The role of adenosine A2A receptors in antidepressant activity in an experimental animal model of depression

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Abstract

Intensive studies on the role of adenosine A2A receptors in Parkinson's disease have been carried out for many years,. These studies have indicated that the antagonists of these receptors not only alleviate motor deficits but also exhibit neuroprotective effects in various animal models. Little is known about the role of these receptors in ailments accompanying Parkinson's disease, such as depression and anxiety. This paper provides a summary of existing research on the role of A2A receptors in comorbid depression in Parkinson's disease.

Keywords:

Parkinson's disease, adenosine, depression, A2A receptor, antidepressant activity

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Introduction

Currently, intensive research is focused on the importance of adenosine A2A receptors in different psychiatric disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), schizophrenia, anxiety and depression [1,2,3]. This applies both to depression as an independent disease entity as well as that accompanying PD. A large body of research has highlighted the implication of A2A receptors in PD. It was shown that adenosine A2A receptor antagonists ameliorated motor dysfunction and exhibited neuroprotective effect in animal models of PD and might also improve cognition [4]. They represent a new promising group of drugs for PD [5]. This paper provides a summary and review of current knowledge concerning the role of adenosine A2A receptors in depression and the mechanisms of action of antidepressant drugs. Particular attention was paid to the role of these receptors in depression coexisting with PD.

Adenosine receptors

Adenosine acts as a neuromodulator in the central nervous system (CNS). Adenosine receptor (AR) family belongs to the large superfamily of G protein-coupled receptors, which activate several different effector systems. Four types of receptors are currently known, A1, A2, A2B and A3. The division of the adenosine receptor subtype is based on their pharmacology and signal transduction mechanisms [6].The division of the A2 receptor into subtype A2A and A2B receptors is associated, respectively, with a high and low affinity of these receptors for adenylate cyclase, the location and the differences in the pharmacological characteristics. Activation of A1 and A3 receptors results in the inhibition of cAMP formation, while A2A and A2B receptors are positively coupled to adenyl cyclase. In addition, A1 and A3 receptor activation results in the formation of inositol 1,4,5 trisphosphate (IP3) and diacylglycerol (DAG). A1 receptors are widely distributed in the CNS and in peripheral tissues. Their high density is observed in the cortex, limbic areas, basal ganglia, cerebellum, midbrain, brainstem, spinal cord. A2B receptors are present on the brain neurons and require high concentration of endogenous adenosine for stimulation. The A3 receptors are widespread in peripheral organs [7], and their density is low in the brain.

Adenosine and depression

As shown by experimental studies, there is a link between adenosine and depression, but it is not fully understood. Berck showed that there

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was a relationship between the function of adenosine A2A receptor in platelets in patients and major depression [8]. Additionally, serum adenosine deaminase activity was decreased in patients with major depression and an inverse relationship between the enzyme activity and the severity of depression was observed.

Depressant or antidepressant effect of adenosine ?

Currently, it is not known exactly whether adenosine exerts a depressant or anti-depressant effect. This is definitely dependent on the receptor and its localization. Adenosine itself and its analogues increase the immobility in the forced swimming test in mice (FST) [9], which indicates their depression-like activity. These effects are reversed by classical antidepressants, such as nortriptyline, desipramine or chlorimipramina.

In contrast, other studies suggested antidepressant–like effect of adenosine and selective A1 and A2 adenosine receptor agonists in two predictive animal models of antidepressant action of drugs in the FST and the tail suspension test (TST). The involvement of adenosine A1 and A2A receptors in the antidepressant-like effect of adenosine was indicated. Pretreatment of mice with caffeine (a non-selective adenosine receptor antagonist), DPCPX (a selective A1 receptor antagonist) and ZM241385 (a selective A2A receptor antagonist) inhibited the decrease in the immobility time caused by adenosine in the FST [10]. In addition, there is evidence showing the participation of the opioid systems, likely dependent on the activation of μ – and δ receptors or the inhibition of κ receptors [11]. It has been suggested the NO-cGMP pathway is involved in this mechanisms [12].

