied by increased excretion of uric acid (Anumonye *et al.*, 1968). The relationship between symptoms of mania and changes in the nucleotide derivatives concentration was confirmed currently, while emphasizing that high serum levels of uric acid is reflected in the increased concentration of the compound in the cerebrospinal fluid (Machado-Vieira *et al.,* 2002; Salvadore *et al.*, 2010; Bowman *et al.*, 2010). In case of depression and bipolar disorder uric acid levels were determined only in serum. The results indicate that depression is accompanied by lowered while affective disorders by the increased concentration of this compound (Kesebir *et al.*, 2014). Perhaps the determination of uric acid in the blood becomes a screening test designed to detect patients during the manic phase (Machado-Vieira *et al.*, 2012).

Allopurinol is a drug that has been used in the treatment of gout for a long time, it inhibits the activity of xanthine oxidase -— an enzyme necessary for uric acid formation. The results indicate that allopurinol may be an effective drug in the treatment of mania, especially while increasing the concentration of uric acid in the blood, which occurs in gout (Machado-Vieira *et al.*, 2001). In a randomized blinded study on 82 patients, they were treated for eight weeks with allopurinol (300 mg daily) or placebo together with lithium and haloperidol (Akhondzadeh *et al.*, 2006). This study showed that allopurinol exerted significant anti-manic effects, which directly confirmed that the disorder of purine metabolism occurs in mania (Akhondzadeh *et al.*, 2006).

## SCHIZOPHRENIA

The symptoms of schizophrenia are divided into positive ones, such as hallucinations and delusions, negative ones, such as: autism, alogia and avolition and cognitive symptoms (Schulz & Andreasen, 1999). Since the etiology of the disease is yet not fully understood, the efforts focus on explaining it in the molecular field. Current hypotheses concerning the etiology of schizophrenia imply the hyperfunction of dopaminergic area within the cerebral cortex and the mesocorticolimbic area and hypofunction of glutamatergic afferents in the prefrontal cortex to the ventral tegmental area (Fuxe *et al.*, 2007; Burnstock *et al.*, 2011). A leading role in the etiology of schizophrenia has been attributed to dopamine (Lau *et al.*, 2013). The participation of dopamine in the etiology of schizophrenia is proved by: anti-psychotic effects of neuroleptics such as antagonists of the dopamine receptor (D2) and psychosis-leading effects of amphetamine and steroids, which stimulate the dopaminergic system. In addition, patients with schizophrenia have an elevated fraction of D2 receptors occupied by endogenous dopamine than normal control subjects (Abi-Dargham *et al.*, 2000). The action of dopamine, however, does not fully explain the pathomechanism of schizophrenia, which is confirmed by the fact that antipsychotic drugs do not affect the negative and cognitive symptoms, and many patients do not respond completely to treatment with D2 receptor antagonists (Wardas, 2008). In our opinion the key factor in the etiology of schizophrenia is adenosine, that regulates secretion of other transmitters and modulators such as: dopamine, glutamate, γ-aminobutyric acid (GABA) and serotonin (Wardas, 2008; Lau *et al.,* 2013). Immunohistochemical studies confirmed colocalization of A2A and D2 receptors and A1 and D1 receptors within the striatum and basal ganglia, which provides a balance between the action of adenosine and dopamine (Ferré, 1997; Azdad *et al.*, 2009). Antagonistic interactions of adenosine and dopamine in the striatum affect, in particular, the motor efficiency in human (Cieślak *et al.*, 2008). This phenomenon is used in the treatment of Parkinson's disease. As yet unknown is the importance of co-localization of A2A and D2 receptors as well as A1 and D1 ones in the brain on psychophysiological and

**Table 2. The patophysiological effects exerted through adenosine receptors activation in the central nervous system.**

| Receptor | Second messenger | Patophysiological effects |
|---|---|---|
| A1 | ↓cAMP<br>↓$IP_3$<br>↑$K^+$, ↓$Ca^{2+}$ | hyperpolarization of neurons, sedative, anticonvulsant, anxiolytic, locomotor depressant |
| A2A | ↑cAMP | inhibition of dopamine-induced effects, pain modulation, immune system modulation |
| A2B | ↑cAMP<br>↑$IP_3$ | modulation of the immune system |
| A3 | ↑cAMP<br>↑$IP_3$ | modulation of inflammatory response, locomotor depressant |

psychopathological processes. On GABAergic neurons D2 receptors coexpress with adenosine A2A and cannabinoid CB1 receptors (Urigüen *et al.*, 2009). The antipsychotic drugs induce down-regulation of CB1 receptors, affect GABA release and contribute to the normalization of cognitive function.

Effects of caffeine, which is a non-selective antagonist of adenosine receptors results in exacerbation of psychotic symptoms and indirectly confirms the involvement of adenosine in the course of schizophrenia (Lucas *et al.*, 1990). In addition, psychotic symptoms are frequent in patients poisoned with theophylline, which is also a non-selective antagonist of adenosine receptors (Lara *et al.*, 2000). The recent publications on the adenosine theory of schizophrenia suggest that maintenance of cortical/hippocampal adenosine homeostasis is essential for effective spatial memory (Singer *et al.*, 2013).

