Purinergic Signalling and Neurological Diseases: An Update

Running title: Purines and brain disorders

Purinergic Signalling and Neurological Diseases: Update

By

Geoffrey Burnstock

Autonomic Neuroscience Centre

Royal Free and University College School of Medicine

Rowland Hill Street

London NW3 2PF

Tel: +44 (0)20 7830 2948

Fax: +44 (0)20 7830 2949

Email: g.burnstock@ucl.ac.uk

and

Department of Pharmacology and Therapeutics,

The University of Melbourne,

Melbourne,

Australia

Abstract: Purinergic signalling, i.e. ATP as an extracellular signalling molecule and cotransmitter in both peripheral and central neurons, is involved in the physiology of neurotransmission and neuromodulation. Receptors for purines have been cloned and characterised, including 4 subtypes of the P1(adenosine) receptor family, 7 subtypes of the P2X ion channel nucleotide receptor family and 8 subtypes of the P2Y G protein-coupled nucleotide receptor family. The roles of purinergic signalling in diseases of the central nervous system and the potential use of purinergic compounds for their treatment are attracting increasing attention. In this review, the focus is on the findings reported in recent papers and reviews to update knowledge in this field about the involvement of purinergic signalling in Alzheimer's, Parkinson's and Huntington's diseases, multiple sclerosis, amyotrophic lateral sclerosis, degeneration and regeneration after brain injury, stroke, ischaemia, inflammation, migraine, epilepsy, psychiatric disorders, schizophrenia, bipolar disorder, autism, addiction, sleep disorders and brain tumours. The use in particular of P2X7 receptor antagonists for the treatment of neurodegenerative diseases, cancer, depression, stroke and ischaemia, A_{2A} receptor antagonists for Parkinson's disease and agonists for brain injury and depression and P2X3 receptor antagonist for migraine and seizures have been recommended. P2Y receptors have also been claimed to be involved in some central nervous disorders.

1. INTRODUCTION

The concept of purinergic signalling, i.e. adenosine 5'-triphosphate (ATP) as an extracellular signalling molecule, was proposed in 1972 [1]. ATP was later shown to be a cotransmitter with established neurotransmitters in both the peripheral and central nervous systems [2, 3]. Receptor families for ATP (P2) and to its breakdown product adenosine (P1) were recognised in 1987 [4]. In the early 1990's, P1 and P2 receptor subtypes were cloned and characterised (see [5]): four subtypes of P1 receptors (A_1, A_{2A}, A_{2B} and A_3); seven subtypes of P2X ion channel receptors (P2X1-7) and eight P2Y G protein-coupled receptors (P2Y$_{1, 2, 4, 6, 11, 12, 13}$ $_{and\ 14}$) are recognised (see [6]).

Reviews have been published previously about purinergic signalling and neurological disorders [7-15]. However, this field is currently attracting much attention, so this review is an update of recent findings.

2. NEURODEGENERATIVE DISEASES

Neurodegeneration is the basis of a wide range of central nervous system (CNS) diseases, involving both neurons and glial cells and inflammation [16] and there is recognition of the participation of purinergic signalling (see [9, 10, 17]). A recent review focuses on the supportive and detrimental roles of P2Y receptors in neurodegeneration [18]. Another review considers nucleotide salvage deficiencies and DNA damage in neurodegenerative diseases [19]. A third review focuses on the neuromodulatory actions mediated by P2X receptors in neurodegenerative diseases [20]. The role of the P2Y-like receptor, GPR17, in CNS remyelination is gaining attention as a novel reparative approach to neurodegenerative diseases [15].

2.1. Alzheimer's disease

Alzheimer's disease is characterised by progressive cognitive impairment, initially with prominent deficits in short term memory. There has been much interest in recent years about the potential of purinergic drugs for the treatment of Alzheimer's disease. Previous studies suggested that both P2X7 and P2Y$_4$ receptor antagonists are potential therapeutic targets for the treatment of Alzheimer's disease [8, 21]. This has received support in recent reviews [20, 22-24]. It has be reported that β-amyloid increases release of ATP which, via P2X receptors, potentiates excitatory synaptic activity; these effects were blocked by P2X antagonists [25]. It has been claimed that adenosine A_3 receptor agonists suppress amyloid-β protein precursor internalization and amyloid-β generation [26]. Hippocampal adenosine A_{2A} receptor up-regulation has been reported to be necessary to trigger memory dysfunction in Alzheimer's disease [27].

2.2. Parkinson's disease

The main focus has been on the involvement of adenosine A_{2A} receptors in Parkinson's disease and their interactions with dopamine receptors, although P2X7 receptor antagonists have also been implicated in this disease [28, 29]. A_{2A} receptor antagonists have been recommended as symptomatic treatment for Parkinson's disease [30, 31]. More recent papers have implicated the involvement of ATP-sensitive potassium channels (K_{ATP}) in Parkinson's disease [32]. A role for P2X1 receptors in Parkinson's pathogenesis has also been reported, perhaps identifying a new therapeutic target [33, 34]. Clinical trials for the use of istradefylline, an A_{2A} antagonist, have been undertaken and it was suggested that it could be an efficacy and safety augmentation drug added on to levodopa or other existing anti-Parkinson's therapies [35]. Later studies have supported this strategy

[36, 37]. A_{2A} receptor blockade prevented rotenone-induced motor impairment in a rat model of parkinsonism and this was taken to reinforce the potential use of A_{2A} receptor antagonists for the treatment of Parkinson's patients [38].

2.3. Huntington's disease

Earlier studies showed that A_{2A} receptor agonists had beneficial effects for Huntington's disease and that P2X7 receptor antagonists prevented neuronal apoptosis and attenuated body weight loss and motor co-ordination effect deficit in Huntington's patients (see [29]). It has been reported that inactivation of adenosine A_{2A} receptors reverses working memory deficits at early stages of Huntington's disease models and it was suggested that A_{2A} receptor antagonists would be novel targets to reverse cognitive deficits in Huntington's patients [39]. In an earlier publication, adenosine A_1 receptor agonists were also considered as a therapeutic target for this disease [40, 41].

2.4. Multiple sclerosis (MS)

Both P2X7 receptors and the P2Y-like GPR17 receptor were shown to be involved in MS [29, 42]. Upregulation of ecto-5'-nucleotidase (CD73) during experimental autoimmune encephalomyelitis, a model of MS, has been reported [43].

2.5. Amyotrophic lateral sclerosis (ALS)

The involvement of A_{2A}, P2X4 and P2X7 receptors in ALS has been described (see [44]). A_1 as well as A_{2A} adenosine receptor subtypes have also been implicated in ALS [45]. Preconditioning with latrepirdine, an adenosine 5'-monophosphate-activated protein kinase activator, has beneficial effects on the progression of the disease in the SOD1 mouse model of ALS [46]. Activation of A_{2A} receptors facilitates neuromuscular transmission in the pre-symptomatic phase of the SOD1 ALS mice, but not in the symptomatic phase [47].

3. BRAIN TRAUMA, INCLUDING STROKE, ISCHAEMIA AND INFLAMMATION

3.1. Brain injury

Traumatic brain injury results in cell death, inflammation and neurologic dysfunction in patients. The roles of purinergic signalling in neurodegeneration following brain injury have been reviewed [29, 48]. Brain stab injury alters ectonucleotidase activities and nucleotide levels in serum [49, 50]. P2X7 receptors play a critical role in radiation-induced brain injury, suggesting that P2X7 receptor antagonists might be effective for the treatment of patients with radiation injury [51]. Evidence has been presented to suggest that astrocytic *p*-connexin 43 promotes neuronic autophagy via activation of P2X7 receptors in the hippocampus, promoting repair of brain injury-induced cognitive deficits [52]. Neuroblasts migrate to sites of brain damage and activation of upregulated $P2Y_1$ receptors contribute to this event [53]. A_{2A} receptor activation has been recommended for the treatment of brain injury and subsequent neuroinflammation [54]. A_{2A} receptors on bone marrow-derived cells are modulators of white matter lesions induced by chronic cerebral hypoperfusion [55].