The effect of antidepressants on the level of adenosine

There is much evidence that adenosine is involved in the mechanism of the antidepressant drug action. Some tricyclic antidepressants are potent inhibitors of cellular uptake of adenosine and may raise the levels of endogenous adenosine. Adenosine is responsible for the inhibitory effect of some antidepressant drugs on glutamate and aspartate release in the prefrontal cortex [13]. As shown in that paper, the effect of amitriptyline and citalopram was attenuated by the administration of the adenosine A1/A2A receptor antagonist, caffeine or by local infusion of the adenosine A1 receptor antagonist, 8-cyclopentyltheophylline (CPT).

Depression in parkinson's disease

Depression accompanies many neurological diseases, such AD, PD, stroke, multiple sclerosis. Depression is one of the primary non-motor symptoms of PD and it is present at all stages in patients with PD. It occurs in early and late stages of this disease [14,15]. Depression is manifested by such symptoms as fatigue, apathy, lack of motivation, psychomotor retardation, sleep disorders and appetite disturbances. The clinical picture of depression associated with PD is characterized by a depressed mood and psychomotor drive, a sense of helplessness, dysphoria, irritability, pessimism, and suicidal thoughts. Less common are, conviction about their own guilt, self-blame and suicidal attempts. Symptoms of depression as an independent disease and coexisting with PD do not differ significantly but there are some subtle differences. Many of the symptoms of both disorders overlap and that is why they are often misinterpreted. For example, bradykinesia, depletion of facial expressions and gestures, monotonous speech can be misinterpreted as symptoms of depression. On the other hand, a reduction in psychomotor drive, eating and sleep disorders, , fatigue (typical features of depression) may be regarded as symptoms of PD [16]. It is not known whether depression in PD is only a psychological reaction to the diagnosis of disease or is a consequence of ongoing neurodegeneration . It is likely that it is caused by a combination of these mechanisms. Depression may precede the diagnosis of PD [16]. Significant deterioration of motor and cognitive functions decrease the quality of life and may contribute to the onset of a depressive episode [17,18]. The symptoms of depression in PD are underlain by dysregulation of dopaminergic, noradrenergic and serotonergic systems in different regions of the brain associated with depression, particularly in the limbic system and the basal ganglia, such as ventral striatum. The ventral striatum is associated with the limbic structures (the amygdala, hippocampus, midline thalamus, and certain regions of the prefrontal cortex) and motor system and it is strongly innervated by mesolimbic dopamine neurons arising from the ventral tegmental area (VTA) [19]. It is also interesting that a partial lesion of the dopaminergic terminals in the ventral striatum may induce

depressive–like symptoms in rats, without any motor disturbances [20].

Damage to dopamine neurons in the nigrostriatal pathway is the basis of an ongoing neurodegenerative process but other mechanisms include partially damaged dopamine neural routes, such as mesolimbic and mesocortical pathways. The emergence of depression in PD may be related to dopaminergic dysfunction. Wu reported that dopamine availability was reduced in the striatum in patients with major depression without PD. Decrease in the number of dopamine neurons in the VTA [21], and in dopaminergic transporter availability in the striatum [22] were observed in PD patients with depression, too [23]. The impaired striatal dopaminergic function in PD was independently related to depressive symptoms and these effect was observed in unmedicated patients [24]. In those patients higher depression scores were associated with a lower striatal 18F-fluorodopa uptake. Depressive symptoms in PD are likely to be associated with changes in serotonin (5-HT – 5-hydroxytryptamine) neurotransmission in the CNS. It has been suggested that vulnerability to depression in PD may be the result of a combination of abnormal 5-HT function and altered network activity in the basal ganglia circuits. Abnormal activity in the basal ganglia in the brain of PD patients would disrupt 5-HT functioning in the cortical and limbic regions through anatomical connections with the midbrain raphe 5-HT neurons. This is reflected by the decreased 5-hydroxyindoleacetic acid (5-HIAA) levels, a 5-HT metabolite, in the cerebral spinal fluid [25]. Likewise, a higher serotonin transporter (5-HTT) binding in the raphe nuclei and limbic structures possibly reflects lower extracellular serotonin levels [26].