To comprehensively analyse the purinergic background of schizophrenia we cannot ignore the ecto-nucleotidases and other ecto-enzymes involved in the nucleotides/nucleosides metabolism. The results of Brunstein and colleagues demonstrated the increased activity of adenosine deaminase, which is involved in the conversion of adenosine to inosine, in the serum of patients with schizophrenia (Brunstein *et al.*, 2007). Moreover, the postmortem studies showed noticeably decreased NTPDase activity (both towards ATP and ADP hydrolysis) in the putamen region, while the activity of ecto-5'-nucleotidase and alkaline phosphatase remained unchanged. In addition, these studies showed diverse expression of ecto-nucleotidases in neurons, glial cells and blood vessels (Aliagas *et al.*, 2013). High NTPDase and ecto-5'-nucleotidase activity on neurons and glial cells confirms the participation of these cells in the extracellular conversion of adenosine. Reduced NTPDase activity in the striatum and an increase in the activity of adenosine deaminase in the blood may explain the decreased levels of adenosine in patients with schizophrenia. Thus, the hypothesis that in the brain of patients with schizophrenia, there is a predominance of the dopaminergic system (hyperdopaminergic state) emerging from the decrease in the extracellular concentration of adenosine (hypoadenosinergic state) is still actual (Lara *et al.*, 2000; Aliagas *et al.*, 2013; Villar-Menéndez *et al.*, 2014). Adenosinergic tone can be reduced or increased by up- and down-regulation of adenosine kinase (ADK) expression, whatraises hopes for the development of new methods for schizophrenia treatments (Singer *et al.*, 2013).

The particular attention is also paid to the role of A1 and A2A receptors, which are expressed at high levels in different regions of the brain (Table 1) and act through different second messengers — Table 2.

The adenosine receptors often form heterodimers with metabotropic receptors for other transmitters and therefore modulate their properties, i.e. affinity for agonist. Several types of such dimers have been described: A1/D1 (Maggio *et al.*, 2009), A2A/D2, A2A/D3 and A2A/mGluR5, and the recently discovered A1/A2A (Ciruela *et al.*, 2006; Fuxe *et al.,* 2007; Cieślak *et al.*, 2008). It is believed that the attachment of adenosine to A1/D1 or A2A/D2 heteromeric complex causes a decrease in the affinity of dopamine receptors for their agonist (Franco *et al.*, 2000). Moreover, the activation of adenosine receptors influences the release of neurotransmitters: at physiological concentrations of adenosine the presynaptic A1 receptor activation results in inhibition of glutamate and dopamine release, while A2A receptor activation increases the release of these transmitters (Machado-Vieira *et al.,* 2002; Burnstock, 2011). In the high concentrations of adenosine A2A receptor reduces A1 receptor affinity for adenosine (Quarta *et al.,* 2004) — Fig. 2.

It is believed that altered metabolism of purines, leading to a reduction in the concentration of extracellular adenosine, may lead to an imbalance between adenosine and dopamine, and the predomination of the dopaminergic system. A probable model for studying these relationships may be blood platelets. Studies of Martini and co-authors have shown that human A2A and D2 receptors are co-expressed in the heteromeric complexes also on the platelets. Analyses of blood platelets of schizophrenic patients can become an useful assay to monitor the interactions of adenosine and dopamine (Martini *et al.*, 2006). Unfortunately, there is lack of such analyses up to date.

It is believed that the blockade of dopamine D2 receptors is an important feature of the action of neuroleptic drugs, what can also suggest the role of D2 receptors in the etiology of schizophrenia (Wardas, 2008; Kapur *et al.*, 2003). This is confirmed by the fact that the administration of amphetamine, which increases the release of dopamine, induces psychotic symptoms

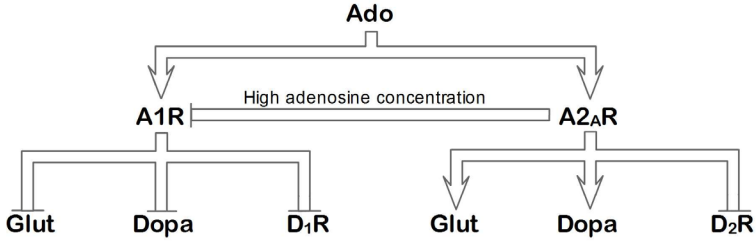


**Figure 2. The influence of adenosine and its receptors activation on the release of glutamate and dopamine and on the dopamine receptors affinity.**
Activation of A1 and A2A receptor lead to regulation (up or down) of glutamate and dopamine release and decrease of dopamine receptors affinity.

(Cherkasova, 2014). In the striatum and the nucleus accumbens region adenosine and dopamine act antagonistically, therefore adenosine receptor agonists have similar behavioral symptoms such as dopamine antagonists (Ferre, 1997; Cieslak *et al.*, 2008). According to this, it can be assumed that the use of antagonists of D2 receptors simultaneously with the A2A receptor agonists or agonists of A2A receptor only may be an effective treatment for schizophrenia.

The decreased concentration of adenosine leads to the increased sensitivity of glutaminergic system. Increased activity of the NMDA receptor triggers the escalation of psychotic, negative and cognitive symptoms of schizophrenia. The studies of Azdad and collaborators have shown that membrane potential transitions in striatal, especially accumbens neurons are controlled by D2 and A2A receptors through specific protein-protein interactions including A2A-D2 receptors heteromerization and regulate NMDA-mediated excitation (Azdad *et al.*, 2009). Simultaneous inhibition of glutamate release through activation of the presynaptic A1 receptors and decrease in the activity of NMDA receptors through activation of postsynaptic A1 receptors (Burnstock *et al.*, 2011; Aliagas *et al.*, 2013) postulates participation of glutamate/adenosine system in the etiology of schizophrenia (Olney & Farber, 1995; Coyle, 2012).

In animal models, the A1 receptor agonists inhibit the release of glutamate from neurons surrounding the forebrain, especially in the area of the prefrontal cortex (Marek, 2009). The results of this study are consistent with the hypothesis that drugs that inhibit the release of glutamate from neuronal limbic circuits, such as the mGlu2 receptor agonists, may be effective antipsychotics (Marek, 2009).

