

Magda Malewska-Kasprzak, Agnieszka Permoda-Osip, Janusz Rybakowski: Disturbances of the purinergic system in affective disorders and schizophrenia*

Abstract

The purinergic system plays a role in the regulation of many psychological processes, including mood and activity. It consists of P1 receptors, with adenosine as the agonist, and P2 receptors, activated by nucleotides (e.g., adenosine 5'-triphosphate – ATP).

Propounded disturbances of uric acid in affective disorders were related to the introduction of lithium for the treatment of these disorders in the 19th and 20th century. At the beginning of the 21st century, new evidence was accumulated concerning a role of uric acid in the pathogenesis and treatment of bipolar disorder (BD). In patients with BD, higher prevalence of gout and increased concentration of uric acid have been found, as well as the therapeutic activity of allopurinol, used as an adjunct to mood stabilizers, has been demonstrated in mania.

In recent years, the research on the role of the purinergic system in the pathogenesis and treatment of affective disorders and schizophrenia focuses on the role of adenosine (P1) receptors and nucleotide (P2) receptors. Activation of adenosine receptors is related to an antidepressant activity. Alterations of P2 receptors are also significant for the pathogenesis of affective disorders. The role of the purinergic system in schizophrenia is related to the effect of adenosine and nucleotide receptors on dopaminergic and glutamatergic neurotransmission. A lot of data indicate that schizophrenia is related to a deficit of the adenosine system. Changes in the purinergic system are also significant for psychopathological symptoms of schizophrenia and for the action of antipsychotic drugs.

Purinergic system and its role in the central nervous system functioning

Uric acid is the final metabolite of purine bases, derived from food, synthesis *de novo* and metabolism of endogenous nucleic acids. It has been found that both uric acid and some purines (e.g., adenosine) may play a role in the regulation of psychological processes, including mood and activity.

In the central nervous system, adenosine 5'-triphosphate (ATP), other nucleotides and adenosine are stored and released into extracellular space from various types of cells: neurons (Fields 2011), astrocytes (Koizumi 2010), and microglia cells (Imura et al. 2013).

Mechanisms of ATP release have been described as an exocytotic vesicular release from nerve terminals (Bodin and Burnstock 2001), involving, among others, calcium ions (Lalo et al. 2014). In vitro studies showed that the activity of astrocytes depends on the release of transmitters, such as glutamate, ATP, and adenosine (Zhang et al. 2007).

The extracellular concentration of ATP increases during neuronal activity under the influence of psychostimulant drugs and in oxygen-glucose deprivation models (OGD) during seizures, as well as inflammations or injuries of the brain (Burnstock et al. 2011; Pintora et al. 1993). Mitochondrial dysfunctions of ATP synthesis **may** be significant for the pathogenesis of neurological and psychiatric illnesses.

Nucleotide receptors, discovered in the 1970s by a British scientist Geoffrey Burnstock, were initially called “purinergic receptors.” When it was found that their activation involves both purine and pyrimidine nucleotides, their name was changed into “nucleotide receptors” and they were divided into two groups, P1 and P2; P1 receptors' agonist is a purine nucleoside – adenosine. Adenosine receptors were divided into A1, A2 and A3 subtypes. P2 receptors, further divided into P2X and P2Y subgroups, are activated by nucleotides. P2X receptors are ionotropic receptors, forming a channel in the cell membrane and activated by ATP. P2Y receptors are metabotropic receptors, G-protein coupled (similarly to P1), activated by ATP, adenosine diphosphate (ADP), uridine triphosphate (UTP), uridine diphosphate (UDP) and sugar derivatives of UDP (Barańska 2014). The release of adenosine, ATP and ADP into the extracellular space exerts an effect on P1 and P2 receptors, localized on neurons and on non-neuronal cells, such as astrocytes, oligodendrocytes, microglia cells and endothelial cells (Fields and Burnstock 2006).

Purinergic transmission plays a significant role in various physiological processes, as well as in numerous pathological states. Purinergic receptors are widely spread in the central nervous system, in neurons and glia cells of the cerebral cortex, in the hypothalamus, basal ganglia, hippocampus and other parts of the limbic system (Burnstock 2008). Purinergic system dysfunctions have been found in many neuropsychiatric conditions, including affective disorders and schizophrenia (Gomes et al. 2011). The current review presents the recent knowledge on the role of the purinergic system in affective disorders and schizophrenia, based on the research performed in the last two decades.