Furthermore, a cholinergic system dysfunction was observed. as evidenced by a reduction in the number of acetylcholine (Ach) receptors in the cingulate cortex and frontoparieto-occipal lobe, and a decreased activity of cortical acetylcholinesterase. Recent studies using magnetic resonance imaging (MRI) and PET techniques also confirmed changes in many brain structures associated with depression in PD [27,28]. Stress (dysfunction of the HPA axis) affects not only on the nigrostriatal pathways but also the mesolimbic and mesocortical pathways and thereby contributes to the severity of neurodegeneration [29]. Stress can cause changes in the brain regions directly associated with depression, such as the hippocampus, prefrontal cortex, amygdala where A2A adenosine receptors are located. It has been observed that elevated levels of cortisol in PD patients may be reduced by levodopa administration [30]. As follows from the above data, depression development in PD is the result of complex disorders of neurotransmission in the CNS.

Therapy of depression in Parkinson's disease

It has been shown that some of the above-mentioned drugs used for the treatment of PD symptoms may also exhibit antidepressant activity. Some of them, like selegiline, amantadine, and pramipexole also show antidepressant activity [31]. Dopamine D2 agonists are an alternative to antidepressant drugs to treat depressive symptoms in PD without adding the risk of adverse events of antidepressants [32]. If the implementation of the above treatment does not bring alleviation in depressive disorder, it is required to apply antidepressants. Research on the efficacy and safety of antidepressants available in PD is incomplete. The selection is based on achieving potentially high benefits in relation to the lowest possible side effects. It should be noted that patients suffering from PD are particularly susceptible to the side effects of antidepressants.

First, it is recommended to use the selective serotonin reuptake inhibitor (SSRI) citalopram, fluvoxamine and sertraline [33]. These drugs are considered to be effective and well tolerated by patients. They significantly reduce the severity of depressive symptoms in PD without compromising the motor skills but are not always effective in treating depression in PD. On the other hand, there is a risk of side effects. During treatment with fluoxetine extrapyramidal symptoms may appear while taking paroxetine carries the risk of cognitive impairment. In addition, co-administration of SSRIs with selegiline increases the risk of serotonin syndrome [34].

Other useful antidepressants belong to the group of mixed serotonin and noradrenaline reuptake inhibitors (milnacipram, venlafaxine), and inhibitors of noradrenaline and dopamine reuptake (maprotiline, trimipramine, bupropion). Drugs with the receptor mechanism of action, such, mianserin, mirtazapine or moclobemide and reversible inhibitors of monoamine oxidase type A, inhibiting serotonin and noradrenaline deamination may be used simultaneously. However, no adequate studies evaluating the

efficacy, side effects and interactions of these drugs in treating depression in PD patients have been carried out. While the combination of dopamine agonists and SSRIs seems to be a safe course of action, it is not recommended to concomitantly use selegiline and moclobemide. In patients with depression in PD with predominant anxiety and insomnia, antidepressants with anxiolytic and sedative effects, paroxetine, mianserin, mirtazapine and tianeptine are preferred.

Tricyclic antidepressants such as, imipramine, nortriptyline [35], desipramine amitriptyline are another group of drugs used in depression accompanying PD. They belong to highly efficient drugs in the treatment of depression. However, due to delayed onset of action of various therapeutic and side effects, especially dangerous in elderly people, their use in PD is limited. Cholinergic component of these drugs is responsible for the appearance of sedation, tremor and downs during therapy. They may also cause cognitive disorders, including attention, concentration and memory deficits, and at the same time they may increase orthostatic hypotension.