Genetic studies conducted by Gotoh and collaborators indicated that the A1 receptor gene polymorphism may be associated with pathophysiological mechanisms underlying the schizophrenia. The authors suggest that the A1 receptor gene polymorphism may be a useful marker of schizophrenia (Gotoh *et al.*, 2009).

A2A receptor activation inhibits the release of γ-aminobutyric acid (GABA) and GABAergic transmission, with a simultaneous increase of GABAergic transmission in the globus pallidus *via* the cAMP-dependent mechanism (Cieślak *et al.*, 2008). It has been shown that patients with schizophrenia have the increased activity (expression) of A2A receptors in the striatum (Deckert *et al.*, 2003). Genetic variation of the ADORA2A gene is associated not only with caffeine sensitivity. Haplotype A is known to be associated with impaired phenotype with the minor or severe CNS disturbances: anxiety induced by caffeine, increased anxiety (Cornelis *et al.*, 2007; Gajewska, 2013; Hohoff, 2014), hyperactivity disorder (Molero, 2013), childhood encephalopathy (Shinohara, 2013), and also schizophrenia (Jagannathan, 2010). The studies of Villar-Menéndez have shown that about fifty percent of patients suffering from schizophrenia have reduced A2AR, at the transcriptional and translational levels (Villar-Menéndez *et al.*, 2014). On the other hand, Hwang and colleagues reported the increased adenosine A2A receptor expression on perivascular astrocytes in the hippocampus of patients with schizophrenia. The presence of this receptor on lymphocytes, suggests its involvement in inflammatory processes (Hwang *et al.*, 2013).

There are only few reports about the possible involvement of ATP in the etiology of schizophrenia. It is believed that ATP activating P2 receptors, particularly P2Y1, causes an increase in dopamine release in the nucleus accumbens (Krugel *et al.*, 2001; Burnstock *et al.*, 2011). Experimental studies on animals have shown that the local administration of P2 receptor antagonist caused a decrease in dopamine release in the nucleus accumbens (Krugel *et al.*, 2001). These results suggest that ATP has a physiologically relevant function in modulating dopaminergic transmission in the mesolimbic system.

## CONCLUDING REMARKS

The experimental results indicate that elements of the purinergic signaling system: purines, purinoreceptors and purines metabolizing ecto-enzymes are involved in psychophysiological processes in health and disease conditions. Despite the lack of comprehensive studies on purine levels in the blood or cerebrospinal fluid of patients with mental disorders, there are indications that some of these compounds (i.e. uric acid), could potentially be markers of psychopathological processes. In patients with altered levels of uric acid, further research focused on nucleotides and nucleosides concentration, ecto-enzymes involved in the metabolism of these compounds and their relationship with markers of inflammation and immune disorders may be recommended.

Currently, it is believed that an imbalance between the concentration of ATP and adenosine in the extracellular space underlies many pathological processes leading to the CNS diseases. The increasing concentration of ecto-ATP in the brain is the danger signal that induces inflammation and apoptosis and stimulation of glutamate release followed by depressive symptoms. To interrupt negative processes initiated by ATP it is necessary to find selective antagonists of ATP-dependent receptors and/or activate ATP conversion to adenosine, which has potent anti-inflammatory activity.

In the brain of patients with schizophrenia, there is a significant decrease in the extracellular concentration of adenosine (hypoadenosinergic state), which effects from the decreased NTPDases activity and increased adenosine deaminase activity. It consequently leads to the predominance of the dopaminergic system (hyperdopaminergic state).

Restoring the balance of the adenosine/dopamine requires: 1/ the use of adenosine receptor agonists, 2/ the use of dopamine antagonists, and 3/ the increase in the concentration of adenosine by stimulating its synthesis and reducing the rate of its degradation.

Difficulties in the development of effective drug to treat schizophrenia base on the fact that all known A2A receptor agonists have significant peripheral side effects, which prevent their use in experimental studies. In view of the adverse effect of A2A receptor agonists on locomotor functions, their combination with D2 receptor antagonists will possibly reduce the incidence of extrapyramidal side effects and will be effective antipsychotics.

Dipyridamole (adenosine transport inhibitor) and allopurinol (xanthine oxidase inhibitor) will cause an increase in the concentration of endogenous adenosine by inhibiting its uptake and metabolic elimination. Both drugs have a beneficial effect in schizophrenia either administered separately or in combination with haloperidol. Regulation of the activity of enzymes involved in the conversion of adenosine (activation of ecto-5'-nucleotidase, and inhibition of adenosine kinase and deaminase) can increase the concentration of this compound in the CNS, and thus also may be an effective treatment for schizophrenia. However, the development of pharmacological treatment of mental disorders is associated with

many difficulties. An important barrier is the lack of a suitable experimental model. Therefore, application of purinergic signaling concerning knowledge may be difficult in practice due to the difficulties in objective evaluation of therapeutic chemicals in relation to psychiatric conditions.

## REFERENCES


Abi-Dargham A, Rodenhiser D, Printz, Y, Zea-Ponce R, Gil L, Kegeles R, Weiss T, Cooper J, Mann R, Van Heertum J, Gorman M, Laruelle (2000) Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci USA* **97**: 8104–8109.

Akhondzadeh S, Milajerdi MR, Amini H, Tehrani-Doost M (2006) Allopurinol as an adjunct to lithium and haloperidol for treatment of patients with acute mania: a double-blind, randomized, placebocontrolled trial. *Bipolar Disord* **8**: 485–489.

Aliagas E, Villar-Menéndez I, Sévigny J, Roca M, Romeu M, Ferrer I, Martín-Satué M, Barrachina M (2013) Reduced striatal ecto-nucleotidase activity in schizophrenia patients supports the "adenosine hypothesis". *Purinergic Signal* **9**: 599–608. doi: 10.1007/s11302-013-9370-7. Epub 2013 Jun 16.