3.2. Stroke

It has been proposed that P2X7 receptor antagonists would be effective to treat the occurrence of post-stroke pain and may be beneficial for the recovery of patients following stroke [56]. A beneficial role for P2X7 receptor activation in acute ischaemic stroke has been reported, by limiting the early oedema formation and possibly by modulating glial responses [57].

3.3. Ischaemia

Extracellular concentrations of ATP and adenosine in the brain increase dramatically during ischaemia that activate both P1 and P2 receptors [58]. Evidence has been presented showing that P2X4 receptors expressed on microglia are involved in the post-ischaemic inflammation in brain ischaemic injury (see [59]). Hypoxic-ischaemic brain injury triggers an inward current and increase in intracellular Ca^{2+} in oligodendrocytes, which is partly mediated by P2X7 receptors (see [60]). Neuronal K_{ATP} channels were reported to mediate hypoxic preconditioning and reduce subsequent neonatal hypoxic-ischaemic brain injury and it was suggested that K_{ATP} channel openers may have therapeutic possibilities [61]. P2X7 antagonists or blockade of pannexin-1 channels attenuates post-ischaemic brain damage [62, 63]. Intranasal administration of guanosine reduced brain damage induced by ischaemia in rats [64].

Both A_{2A} receptor agonists and antagonists have been claimed to be protective against ischaemic brain injury (see [65]). In a recent paper, A_1 receptors were reported to contribute to immune regulation after neonatal hypoxic ischaemic brain injury [66].

3.4. Inflammation

Recent reviews summarise the importance of inflammation in the responses to brain injury and disease, including bacterial infection and neurological disorders and the involvement of P1 and P2 receptors [67, 68] and of P2X7 receptors in particular [69].

4. NEUROPROTECTION AND NEUROREGENERATION

4.1. Neuroprotection

Recent reviews explore this topic [17, 29, 70]. Both blockade of ATP activation of P2X and P2Y receptors and the action of adenosine, after ectoenzymatic breakdown of ATP released from cells in the CNS, are claimed to be neuroprotective. Activation of the pannexin 1/P2X7 receptor complex appears to play a role in the neuroprotective mechanism of ischaemic pre- and post-conditioning [63]. It has been suggested that dietary docosahexaenoic acid may act as a purinergic modulator via P2X receptors to protect against neurodegenerative diseases [71]. Neuroprotection has been claimed to be mediated by $P2Y_{13}$ nucleotide receptors in neurons [72]. A recent study showed that microglia-mediated neuroprotection depends on ATP-activated P2X7 receptors and induction of tumour necrosis factor-α release [73]. Blockade of P2X7 receptors provides neuroprotection to various neurological disorders, including stroke, traumatic brain injury and subarachnoid haemorrhage [74].

Recent reviews have focussed on the roles played by P2X4 and P2X7 receptors [75] and A_{2A} receptors [76] in neurodegeneration and neuroprotection.

4.2. Neuroregeneration

6

A recent review focussed on neuroregeneration is available [29]. Activation of P2Y$_2$ receptors promotes regeneration of both nerves and glial cells and the P2Y-like GPR17 receptor promotes regeneration of oligodendrocytes. Activation of neural stem cells results in neuroregeneration, probably via P2X4 and P2X7 receptors. Lysosome-mediated ATP exocytosis and calcium signalling appear to play a role in astrocytic responses and may benefit the optimization of scaffold design for CNS healing [77].

4.3. Migraine

The involvement of ATP in migraine was first considered in a vascular theory for this disorder (see [10, 78]). Later, the involvement of P2X3 receptors in brain areas that mediate nociception, such as the trigeminal nucleus and thalamus, was explored [79] and the interaction with P2Y$_1$ receptors in trigeminal neurons. The therapeutic potential of P2X7 antagonists for the treatment of migraine has also been proposed [80], as well as P2X3 and P2X2/3 receptor antagonists [81]. A review of the roles of purinergic signalling in the aetiology of migraine concluded that 'purinergic receptors can be an excellent target for pharmacologists constructing new antimigraine therapeutics' [82].

4.4. Epileptic seizures

Early attention was on the role of P1 adenosine receptors in epileptic seizures, but more recently P2X4 and P2X7 receptor antagonists have been explored as neuroleptic agents [8, 83, 84]. P2Y$_{12}$ knockout mice exhibited reduced seizure-induced increases in microglial process numbers and worsened kainate-induced seizure behaviours [85]. It has been suggested that the antiepileptic effects of deep brain stimulation may be mediated by adenosine [86]. Experiments support a role for post-transcriptional regulation of the P2X7 receptors and it was suggested that therapeutic targeting of microRNA-22 may prevent inflammation and development of epilepsy [87]. Upregulated expression of P2X3 receptors was demonstrated in both epileptic humans and rats and it was suggested that P2X3 receptor antagonists may represent novel therapeutic targets for antiepileptic drugs [88]. Microelectrode biosensors have been used to measure the release of ATP and adenosine during on-going epileptiform activity [89]. Increased levels of ATP were shown during epileptic seizures, which were not of neuronal origin [90]. An insightful Editorial was published recently about purinergic signalling-induced neuroinflammation in epilepsy [91].

5. PSYCHIATRIC DISORDERS

Antipsychotic drugs, such as haloperidol, chlorpromazine and fluspirilene, inhibited ATP-evoked responses mediated by P2X receptors. Such antipsychotic drugs have a therapeutic effect by suppressing dopaminergic hyperactivity through inhibition of P2X-mediated effects (see [8]). Haloperidol was shown to be an inhibitor of NTPDase and adenosine deaminase activities in zebrafish brain [92]. Reviews concerned with the roles of purinergic signalling in psychiatric disorders, including schizophrenia, bipolar disorder, depression and addiction, as well as autism (a developmental disorder), have been published [93-95]. A recent review raises the possibility that increases in adenosine concentrations in the brain by increasing activation of NTPDases, inhibition of adenosine deaminase and/or adenosine kinase, as well as the use of P1 receptor agonists, might be beneficial in therapy of psychiatric disorders [96].

5.1. Schizophrenia

Most attention has been paid to adenosine neuromodulation in schizophrenia (see [97, 98]). For example, deletion of A_{2A} receptors from astrocytes disrupts glutamate homeostasis leading to psychomotor and cognitive impairment, relevant to schizophrenia [99]. However, there is also evidence that P2X7 receptors and pannexin 1 channels are involved (see [10, 100]).

5.2. Bipolar disorder

There is increasing evidence that P2X7 receptors, mediating neuroinflammation, via the activity of microglia, play a role in bipolar disorder (see [101-103]). Increased serum levels of uric acid have been demonstrated in different phases of bipolar disorder in patients [104] and those patients treated with lithium [105]. This implied that dysregulation of the purinergic system may occur during manic episodes and suggested that increased uric acid levels may be a useful marker for the manic phase of bipolar disorder. It has been claimed that purinergic modulators that lower uric acid levels could play a role in clinical practice [106].

5.3. Mood disorder

Reviews are available describing the roles of both P1 (A_1 and A_{2A}) and P2X7 receptors in mood disorders [9, 107-109].

Antidepressant and anticompulsive effects of P2X7 antagonists have been reported [110]. P2X2 receptors in the medial prefrontal cortex were shown to mediate the antidepressant-like effects of ATP released from astrocytes [111]. Brilliant blue G, a P2X7 receptors antagonist, had anti-inflammatory and antidepressant effects in mice after lipopolysaccharide administration [112]. The P2X7 receptor antagonist, A-804598, was shown to have an impact on the neuroimmune and behavioural consequences of stress [113]. A mutation causing increased K_{ATP} channel activity was reported to lead to reduced anxiety in mice [114].