Purinergic system dysfunctions in affective disorders

The relations between BD and purinergic system dysfunction concerned initially the disturbances of uric acid. This was related to the introduction of lithium as a treatment for

affective disorders. A Danish scientist, Carl Lange, suggested in 1886 that an excess of uric acid played a role in the pathogenesis of depression and proposed a therapeutic use of lithium, as lithium urate is one of best soluble urates. In 1949, an Australian psychiatrist, John Cade, introduced lithium as a treatment for manic states, suggesting beforehand that these states are characterized by increased excretion of urates (Malewska et al.2016).

The premises for a significance of uric acid in the pathogenesis of bipolar disorder are epidemiological, clinical and therapeutic. An epidemiological study performed by Chung et al. (2010) in Taiwan, covering 24,262 patients with BD and 121,310 patients in the control group, and followed up during the period of 2000-2006, found that gout occurred among 16.4% of the patients with BD and in 13.6% of the patients of the control group. The risk of developing gout during the 6-year follow-up period was 1.19% higher for patients with BD than for the control group (95% confidence interval (CI) = 1.10-1.24, $p < 0.001$).

Salvadore et al. (2010) observed that patients with the first episode of mania had increased levels of uric acid which might indicate that the purinergic system dysfunctions may occur even in the early phases of BD. Recent analyses, performed by Bartoli et al. (2016, 2017) found that patients with BD have a significantly increased concentration of uric acid in comparison with healthy control subjects and with patients suffering from depression. Albert et al. (2015) reported a significantly higher concentration of uric acid in BD in comparison with obsessive-compulsive disorder or schizophrenia. In patients with BD, no difference between acute phase and remission was observed. A recent study has shown that the concentration of uric acid is significantly higher in people with the first episode of mania compared to the control group and negatively correlates with the improvement of the clinical state after one month of treatment (Chatterjee et al.2018). In our study, comparing uric acid concentration in patients with BD during mania, depression and remission, no significant differences were found. However, hyperuricemia was observed in more than one-third of patients during depressive episode (Malewska et al.2017).

Allopurinol, used for the treatment of gout, acts by inhibiting the enzyme, xanthine oxidase, which results in reducing the level of uric acid. In a double-blind, randomized, placebo-controlled trial, including patients with mania (moderate to acute), it was found that addition of allopurinol to lithium or haloperidol, during eight weeks, resulted in a greater reduction of agitation and symptoms of mania, assessed by the Young Mania Rating Scale (YMRS), compared to the control group, where placebo was added (Akhondzadeh et al. 2006). The study performed by Machado-Vieira et al. (2008) estimated the efficacy and tolerance to allopurinol (600 mg/day) and dipyridamole (200 mg/day) combined with lithium

in the treatment of acute manic episode. The study lasted four weeks, was randomized and double-blind, placebo-controlled. The results indicated that obtained reduction in the YMRS scale was significantly greater in case of added allopurinol than dipyridamole or placebo. Antimanic effects of allopurinol correlated with a decrease of uric acid concentration. The results of these two studies suggest that allopurinol may be synergistic with lithium in the treatment of manic episodes in patients with BD.

The study of Jahangard et al. (2014) including 57 patients with manic episode investigated potential benefits of allopurinol (600 mg/day) compared with placebo for augmenting the antimanic effect of sodium valproate (15-20 mg/kg/day). Compared to the control group receiving placebo, both symptoms of mania and uric acid concentration decreased significantly in the group of patients where allopurinol was added. The probability of remission after four weeks of treatment was 23 times higher in the group receiving allopurinol and lower uric acid concentration after four weeks was associated with symptom improvement. Thus, in the treatment of acute mania, allopurinol could act in synergy with sodium valproate.

Experimental studies also showed an antidepressant effects of allopurinol. Özgür et al. (2015) compared the effects of allopurinol with those of fluoxetine in a forced swimming test in rats after 14 days of drug administration. Both allopurinol and fluoxetine caused a decrease in the duration of immobility, with similar efficacy. However, no significant differences in the antidepressant effect between the combined therapy versus single drug therapy were found. A meta-analysis of Bartoli et al. (2017), proved the beneficial effect of using allopurinol for an augmentation of the treatment of mania.

Current research on the role of the purinergic system in the pathogenesis of affective disorders has been mainly focused on the abnormalities of adenosine receptors (P1) and nucleotide receptors (P2) (Ortiz et al. 2015). The activation of adenosine receptor causes a reduction of neuronal excitability, a decrease of uric acid concentration and inhibition of calcium-dependent release of excitatory neurotransmitters. Experimental studies found that lithium increases the level of adenosine by inhibiting the activity of ectonucleotidase (Oliveira et al. 2011). It was also found that the agonists of adenosine system, cyclohexyladenosine (CHA) and (N6-[2-(3,5-di-methoxyphenyl)-2-(2-methylphenyl)-ethyl] adenosine (DMPA), exert an antidepressant effect in the forced swimming test (Kaster et al. 2004). Sleep deprivation causes an increase of adenosine signalling in the brain. S-adenosyl-l-methionine, a precursor of adenosine, has a similar effect (De Berardis et al. 2013).

