

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Role and Development of the Antagonist of Adenosine A_{2A} in Parkinson's Disease

*Widya Dwi Aryati, Nabilah Nurtika Salamah,
Rezi Riadhi Syahdi and Arry Yanuar*

Abstract

Adenosine is a neuromodulator that regulates the body's response to dopamine and another neurotransmitter in the brain that is responsible for motoric, emotion, learning, and memory function. Adenosine is a G-protein-coupled receptor and has four subtypes, which are A₁, A_{2A}, A_{2B}, and A₃. Adenosine A_{2A} is located in the striatum of the brain. Antagonist interferes with GABA releasing, modulates acetylcholine and releases dopamine, and also facilitates dopamine receptor's signaling. Therefore, it can reduce motoric symptoms in Parkinson's disease. Adenosine A_{2A} antagonist is also believed to have neuroprotective effects. Several compounds have been reported and have undergone clinical test as selective adenosine A_{2A} antagonists, including istradefylline, preladenant, tozadenant, vipadenant, ST-1535, and SYN-115. Nonselective adenosine A_{2A} antagonists from natural compounds are caffeine and theophylline.

Keywords: adenosine A_{2A}, selective adenosine A_{2A} antagonists, Parkinson's disease, neuroprotective, natural compounds

1. Introduction

Adenosine is a neuromodulator that coordinates responses to dopamine and other neurotransmitters in areas of the brain responsible for motor function, mood, learning, and memory [1]. Adenosine consists of four receptor subtypes: A₁, A_{2A}, A_{2B}, and A₃ belonging to the superfamily of G-protein-coupled receptor. Adenosine A₁ and A₃ receptors are coupled to inhibitory G proteins, while A_{2A} and A_{2B} receptors are coupled to stimulatory G proteins [2].

Adenosine A₁ receptor can be found in adipose tissue, heart muscle, and inflammatory cells. The receptor mostly expressed by the central nervous system such as neocortex, cerebellum, hippocampus, and dorsal horn of the spinal cord [3]. The pre- and postsynaptic nerve terminals, mast cells, airway smooth muscle, and circulating leukocytes are the places where adenosine A₂ receptor can be found. As the more widely dispersed receptor, adenosine A₂ is divided into two receptors on the basis of high- and low-affinity for adenosine, A_{2A} and A_{2B} [4]. Striatal neurons are where the adenosine A_{2A} are highly enriched; however its lower levels can also be found in glial cells and neurons outside the striatum [5]. The adenosine A_{2B} receptors are highly expressed in the gastrointestinal tract, bladder, lung, and on mast

cells. The most widely dispersed receptor is the A_3 receptor which can be found in the kidney, testis, lung, mast cells, eosinophils, neutrophils, heart, and the brain cortex [4].

Adenosine A_{2A} receptors are found to be concentrates in GABAergic medium-sized spiny neurons in the dopamine-rich regions of the brain. The protein translated in the adenosine A_{2A} is carried by many other tissues such as blood vessels, endothelial, lymphoid cells, smooth muscle cells, and several neurons in sympathetic and parasympathetic systems [6]. Therefore, the dispersion of adenosine A_{2A} is not limited to the medium spiny neurons in the basal ganglia. It stimulates the modulation of cAMP production and increases the level of adenylyl cyclase. This receptor is essential in giving the medium of vasodilation of coronary arteries which then supports the combination of new blood vessels and giving protection for tissues from indirect inflammatory damage [7]. The role of the A_{2A} in the brain includes influencing the activity within the indirect pathway of the basal ganglia. The A_{2A} has complicated actions because it colocalizes and is physically combined with other unrelated G-protein-coupled receptors. Therefore, it can form heterodimers such as dopamine D_2/A_{2A} , and D_3/A_{2A} , cannabinoid CB_1/A_{2A} , and glutamate mGluR5/ A_{2A} , as well as $CB_1/A_{2A}/D_2$ heterotrimers [7].

The pathways which give signals used by the A_{2A} receptor depend on the location of the cell and tissue, the specific G protein which couples it, and the signaling in the cell. The brain also carries the A_{2A} receptor in which it plays an important role in regulating the glutamate and releasing the dopamine [8]. In the striatopallidal neurons, dopamine D_2 receptors are colocalized with adenosine A_{2A} receptors. Adenosine A_{2A} receptor activity that mediates stimulation and D_2 receptors that mediate inhibition in the striatopallidal pathway are balanced [9]. The adenosine A_{2A}