An A_{2A} receptor antagonist was reported to have antidepressant activity [93]. It was claimed that creatine and ketamine had antidepressant effects, probably mediated by activation of A_1 and A_{2A} receptors [115]. Caffeine, acting as an antagonist at A_{2A} receptors, prevented depression and memory dysfunction triggered by chronic stress [116]. It was reported that striatal and extrastriatal A_{2A} receptors in the forebrain regulate fear responses in mice [117]. Adenosine, via A_{2A} receptors, increased interleukin 1β in the brain contributing to anxiety [118]. Administration of a derivative of adenosine, WS0701, alleviated anxiety and fear in a mouse model of posttraumatic stress disorder [119]. In the aetiology of anxiety disorders and addiction, the basolateral amygdala plays a critical role and adenosine, via activation of A_{2A} receptors, facilitated basolateral amygdala pyramidal cell output [120].

5.4. Autism

Both adenosine and suramin, a non-selective antagonist of ATP, have been claimed to reverse autism-like behaviours [121-123].

5.5. Addiction

There is experimental evidence that targeting A_{2A} receptors may offer innovative translational strategies for combating drug addiction [124]. It is generally accepted that behavioural sensitization in animals provides a

model for drug craving believed to underlie addiction in humans and sensitization to amphetamine was interrupted by P2Y$_1$ receptor blockade in the mesocortico-limbic dopaminergic system [125]. Striatopallidal A$_{2A}$ receptor signalling in the dorsomedial striatum may be a therapeutic target to reverse abnormal habit formation associated with drug addiction [126]. Caffeine, an adenosine receptor antagonist, potentiates the addictive effects of drugs of abuse, including cocaine, amphetamine derivatives and energy drinks with alcohol [127].

5.5.1. Opiates

Treatment of rodents with the P2X7 receptor antagonist, 2',3'-O-(2,4,6-trinitrophenyl) adenosine 5'-triphosphate (TNP-ATP), diminished opioid tolerance, in part by inhibiting excitatory amino acid release [128]. Opiate-induced changes in brain adenosine levels may explain some of the neurobehavioral features associated with opiate addiction and withdrawal [129]. Heroin administration may enhance the catabolism and inhibit the anabolism of purine nucleotides in the brain [130].

5.5.2. Cocaine

Adenosine, acting via A$_{2A}$ receptors, regulated addiction induced by cocaine [131]. Enhancement of dopamine function via A$_{2A}$ receptor blockade was suggested for reducing the neurobehavioral deficits associated with chronic cocaine addiction [132]. Females have a higher sensitivity and thus higher vulnerability to cocaine abuse compared to males; treatment with adenosine receptor antagonists was identified as a possible treatment [133]. Cocaine self-administration differentially affects A$_{2A}$-D$_2$ receptor-receptor interactions in the dorsal striatum, which would contribute to the development of compulsive drug seeking [134].

5.5.3. Methamphetamine

Methamphetamine transiently increased the expression of the ATP-binding cassette transporter ABCB1 [135]. Striatal A$_{2A}$ and glutamate (mGlu5) receptor interactions modulate the psychomotor and drug-seeking effects of methamphetamine [136]. Methamphetamine self-administration produces selective alterations in adenosine receptor expression in the nucleus accumbens and stimulation of adenosine receptors reduces several behavioural indices of methamphetamine addiction [137]. A$_{2A}$ receptor antagonism in dorsomedial striatum reduces methamphetamine-induced deficits [138]. Adenosine A$_{2A}$ receptors are needed to integrate rewarding and motivational behaviours of methamphetamine [139].

5.5.4. Nicotine

Treatment with A$_{2A}$ receptor agonists can help counteract the nicotine addiction [140].

5.5.5. Alcohol

A$_{2A}$ receptors were suggested to be a potential target for the treatment of alcohol abuse [141, 142]. A review focussed on the regulation of adenosine signalling in striatal circuits in alcohol addiction is available [143]. A$_1$ receptor signalling may play a role in regulating basolateral amygdala excitability, contributing to the pathophysiology of alcohol addiction [144]. P2X4 receptors have been claimed to modulate synaptic signalling associated with alcohol addiction [145]. A recent review about alcohol addiction includes consideration of the role of adenosine [146].

6. NEUROPATHIC PAIN

Evidence for the involvement of both P1 and P2 receptors in neuropathic pain has been reviewed [9, 147-149]. The discovery by Inoue and colleagues that antagonists to P2X4 and P2X7 receptors on microglia were effective against neuropathic pain was particularly important (see [150, 151]). P1 and P2Y receptors have also been shown to be involved (see [152]). A_3 receptor agonists prevent the development of neuropathic pain [153]. Glial $P2Y_2$ receptors have been proposed as potential targets for the management of trigeminal-related pain [154]. An interaction between pannexin 1 and P2X7 receptors has been implicated in chronic pain [155]. The expression levels of P2X1 and P2X5 receptors increased in neuropathic pain [156].

7. COGNITIVE IMPAIRMENT

Earlier papers reported the involvement of P1 receptors in the cognitive impairment associated with Alzheimer's disease as well as physiological aging (see [9, 157]). It has been suggested that blockade of either A_1 or A_{2A} receptors may be potentially effective for the treatment of attention-deficit hyperactivity disorder. P2X7 receptors were also implicated. In a recent review, knowledge of the role of glial purinergic signalling in cognitive-related neurological diseases is discussed [158]. Activation of $P2Y_1$ receptors in the medial prefrontal cortex impairs cognition [159, 160]. TNP-ATP, a selective antagonist at P2X1 and P2X3 receptors, was beneficial for the treatment of neonatal hypoxia-induced hypomyelination and cognitive decline ([161]; see also the review by Guzman and Gerevich [162]).

8. BRAIN TUMOURS

Neuroblastoma, a tumour in childhood, expresses P2X7 receptors, which appear to mediate proliferation [163]. In a later paper, it was reported that P2X7 receptors mediate modulation of myeloid-derived suppressor cell functions in the neuroblastoma microenvironment [164]. Data was presented to suggest that the P2X7 receptor is an upstream regulator of the main signalling pathways involved in neuroblastoma growth, metabolic activity and angiogenesis and it was suggested that it may be a promising therapeutic target for neuroblastoma treatment [165]. The effect of temozolomide, an antitumor agent, was potentiated by the antiproliferative actions of antagonists to A_3, $P2Y_1$ and P2X7 receptors [166].

P2X7 receptors were found to be over-expressed in human gliomas and antagonists resulted in a decrease in tumour cell number, suggesting that they may be a therapeutic target for human glioma proliferation [167]. CD38, a multifunctional enzyme, decreased intracellular levels of ATP and mediated reduction of C6 glioma cells and it was suggested that P2X receptors contributed to this action [168]. It was claimed that K_{ATP} channels are associated with cell proliferation and tumorigenesis of human glioma [169]. Extracellular nucleotides control glioma growth via P2X7 and $P2Y_6$ receptor activation, resulting in secretion of inflammatory cytokines; growth was reduced with antagonists to these receptors [170]. A_{2A} and P2X7 receptor activation is necessary for release of cytokines by macrophages exposed to glioma-conditioned medium; this was prevented by antagonists to these receptors [171]. BMS-536924, an ATP-competitive insulin-like growth factor receptor inhibitor, decreased viability and migration of glioma cells *in vitro* and suppressed tumour growth *in vivo* [172].

9. NEUROAIDS

It has been suggested that P2X4 receptors may be novel therapeutic targets for restricting synaptodendritic injury and neurodegeneration that accompanies neuroAIDS and opiate abuse [173]. Astrocytes mediate HIV-1 Tat-induced neuronal damage via P2X7 receptors and P2X receptor antagonists reduced HIV Tat-induced neuronal death, suggesting that it would be a novel target for therapeutic management of neuroAIDS [174].

10. SLEEP DISORDERS

Evidence was presented to suggest that $P2Y_{11}$ receptors are associated with narcolepsy [175]. Endothelial dysfunction in cerebral arteries, due to reduced dilation to ATP, occurred in a rat model of obstructive sleep apnoea [176]. Adenosine was identified as one of the players in the regulation and maintenance of sleep-wake dependent changes in neural activities; dysregulation leads to sleep-wake disorders [177].