The modern therapy of depression still has a limited number of effective and safe drugs. Considering the complex mechanism of action and difficulties related to treatment with antidepressant drugs, new therapeutics are searched for, taking into account a variety of chemical structures and affinities for dopaminergic, serotoninergic, glutamatergic and adenosine receptors.

The importance of adenosine A2A receptors for development of depression

It has been proposed that adenosine A2A receptors may be involved in the pathomechanisms of depression and depressive – like behavior in animals. What is the relationship between adenosine A2A receptors and depression? So far, the answer to this question has not been found. The role adenosine A2A receptor in depression is not fully elucidated [36]. Likely, location of these receptors in the CNS may determine their involvement in the mechanisms of depression.

Pre – and postsynaptic adenosine A2A receptor, the role in neurotransmission in the CNS

Adenosine A2A receptors are mainly located in the dorsal and ventral striatum in both humans, rodents and monkeys [37]. The ventral striatum is strongly innervated by dopaminergic fibers from the VTA (A10 cell group), known as the mesolimbic dopamine (DA) system, and has the highest density of serotonergic inputs in the striatum [19]. Perhaps adenosine A2A receptors located in those parts of the striatum mediate antidepressant effects. Within the striatum they are located predominantly post-synaptically on GABA(gamma aminobutyric acid)-ergic striatopallidal neurons. Striatal A2A receptors are richly expressed in a subpopulation of medium–sized spiny (MSNs) GABAergic neurons in the "indirect" striatal output pathway [38] where they co-localize with D2 receptors [39]. These findings indicated that A2A receptors might modulate GABAergic signaling within the rat striatum. In vivo studies have shown that A2A receptor stimulation increases GABA release whereas their blockade decreases GABA release in the striatum and globus pallidus GP [40]. Participation of A2A receptor in the regulation of the activity of GABAergic neurons is relevant in the therapy of PD. Striatal A2A receptors may interact synergistically with metabotropic glutamate 5 receptors (mGlu5) and cannabinoid receptors (CB1) [41]. Additionally, they may interact antagonistically with dopamine D2 receptors (D2Rs) [42] opposing the N-methyl-D-aspartate receptor (NMDA) function. Co-localization of A2A and D2 receptors on the striopallidal GABAergic neurons is the basis for negative interaction between adenosine and DA. As a result of these interactions, the adenosine A2A receptor blockade increases dopaminergic transmission. It has been used in many studies focused on the treatment of PD. These receptors are concentrated in the areas where the dopaminergic innervation dominates but were not identified on the dopaminergic neurons. Adenosine A2A antagonists had no effect on the basal dopamine (DA) level, but enhanced L-DOPA–induced elevations in extracellular DA levels in the striatum [43]. This is an evidence that A2A receptors and their antagonists only indirectly regulate DA release in the striatum. In addition, A2A receptors are present on cholinergic interneurons in the striatum where they modulate Ach release [44]. Outside of the striatum, A2A receptors are also expressed on neurons in the hippocampus and the cortex Rosin et al., 1998). In those structures, they have presynaptic location and may control the release of many neurotransmitters, like glutamate (Glu), noradrenaline (NA), ACh and

GABA. A2A receptors may modulate Glu release with opposing effects at different sites, such as striatopallidal neurons and Glu-ergic terminals, and glia transporters.

In summary, A2A receptors, depending on the localization, modulate (potentiate or inhibit) the release of many neurotransmitters in the CNS. This suggests that stimulation or blockade respectively, of these receptors could directly or indirectly affect the abnormal neurotransmission in depression. However, this problem requires a thorough examination.