Anumonye A, Reading HW, Knight F, Ashcroft GW (1968) Uric-acid metabolism in manic-depressive illness and during lithium therapy. *Lancet* **1**: 1290–1293.

Azdad K, Gall D, Woods AS, Ledent C, Ferré S, Schiffmann SN (2009) Dopamine D2 and adenosine A2A receptors regulate NMDA-mediated excitation in accumbens neurons through A2A-D2 receptor heteromerization. *Neuropsychopharmacology* **34**: 972–986. doi: 10.1038/npp.2008.144. Epub 2008 Sep 17.

Backlund L, Nikamo P, Hukic DS, Ek IR, Träskman-Bendz L, Landén M, Edman G, Schalling M, Frisén L, Osby U (2011) Cognitive manic symptoms associated with the P2RX7 gene in bipolar disorder. *Bipolar Disord* **13**: 500–508. doi: 10.1111/j.1399-5618.2011.00952.x.

Backlund L, Lavebratt C, Frisén L, Nikamo P, Hukic Sudic D, Träskman-Bendz L, Landén M, Edman G, Vawter MP, Ösby U, Schalling M (2012) P2RX7: expression responds to sleep deprivation and associates with rapid cycling in bipolar disorder type 1. *PLoS One* **7**: e43057. doi: 10.1371/journal.pone.0043057. Epub 2012 Aug 28.

Bannerman DM, Good MA, Butcher SP, Ramsay M, Morris RG (1995) Distinct components of spatial learning revealed by prior training and NMDA receptor blockade. *Nature* **378**: 182–186.

Barden N, Harvey M, Gagné B, Shink E, Tremblay M, Raymond C, Labbé M, Villeneuve A, Rochette D, Bordeleau L, Stadler H, Holsboer F, Müller-Myhsok B (2006) Analysis of single nucleotide polymorphisms in genes in the chromosome 12Q24.31 region points to P2RX7 as a susceptibility gene to bipolar affective disorder. *Am J Med Genet B Neuropsychiatr Genet* **141B**: 374–382.

Bettio LE, Cunha MP, Budni J, Pazini FL, Oliveira Á, Colla AR, Rodrigues AL (2010) Guanosine produces an antidepressant-like effect through the modulation of NMDA receptors, nitric oxide-cGMP and PI3K/mTOR pathways. *Behav Brain Res* **234**: 137–148. doi: 10.1016/j.bbr.2012.06.021. Epub 2012 Jun 26.

Bowman GL, Shannon J, Frei B, Kaye JA, Quinn JF (2010) Uric acid as CNS antioxidant. *J Alzheimers Dis* **19**: 1331–1336. doi: 10.3233/JAD-2010-1330.

Brocardo Pde S, Budni J, Lobato KR, Kaster MP, Rodrigues AL (2008) Antidepressant-like effect of folic acid: Involvement of NMDA receptors and L-arginine-nitric oxide-cyclic guanosine monophosphate pathway. *Eur J Pharmacol* **598**: 37–42. doi: 10.1016/j.ejphar.2008.08.033. Epub 2008 Sep 3.

Brunstein MG, Silveira EM Jr, Chaves LS, Machado H, Schenkel O, Belmonte-de-Abreu P, Souza DO, Lara DR (2007) Increased serum adenosine deaminase activity in schizophrenic receiving antipsychotic treatment. *Neurosci Lett* **414**: 61–64. Epub 2007 Jan 8.

Burnstock G (1978) Cell Membrane Receptors for Drugs and Hormones: A Multidisciplinary Approach. Straub RW, Bolis L, eds. Raven Press, New York. pp. 107–118.

Burnstock G, Kennedy C (1985) Is there a basis for distinguishing two types of P2-purinoceptor? *Gen. Pharmacol* **16**: 433–440.

Burnstock G (2007) Physiology and pathophysiology of purinergic neurotransmission. *Physiol Rev* **87**: 659–797.

Burnstock G (2008) Purinergic signalling and disorders of the central nervous system. *Nat Rev Drug Discov* **7**: 575–590. doi: 10.1038/nrd2605.

Burnstock G, Kruger U, Abbracchio M, Illes P (2011) Purinergic signaling: From normal behaviour to pathological brain function. *Progr Neurobiol* **95**: 229–274. doi: 10.1016/j.pneurobio.2011.08.006. Epub 2011 Sep 1.

Cieślak M, Komoszyński M, Wojtczak A (2008) Adenosine A(2A) receptors in Parkinson's disease treatment. *Purinergic Signal* **4**: 305–312. doi: 10.1007/s11302-008-9100-8. Epub 2008 Apr 26.

Cieślak M, Kukulski F, Komoszyński M (2011) Emerging role of extracellular nucleotides and adenosine in multiple sclerosis. *Purinergic Signal* **7**: 393–402. doi: 10.1007/s11302-011-9250-y. Epub 2011 Jul 27.

Cieślak M, Czarnecka J, Roszek K, Komoszyński M (2015) The role of purinergic signalling in the etiology of migraine and novel antimigraine treatment. *Purinergic Signal* **11**: 307–316. doi: 10.1007/s11302-015-9453-8. Epub 2015 May 10.

Ciruela F, Casadó V, Rodrigues RJ, Luján R, Burgueño J, Canals M, Borycz J, Rebola N, Goldberg SR, Mallol J, Cortés A, Canela EI, López-Giménez JF, Milligan G, Lluis C, Cunha RA, Ferré S, Franco R (2006) Presynaptic control of striatal glutamatergic neurotransmission by adenosine A1-A2A receptor heteromers. *J Neurosci* **26**: 2080–2087.