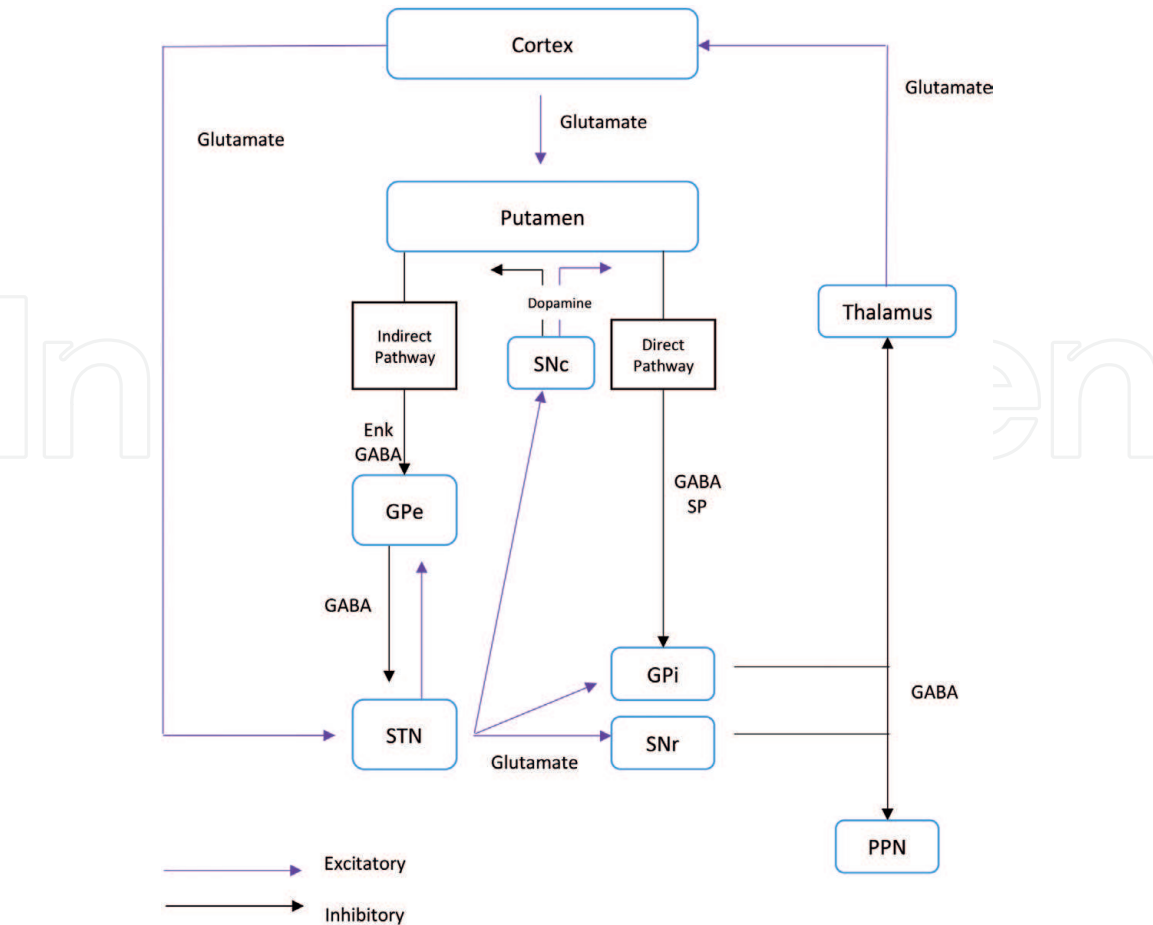


Figure 1.
Basal ganglia circuitry in normal conditions.

likely affects motor activity by acting at different levels of the basal ganglia network. The basal ganglia comprise the striatum (putamen), the globus pallidus externa (GPe), the globus pallidus interna (GPi), substantia nigra pars compacta (SNc), substantia nigra reticulata (SNr), and the subthalamic nucleus (STN). The striatum is represented by medium-sized spiny projection neurons (MSNs), accounting for almost 95% of striatal neurons and using γ -aminobutyric acid (GABA) as neurotransmitter. The GABAergic spiny neurons give rise to the two main striatal efferent circuits: the striatonigral and the striatopallidal pathway. The neurons of the striatonigral (direct) pathway contain the neuropeptide substance P and dynorphin and mainly express D₁ receptors; this pathway directly projects from the striatum to the GPi/SNr. The neurons of the striatopallidal (indirect) pathway containing the neuropeptide, enkephalin (ENK), predominantly express D₂ receptors; this circuit connects the striatum with the GPi/SNr via synaptic connections in the GPe and STN in **Figure 1**. Dopamine modulates motor coordination and fine movements by facilitating the action of the direct pathway on stimulatory D₁ receptors and by inhibiting indirect pathway function acting on inhibitory D₂ receptors [10].

The adenosine A_{2A} receptor has agonists and antagonists of which the roles are potentiating and inhibiting, respectively. The D₂ receptor agonist has effects on motor activity, the releasing of neurotransmitter, and the expression of striatal of c-Fos, a factor of transcription which is used as neuronal activity's indirect marker [11]. The adenosine A_{2A} receptor has a key role in regulating the striatal dopaminergic neurotransmission which produces substances that are valuable to treat neurological disorders that are relevant with dopaminergic dysfunction.