Evidence for the participation of A2A receptors in the antidepressant-like mechanisms

A2A receptors are involved in the regulation of animal behavior such as anxiety, catalepsy, depression-like behavior [3]. The activation of these receptors induces catalepsy and has anxiolytic activity. On the other hand, mice lacking this receptor are aggressive, have reduced sensitivity to pain, elevated blood pressure and increased platelet aggregation [45]. Chronic stress may be not only a cause of depression but also may alter the expression of A2A receptor in the CNS [46]. Unpredictable chronic mild stress (UCMS) promoted an up-regulation of A2A adenosine receptors in the striatum and induced depressive-like behavior. The chronic-restraint stress (CRS) had no effect on the striatal A2A adenosine receptors. Moreover, chronic unpredictable stress decreased dopamine levels in the striatum, nucleus accumbens, and frontal cortex [47].

In an attempt to explain the participation of A2A receptors in the mechanisms of depression, attention is paid to the role of A1/A2A receptors in the modulation of 5-HT release in the hippocampus [48] and reversing morphological, behavioral and electrophisiological effects of sub-chronic stress or maternal separation stress (early life stress model) by A2A antagonist in CNS [49]. The results of those studies clearly indicate the role of A2A receptor not only in the stress associated – impairments but in restoring the normal function of the HPA axis. Moreover, involvement of adenosine in the control of the release of CRH, cortisol and corticosterone, and hippocampal glucocorticoid receptor expression supports the participation of A2A receptors in the control of the HPA axis [49]. Thus, it may be one of possible mechanisms of antidepressant action of the compounds with affinity for A2A receptors.

Another important argument in favor of the participation of A2A receptors in the effects of antidepressants is related to newly discovered interactions of brain derived neurotrophic factor (BDNF) and its TrkB receptors with A2A receptors. BDNF plays critical roles in the CNS, being implicated in trophic functions, neurotransmission and synaptic plasticity. In accordance with the neurotrophic hypothesis of depression, the level of BDNF is lowered in patients with depression. Clinical studies showed the reduced serum BDNF level while post mortem research revealed its increased level in the hippocampus in patients treated with antidepressants [50]. Also studies in animal models of depression showed the reduced expression of mRNA coding for BDNF and TrkB receptor in the hippocampus and cerebral cortex. BDNF produces antidepressant effects in behavioral models of depression, too [51].

It is postulated that A2A receptors play a pivotal role in regulating the function of BDNF and maintaining the appropriate level. The cross-talk between adenosine A2A and TrkB receptors has been carefully investigated in the CNS. Adenosine A2A receptors are colocalized with TrkB receptors in many brain regions, particularly in the cortex and hippocampus where their interaction with adenosine A2A receptors has been recently reported. It has been suggested that A2A receptor stimulation up-regulates BDNF expression [52]. So far, the importance of this interaction was evidenced in normal control and in Huntington's disease [53]. It is likely too that the activation of A2A receptor modulates BDNF production in rat primary cortical neurons. CGS 21680 (4-[2-[[6-amino-9-(N-ethyl-β-D-ribofuranuronamidosyl)-9H-purin-2-yl]amino] ethyl]-benzene propanoic acid), an adenosine A2A receptor agonist, induced BDNF expression and release [54]. Since A2A receptor stimulation increases the level of BDNF [10], it is possible to speculate that these receptors and adenosine are involved in the antidepressant effect. These interactions seem to be also relevant to Parkinson's disease, in particular for glial cell line-derived neutrophic factor (GDNF) therapy. However, earlier studies investigating the cross-talk between A2A receptor antagonists and neutrophic factor did not confirm its impact on antidepressant activity. ZM 241385–induced blockade of A2A receptor or A2A receptor knockout (KO) is accompanied by decreased levels of BDNF. No changes were observed in the level of TrkB receptor in the

hippocampus [55]. A2A KO mice showed the reduced BDNF levels in the hippocampus and striatum, but not in the cerebral cortex suggesting that A2A receptor may not be involved in BDNF expression in the cerebral cortex [55]. These data are ambiguous and contrary to the generally accepted role of BDNF in depression and require additional testing.