Collingridge GL (1994) Long-term potentiation. A question of reliability. *Nature* **371**: 652–653.

Collingridge GL, Bliss TV (1995) Memories of NMDA receptors and LTP. *Trends Neurosci* **18**: 54–56.

Cornelis MC, El-Sohemy A, Campos H (2007) Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. *Am J Clin Nutr* **86**: 240–244.

Coyle JT (2012) NMDA receptor and schizophrenia: a brief history. *Schizophr Bull* **38**: 920–926. doi: 10.1093/schbul/sbs076.

Cotrina ML, Lin JH, López-García JC, Naus CC, Nedergaard M (2000) ATP-mediated glia signaling. *J Neurosci* **20**: 2835–2844.

Csölle C, Baranyi M, Zsilla G, Kittel A, Goloncser F, Illes P, Papp E, Vizi E, Sperlagh B (2013) Neurochemical changes in the mouse hippocampus underlying the antidepressant effect of genetic deletion of P2X7 receptors. *PLoS One* **8**: e66547. Print 2013.

Cunha RA (2005) Neuroprotection by adenosine in the brain: From A(1) receptor activation to A (2A) receptor blockade. *Purinergic Signal* **1**: 111–134. doi: 10.1007/s11302-005-0649-1. Epub 2005 Mar 17.

Czarnecka J, Roszek K, Jabłoński A, Smoliński DJ, Komoszyński M (2011) Some aspects of purinergic signaling in the ventricular system of porcine brain. *Acta Vet Scand* **13**: 53–54. doi: 10.1186/1751-0147-53-54.

Cherkasova MV, Faridi N, Casey KF, O'Driscoll GA, Hechtman L, Joober R, Baker GB, Palmer J, Dagher A, Leyton M, Benkelfat C (2014) Amphetamine-induced dopamine release and neurocognitive function in treatment-naive adults with ADHD. *Neuropsychopharmacology* **39**: 1498–1507. doi: 10.1038/npp.2013.349. Epub 2013 Dec 30.

Deckert J, Brenner M, Durany N, Zöchling R, Paulus W, Ransmayr G, Tatschner T, Danielczyk W, Jellinger K, Riederer P (2003) Up-regulation of striatal adenosine A(2A) receptors in schizophrenia. *Neuroreport* **14**: 313–316.

Del Puerto A, Wandosell F, Garrido JJ (2013) Neuronal and glial purinergic receptors functions in neuron development and brain disease. *Front Cell Neurosci* **7**: 197. doi: 10.3389/fncel.2013.00197.

Di Virgilio F (2007) Purinergic signaling in the immune system. A brief update. *Purinergic Signal* **3**: 1–3. doi: 10.1007/s11302-006-9048-5. Epub 2007 Feb 6.

Di Virgilio F, Ceruti S, Bramanti P, Abbracchio MP (2009) Purinergic signalling in inflammation of the central nervous system. *Trends Neurosciences* **2**: 79–87. doi: 10.1016/j.tins.2008.11.003. Epub 2009 Jan 8.

Erhardt A, Lucae S, Unschuld PG, Ising M, Kern N, Salyakina D, Lieb R, Uhr M, Binder EB, Keck ME, Müller-Myhsok B, Holsboer F (2007) Association of polymorphisms in P2RX7 and CaMKKb with anxiety disorders. *J Affect Disord* **101**: 159–168. Epub 2007 Jan 2.

Ferré S (1997) Adenosine-dopamine interactions in the ventral striatum. Implications for the treatment of schizophrenia. *Psychopharmacology (Berl)* **133**: 107–120.

Franco R, Ferré S, Agnati L, Torvinen M, Ginés S, Hillion J, Casadó V, Lledó P, Zoli M, Lluis C, Fuxe K (2000) Evidence for adenosine/dopamine receptor interactions: indications for heteromerization. *Neuropsychopharmacology* **23**: S50–S59.

Frau L, Borsini F, Wardas J, Khairnar AS, Schintu N, Morelli M (2011) Neuroprotective and anti-inflammatory effects of the adenosine A(2A) receptor antagonist ST1535 in a MPTP mouse model of Parkinson's disease. *Synapse* **65**: 181–188. doi: 10.1002/syn.20833.

Fredholm BB, Chen JF, Cunha RA, Svenningsson P, Vaugeois JM (2005) Adenosine and brain function. *Int Rev Neurobiol* **63**: 191–270.

Fuller SJ, Stokes L, Skarratt KK, Gu BJ, Wiley JS (2009) Genetics of the P2X7 receptor and human disease. *Purinergic Signal* **5**: 257–262. doi: 10.1007/s11302-009-9136-4. Epub 2009 Mar 25.

Fuxe K, Canals M, Torvinen M, Marcellino D, Terasmaa A, Genedani S, Leo G, Guidolin D, Diaz-Cabiale Z, Rivera A, Lundstrom L, Langel U, Narvaez J, Tanganelli S, Lluis C, Ferré S, Woods A, Franco R, Agnati LF (2007) Intramembrane receptor-receptor interactions: a novel principle in molecular medicine. *J Neural Transm* **114**: 49–75. Epub 2006 Oct 27.

Gajewska A, Blumenthal TD, Winter B, Herrmann MJ, Conzelmann A, Mühlberger A, Warrings B, Jacob C, Arolt V, Reif A, Zwanzger P, Pauli P, Deckert J, Domschke K (2013) Effects of ADORA2A gene variation and caffeine on prepulse inhibition: a multi-level risk model of anxiety. *Prog Neuropsychopharmacol Biol Psychiatry* **40**: 115–121. doi: 10.1016/j.pnpbp.2012.08.008. Epub 2012 Aug 23.

