Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 37

Thomas A. Ban

Lithium

6. Action

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Contents

*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, Morizawa, Komatsu 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, Palygin, Rasooli-Nejad 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, Chen, Zhou 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, Krügel, Abbracchio and Illes 2011; Pintora. Porras, Mora and Miras-Portugal 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, Kaster, Tomé 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, Jasińska and Rybakowski 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, Huang and Lin (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, Viale, Luckenbaugh 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,

Crocamo, Mazza et al. (2016) and Bartoli, Crocamo C, Dakanalis et al. (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, De Cori, Aguglia 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, Ghosal, Mitra 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, Permoda-Osip, Kasprzak 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, Milajerdi, Amini et al. 2006). The study performed by Machado-Vieira, Soares, Lara 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 by synergistic with lithium in the treatment of manic episodes in patients with BD.

The study of Jahangard, Soroush, Haghighi 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. Gürbüz Özgür, Aksu, Birincioğlu and Dost (2015) compared the effects of allopurinol with these 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, Crocamo, Clerici and Carrà (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, Ulrich, Zarate 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 Rda, Seibt, Rico 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, Rosa, Rosso 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, Marini, Serroni et al. 2013).

Both sleep deprivation and electroconvulsive therapy cause an increase in adenosine A1 receptors (Elmenhorst, Meyer, Winz 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, Jacintho Moritz, Vasconcelos-Moreno 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, Fries, de Aguiar 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, Camp, Hensel 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, Kittel and Sperlágh 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, Spies, Regenthal et al. 2004) and are important for antidepressant and anxiolytic effects (Kittner, Franke, Fischer 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, Brenner, Durany 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, Nöthen, Bryant 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, Fredholm, Morelli et al. 1997; Ferré, Ciruela, Quiroz et al. 2007; Rimondini, Ferré, Ogren and Fuxe 1997; Shen, Coelho, Ohtsuka et al. 2008; Villar-Menéndez, Díaz-Sánchez, Blanch et al. 2014). On the other hand, adenosine antagonists, such as caffeine, exert similar 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 dipyridamole 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, Shasavand, Jamilian et al. 2000; Weiser, Gershon, Rubinstein et al. 2012; Wonodi, Gopinath, Liu et al. 2011).

In animal models, A1 and A2A receptor agonists decrease behavioral activity caused by NMDA receptor antagonists (Popoli and Pepponi 2012; Sills, Azampanah and Fletcher 1999) and agonists of A2A receptors enhance glutamate release in glutamatergic neuronal endings of the striatum (De Mendonça, Sebastião and Ribeiro 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, Melone, Vallejo-Illarramendi and Conti 2005; Smith, Haroutunian, Davis and Meador-Woodruff 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, Shen, Augusto et al. 2015).

Zhang, Abdallah, Wang 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, Turčin, Dolžan, Porcelli, Serretti and Plesničar (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, Schmidt, Franke et al. 2010). Activation of these receptors also causes the hypofunction of NMDA receptors in the prefrontal cortex (Gonzalez-Burgos and Lewis 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 a euphorigenic effect, similar to that of dopamine (Krügel, Kittner and Illes 1999; Zhang, Yamashita, Ohshita 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, Csölle, Calovi 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, Leboyer, Gaman et al. 2015; Rajan, Zalpuri, Harrington 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, Permoda-Osip, Kasprzak 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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Janusz K. Rybakowski's additional information

A commentary on Walter Felber's paper on Lithium prevention of depression 100 years ago -- an ingenious misconception, published in 1987

Werner Felber's paper, *Die Lithiumprophylaxe der Depression vor 100 Jahren - ein genialem Irrtum*, was published a year after the 100th anniversary of Carl Lange's treatise on the periodic depressive states: *Om Periodiske Depressionstilstande og deres Patogenese* (Lange 1886). Lange's monograph was reproduced nine years later in German, translated by Hans Kurella, as *Periodische Depressionzustände und ihre Pathogenesis auf dem Boden der harnsauren Diathese* (On periodical depressions and their pathogenesis in the context of uric acid abnormality) (Lange 1895). Johan Schioldann's English translation appeared more than a 100 years later, in the beginning of the 21st century (Schioldann 2001).