CONCLUSIONS

This review has aimed at updating information about the roles of purinergic signalling in a wide variety of disorders of the CNS. The use of P2X7 and A_{2A} receptor antagonists for therapeutic treatment in particular is gaining attention.

LIST OF ABBREVIATIONS:

ATP - Adenosine 5'-triphosphate

ALS - Amyotrophic lateral sclerosis

CNS – Central nervous system

MS - Multiple sclerosis

CONFLICT OF INTEREST

The author confirms that this article content has no conflicts of interest.

REFERENCES

[1]   Burnstock G. Purinergic nerves. Pharmacol Rev 1972; 24: 509-81.

[2]   Burnstock G. Do some nerve cells release more than one transmitter? Neuroscience 1976; 1: 239-48.

[3]   Burnstock G. The Erasmus Lecture 2012, Academia Europaea. The concept of cotransmission: focus on ATP as a cotransmitter and its significance in health and disease. Eur Rev 2014; 22: 1-17.

[4]   Burnstock G. A basis for distinguishing two types of purinergic receptor. In: Straub RW, Bolis L, eds. Cell Membrane Receptors for Drugs and Hormones: A Multidisciplinary Approach. New York: Raven Press 1978: 107-118.

[5]   Ralevic V, Burnstock G. Receptors for purines and pyrimidines. Pharmacol Rev 1998; 50: 413-92.

[6]   Burnstock G. Purine and pyrimidine receptors. Cellular and Molecular Life Sciences 2007; 64: 1471-83.

[7]   Burnstock G. Purinergic signalling and disorders of the central nervous system. Nature Reviews Drug Discovery 2008; 7: 575-90.

[8]   Burnstock G. Physiopathological roles of P2X receptors in the central nervous system. Curr Med Chem 2015; 22: 819-44.

[9]   Burnstock G, Krügel U, Abbracchio MP, Illes P. Purinergic signalling: from normal behaviour to pathological brain function. Prog Neurobiol 2011; 95: 229-74.

[10]   Burnstock G, Verkhratsky A. Purinergic signalling and the nervous system. Heidelberg/Berlin: Springer 2012; pp. 1-715.

[11]   Chiu GS, Freund GG. Modulation of neuroimmunity by adenosine and its receptors: metabolism to mental illness. Metabolism 2014; 63: 1491-8.

[12]   Puchalowicz K, Tarnowski M, Baranowska-Bosiacka I, Chlubek D, Dziedziejko V. P2X and P2Y receptors-role in the pathophysiology of the nervous system. Int J Mol Sci 2014; 15: 23672-704.

[13]   Boison D, Aronica E. Comorbidities in neurology: is adenosine the common link? Neuropharmacology 2015; 97: 18-34.

[14]   Tewari M, Seth P. Emerging role of P2X7 receptors in CNS health and disease. Ageing Res Rev 2015; 24: 328-42.

[15]   Fumagalli M, Lecca D, Abbracchio MP. CNS remyelination as a novel reparative approach to neurodegenerative diseases: The roles of purinergic signaling and the P2Y-like receptor GPR17. Neuropharmacology 2016; 104: 82-93.

[16]   Rama Rao KV, Kielian T. Neuron-astrocyte interactions in neurodegenerative diseases: Role of neuroinflammation. Clin Exp Neuroimmunol 2015; 6: 245-63.

[17]   Illes P, Verkhratsky A. Purinergic neurone-glia signalling in cognitive-related pathologies. Neuropharmacology 2016; 104: 62-75.

[18]   Förster D, Reiser G. Supportive or detrimental roles of P2Y receptors in brain pathology?--The two faces of P2Y receptors in stroke and neurodegeneration detected in neural cell and in animal model studies. Purinergic Signal 2015; 11: 441-54.

[19]   Fasullo M, Endres L. Nucleotide salvage deficiencies, DNA damage and neurodegeneration. Int J Mol Sci 2015; 16: 9431-49.

[20]   Sáez-Orellana F, Godoy PA, Silva-Grecchi T, Barra KM, Fuentealba J. Modulation of the neuronal network activity by P2X receptors and their involvement in neurological disorders. Pharmacol Res 2015; 101: 109-15.

[21]   Li HQ, Chen C, Dou Y *et al.* P2Y$_4$ receptor-mediated pinocytosis contributes to amyloid beta-induced self-uptake by microglia. Mol Cell Biol 2013; 33: 4282-93.

[22]   Miras-Portugal MT, Diaz-Hernandez JI, Gomez-Villafuertes R, Diaz-Hernandez M, Artalejo AR, Gualix J. Role of P2X7 and P2Y$_2$ receptors on α-secretase-dependent APP processing: Control of amyloid plaques formation "*in vivo*" by P2X7 receptor. Comput Struct Biotechnol J 2015; 13: 176-81.

[23]   Erb L, Cao C, Ajit D, Weisman GA. P2Y receptors in Alzheimer's disease. Biol Cell 2015; 107: 1-21.

[24]   Woods LT, Ajit D, Camden JM, Erb L, Weisman GA. Purinergic receptors as potential therapeutic targets in Alzheimer's disease. Neuropharmacology 2016; 104: 169-79.

[25]   Sáez-Orellana F, Godoy PA, Bastidas CY *et al.* ATP leakage induces P2XR activation and contributes to acute synaptic excitotoxicity induced by soluble oligomers of β-amyloid peptide in hippocampal neurons. Neuropharmacology 2016; 100: 116-23.

[26]   Li S, Geiger NH, Soliman ML, Hui L, Geiger JD, Chen X. Caffeine, through adenosine A3 receptor-mediated actions, suppresses amyloid-β protein precursor internalization and amyloid-β generation. J Alzheimers Dis 2015; 47: 73-83.

[27]   Cunha R. Hippocampal adenosine A2A receptor up-regulation isnecessary and sufficient to trigger memory dysfunction inAlzheimer's disease. Journal of Neurochemistry 2015; 134: 322.

[28]   Jörg M, Scammells PJ, Capuano B. The dopamine D$_2$ and adenosine A$_{2A}$ receptors: past, present and future trends for the treatment of Parkinson's disease. Curr Med Chem 2014; 21: 3188-210.

[29]   Burnstock G. Purinergic signalling in neuroregeneration. Neural Regeneration Research 2015; 10: 1919.

[30]   Jenner P. An overview of adenosine A$_{2A}$ receptor antagonists in Parkinson's disease. Int Rev Neurobiol 2014; 119: 71-86.

[31]   Mori A. Mode of action of adenosine A$_{2A}$ receptor antagonists as symptomatic treatment for Parkinson's disease. Int Rev Neurobiol 2014; 119: 87-116.

[32]   Dragicevic E, Schiemann J, Liss B. Dopamine midbrain neurons in health and Parkinson's disease: emerging roles of voltage-gated calcium channels and ATP-sensitive potassium channels. Neuroscience 2015; 284: 798-814.

[33]   Gan M, Moussaud S, Jiang P, McLean PJ. Extracellular ATP induces intracellular alpha-synuclein accumulation via P2X1 receptor-mediated lysosomal dysfunction. Neurobiol Aging 2015; 36: 1209-20.

[34]   Navarro G, Borroto-Escuela DO, Fuxe K, Franco R. Purinergic signaling in Parkinson's disease. Relevance for treatment. Neuropharmacology 2016; 104: 161-8.

[35]   Tao Y, Liang G. Efficacy of adenosine A2A receptor antagonist istradefylline as augmentation for Parkinson's disease: a meta-analysis of randomized controlled trials. Cell Biochem Biophys 2015; 71: 57-62.

[36] Uchida S, Soshiroda K, Okita E *et al.* The adenosine A2A receptor antagonist, istradefylline enhances the anti-parkinsonian activity of low doses of dopamine agonists in MPTP-treated common marmosets. Eur J Pharmacol 2015; 747: 160-5.