Gomes CV, Kaster MP, Tomé AR, Agostinho PM, Cunha RA (2011) Adenosine receptors and brain diseases: neuroprotection and neurodegeneration. *Biochim Biophys Acta* **1808**: 1380–1399. doi: 10.1016/j.bbamem.2010.12.001. Epub 2010 Dec 9.

Gotoh L, Mitsuyasu H, Kobayashi Y, Oribe N, Takata A, Ninomiya H, Stanton VP Jr, Springett GM, Kawasaki H, Kanba S (2009) Association analysis of adenosine A1 receptor gene (ADORA1) polymorphisms with schizophrenia in a Japanese population. *Psychiatr Genet* **19**: 328–335. doi: 10.1097/YPG.0b013e3283328e26.

Green EK, Grozeva D, Raybould R, Elvidge G, Macgregor S, Craig I, Farmer A, McGuffin P, Forty L, Jones L, Jones I, O'Donovan MC, Owen MJ, Kirov G, Craddock N (2009) P2RX7: A bipolar and unipolar disorder candidate susceptibility gene? *Am J Med Genet B Neuropsychiatr Genet* **150B**: 1063–1069. doi: 10.1002/ajmg.b.30931.

Hejjas K, Szekely A, Domotor E, Halmai Z, Balogh G, Schilling B, Sarosi A, Faludi G, Sasvari-Szekely M, Nemoda Z (2009) Association between depression and the Gln460Arg polymorphism of P2RX7 gene: a dimensional approach. *Am J Med Genet B Neuropsychiatr Genet* 2009 **150B**: 295–299. doi: 10.1002/ajmg.b.30799.

Hohoff C, Garibotto V, Elmenhorst D, Baffa A, Kroll T, Hoffmann A, Schwarte K, Zhang W, Arolt V, Deckert J, Bauer A (2014) Association of adenosine receptor gene polymorphisms and *in vivo* adenosine A1 receptor binding in the human brain. *Neuropsychopharmacology* **39**: 2989–2999. doi: 10.1038/npp.2014.150. Epub 2014 Jun 19.

Hwang Y, Kim J, Shin JY, Kim JI, Seo JS, Webster MJ, Lee D, Kim S (2013) Gene expression profiling by mRNA sequencing reveals increased expression of immune/inflammation-related genes in the hippocampus of individuals with schizophrenia. *Transl Psychiatry* **29**: 3: e321. doi: 10.1038/tp.2013.94.

Jagannathan K, Calhoun VD, Gelernter J, Stevens MC, Liu J, Bolognani F, Windemuth A, Ruaño G, Assaf M, Pearlson GD (2010) Genetic associations of brain structural networks in schizophrenia: a preliminary study. *Biol Psychiatry* **68**: 657–666. doi: 10.1016/j.biopsych.2010.06.002. Epub 2010 Aug 5.

Kapur S, Mamo D (2003) Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Prog Neuropsychopharmacol Biol Psychiatry* **27**: 1081–1090.

Kaster MP, Machado DG, Santos AR, Rodrigues AL (2012) Involvement of NMDA receptors in the antidepressant-like action of adenosine. *Pharmacol Rep* **64**: 706–713.

Kesebir S, Tatlıdil Yaylacı E, Süner O, Gültekin BK (2014) Uric acid levels may be a biological marker for the differentiation of unipolar and bipolar disorder: the role of affective temperament. *J Affect Disord* **165**: 131–134. doi: 10.1016/j.jad.2014.04.053. Epub 2014 May 4.

Kovács Z, Dobolyi A, Kékesi KA, Juhász G (2013) 5'-nucleotidases, nucleosides and their distribution in the brain: pathological and therapeutic implications. *Curr Med Chem* **20**: 4217–4240.

Kraepelin E (1921) Manic-depressive insanity and paranoia. E. & S. Livingstone, Edinburgh.

Krügel U, Kittner H, Illes P (2001) Mechanisms of adenosine 5'-triphosphate-induced dopamine release in the rat nucleus accumbens *in vivo*. *Synapse* **39**: 222–232.

Kukulski F, Sevigny J, Komoszyński M (2004) Comparative hydrolysis of extracellular adenine nucleotides and adenosine in synaptic membranes from porcine brain cortex, hippocampus, cerebellum and medulla oblongata. *Brain Res* **1030**: 49–56.

Langer D, Hammer K, Koszalka P, Schrader J, Robson S, Zimmermann H (2008) Distribution of ectonucleotidases in the rodent brain revisited. *Cell Tissue Res* **334**: 199–217. doi: 10.1007/s00441-008-0681-x. Epub 2008 Oct 9.

Lara DR, Souza DO (2000) Schizophrenia: a purinergic hypothesis. *Med Hypotheses* **54**: 157–166.

Lara DR, Brunstein MG, Ghisolfi ES, Lobato MI, Belmonte-de-Abreu P, Souza DO (2001) Allopurinol augmentation for poorly responsive schizophrenia. *Int Clin Psychopharmacol* **16**: 235–237.

Lara DR, Dall'Igna OP, Ghisolfi ES, Brunstein MG (2006) Involvement of adenosine in the neurobiology of schizophrenia and its therapeutic implications. *Prog Neuropsychopharmacol Biol Psychiatry* **30**: 617–629. Epub 2006 Mar 6.

Lau CI, Wang HC, Hsu JL, Liu ME (2013) Does the dopamine hypothesis explain schizophrenia? *Rev Neurosci* **24**: 389–400. doi: 10.1515/revneuro-2013-0011.