Adenosine A2A receptor antagonists – novel therapeutic strategies in PD

Taking into account the coexistence of depression and PD, new, more efficient and safe medications which cause far fewer side effects and do not interacting with other drugs, are constantly searched for. Recently, much attention has been paid to adenosine A2A receptor antagonists. They represent a new class of non-dopaminergic antiparkinsonian therapy. At present, intensively studied compounds belong to two different groups, the xanthine – or non-xanthine based derivatives [56]. It is believed that the beneficial effects of adenosine A2A receptor antagonists in reducing the symptoms typical of PD, are a result of normalization of DA deficit in neural pathways [5]. Confirmation of this hypothesis is provided by data on GABA release and GAD 67 level, as an indicator of neuronal activity of GABAergic neurons in the basal ganglia [57]. Currently, some of the tested compounds are in clinical trials. These are SCH – 420814 (Privadenant; 2-(furan-2-yl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl] piperazin-1-yl] ethyl]-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]-pyrimi din-5-amine), BHB014 (Biogen; V2006; 3-(4-amino-3-methylbenzyl)-7-(2-furyl)-3H-[1,2,3] triazolo[4,5 – d]pyrimidine-5-amine), KW-6002 (Istradefylline; 8-[(1E)-2-(2-(3,4-dimethoxyphenyl) ethenyl]-1,3-diethyl-3,7-dihydro-7-methyl-1H-purine-2,6-dione) [5].

An important argument in favor of this new form of therapy in PD comes from demonstration of its positive effect in movement disorders. Adenosine A2A antagonists reversed the cataleptic effects of haloperidol [58]. These drugs lessened motor deficits in animal models of PD (after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP or 6-hydroxydopamine; 6-OHDA), potentiating L-DOPA–induced rotation in 6-OHDA–lesioned rats without inducing dyskinesia [59-63], reduced muscle stiffness caused by haloperidol or reserpine administration, and intensified the effects of L-DOPA in bearing stiffness induced by haloperidol. A2A antagonists may be effective not only as monotherapy but also in combination with L-DOPA or dopamine agonist therapy. Some of these compounds suppressed tacrine–induced tremors [64]. Additionally, the A2A antagonists might have some neuroprotective effects. It is believed that a different mechanism of action is involved in this neuroprotective effect which is not related to improvement in motor deficits. It probably involves other adenosine receptor populations, for example, presynaptic A2A receptors regulating glutamate release or receptors present on glia cells [1]. Both the antiparkinsonian and neuroprotective effects are important for the use of these compounds in the treatment of PD.

Adenosine A2A antagonists in animal models of depression

Over 10 years ago, Sarges et al., suggested antidepressant properties of the most potent and A1 or A2 selective non-xanthine adenosine antagonists [65]. At the moment, there is still little research concerning the role of A2A receptor in depression. According to recent research, some of the selective adenosine A2A antagonists exhibit antidepressant – like activity in animal models, with high predictive validity. Promising results were obtained for the following compounds, SCH – 58261, ZM – 241385 (4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-a][1,3,5]triazin-5-ylamino] ethyl)phenol), KW-6002 [36,66], SCH – 412348([7-[2-[4-2,4-difluorophenyl]-1-piperazinyl]ethyl]-2-(2-furanyl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine]) and preladenant (SCH – 420814) [67]. These compounds reduced the immobility time in the tail suspension test and in the forced swimming test in mice (putatively involving cortex). This was confirmed by studies conducted in A2A receptor KO mice [36]. It is suggested that D2 receptors and dopamine transmission in the frontal cortex and nucleus accumbens are involved in the anti-immobility effect elicited by some A2A adenosine antagonist [36]. This is supported by the fact that some antidepressant drugs increased extracellular dopamine level in the prefrontal cortex and indirectly affected the release of DA in the striatum [43, 68]. According to this, SCH 58261 and MSX-3 (adenosine A2A antagonists) reversed the effects of haloperidol on immobility in the forced swimming test and on effort-related choice in rat, respectively [36]. While istradefylline itself induced antidepressant-like effect in LH rats [69], MSX-3 alone was devoid of effects on effort-related behavior.