[37] Vorovenci RJ, Antonini A. The efficacy of oral adenosine A_{2A} antagonist istradefylline for the treatment of moderate to severe Parkinson's disease. Expert Rev Neurother 2015; 15: 1383-90.

[38] Fathalla AM, Soliman AM, Ali MH, Moustafa AA. Adenosine A_{2A} receptor blockade prevents rotenone-induced motor impairment in a rat model of parkinsonism. Front Behav Neurosci 2016; 10: 35.

[39] Li W, Silva HB, Real J *et al.* Inactivation of adenosine A_{2A} receptors reverses working memory deficits at early stages of Huntington's disease models. Neurobiol Dis 2015; 79: 70-80.

[40] Ferrante A, Martire A, Pepponi R *et al.* Expression, pharmacology and functional activity of adenosine A_1 receptors in genetic models of Huntington's disease. Neurobiol Dis 2014; 71: 193-204.

[41] Lee CF, Chern Y. Adenosine receptors and Huntington's disease. Int Rev Neurobiol 2014; 119: 195-232.

[42] Plemel JR, Keough MB, Duncan GJ *et al.* Remyelination after spinal cord injury: is it a target for repair? Prog Neurobiol 2014; 117: 54-72.

[43] Lavrnja I, Laketa D, Savic D *et al.* Expression of a second ecto-5'-nucleotidase variant besides the usual protein in symptomatic phase of experimental autoimmune encephalomyelitis. J Mol Neurosci 2015; 55: 898-911.

[44] Volonté C, Apolloni S, Parisi C, Amadio S. Purinergic contribution to amyotrophic lateral sclerosis. Neuropharmacology 2016; 104: 180-93.

[45] Nascimento F, Sebastião AM, Ribeiro JA. Presymptomatic and symptomatic ALS SOD1(G93A) mice differ in adenosine A_1 and A_{2A} receptor-mediated tonic modulation of neuromuscular transmission. Purinergic Signal 2015; 11: 471-80.

[46] Coughlan KS, Mitchem MR, Hogg MC, Prehn JH. "Preconditioning" with latrepirdine, an adenosine 5'-monophosphate-activated protein kinase activator, delays amyotrophic lateral sclerosis progression in SOD1(G93A) mice. Neurobiol Aging 2015; 36: 1140-50.

[47] Nascimento F, Pousinha PA, Correia AM, Gomes R, Sebastião AM, Ribeiro JA. Adenosine A_{2A} receptors activation facilitates neuromuscular transmission in the pre-symptomatic phase of the SOD1(G93A) ALS mice, but not in the symptomatic phase. PLoS One 2014; 9: e104081.

[48] Hu X, Liou AK, Leak RK *et al.* Neurobiology of microglial action in CNS injuries: receptor-mediated signaling mechanisms and functional roles. Prog Neurobiol 2014; 119-120: 60-84.

[49] Parabucki A, Savic D, Laketa D *et al.* Expression of major ectonucleotidases after cortical stab brain injury in rats: a real-time PCR study. Arch Biol Sci Belgrade 2014; 66: 149-55.

[50] Laketa D, Savic J, Bjelobaba I *et al.* Brain injury alters ectonucleotidase activities and adenine nucleotide levels in rat serum. Journal of Medical Biochemistry 2015; 34: 215-22.

[51] Xu P, Xu Y, Hu B *et al.* Extracellular ATP enhances radiation-induced brain injury through microglial activation and paracrine signaling via P2X7 receptor. Brain Behav Immun 2015; 50: 87-100.

[52] Sun L, Gao J, Zhao M *et al.* A novel cognitive impairment mechanism that astrocytic *p*-connexin 43 promotes neuronic autophagy via activation of P2X7R and down-regulation of GLT-1 expression in the hippocampus following traumatic brain injury in rats. Behav Brain Res 2015; 291: 315-24.

[53] Cao L, Pu J, Scott RH, Ching J, McCaig CD. Physiological electrical signals promote chain migration of neuroblasts by up-regulating P2Y1 purinergic receptors and enhancing cell adhesion. Stem Cell Rev 2015; 11: 75-86.

[54] Dai SS, Zhou YG. Adenosine 2A receptor: a crucial neuromodulator with bidirectional effect in neuroinflammation and brain injury. Rev Neurosci 2011; 22: 231-9.

[55] Ran H, Duan W, Gong Z *et al.* Critical contribution of adenosine A_{2A} receptors in bone marrow-derived cells to white matter lesions induced by chronic cerebral hypoperfusion. J Neuropathol Exp Neurol 2015; 74: 305-18.

[56] Kuan YH, Shih HC, Tang SC, Jeng JS, Shyu BC. Targeting P_2X_7 receptor for the treatment of central post-stroke pain in a rodent model. Neurobiol Dis 2015; 78: 134-45.

[57] Kaiser M, Penk A, Franke H *et al.* Lack of functional P2X7 receptor aggravates brain edema development after middle cerebral artery occlusion. Purinergic Signal 2016.

[58] Pedata F, Dettori I, Coppi E *et al.* Purinergic signalling in brain ischemia. Neuropharmacology 2016; 104: 105-30.

[59] Cheng RD, Ren JJ, Zhang YY, Ye XM. P2X4 receptors expressed on microglial cells in post-ischemic inflammation of brain ischemic injury. Neurochem Int 2014; 67: 9-13.

[60] Fern RF, Matute C, Stys PK. White matter injury: Ischemic and nonischemic. Glia 2014; 62: 1780-9.

[61] Sun HS, Xu B, Chen W *et al.* Neuronal K_{ATP} channels mediate hypoxic preconditioning and reduce subsequent neonatal hypoxic-ischemic brain injury. Exp Neurol 2015; 263: 161-71.

[62] Cisneros-Mejorado A, Gottlieb M, Cavaliere F *et al.* Blockade of P2X7 receptors or pannexin-1 channels similarly attenuates postischemic damage. J Cereb Blood Flow Metab 2015; 35: 843-50.

[63] Mahi N, Kumar A, Jaggi AS, Singh N, Dhawan R. Possible role of pannexin 1/P_2x_7 purinoceptor in neuroprotective mechanism of ischemic postconditioning in mice. J Surg Res 2015; 196: 190-9.

[64] Ramos DB, Muller GC, Rocha GB *et al.* Intranasal guanosine administration presents a wide therapeutic time window to reduce brain damage induced by permanent ischemia in rats. Purinergic Signal 2016; 12: 149-59.

[65] Pedata F, Pugliese AM, Coppi E *et al.* Adenosine A_{2A} receptors modulate acute injury and neuroinflammation in brain ischemia. Mediators Inflamm 2014; 2014: 805198.

[66] Winerdal M, Winerdal ME, Wang YQ, Fredholm BB, Winqvist O, Ådén U. Adenosine A_1 receptors contribute to immune regulation after neonatal hypoxic ischemic brain injury. Purinergic Signal 2016; 12: 89-101.

[67] Fiebich BL, Akter S, Akundi RS. The two-hit hypothesis for neuroinflammation: role of exogenous ATP in modulating inflammation in the brain. Front Cell Neurosci 2014; 8: 260.

[68] Beamer E, Göröncsér F, Horváth G *et al.* Purinergic mechanisms in neuroinflammation: An update from molecules to behavior. Neuropharmacology 2016; 104: 94-104.

15

[69] Burnstock G. P2X ion channel receptors and inflammation. Purinergic Signalling 2016; 12: 59-67.

[70] Rodrigues RJ, Tomé AR, Cunha RA. ATP as a multi-target danger signal in the brain. Front Neurosci 2015; 9: 148.

[71] Molz S, Olescowicz G, Kraus JR, Ludka FK, Tasca CI. Purine receptors are required for DHA-mediated neuroprotection against oxygen and glucose deprivation in hippocampal slices. Purinergic Signal 2015; 11: 117-26.