Felber's paper consists of six parts: 1) Preface; 2) Short biography of Carl Lange and the German translator of his book, Hans Kurella; 3) Remarks on Lange's description of periodic depression; 4) Practical aspects of lithium therapy as performed by Carl Lange; 5) The reasons for the oblivion of epochal achievement; and 6) The pathway to lithium re-discovery.

In the preface, Felber underlined the significance of the Carl Lange's treatise of 1886 which became known to the wider public several years later thanks to German translation by Hans Kurella. The "uric acid diathesis" concept put forward in Lange's treatise provided the basis for long-term lithium administration in periodic depression. Felber estimates that during the 20 years of his psychiatric ambulatory practice Lange treated about 2,000 of such patients with lithium.

In the second part, the short biographies of Carl Lange (1834-1900) and Hans Kurella (1858-1916) were provided. The latter, a German psychiatrist promoted by Karl Kahlbaum,

was a keen translator of neurological, psychiatric, anthropological and sociopolitical works of foreign authors, among them Scandinavian and Italian.

The remarks on Lange's description of periodic depression pay great tribute to the clinical astuteness of the Danish physician. Mental and somatic symptoms of depression were delineated, most of which comply with contemporary diagnostic criteria of depression. Among the first are, among others, mental stiffness or paralysis, inability to initiate motor or mental activity, lack of spirits and concomitant anxiety. Within the second group, variable painful symptoms, vegetative disturbances, loss of weight and abnormalities of sleep are listed. In his treatise, Lange also points at circadian mood changes, with the worse mood in the morning in a majority of patients. Felber also mentions Lange's observations on the periodicity and natural course of the illness which are to a great extent similar to contemporary views on the major depressive disorder of mild to moderate intensity.

In the fourth part, Felber describes lithium administration outlined by Carl Lange, regarding dose and method of administration. The drug was given as lithium carbonate powder, 8-40 mmol lithium per day, in 3-4 doses. The daily amount of lithium is therefore comparable to what is used today. Lithium carbonate was dissolved in water or lemonade. In the end, Felber quotes Lange's statement that long-term treatment with lithium caused a disappearance or decrease of depressive episodes with significant prolongation of remission, although in most cases, the illness was not fully cured.

In the fifth part of the paper, Felber argues that the forgotten reason for introducing lithium into treatment of mood disorders by Lange was that the idea of uric acid diathesis behind it was false and was refuted by both psychiatrists and practitioners of general medicine where this kind of diathesis was a basis for using lithium in the treatment of rheumatic diseases.

In his final part (6), Felber mentions John Cade who related to Garrod's work on using lithium in gout on account of the suspected excess of uric acid in this condition (Garrod 1859). However, he did not mention the full story of Cade's experiments which gave rise to the introduction of lithium into contemporary psychiatry. One of Cade's premises was based on the excess of uric acid in manic patients. In the last paragraph of the paper, in relation to Carl Lange's work, Felber speculates about the discrepancy between theory and practice, showing how a false theory could sometimes result in a spectacular clinical achievement.

However, as far as pathogenesis of psychiatric disorders is concerned, the situation nowadays is entirely different from that of 30 years ago when Falber was writing his paper. In the recent two decades it has been found that both uric acid, as the final metabolite of purine bases, and some purines (e.g., adenosine), may play a role in the regulation of psychological

processes, including mood and activity. Concomitantly, new evidence has been accumulated concerning a role of uric acid in the pathogenesis and treatment of bipolar disorder (BD). In patients with BD, a higher prevalence of gout and increased concentration of uric acid have been found, and the therapeutic efficacy of allopurinol, used as an adjunct to mood stabilizers, has been demonstrated in mania. In recent years, research on the role of the purinergic system in the pathogenesis and treatment of mood disorders (and also schizophrenia) has focused on the role of adenosine (P1) receptors and nucleotide (P2) receptors. Activation of adenosine receptors is related to antidepressant activity. Alterations of P2 receptors (mostly P2X7 receptors) has been found significant for the pathogenesis of mood disorders, especially bipolar disorder (Malewska-Kasprzak, Permoda-Osip, Rybakowski 2018). Therefore, a direct connection between uric acid and bipolar disorder, and indirectly with lithium, as the main therapeutic modality in this disorder can no longer be denied.

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