Lazarowski ER (2012) Vesicular and conductive mechanisms of nucleotide release. *Purinergic Signal.* **8**: 359-373. doi: 10.1007/s11302-012-9304-9. Epub 2012 Apr 12.

Lucas PB, Pickar D, Kelsoe J, Rapaport M, Pato C, Hommer D (1990) Effects of the acute administration of caffeine in patients with schizophrenia. *Biol Psychiatry* **28**: 35–40.

Machado-Vieira R, Lara DR, Souza DO, Kapczinski F (2001) Therapeutic efficacy of allopurinol in mania associated with hyperuricemia. *J Clin Psychopharmacol* **21**: 621–622.

Machado-Vieira R, Lara DR, Souza DO, Kapczinski F (2002) Purinergic dysfunction in mania: an integrative model. *Med Hypotheses* **58**: 297–304.

Machado-Vieira R (2012) Purinergic system in the treatment of bipolar disorder: uric acid levels as a screening test in mania. *J Clin Psychopharmacol* **32**: 735–736.

Maggio R, Aloisi G, Silvano E, Rossi M, Millan MJ (2009) Heterodimerization of dopamine receptors: new insights into functional and therapeutic significance. *Parkinsonism Relat Disord* **15** (Suppl 4): S2–S7. doi: 10.1016/S1353-8020(09)70826-0.

Maj J, Rogóz Z, Skuza G (1992) The effects of combined treatment with MK-801 and antidepressant drugs in the forced swimming test in rats. *Pol J Pharmacol Pharm* **44**: 217–226.

Malarkey EB, Parpura V (2008) Mechanisms of glutamate release from astrocytes. *Neurochem Int* **52**: 142–154. Epub 2007 Jun 26.

Marek GJ (2009) Activation of adenosine(1) (A(1)) receptors suppresses head shakes induced by a serotonergic hallucinogen in rats. *Neuropharmacology* **56**: 1082–1087. doi: 10.1016/j.neuropharm.2009.03.005. Epub 2009 Mar 24.

Martinez JM, Garakani A, Yehuda R, Gorman JM (2012) Proinflammatory and „resiliency" proteins in the CSF of patients with major depression. *Depress Anxiety* **29**: 32–38. doi: 10.1002/da.20876. Epub 2011 Sep 2.

Martini C, Tuscano D, Trincavelli ML, Cerrai E, Bianchi M, Ciapparelli A, Lucioni A, Novelli L, Catena M, Lucacchini A, Cassano GB, Dell'Osso L (2006) Upregulation of A2A adenosine receptors in platelets from patients affected by bipolar disorders under treatment with classical antipsychotics. *J Psychiatr Res* **40**: 81–88.

McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A (2003). The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* **60**: 497–502.

Molero Y, Gumpert C, Serlachius E, Lichtenstein P, Walum H, Johansson D, Anckarsäter H, Westberg L, Eriksson E, Halldner L (2013) A study of the possible association between adenosine A2A receptor gene polymorphisms and attention-deficit hyperactivity disorder traits. *Genes Brain Behav* **12**: 305–310. doi: 10.1111/gbb.12015. Epub 2013 Mar 7.

Nishizaki T (2004) ATP- and adenosine-mediated signaling in the central nervous system: adenosine stimulates glutamate release from astrocytes *via* A2a adenosine receptors. *J Pharmacol Sci* **94**: 100–102.

Olney JW, Farber NB (1995) Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry* **52**: 998–1007.

Palucha A, Pilc A (2005) The involvement of glutamate in the pathophysiology of depression. *Drug News Perspect* **18**: 262–268.

Pochwat B, Szewczyk B, Sowa-Kucma M, Siwek A, Doboszewska U, Piekoszewski W, Gruca P, Papp M, Nowak G (2014) Antidepressant-like activity of magnesium in the chronic mild stress model in rats: alterations in the NMDA receptor subunits. *Int J Neuropsychopharmacol* **17**: 393–405. doi: 10.1017/S1461145713001089. Epub 2013 Sep 26.

Poleszak E, Wośko S, Serefko A, Szopa A, Wlaź A, Szewczyk B, Nowak G, Wlaź P (2013) Effects of ifenprodil on the antidepressant-like activity of NMDA ligands in the forced swim test in mice. *Prog Neuropsychopharmacol Biol Psychiatry* **46**: 29–35. doi: 10.1016/j.pnpbp.2013.06.001. Epub 2013 Jun 14.

Quarta D, Ferré S, Solinas M, You ZB, Hockemeyer J, Popoli P, Goldberg SR (2004) Opposite modulatory roles for adenosine A1 and A2A receptors on glutamate and dopamine release in the shell of the nucleus accumbens. Effects of chronic caffeine exposure. *J Neurochem* **88**: 1151–1158.

Ralevic V, Burnstock G (1998) Receptors for purines and pyrimidines. *Pharmacol Rev* **50**: 413–492.

Raison CL, Miller AH (2013) Role of inflammation in depression: implications for phenomenology, pathophysiology and treatment. *Mod Trends Pharmacopsychiatri* **28**: 33–48. doi: 10.1159/000343966. Epub 2013 Feb 27.

Rieger DK, Costa AP, Budni J, Moretti M, Barbosa SG, Nascimento KS, Teixeira EH, Cavada BS, Rodrigues AL, Leal RB (2014) Antidepressant-like effect of *Canavalia brasiliensis* (ConBr) lectin in mice: Evidence for the involvement of the glutamatergic system. *Pharmacol Biochem Behav* **122**: 53–60. doi: 10.1016/j.pbb.2014.03.008. Epub 2014 Mar 18.