[72] Pérez-Sen R, Queipo MJ, Morente V, Ortega F, Delicado EG, Miras-Portugal MT. Neuroprotection mediated by P2Y$_{13}$ nucleotide receptors in neurons. Comput Struct Biotechnol J 2015; 13: 160-8.

[73] Masuch A, Shieh CH, van Rooijen N, van Calker D, Biber K. Mechanism of microglia neuroprotection: Involvement of P2X7, TNFα, and valproic acid. Glia 2016; 64: 76-89.

[74] Zhao H, Zhang X, Dai Z *et al.* P2X7 receptor suppression preserves blood-brain barrier through inhibiting RhoA activation after experimental intracerebral hemorrhage in rats. Sci Rep 2016; 6: 23286.

[75] Miras-Portugal MT, Gomez-Villafuertes R, Gualix J *et al.* Nucleotides in neuroregeneration and neuroprotection. Neuropharmacology 2016; 104: 243-54.

[76] Ribeiro FF, Xapelli S, Miranda-Lourenco C *et al.* Purine nucleosides in neuroregeneration and neuroprotection. Neuropharmacology 2016; 104: 226-42.

[77] Singh AV, Raymond M, Pace F *et al.* Astrocytes increase ATP exocytosis mediated calcium signaling in response to microgroove structures. Sci Rep 2015; 5: 7847.

[78] Haanes KA, Edvinsson L. Expression and characterization of purinergic receptors in rat middle meningeal artery-potential role in migraine. PLoS One 2014; 9: e108782.

[79] Hullugundi SK, Ansuini A, Ferrari MD, van den Maagdenberg AM, Nistri A. A hyperexcitability phenotype in mouse trigeminal sensory neurons expressing the R192Q Cacna1a missense mutation of familial hemiplegic migraine type-1. Neuroscience 2014; 266: 244-54.

[80] Gölöncsér F, Sperlágh B. Effect of genetic deletion and pharmacological antagonism of P2X7 receptors in a mouse animal model of migraine. J Headache Pain 2014; 15: 24.

[81] Kilinc E, Koroleva K, Guerrero Toro C, Töre F, Giniatullin R. The role of adenosine triphosphate and its receptors in migraine pathophysiology. Acta Physiologica 2015; 215: 44.

[82] Cieslak M, Czarnecka J, Roszek K, Komoszynski M. The role of purinergic signaling in the etiology of migraine and novel antimigraine treatment. Purinergic Signal 2015; 11: 307-16.

[83] Mesuret G, Engel T, Hessel EV *et al.* P2X7 receptor inhibition interrupts the progression of seizures in immature rats and reduces hippocampal damage. CNS Neurosci Ther 2014; 20: 556-64.

[84] Engel T, Alves M, Sheedy C, Henshall DC. ATPergic signalling during seizures and epilepsy. Neuropharmacology 2016; 104: 140-53.

[85] Eyo UB, Peng J, Swiatkowski P, Mukherjee A, Bispo A, Wu LJ. Neuronal hyperactivity recruits microglial processes via neuronal NMDA receptors and microglial P2Y12 receptors after status epilepticus. J Neurosci 2014; 34: 10528-40.

[86] Miranda MF, Hamani C, de Almeida AC *et al.* Role of adenosine in the antiepileptic effects of deep brain stimulation. Front Cell Neurosci 2014; 8: 312.

[87] Jimenez-Mateos EM, Arribas-Blazquez M, Sanz-Rodriguez A *et al.* microRNA targeting of the P2X7 purinoceptor opposes a contralateral epileptogenic focus in the hippocampus. Sci Rep 2015; 5: 17486.

[88] Zhou X, Ma LM, Xiong Y *et al.* Upregulated P2X3 receptor expression in patients with intractable temporal lobe epilepsy and in a rat model of epilepsy. Neurochem Res 2016; 41: 1263-73.

[89] Frenguelli BG, Wall MJ. Combined electrophysiological and biosensor approaches to study purinergic regulation of epileptiform activity in cortical tissue. J Neurosci Methods 2016; 260: 202-14.

[90] Lietsche J, Imran I, Klein J. Extracellular levels of ATP and acetylcholine during lithium-pilocarpine induced status epilepticus in rats. Neurosci Lett 2016; 611: 69-73.

[91] Engel T. Purinergic signaling-induced neuroinflammation and status epilepticus. Expert Rev Neurother 2016; 1-3.

[92] Seibt KJ, Oliveira RL, Bogo MR, Senger MR, Bonan CD. Investigation into effects of antipsychotics on ectonucleotidase and adenosine deaminase in zebrafish brain. Fish Physiol Biochem 2015; 41: 1383-92.

[93] Yamada K, Kobayashi M, Kanda T. Involvement of adenosine A_{2A} receptors in depression and anxiety. Int Rev Neurobiol 2014; 119: 373-93.

[94] Lindberg D, Shan D, Ayers-Ringler J *et al.* Purinergic signaling and energy homeostasis in psychiatric disorders. Curr Mol Med 2015; 15: 275-95.

[95] Krügel U. Purinergic receptors in psychiatric disorders. Neuropharmacology 2016; 104: 212-25.

[96] Cieslak M, Czarnecka J, Roszek K. The roles of purinergic signaling in psychiatric disorders. Acta Biochim Pol 2016; 63: 1-9.

[97] Rial D, Lara DR, Cunha RA. The adenosine neuromodulation system in schizophrenia. Int Rev Neurobiol 2014; 119: 395-449.

[98] Ciruela F, Fernández-Dueñas V, Contreras F et al. Adenosine in the neurobiology of schizophrenia: potential adenosine receptor-based pharmacotherapy. In: Gargiulo PÁ, Arroyo HLM, Eds.; Psychiatry and Neuroscience Update: Bridging the Divide. Springer International Publishing: Cham, 2015; pp. 375-388.

[99] Matos M, Shen HY, Augusto E *et al.* Deletion of adenosine A_{2A} receptors from astrocytes disrupts glutamate homeostasis leading to psychomotor and cognitive impairment: relevance to schizophrenia. Biol Psychiatry 2015; 78: 763-74.

[100] Avendano BC, Montero TD, Chávez CE, von Bernhardi R, Orellana JA. Prenatal exposure to inflammatory conditions increases Cx43 and Panx1 unopposed channel opening and activation of astrocytes in the offspring effect on neuronal survival. Glia 2015; 63: 2058-72.

[101] Gubert C, Fries GR, Wollenhaupt de Aguiar B *et al.* The P2X7 purinergic receptor as a molecular target in bipolar disorder. Neuropsychiatry and Neuropsychology 2013; 8: 1-7.

[102] Gubert C, Fries GR, Pfaffenseller B *et al.* Role of P2X7 receptor in an animal model of mania induced by D-amphetamine. Mol Neurobiol 2016; 53: 611-20.

[103] Barron ML, Werry EL, McGregor IS, Kassiou M. P2X7 in bipolar and depressive disorders. In: Weiss N, Koschak A, Eds.; Pathologies of Calcium Channels. Springer: Berlin Heidelberg, 2014; pp. 635-661.

[104] Albert U, De Cori D, Aguglia A, Barbaro F, Bogetto F, Maina G. Increased uric acid levels in bipolar disorder subjects during different phases of illness. J Affect Disord 2015; 173: 170-5.

[105] Muti M, Del Grande C, Musetti L *et al.* Serum uric acid levels and different phases of illness in bipolar I patients treated with lithium. Psychiatry Res 2015; 225: 604-8.

[106] Bartoli F, Crocamo C, Gennaro GM *et al.* Exploring the association between bipolar disorder and uric acid: A mediation analysis. J Psychosom Res 2016; 84: 56-9.

[107] Sperlagh B, Csolle C, Ando RD, Goloncser F, Kittel A, Baranyi M. The role of purinergic signaling in depressive disorders. Neuropsychopharmacol Hung 2012; 14: 231-8.