The topology of G-protein-coupled receptor is displayed in the structure of the adenosine A_{2A} receptor. These receptors have a central core which consists of seven

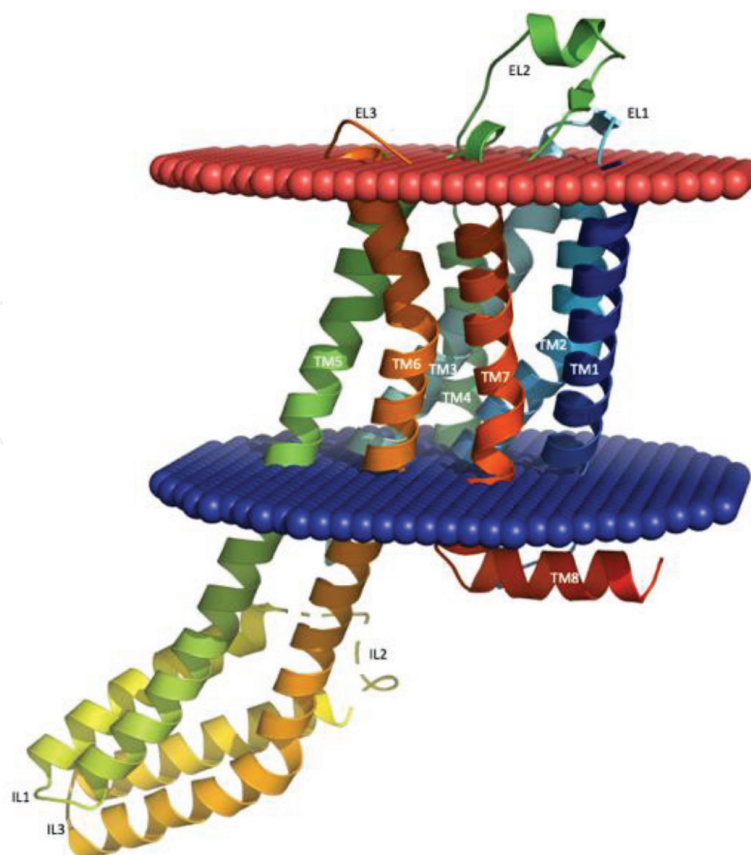


Figure 2.
 Crystal structure of the adenosine A_{2A} receptor (4E1Y) shown in the membrane structure. The extracellular and intracellular parts of the membrane are shown in red and blue beads, respectively. The disorder residues of intracellular loop (IL2) are modeled in dashed line.

transmembrane helices (7TM). Each of the TM is mainly α -helical and consists of 20–27 amino acids. Three intracellular (IL1, IL2, and IL3) and three extracellular (EL1, EL2, and EL3) loops connect each of the TM domain. A short helix TM8 runs parallel to the cytoplasmic surface of the membrane. The adenosine A_{2A} receptor has differences in length and N-terminal extracellular domain function, their domain of C-terminal intracellular, and their loops of intracellular/extracellular. These differences are shown in **Figure 2**.

2. The role of adenosine A_{2A} in Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative disorder in the brain, marked by motoric symptoms [12]. The motoric symptoms in PD are resting tremor, rigidity, bradykinesia, and postural disorder. Besides motoric symptoms, PD also has non-motoric symptoms such as depression, hallucination, sleeping disorder, and decreasing cognitive and sensory functions. The main pathological characteristic of PD is the loss of dopaminergic neurons in *substantia nigra pars compacta*, a region in the brain that controls all the body movement and forms the dopamine. The development of PD also includes the formation of Lewy body, a deposit of cytoplasmic, eosinophilic neuronal inclusions, composed of the presynaptic protein α -synuclein [13, 14].

The current therapy of PD is targeted at dopamine replacement, thereby decreasing the motor symptoms. It includes precursor of dopamine (levodopa), dopamine agonists [15, 16] monoamine oxidase type B (MAO-B) inhibitors [17], and catechol-O-methyltransferase (COMT) inhibitors [17, 18]. These agents produce undesirable side effects such as on-off effects, hallucinations, and dyskinesia. These effects get more severe as the treatment continued. The efficacy of these agents is also decreasing as the disease progressed [19].

Because of the undesirable side effects of dopamine replacement therapy, the non-dopaminergic therapy is continuously being explored. One of the approaches is selective adenosine A_{2A} antagonist [20, 21]. Adenosine A_{2A} receptors are found mainly in the striatum of rat [22, 23], which has similar distribution with the human brain [24, 25]. In the striatum, adenosine A_{2A} receptors are colocalized with dopamine D_2 receptors. These two receptors have opposite effect on motoric function [26]. The activation of adenosine A_{2A} receptors will inhibit the signaling of dopamine D_2 receptors, and conversely, the inhibition of signaling of adenosine A_{2A} receptors will increase the activation of dopamine D_2 receptors, therefore facilitating dopamine D_2 -mediated responses [11]. The inhibition of adenosine A_{2A} receptors showed motoric improvement in animal models of PD [27–30]. This also has desirable effect on long-term levodopa treatment such as decreasing the dyskinesia and increasing the therapeutic effect on levodopa [31, 32].