Robson S., Sevigny J., Zimmermann H (2006) The E-NTPDase family of ectonucleotidases: structure function relationships and pathophysiological significance. *Purinergic Signal* **2**: 409–430. doi: 10.1007/s11302-006-9003-5. Epub 2006 May 30.

Saitoh M, Shinohara M, Ishii A, Ihara Y, Hirose S, Shiomi M, Kawawaki H, Kubota M, Yamagata T, Miyamoto A, Yamanaka G, Amemiya K10, Kikuchi K, Kamei A, Akasaka M, Anzai Y, Mizuguchi M (2015) Clinical and genetic features of acute encephalopathy in children taking theophylline. *Brain Dev* **37**: 463–470. doi: 10.1016/j.braindev.2014.07.010. Epub 2014 Aug 23.

Salvadore G, Viale CI, Luckenbaugh DA, Zanatto VC, Portela LV, Souza DO, Zarate CA Jr, Machado-Vieira R (2010) Increased uric acid levels in drug-naïve subjects with bipolar disorder during a first manic episode. *Prog Neuropsychopharmacol Biol Psychiatry* **34**: 819–821. doi: 10.1016/j.pnpbp.2010.02.027. Epub 2010 Mar 3.

Schmidt AP, Lara DR, de Faria Maraschin J, da Silveira Perla A, Onofre Souza D (2000) Guanosine and GMP prevent seizures induced by quinolinic acid in mice. *Brain Res* **864**: 40–43.

Schmidt AP, Tort AB, Souza DO, Lara DR (2008) Guanosine and its modulatory effects on the glutamatergic system. *Eur Neuropsychopharmacol* **18**: 620–622. doi: 10.1016/j.euroneuro.2008.01.007. Epub 2008 Mar 10.

Schultz SK, Andreasen NC (1999) Schizophrenia. *Lancet* **353**: 1425–1430.

Shinohara M, Saitoh M, Nishizawa D, Ikeda K, Hirose S, Takanashi J, Takita J, Kikuchi K, Kubota M, Yamanaka G, Shiihara T, Kumakura A, Kikuchi M, Toyoshima M, Goto T, Yamanouchi H, Mizuguchi M (2013) ADORA2A polymorphism predisposes children to encephalopathy with febrile status epilepticus. *Neurology* **80**: 1571–1576. doi: 10.1212/WNL.0b013e31828f18d8. Epub 2013 Mar 27.

Singer P, Zhang C, Boison D, Yee BK. (2013) Dysregulation of brain adenosine is detrimental to the expression of conditioned freezing but not general Pavlovian learning. *Pharmacol Biochem Behav* **104**: 80–89. doi: 10.1016/j.pbb.2012.12.012. Epub 2013 Jan 2.

Soronen P, Mantere O, Melartin T, Suominen K, Vuorilehto M, Rytsälä H, Arvilommi P, Holma I, Holma M, Jylhä P, Valtonen HM, Haukka J, Isometsä E, Paunio (2011) P2RX7 gene is associated consistently with mood disorders and predicts clinical outcome in three clinical cohorts. *Am J Med Genet B Neuropsychiatr Genet* **156B**: 435–447. doi: 10.1002/ajmg.b.31179. Epub 2011 Mar 22.

Sperlagh B., Illes P (2007) Purinergic modulation of microglial cell activation. *Purinergic Signal* **3**: 117–127. doi: 10.1007/s11302-006-9043-x. Epub 2006 Dec 19.

Stoeckel ME, Uhl-Bronner S, Hugel S, Veinante P, Klein MJ, Mutterer J, Freund-Mercier MJ, Schlichter R (2003) Cerebrospinal fluid-contacting neurons in the rat spinal cord, a γ-aminobutyric acidergic system expressing the P2X2 subunit of purinergic receptors, PSA-NCAM, and GAP-43 immunoreactivities: light and electron microscopic study. *J Comp Neurol* **457**: 159–174.

Urigüen L, García-Fuster MJ, Callado LF, Morentin B, La Harpe R, Casadó V, Lluis C, Franco R, García-Sevilla JA, Meana JJ (2009) Immunodensity and mRNA expression of A2A adenosine, D2 dopamine, and CB1 cannabinoid receptors in postmortem frontal cortex of subjects with schizophrenia: effect of antipsychotic treatment. *Psychopharmacology (Berl)* **206**: 313–324. doi: 10.1007/s00213-009-1608-2. Epub 2009 Aug 4.

Viikki M, Kampman O, Anttila S, Illi A, Setälä-Soikkeli E, Huuhka M, Mononen N, Lehtimäki T, Leinonen E (2011) P2RX7 polymorphisms Gln460Arg and His155Tyr are not associated with major depressive disorder or remission after SSRI or ECT. *Neurosci Lett* **493**: 127–130. doi: 10.1016/j.neulet.2011.02.023. Epub 2011 Feb 16.

Villar-Menéndez I, Díaz-Sánchez S, Blanch M, Albasanz JL, Pereira-Veiga T, Monje A, Planchat LM, Ferrer I, Martín M, Barrachina M (2014) Reduced striatal adenosine A2A receptor levels define a molecular subgroup in schizophrenia. *J Psychiatr Res* **51**: 49–59.

Wei C, Li W, Chen J (2011) Normal and abnormal functions of adenosine receptors in the central nervous system revealed by genetic knockout studies. *BBA Biomembranes* **1808**: 1358–1379. doi: 10.1016/j.jpsychires.2013.12.013. Epub 2014 Jan 7.

Wardas J (2008) Potential role of adenosine A2A receptors in the treatment of schizophrenia. *Front Biosci* **13**: 4071–4096.

Watkins J, Collingridge G (1994) Phenylglycine derivatives as antagonists of metabotropic glutamate receptors. *Trends Pharmacol Sci* **15**: 333–342.