[108] Yamada K, Kobayashi M, Shiozaki S *et al.* Antidepressant activity of the adenosine A_{2A} receptor antagonist, istradefylline (KW-6002) on learned helplessness in rats. Psychopharmacology (Berl) 2014; 231: 2839-49.

[109] Ortiz R, Ulrich H, Zarate CA, Jr., Machado-Vieira R. Purinergic system dysfunction in mood disorders: a key target for developing improved therapeutics. Prog Neuropsychopharmacol Biol Psychiatry 2015; 57: 117-31.

[110] Pereira VS, Casarotto PC, Hiroaki-Sato VA, Sartim AG, Guimarães FS, Joca SR. Antidepressant- and anticompulsive-like effects of purinergic receptor blockade: involvement of nitric oxide. Eur Neuropsychopharmacol 2013; 23: 1769-78.

[111] Cao X, Li LP, Wang Q *et al.* Astrocyte-derived ATP modulates depressive-like behaviors. Nat Med 2013; 19: 773-7.

[112] Ma M, Ren Q, Zhang JC, Hashimoto K. Effects of brilliant blue G on serum tumor necrosis factor-α levels and depression-like behavior in mice after lipopolysaccharide administration. Clin Psychopharmacol Neurosci 2014; 12: 31-6.

[113] Catanzaro JM, Hueston CM, Deak MM, Deak T. The impact of the $P2X_7$ receptor antagonist A-804598 on neuroimmune and behavioral consequences of stress. Behav Pharmacol 2014; 25: 582-98.

[114] Lahmann C, Clark RH, Iberl M, Ashcroft FM. A mutation causing increased K_{ATP} channel activity leads to reduced anxiety in mice. Physiol Behav 2014; 129: 79-84.

[115] Cunha MP, Pazini FL, Rosa JM *et al.* Creatine, similarly to ketamine, affords antidepressant-like effects in the tail suspension test via adenosine A_1 and A_{2A} receptor activation. Purinergic Signal 2015; 11: 215-27.

[116] Kaster MP, Machado NJ, Silva HB *et al.* Caffeine acts through neuronal adenosine A2A receptors to prevent mood and memory dysfunction triggered by chronic stress. Proc Natl Acad Sci U S A 2015; 112: 7833-8.

[117] Wei CJ, Augusto E, Gomes CA *et al.* Regulation of fear responses by striatal and extrastriatal adenosine A_{2A} receptors in forebrain. Biol Psychiatry 2014; 75: 855-63.

[118] Chiu GS, Darmody PT, Walsh JP *et al.* Adenosine through the A2A adenosine receptor increases IL-1β in the brain contributing to anxiety. Brain Behav Immun 2014; 41: 218-31.

[119] Huang ZL, Liu R, Bai XY *et al.* Protective effects of the novel adenosine derivative WS0701 in a mouse model of posttraumatic stress disorder. Acta Pharmacol Sin 2014; 35: 24-32.

[120] Rau AR, Ariwodola OJ, Weiner JL. Postsynaptic adenosine A2A receptors modulate intrinsic excitability of pyramidal cells in the rat basolateral amygdala. Int J Neuropsychopharmacol 2015; 18: 1-13.

[121] Masino SA, Kawamura M, Jr., Cote JL, Williams RB, Ruskin DN. Adenosine and autism: a spectrum of opportunities. Neuropharmacology 2013; 68: 116-21.

[122] Naviaux JC, Schuchbauer MA, Li K *et al.* Reversal of autism-like behaviors and metabolism in adult mice with single-dose antipurinergic therapy. Transl Psychiatry 2014; 4: e400.

[123] Naviaux JC, Wang L, Li K *et al.* Antipurinergic therapy corrects the autism-like features in the Fragile X (*Fmr1* knockout) mouse model. Mol Autism 2015; 6: 1.

[124] Filip M, Zaniewska M, Frankowska M, Wydra K, Fuxe K. The importance of the adenosine A_{2A} receptor-dopamine D_2 receptor interaction in drug addiction. Curr Med Chem 2012; 19: 317-55.

[125] Krügel U, Köles L, Illes P. Integration of neuronal and glial signalling by pyramidal cells of the rat prefrontal cortex; control of cognitive functions and addictive behaviour by purinergic mechanisms. Neuropsychopharmacol Hung 2013; 15: 206-13.

[126] Li Y, He Y, Chen M *et al.* Optogenetic activation of adenosine A2A receptor signaling in the dorsomedial striatopallidal neurons suppresses goal-directed behavior. Neuropsychopharmacology 2016; 41: 1003-13.

[127] Ferrée S. Mechanisms of the psychostimulant effects of caffeine: implications for substance use disorders. Psychopharmacology (Berl) 2016; 233: 1963-79.

[128] Tai YH, Cheng PY, Tsai RY, Chen YF, Wong CS. Purinergic P2X receptor regulates *N*-methyl-D-aspartate receptor expression and synaptic excitatory amino acid concentration in morphine-tolerant rats. Anesthesiology 2010; 113: 1163-75.

[129] Wu M, Sahbaie P, Zheng M *et al.* Opiate-induced changes in brain adenosine levels and narcotic drug responses. Neuroscience 2013; 228: 235-42.

[130] Li K, He HT, Li HM, Liu JK, Fu HY, Hong M. Heroin affects purine nucleotides metabolism in rat brain. Neurochem Int 2011; 59: 1104-8.

[131] Wells L, Opacka-Juffry J, Fisher D, Ledent C, Hourani S, Kitchen I. In vivo dopaminergic and behavioral responses to acute cocaine are altered in adenosine A_{2A} receptor knockout mice. Synapse 2012; 66: 383-90.

[132] Moeller FG, Steinberg JL, Lane SD *et al.* Increased orbitofrontal brain activation after administration of a selective adenosine A_{2A} antagonist in cocaine dependent subjects. Front Psychiatry 2012; 3: 44.

[133] Broderick PA, Malave LB. Cocaine shifts the estrus cycle out of phase and caffeine restores it. J Caffeine Res 2014; 4: 109-13.

[134] Pintsuk J, Borroto-Escuela DO, Pomierny B *et al.* Cocaine self-administration differentially affects allosteric A2A-D2 receptor-receptor interactions in the striatum. Relevance for cocaine use disorder. Pharmacol Biochem Behav 2016; 144: 85-91.

[135] ElAli A, Urrutia A, Rubio-Araiz A *et al.* Apolipoprotein-E controls adenosine triphosphate-binding cassette transporters ABCB1 and ABCC1 on cerebral microvessels after methamphetamine intoxication. Stroke 2012; 43: 1647-53.

19

[136] Wright SR, Zanos P, Georgiou P *et al.* A critical role of striatal A2A R-mGlu R interactions in modulating the psychomotor and drug-seeking effects of methamphetamine. Addict Biol 2016; 21: 811-25.

[137] Kavanagh KA, Schreiner DC, Levis SC, O'Neill CE, Bachtell RK. Role of adenosine receptor subtypes in methamphetamine reward and reinforcement. Neuropharmacology 2015; 89: 265-73.

[138] Furlong TM, Supit AS, Corbit LH, Killcross S, Balleine BW. Pulling habits out of rats: adenosine 2A receptor antagonism in dorsomedial striatum rescues meth-amphetamine-induced deficits in goal-directed action. Addict Biol 2015.

[139] Chesworth R, Brown RM, Kim JH, Ledent C, Lawrence AJ. Adenosine 2A receptors modulate reward behaviours for methamphetamine. Addict Biol 2016; 21: 407-21.

[140] Jastrzebska J, Nowak E, Smaga I *et al.* Adenosine A_{2A} receptor modulation of nicotine-induced locomotor sensitization. A pharmacological and transgenic approach. Neuropharmacology 2014; 81: 318-26.

[141] Micioni Di Bonaventura MV, Cifani C, Lambertucci C *et al.* Effects of A_2A adenosine receptor blockade or stimulation on alcohol intake in alcohol-preferring rats. Psychopharmacology (Berl) 2012; 219: 945-57.