3. Adenosine A_{2A} receptor antagonist as a neuroprotective

For years, adenosine-dopamine interactions have been investigated in order to observe their relevance for treatment of central nervous system (CNS) disorders [33]. It is assumed that adenosine A_1 receptors (A_1 Rs) play an important role in neuroprotection as their activation at the onset of neuronal injury has shown to reduce brain damage in adult animal model. Vice versa, their blockade aggravates the damage. In other hand, adenosine A_2 receptors (A_{2A} Rs) are shown to be upregulated in harmful brain conditions, and their blockade shows brain neuroprotection in studied animals [34]. The blockade of A_{2A} Rs alleviates the long-term

burden of brain disorders in different neurodegenerative conditions, namely, ischemia, epilepsy, and Parkinson's and Alzheimer's disease, through its control on neuronal cell death [35].

A_{2A}Rs have been shown to be viable in serving as alternative non-dopaminergic strategy of Parkinson's disease treatment because of their limited distribution in the striatum and the intense interaction between adenosine and dopamine receptors in the brain. A_{2A}Rs antagonists were shown to improve motor function in different animal models (primates and rodents), alone or co-administered with dopaminomimetic drugs, levodopa, or dopamine agonists [35]. Based on rigorous preclinical animal studies, istradefylline (KW6002) has shown its promising ability to increase motor activity in PD of the advanced stage in clinical phase IIB trial [36]. It became the first therapeutic agent developed to target A_{2A}Rs, and other similar compounds will be available in near future [37].

The recent meta-analysis (n = 6) suggested that 20 mg of istradefylline improves unified Parkinson's disease ranking scale (UPDRS) III. Meanwhile at 40 mg per day, istradefylline could alleviate off time and motor symptoms derived from Parkinson's disease [38]. Phase 3 study (613 randomized patients), done by Isaacson et al. concluded that greater reduction from baseline in total hours off time/day were shown at all-time points for istradefylline 20 and 40 mg/day, compared to placebo. However, future development is needed as the study has not yet reached statistical significance [39].

In the case of Parkinson's disease, microglia has been suggested to be the most likely cell type to be targeted by A_{2A}Rs antagonists [40]. In vitro and in vivo studies showed that local neuroinflammation make glial cells (especially microglial cells) particularly sensitive to A_{2A}R modulation [41]. Previous research done by Gao and Phillis is the first study to demonstrate nonselective A_{2A}R antagonist action in reducing cerebral ischemic injury in the gerbil, following global forebrain ischemia [42]. After that, many studies have reported the neuroprotective of A_{2A}R antagonists in different models of ischemia [43].

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that is indicated by the progressive loss of memory and other cognitive functions, leading to dementia [44, 45]. Adenosine can control and integrate cognition and memory [46]. Both A₁Rs and A_{2A}Rs, mainly located in synapses, control the release of neurotransmitters which are involved in memory or other cognitive processes [34, 47]. Methylxanthine was discovered to act as nonselective adenosine receptors antagonist. Caffeine, the most famous methylxanthine found in common beverages, is the most widely consumed psychoactive drug. Maia and de Mendonca presented the first epidemiological data showing that the incidence of AD is inversely proportioned with coffee consumption [48]. Several other studies also show this inverse relationship [49–51]. Animal models also shown that caffeine intake may be beneficial for AD. In a study, a 6-month period of 0.3 g/L caffeine intake alleviated the cognitive deficits found in AD transgenic mice (APPsw). Furthermore, these mice culture neurons showed the reduced production of A β _{1–40} and A β _{1–42} peptides [52]. A_{2A}Rs antagonists and/or caffeine prophylactic and long-term neuroprotective process are suggested to be based on inhibition of reactive oxygen species activity, tau pathology, and A β production by neuronal cells [53].

A_{2A}Rs antagonist may also serve as antidepressants, as observed in animal model of antidepressants screening test done by El-Yacoubi et al. [54, 55]. In both tests, A_{2A}Rs antagonists prolong escape-directed behavior. Additionally, potential role as antidepressants was also observed in attenuated behavioral despairs displayed in both tests [55]. The relation between adenosine and depression in preclinical models was obtained from the genetic manipulation model of A_{2A}R. Genetic depletion of A_{2A}Rs resulted in antidepressant-like phenotype in animal models [55]. The

A_{2A}Rs blockade also relieves stress-induced early hippocampal modifications [56]. However, the effect of adenosine neuromodulation system in depression is complex, as it has the ability to modulate several other neurotransmission systems [35].

As addressed in previous paragraphs, A_{2A}R emerges as potential target candidate in various disorders. This is majorly caused by its unique interaction with D2 receptors, a major psychoactive drug target. Important roles of A_{2A}R were also observed in its robust neuroprotective activity, in which it mainly acts in the normalization of glutaminergic synapses, the control of mitochondria-induced apoptosis, and the control of neuroinflammation [35].

4. Current sources of the adenosine A_{2A} antagonist

The treatment of PD currently focuses on symptom management with dopaminergic therapy, such as dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) (in combination with peripheral decarboxylase inhibitors) and dopamine agonists [57]. Although L-DOPA is beneficial in patients with PD, with time, the span of the effect is shortened, the response becomes less probable, and involuntary muscle movements or, in a severe situation, dystonia can emerge [57]. These problems highlight the urgent medical need for an alternative mode of therapeutic intervention that can relieve the symptoms of the disorder while also allowing a decrease in the occurrence of side effects.