Both sleep deprivation and electroconvulsive therapy cause an increase in adenosine A1 receptors (Elmenhorst et al. 2007). The activation of A1 receptors has an inhibiting effect on N-methyl-D-aspartate (NMDA) receptors. Experimental studies demonstrated that such an effect is associated with antidepressant activity and activation of neuronal plasticity. Adenosine A2 receptors modulate dopaminergic signalling in subcortical structures of the brain and their activation is associated with the weakening of motivational and motor skills. In turn, inhibition of these receptors, e.g., by bupropion, is associated with an antidepressant effect. Thus, the antidepressant effect can be obtained both by adenosine A1 receptors activation and A2 receptors inhibition. In turn, Gubert et al. (2016) showed that the concentration of adenosine is lower in bipolar patients compared to the control group and pointed to its negative correlation with the severity of depression. It was also found that a greater functional impairment was associated with lower levels of adenosine.

Some research also found that P2 receptors, activated by extracellular ATP, are of significance for the pathogenesis of BD. Gubert et al. (2013) presented the role of the P2X7 receptor which mediates in the processes of apoptosis, proliferation and release of proinflammatory cytokines, as well as in mechanisms of neurotransmission and neuromodulation. The release of proinflammatory cytokines may be important for the pathogenesis of BD, most significantly with the microglia P2X7 receptor activation. The gene of the P2X7 receptor is located on the chromosome 12q23-24, which is described as a potential susceptibility locus for affective disorders (Abkevich et al. 2003). Moreover, it was found that specific genotypes of the P2X7 receptor, e.g., two haplotypes containing A348T, might increase the risk for affective disorders. Recent animal studies have shown that P2X7 receptor is associated with learned helplessness model of depression in mice (Otrokocsi et al, 2017).

There is also data concerning the pathogenetic role of the P2Y1 receptor in affective disorders. This receptor, located on astrocytes, modulates presynaptic, calcium-dependant release of glutamine. The experimental research found that P2Y1 receptors on neurons play a role in motivational processes (Krügel et al. 2004) and are important for antidepressant and anxiolytic effects (Kittner et al. 2003).

Purinergic system dysfunctions in schizophrenia

The role of the purinergic system in schizophrenia is related to the effects of adenosine and nucleotide receptors on dopaminergic and glutamatergic signalling. Many data have indicated that schizophrenia may be related to a deficit in the adenosine system (Deckert et

al.2003). As early as 20 years ago, the association between polymorphism of adenosine A2A receptor gene, located on chromosome 22q, and susceptibility to schizophrenia was reported (Deckert et al.1997).

Stimulation of adenosine system exerts an anti-dopaminergic and pro-glutamatergic effect. Adenosine and A2A receptor agonists have similar activity as dopamine antagonists (Ferré et al. 1997, 2007; Rimondini et al.1997; Shen et al. 2008; Villar-Menéndez et al.2014). On the other hand, adenosine antagonists, such as caffeine,exertsimilar effects to those of psychostimulants by increasing dopamine concentration in the striatum. By forming the A2A / D2 heteromers, a decrease of adenosine may cause an increase in dopamine. A reduction of the A2A receptors at the level of transcription and DNA methylation, coding the A2A receptor gene, was found in schizophrenic patients. In some papers, it was shown that dipyrindamole and allopurinol, which enhance adenosine system by inhibiting cellular uptake and metabolic elimination of adenosine, can potentiate the effects of antipsychotic drugs in schizophrenia (Akhondzadeh et al. 2000; Weiser et al. 2012; Wonodi et al. 2011).

In animal models, A1 and A2A receptor agonists decrease behavioral activity caused by NMDA receptor antagonists (Popoli et al. 2012; Sills et al. 1999) and agonists of A2A receptors enhance glutamate release in glutamatergic neuronal endings of the striatum (De Mendonça et al.1995). A post-mortem study of schizophrenia patients found that an increase of mRNA glutamine transporter in astrocytes is associated with the functioning of the A2A receptors (Matute et al.2005; Smith et al.2001). Recent *in vivo* studies concerning A2A receptors indicate that glutamatergic system dysfunctions may depend on impaired signalling from astrocytes to neurons. In the study of mice with A2A receptors removed from astrocytes, inhibition of psychomotor functions and memory after administration of the NMDA receptor antagonist, MK-801, as well as suppression of glutamine transporter activity were observed (Matos et al. 2015).

