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 triphosphohydrolases), 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 confirmed 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 (Lazarski, 2012). The concentration of ecto-purine 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 deamminated 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
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 psychopathological 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-
The chromosome reexpression in brain neurons and oligodendrocytes in the spinal cord, astrocytes is widely distributed but low expression levels in sensory neurons, nucleus tractus solarius neurons, and in the brain neurons and oligodendrocytes in the spinal cord, astrocytes is widely distributed but low expression levels in sensory neurons, nucleus tractus solarius neurons, astrocytes.

In CNS neurons, motor neurons in spinal cord, astrocytes, high levels in dopaminergic neurons, thalamic nucleus, hypothalamus and substantia nigra, the 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 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 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, 2008). 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 (Giessler 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, 2008; 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 ensiformis, 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 & Pile, 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 anti-psychotic 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, Anumoney found that remission of manic symptoms is accompanied by increased excretion of uric acid (Anumoney 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 (Keszthelyi 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 (Akhoundzadeh 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 (Akhoundzadeh 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, y-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 (Cieslak 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
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 concentrations 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, which raises 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 predominance 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.

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

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Second messenger</th>
<th>Patophysiological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>cAMP, K+, Ca2+</td>
<td>hyperpolarization of neurons, sedative, anticonvulsant, anxiolytic, locomotor depressant</td>
</tr>
<tr>
<td>A2A</td>
<td>cAMP, IP, cAMP</td>
<td>inhibition of dopamine-induced effects, pain modulation, immune system modulation</td>
</tr>
<tr>
<td>A2B</td>
<td>cAMP, IP</td>
<td>modulation of the immune system</td>
</tr>
<tr>
<td>A3</td>
<td>cAMP, IP</td>
<td>modulation of inflammatory response, locomotor depressant</td>
</tr>
</tbody>
</table>

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**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.
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 glutamergic 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 (Cieslak 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; Gajewksa, 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.

Dipiridamole (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.

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