Among the non-dopaminergic therapies investigated for the treatment of PD, the adenosine A_{2A} receptor antagonists show very convincingly for two main reasons: their selective and restricted localization in the basal ganglia circuitry and their interaction with dopaminergic receptors. In another word, inhibition of the interaction of adenosine with the A_{2A} receptor may provide a potential treatment for PD.

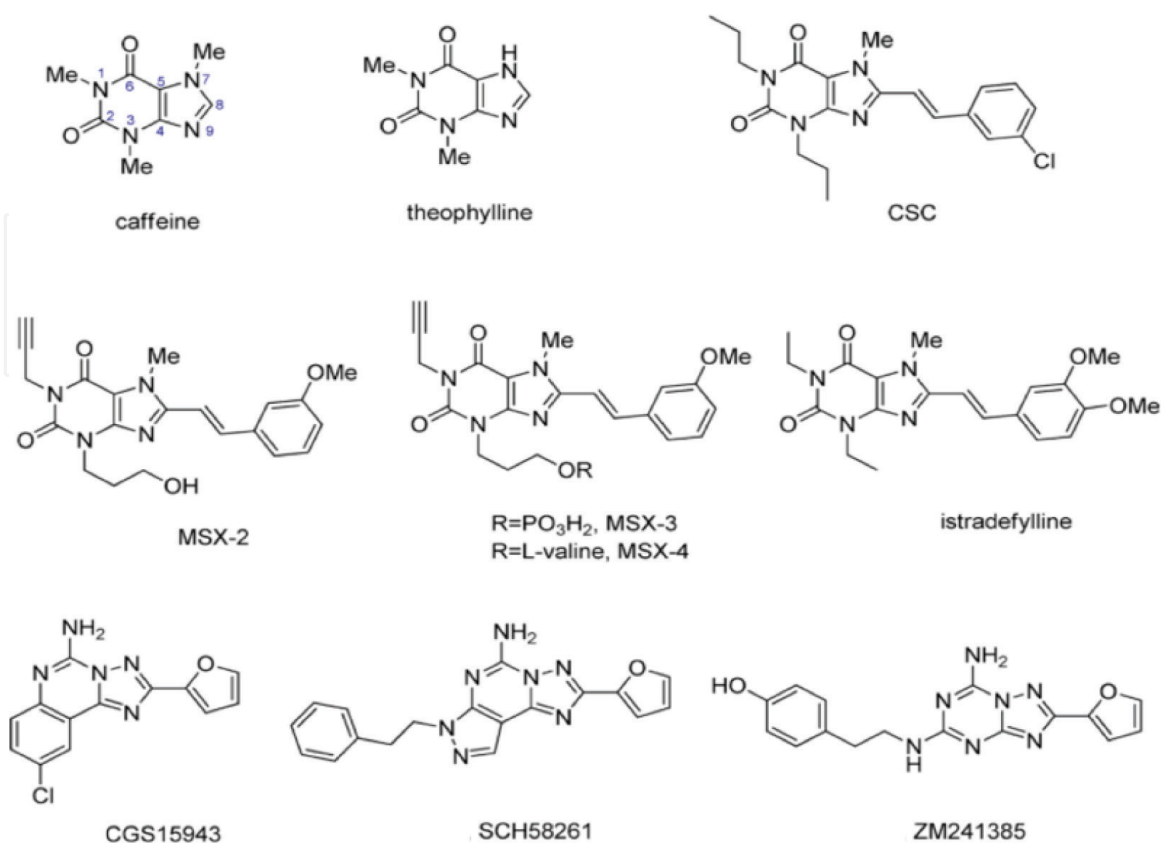


Figure 3.
Adenosine A_{2A} inhibitors.

Many highly selective A_{2A} antagonists, both xanthine and non-xanthine derivatives, have been created, and some of them are being investigated as treatment for subjects with PD in various stage of clinical trials (**Figure 3**) [7, 19, 58–61]. Caffeine as a xanthine derivate is developed as a lead compound for the design of antagonist of adenosine A_{2A} receptor [62]. Experimental model using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism is known to be an evidence that caffeine have a protective effect in Parkinson's disease [36, 63]. Some A_{2A} antagonists have progressed to clinical trials by various pharmaceutical companies including istradefylline [59], PBS-509, ST1535 and its metabolite ST4206, tozadenant, V81444, preladenant, and vipadenant [64]. Several studies of novel series of 2-aminoimidazo[4,5-b]pyridine-derivatives [65], arylindenopyrimidine [66], and bicyclic aminoquinazoline derivatives [67] as adenosine A_{2A} antagonists are reported.

Various computational methods were used to study neuroprotective effect from adenosine A_{2A} antagonists such as pharmacophore model [68], QSAR, molecular docking [69–71], and molecular dynamics [72, 73]. Orally bioavailable adenosine A_{2A} receptor antagonists have been studied for its QSAR and pharmacokinetics properties [74].

The study of structure-kinetics relationship (SKR) is done as a complement to a SAR analysis at the adenosine A_{2A} receptor. The series of 24 triazolotriazine derivatives showing a similar binding kinetics to the putative antagonist ZM241385 (4-(2-((7-amino-2-(furan-2-yl)-[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl)amino)ethyl)phenol) revealed minor affinity changes, although they varied substantially in their dissociation rates from the receptor [75].