Zhang et al. (2012) assessed a relationship between the adenosine gene A2A receptor expression and the results of sensory gating in schizophrenia patients, before and after 6-week antipsychotic treatment, compared with healthy subjects. Before treatment, schizophrenia patients exhibited sensory gating impairment in comparison with healthy patients. However, there was no difference in A2A receptors expression. After treatment, schizophrenia patients had increased expression of the receptors (up-regulation) which correlated with the initial amplitude of P50, the measure of sensory gating. Recently, Turčinet al. (2016) studied an association between genes of adenosine A1, A2A, and A3 receptors and psychopathological symptoms and antipsychotic drugs side effects in 127 chronic schizophrenia patients.

Association with psychopathological effects was found in relation to A1 and A2A receptors, whereas the association with akathisia was related to all three receptors. Association with tardive dyskinesia was found about the A3 receptor.

Besides adenosine receptors, much data also points to a significance of nucleotide receptors in the pathogenesis and treatment of schizophrenia. In contrast to adenosine receptors, stimulation of nucleotide receptors exerts a pro-dopaminergic and anti-glutamatergic effect. Experimental studies found that stimulation of the P2 receptors causes behavioral activation and their inhibition prevents such an activation. Stimulation of P2Y1 receptors in the prefrontal cortex is related to an increase in dopamine release from the ventral tegmental area (Guzman et al. 2010). Activation of these receptors also causes the hypofunction of NMDA receptors in the prefrontal cortex (Gonzalez-Burgos et al.2008). It was demonstrated that antipsychotic drugs, such as haloperidol and chlorpromazine, inhibit ATP-evoked stimulation via P2X receptors without blocking the D2 dopamine receptors. In contrast, application of ATP or non-selective P2X/Y receptor agonist, 2-methylthio ATP, into the rat striatum increases dopamine levels and exerts euphorogenic effect, similar to that of dopamine (Krügel et al. 1999; Zhang et al.1995). Stimulation of P2 receptors via endogenous ATP probably plays a role in an activating effect of amphetamine. On the other hand, blocking P2 receptors may contribute to preventing the development of dopaminergic hyperactivity. Koványi et al. (2016) examined for the first time the role of P2X7 in an animal model of schizophrenia. Using the phencyclidine induced schizophrenia model, they showed that P2X7 can make a potential therapeutic target in schizophrenia.

The research on uric acid concentration in schizophrenia patients can also be mentioned. In some studies, an increased concentration of uric acid during acute phase of the illness was found (Nagamine 2010). Recent research has pointed out to a relationship between increased uric acid concentration and the risk of metabolic syndrome in schizophrenia patients (Godin et al. 2015; Rajan et al. 2016). In our own study, we did not find any differences in uric acid concentration in schizophrenia patients between an acute and remission phases of the illness. Uric acid concentration in schizophrenia patients did not also differ from the concentration in patients with bipolar disorder (Malewska et al.2017).

Summary

Disturbances of purinergic system in affective disorders and schizophrenia are related to uric acid and adenosine and nucleotide receptors. Propounded disturbances of uric acid in affective disorders were related to the introduction of lithium for the treatment of these

disorders in the 19th and 20th century. At the beginning of the 21st century, new evidence was found, for the role of uric acid in pathogenesis and treatment of BD. The more frequent occurrence of gout and increased concentration of uric acid was found in patients with BD. The efficacy of allopurinol, used as an augmentation of mood stabilizers in mania, was also observed.

In recent years, the research on the role of the purinergic system in the pathogenesis and treatment of affective disorders and schizophrenia has mainly focused on the role of adenosine (P1) receptors and nucleotide (P2) receptors. Adenosine receptors activation is related to an antidepressant activity. Alterations in P2 receptors are also significant for the pathogenesis of affective disorders. The role of the purinergic system in schizophrenia is related to the effects of adenosine and nucleotide receptors on dopaminergic and glutamatergic signalling. Much data have indicated that schizophrenia is related to a deficit of the adenosine system. Alterations in the purinergic system are also significant for psychopathological symptoms of schizophrenia and the effects of antipsychotic drugs.

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*From the Department of Adult Psychiatry and Department of Child and Adolescent Psychiatry, Poznan University of Medical Sciences, Poznan, Poland.

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