[142] Houchi H, Persyn W, Legastelois R, Naassila M. The adenosine A2A receptor agonist CGS 21680 decreases ethanol self-administration in both non-dependent and dependent animals. Addict Biol 2013; 18: 812-25.

[143] Nam HW, Bruner RC, Choi DS. Adenosine signaling in striatal circuits and alcohol use disorders. Mol Cells 2013; 36: 195-202.

[144] Rau AR, Ariwodola OJ, Weiner JL. Presynaptic adenosine A_1 receptors modulate excitatory transmission in the rat basolateral amygdala. Neuropharmacology 2014; 77: 465-74.

[145] Franklin KM, Asatryan L, Jakowec MW, Trudell JR, Bell RL, Davies DL. P2X4 receptors (P2X4Rs) represent a novel target for the development of drugs to prevent and/or treat alcohol use disorders. Front Neurosci 2014; 8: 176.

[146] Michalak A, Biala G. Alcohol dependence--neurobiology and treatment. Acta Pol Pharm 2016; 73: 3-12.

[147] McGaraughty S, Jarvis MF. Purinergic control of neuropathic pain. Drug Dev Res 2006; 67: 376-88.

[148] Magni G, Ceruti S. The purinergic system and glial cells: emerging costars in nociception. Biomed Res Int 2014; 2014: 495789.

[149] Burnstock G. Purinergic mechanisms and pain. In: Barrett JE, Ed.; Pharmacological Mechanisms and the Modulation of Pain. Elsevier: Amsterdam, 2016; pp. 91-137.

[150] Trang T, Beggs S, Salter MW. ATP receptors gate microglia signaling in neuropathic pain. Exp Neurol 2012; 234: 354-61.

[151] Tsuda M. Microglia in the spinal cord and neuropathic pain. J Diabetes Investig 2016; 7: 17-26.

[152] Burnstock G, Sawynok J. ATP and adenosine receptors and pain. In: Beaulieu P, Lussier D, Porreca F, Dickenson AH, Eds.; Pharmacology of Pain. IASP Press: Seattle, 2010; pp. 303-326.

[153] Janes K, Esposito E, Doyle T *et al.* A3 adenosine receptor agonist prevents the development of paclitaxel-induced neuropathic pain by modulating spinal glial-restricted redox-dependent signaling pathways. Pain 2014; 155: 2560-7.

[154]   Magni G, Merli D, Verderio C, Abbracchio MP, Ceruti S. P2Y$_2$ receptor antagonists as anti-allodynic agents in acute and sub-chronic trigeminal sensitization: role of satellite glial cells. Glia 2015; 63: 1256-69.

[155]   Bravo D, Maturana CJ, Pelissier T, Hernández A, Constandil L. Interactions of pannexin 1 with NMDA and P2X7 receptors in central nervous system pathologies: Possible role on chronic pain. Pharmacol Res 2015; 101: 86-93.

[156]   Chen L, Liu YW, Yue K *et al.* Differential expression of ATP-gated P2X receptors in DRG between chronic neuropathic pain and visceralgia rat models. Purinergic Signal 2016; 12: 79-87.

[157]   Chen JF. Adenosine receptor control of cognition in normal and disease. Int Rev Neurobiol 2014; 119: 257-307.

[158]   Illes P, Verkhratsky A, Burnstock G, Sperlagh B. Purines in neurodegeneration and neuroregeneration. Neuropharmacology 2016; 104: 1-3.

[159]   Koch H, Bespalov A, Drescher K, Franke H, Krügel U. Impaired cognition after stimulation of P2Y$_1$ receptors in the rat medial prefrontal cortex. Neuropsychopharmacology 2015; 40: 305-14.

[160]   Carmo MR, Simões AP, Fonteles AA, Souza CM, Cunha RA, Andrade GM. ATP P2Y1 receptors control cognitive deficits and neurotoxicity but not glial modifications induced by brain ischemia in mice. Eur J Neurosci 2014; 39: 614-22.

[161]   Xiao J, Huang Y, Li X *et al.* TNP-ATP is beneficial for treatment of neonatal hypoxia-induced hypomyelination and cognitive decline. Neurosci Bull 2016; 32: 99-107.

[162]   Guzman SJ, Gerevich Z. P2Y Receptors in Synaptic Transmission and Plasticity: Therapeutic Potential in Cognitive Dysfunction. Neural Plast 2016; 2016: 1207393.

[163]   Raffaghello L, Chiozzi P, Falzoni S, Di VF, Pistoia V. The P2X$_7$ receptor sustains the growth of human neuroblastoma cells through a substance P-dependent mechanism. Cancer Res 2006; 66: 907-14.

[164]   Bianchi G, Vuerich M, Pellegatti P *et al.* ATP/P2X7 axis modulates myeloid-derived suppressor cell functions in neuroblastoma microenvironment. Cell Death Dis 2014; 5: e1135.

[165]   Amoroso F, Capece M, Rotondo A *et al.* The P2X7 receptor is a key modulator of the PI3K/GSK3β/VEGF signaling network: evidence in experimental neuroblastoma. Oncogene 2015; 34: 5240-51.

[166]   D'Alimonte I, Nargi E, Zuccarini M *et al.* Potentiation of temozolomide antitumor effect by purine receptor ligands able to restrain the in vitro growth of human glioblastoma stem cells. Purinergic Signal 2015; 11: 331-46.

[167]   Monif M, O'Brien TJ, Drummond KJ, Reid CA, Liubinas SV, Williams DA. P2X7 receptors are a potential novel target for anti-glioma therapies. Journal of Inflammation 2014; 11: 25.

[168]   Ma Y, Jiang J, Ying W. CD38 mediates the intracellular ATP levels and cell survival of C6 glioma cells. Neuroreport 2014; 25: 569-73.

[169]   Ru Q, Tian X, Wu YX, Wu RH, Pi MS, Li CY. Voltage-gated and ATP-sensitive K$^+$ channels are associated with cell proliferation and tumorigenesis of human glioma. Oncol Rep 2014; 31: 842-8.

[170]   Braganhol E, Kukulski F, Lévesque SA *et al.* Nucleotide receptors control IL-8/CXCL8 and MCP-1/CCL2 secretions as well as proliferation in human glioma cells. Biochim Biophys Acta 2015; 1852: 120-30.

[171]   Bergamin LS, Braganhol E, Figueiró F *et al.* Involvement of purinergic system in the release of cytokines by macrophages exposed to glioma-conditioned medium. J Cell Biochem 2015; 116: 721-9.

[172]   Zhou Q. BMS-536924, an ATP-competitive IGF-1R/IR inhibitor, decreases viability and migration of temozolomide-resistant glioma cells in vitro and suppresses tumor growth in vivo. Onco Targets Ther 2015; 8: 689-97.

[173]   Sorrell ME, Hauser KF. Ligand-gated purinergic receptors regulate HIV-1 Tat and morphine related neurotoxicity in primary mouse striatal neuron-glia co-cultures. J Neuroimmune Pharmacol 2014; 9: 233-44.

[174]   Tewari M, Monika, Varghse RK, Menon M, Seth P. Astrocytes mediate HIV-1 Tat-induced neuronal damage via ligand-gated ion channel P2X7R. J Neurochem 2015; 132: 464-76.

[175]   Kornum BR, Kawashima M, Faraco J *et al.* Common variants in *P2RY11* are associated with narcolepsy. Nat Genet 2011; 43: 66-71.

[176]   Crossland RF, Durgan DJ, Lloyd EE *et al.* A new rodent model for obstructive sleep apnea: effects on ATP-mediated dilations in cerebral arteries. Am J Physiol Regul Integr Comp Physiol 2013; 305: R334-R342.

[177]   Holst SC, Valomon A, Landolt HP. Sleep pharmacogenetics: personalized sleep-wake therapy. Annu Rev Pharmacol Toxicol 2016; 56: 577-603.