5. Future direction of drug discovery of Parkinson's disease

Various studies have been conducted in the discovery of Parkinson's drugs against the target A_{2A} receptors. The discovery of drugs assisted by computers has accelerated in obtaining lead compounds. Apparently, this method takes a lot of consideration before entering the preclinical and clinical phases. It is because this computational method is more able to describe the answer in preparing the next design. This method can also make various predictions of activities that are difficult to do in the absence of chemical compounds before they are synthesized. In silico prediction of various pharmacokinetic parameters and toxicity can also be done faster. All of these things can provide a better picture of getting a cure for Parkinson's disease.

6. Conclusions

A_{2A} receptors emerge as potential target candidate in various disorders, caused by its unique interaction with D2 receptors, a major psychoactive drug target. Various studies have been conducted in the discovery of Parkinson's drugs against the target A_{2A} receptors. In silico study brings a new approach of study with A_{2A} receptors.

Acknowledgements

This work was supported by *Hibah Publikasi Internasional Terindeks Untuk Tugas Akhir Mahasiswa UI (PITTA)* 2018 by Universitas Indonesia.

Conflict of interest

The authors declare that they have no conflict of interest or involvement with any organization of affiliation.

IntechOpen

IntechOpen

Author details

Widya Dwi Aryati, Nabilah Nurtika Salamah, Rezi Riadhi Syahdi
and Arry Yanuar*

Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia

*Address all correspondence to: arry.yanuar@ui.ac.id

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Latini S, Pedata F. Adenosine in the central nervous system: Release mechanisms and extracellular concentrations. *Journal of Neurochemistry*. 2008;**79**:463-484
- [2] Stiles GL. Adenosine receptors. *Journal of Biological Chemistry*. 1992;**267**:6451-6454
- [3] Townsend-Nicholson A, Baker E, Schofield PR, Sutherland GR. Localization of the adenosine A₁ receptor subtype gene (ADORA1) to chromosome 1q32.1. *Genomics*. 1995;**26**:423-425
- [4] Livingston M, Heaney LG, Ennis M. Adenosine, inflammation and asthma? A review. *Inflammation Research*. 2004;**53**:171-178
- [5] Boison D, Singer P, Shen H-Y, Feldon J, Yee BK. Adenosine hypothesis of schizophrenia—Opportunities for pharmacotherapy. *Neuropharmacology*. 2012;**62**:1527-1543
- [6] Fredholm BB, Cunha RA, Svenningsson P. Pharmacology of adenosine A_{2A} receptors and therapeutic applications. *Current Topics in Medicinal Chemistry*. 2003;**3**:413-426
- [7] de Lera Ruiz M, Lim Y-H, Zheng J. Adenosine A_{2A} receptor as a drug discovery target. *Journal of Medicinal Chemistry*. 2014;**57**:3623-3650
- [8] Kull B, Svenningsson P, Fredholm BB. Adenosine A_{2A} receptors are colocalized with and activate golf in rat striatum. *Molecular Pharmacology*. 2000;**58**:771-777
- [9] Torvinen M et al. Adenosine A_{2A} receptor and dopamine D₃ receptor interactions: evidence of functional A_{2A}/D₃ heteromeric complexes. *Molecular Pharmacology*. 2005;**67**:400-407
- [10] Schapira AHV. Present and future drug treatment for Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2005;**76**:1472-1478
- [11] Pollack AE, Fink JS. Adenosine antagonists potentiate D2 dopamine-dependent activation of Fos in the striatopallidal pathway. *Neuroscience*. 1995;**68**:721-728
- [12] Lozano AM, Lang AE, Hutchison WD, Dostrovsky JO. New developments in understanding the etiology of Parkinson's disease and in its treatment. *Current Opinion in Neurobiology*. 1998;**8**:783-790
- [13] Savitt JM. Diagnosis and treatment of Parkinson disease: Molecules to medicine. *Journal of Clinical Investigation*. 2006;**116**:1744-1754
- [14] Dauer W, Przedborski S. Parkinson's disease. *Neuron*. 2003;**39**:889-909
- [15] Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. *Lancet Neurology*. 2009;**8**:929-937
- [16] Yamamoto M, Schapira AH. Dopamine agonists in Parkinson's disease. *Expert Review of Neurotherapeutics*. 2008;**8**:671-677
- [17] Olanow CW, Stocchi F. COMT inhibitors in Parkinson's disease: Can they prevent and/or reverse levodopa-induced motor complications? *Neurology*. 2004;**62**:S72-S81
- [18] Gordin A, Brooks DJ. Clinical pharmacology and therapeutic use of COMT inhibition in Parkinson's disease. *Journal of Neurology*. 2007;**254**:IV37-IV48
- [19] Shook BC, Jackson PF. Adenosine A_{2A} receptor antagonists and Parkinson's

disease. *ACS Chemical Neuroscience*. 2011;**2**:555-567

[20] Schwarzschild MA, Agnati L, Fuxe K, Chen J-F, Morelli M. Targeting adenosine A_{2A} receptors in Parkinson's disease. *Trends in Neurosciences*. 2006;**29**:647-654