In addition, D2 receptor agonist, pramipexole, alleviated symptoms of depression [70]. The mechanism by which A2A receptor antagonists act as antidepressants probably involves the interaction with D2 receptors in the frontal cortex and/or in the striatum. A2A receptors stimulate adenylyl-cyclase and activate the cyclic adenosine monophosphate (cAMP) signaling pathway. The activation of D2 receptor inhibits the effects of A2A receptor stimulation on adenylyl cyclase. This antagonistic A2A–D2 receptor interaction may also involve the formation of A2A–D2 heterodimers, which modulates neuronal excitability and neurotransmitter release. However, recent findings do not unambiguously confirm the participation of D2 receptors or adrenergic, serotonergic neurotransmission in the mechanism of antidepressant-like activity of istradefylline [66,70].

Mechanisms of action of antidepressants are associated with the regulation of the HPA axis. Consequently, the effect of istradefylline on the stress axis was also investigated. As that research showed, antidepressant-like effects of low doses of istradefylline were suppressed by the combined administration with corticosterone, without influencing motor activity [66]. Acute or chronic oral administration of istradefylline ameliorated the depressive behavior of rats in the predictive learned helplessness (LH) model to a degree comparable to chronic treatment with antidepressant drugs [70]. It is difficult to determine which structures within the brain are responsible for the antidepressant effects of A2A receptor antagonists, since the local injection of the A2A agonist CGS 2168 to the nucleus accumbens, caudate – putamen or the paraventricular nucleus of the hypothalamus reversed the effect of istradefylline in this model. Caffeine, a nonselective A1 and A2A antagonist, in low doses has a stimulating effect on mood. It simultaneously increased NA turnover and caused down-regulation of beta receptors in the brain and at low, acute doses enhanced locomotor activity of the animals [36]. Despite such property, its antidepressant action and its effects in the forced swim test should not be attributed to that ability and are deemed to be false positive. Therefore, the suggestion arises that selective A2A receptor antagonists could also have non-specific effects in the screening assays. Thus, it seems necessary to distinguish the escape directed behavior from a nonspecific locomotor stimulant effect elicited by selective adenosine A2A antagonists. It was also demonstrated that a long-term exposure to caffeine, a non-selective adenosine antagonist, exerted an antidepressant activity in the chronic unpredictable stress model. Caffeine reversed the depressive–like behaviors, like decreased sucrose consumption and increased immobility in the forced swimming test. It was accompanied by increased hippocampal dopamine and serotonin levels [71].

Conclusions

The mechanism of antidepressant action of the compounds with affinity for A2A receptors has not been fully elucidated. Most likely, it is related to the location of these receptors or to the A2A receptor interactions with other receptors and their participation in the modulation of neurotransmission in the CNS. Perhaps there are other molecular mechanisms not yet thoroughly known. Adenosine A2A antagonists are a new group of drugs that not only can be effective in the treatment of PD but probably in coexisting depression in PD. However, it may take a lot of time before they can be applied in practice, because such complex therapy still requires extensive research. In addition, the side effects of such therapy should be carefully examined in animal models of depression.

Resumo

Intensivaj studoj pri la rolo de adenozinaj A2A-receptoroj en Parkinson-malsano estis ekzamenitaj dum multaj jaroj. Ĉi tiuj studoj indikis, ke la antagonistoj de ĉi tiuj receptoroj ne nur malfortigas movefikon, sed ankaŭ montras neŭroprotektivajn efektojn en diversaj bestaj modeloj. Malmulton oni scias pri la rolo de ĉi tiuj receptoroj en malsanoj, kiuj akompanas la Parkinson-malsanon, kiel ekzemple depresio kaj angoro. En ĉi tiu artikolo oni provizas resumon de ekzistantaj esploradoj pri la rolo de A2A-receptoroj en kunekzistanta depresio en Parkinson-malsano.

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