[21] Salamone JD. Facing dyskinesia in Parkinson disease: Nondopaminergic approaches. *Drugs Future*. 2010;**35**:567

[22] Rosin DL, Robeva A, Woodard RL, Guyenet PG, Linden J. Immunohistochemical localization of adenosine A_{2A} receptors in the rat central nervous system. *Journal of Comparative Neurology*. 1998;**401**:163-186

[23] Fredholm BB, Svenningsson P. Striatal adenosine A_{2A} receptors—Where are they? What do they do? *Trends in Pharmacological Sciences*. 1998;**19**:46-47

[24] Ishiwata K et al. First visualization of adenosine A_{2A} receptors in the human brain by positron emission tomography with [¹¹C]TMSX. *Synapse*. 2005;**55**:133-136

[25] Svenningsson P, Hall H, Sedvall G, Fredholm BB. Distribution of adenosine receptors in the postmortem human brain: An extended autoradiographic study. *Synapse*. 1997;**27**:322-335

[26] Fink JS et al. Molecular cloning of the rat A₂ adenosine receptor: Selective co-expression with D₂ dopamine receptors in rat striatum. *Molecular Brain Research*. 1992;**14**:186-195

[27] Chen J-F et al. Neuroprotection by caffeine and A_{2A} adenosine receptor inactivation in a model of Parkinson's disease. *Journal of Neuroscience*. 2001;**21**:RC143-RC143

[28] Grondin R et al. Antiparkinsonian effect of a new selective adenosine A_{2A}

receptor antagonist in MPTP-treated monkeys. *Neurology*. 1999;**52**:1673-1673

[29] Ongini E et al. Dual actions of A_{2A} adenosine receptor antagonists on motor dysfunction and neurodegenerative processes. *Drug Development Research*. 2001;**52**:379-386

[30] Ikeda K, Kurokawa M, Aoyama S, Kuwana Y. Neuroprotection by adenosine A_{2A} receptor blockade in experimental models of Parkinson's disease. *Journal of Neurochemistry*. 2002;**80**:262-270

[31] Kanda T et al. Combined use of the adenosine A_{2A} antagonist KW-6002 with l-DOPA or with selective D1 or D2 dopamine agonists increases antiparkinsonian activity but not dyskinesia in MPTP-treated monkeys. *Experimental Neurology*. 2000;**162**:321-327

[32] Hauser RA, Hubble JP, Truong DD. Randomized trial of the adenosine A_{2A} receptor antagonist istradefylline in advanced PD. *Neurology*. 2003;**61**:297-303

[33] Fuxe K et al. Adenosine-dopamine interactions in the pathophysiology and treatment of CNS disorders. *CNS Neuroscience and Therapeutics*. 2010;**16**:e18-e42

[34] Cunha RA. Neuroprotection by adenosine in the brain: From A₁ receptor activation to A_{2A} receptor blockade. *Purinergic Signal*. 2005;**1**:111-134

[35] Gomes CV, Kaster MP, Tomé AR, Agostinho PM, Cunha RA. Adenosine receptors and brain diseases: Neuroprotection and neurodegeneration. *Biochimica et Biophysica Acta (BBA)—Biomembranes*. 2011;**1808**:1380-1399

[36] Kalda A, Yu L, Oztas E, Chen J-F. Novel neuroprotection by caffeine and adenosine A_{2A} receptor antagonists

in animal models of Parkinson's disease. *Journal of the Neurological Sciences*. 2006;**248**:9-15

[37] Yamada K, Kobayashi M, Kanda T. Chapter Fifteen - Involvement of Adenosine A_{2A} Receptors in Depression and Anxiety. *International Review of Neurobiology*. 2014;**119**:373-393. DOI: 10.1016/B978-0-12-801022-8.00015-5

[38] Sako W, Murakami N, Motohama K, Izumi Y, Kaji R. The effect of istradefylline for Parkinson's disease: A meta-analysis. *Scientific Reports*. 2017;**7**:18018

[39] Isaacson S et al. Efficacy and safety of istradefylline in moderate to severe Parkinson's disease: A phase 3, multinational, randomized, double-blind, placebo-controlled trial (i-step study). *Journal of the Neurological Sciences*. 2017;**381**:351-352

[40] Franco R, Navarro G. Adenosine A_{2A} receptor antagonists in neurodegenerative diseases: Huge potential and huge challenges. *Frontiers in Psychiatry*. 2018;**9**(1-5)

[41] Chen J-F, Pedata F. Modulation of ischemic brain injury and neuroinflammation by adenosine A_{2A} receptors. *Current Pharmaceutical Design*. 2008;**14**:1490-1499

[42] Gao Y, Phillis JW. CGS 15943, An adenosine A₂ receptor antagonist, reduces cerebral ischemic injury in the Mongolian gerbil. *Life Sciences*. 1994;**55**:PL61-PL65

[43] Pedata F et al. Adenosine A_{2A} receptors modulate acute injury and neuroinflammation in brain ischemia. *Mediators of Inflammation*. 2014;**805198**:2014

[44] Kalaria RN et al. Alzheimer's disease and vascular dementia in developing countries: Prevalence, management, and risk factors. *The Lancet Neurology*. 2008;**7**:812-826

[45] Lesne S. Toxic oligomer species of amyloid- β in Alzheimer's disease, a timing issue. *Swiss Medical Weekly*. 2014;**298**:789-791

[46] Cunha RA, Agostinho PM. Chronic caffeine consumption prevents memory disturbance in different animal models of memory decline. *Journal of Alzheimer's Disease*. 2010;**20**:S95-S116

[47] Ribeiro JA, Sebastião AM, de Mendonça A. Adenosine receptors in the nervous system: Pathophysiological implications. *Progress in Neurobiology*. 2002;**68**:377-392

[48] Maia L, de Mendonça A. Does caffeine intake protect from Alzheimer's disease? *European Journal of Neurology*. 2002;**9**:377-382

[49] Ritchie K et al. The neuroprotective effects of caffeine: A prospective population study (the Three City Study). *Neurology*. 2007;**69**:536-545

[50] Santos C, Costa J, Santos J, Vaz-Carneiro A, Lunet N. Caffeine intake and dementia: systematic review and meta-analysis. *Journal of Alzheimer's Disease*. 2010;**20**:S187-S204

[51] Smith AP. Caffeine, cognitive failures and health in a non-working community sample. *Human Psychopharmacology Clinical and Experimental*. 2009;**24**:29-34

[52] Arendash GW et al. Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain β -amyloid production. *Neuroscience*. 2006;**142**:941-952

[53] Marzagalli R, Castorina A. The seeming paradox of adenosine receptors as targets for the treatment of Alzheimer's disease: Agonists or antagonists? *Neural Regeneration Research*. 2015;**10**:205

[54] Cantwell R, Cox JL. Psychiatric disorders in pregnancy and the

puerperium. *Current Obstetrics & Gynaecology*. 2006;**16**:14-20

[55] El Yacoubi M et al. Adenosine A_{2A} receptor antagonists are potential antidepressants: evidence based on pharmacology and A_{2A} receptor knockout mice. *British Journal of Pharmacology*. 2001;**134**:68-77

[56] Cunha GMA, Canas PM, Oliveira CR, Cunha RA. Increased density and synapto-protective effect of adenosine A_{2A} receptors upon sub-chronic restraint stress. *Neuroscience*. 2006;**141**:1775-1781

[57] Olanow CW et al. Levodopa in the treatment of Parkinson's disease: Current controversies. *Movement Disorders*. 2004. DOI: 10.1002/mds.20243

[58] Armentero MT et al. Past, present and future of A_{2A} adenosine receptor antagonists in the therapy of Parkinson's disease. *Pharmacology & Therapeutics*. 2011. DOI: 10.1016/j.pharmthera.2011.07.004

[59] Jenner P. Istradefylline, a novel adenosine A_{2A} receptor antagonist, for the treatment of Parkinson's disease. *Expert Opinion on Investigational Drugs*. 2005. DOI: 10.1517/13543784.14.6.729

[60] Pinna A. Novel investigational adenosine A_{2A} receptor antagonists for Parkinson's disease. *Expert Opinion on Investigational Drugs*. 2009. DOI: 10.1517/13543780903241615

[61] Hickey P, Stacy M. Adenosine A_{2A} antagonists in Parkinson's disease: What's next? *Current Neurology and Neuroscience Reports*. 2012;**12**:376-385

[62] Petzer JP, Petzer A. Caffeine as a lead compound for the design of therapeutic agents for the treatment of Parkinson's disease. *Current Medicinal Chemistry*. 2015. DOI: 10.2174/0929867322666141215160015

[63] Munoz DG, Fujioka S. Caffeine and Parkinson disease: A possible diagnostic and pathogenic breakthrough. *Neurology*. 2018. DOI: 10.1212/WNL.0000000000004898

[64] Pinna A. Adenosine A_{2A} receptor antagonists in Parkinson's disease: Progress in clinical trials from the newly approved istradefylline to drugs in early development and those already discontinued. *CNS Drugs*. 2014;**28**:455-474

[65] McGuinness BF et al. Discovery of 2-aminoimidazopyridine adenosine A_{2A} receptor antagonists. *Bioorganic & Medicinal Chemistry Letters*. 2010;**20**:6845-6849

[66] Attack JR et al. JNJ-40255293, a novel adenosine A_{2A}/A₁ antagonist with efficacy in preclinical models of Parkinson's disease. *ACS Chemical Neuroscience*. 2014;**5**:1005-1019

[67] Zhou G et al. Bioorganic & medicinal chemistry letters discovery of aminoquinazoline derivatives as human A_{2A} adenosine receptor antagonists. *Bioorganic & Medicinal Chemistry Letters*. 2016;**26**:1348-1354

[68] Khanfar MA, Al-Qtaishat S, Habash M, Taha MO. Discovery of potent adenosine A_{2A} antagonists as potential anti-Parkinson disease agents. Non-linear QSAR analyses integrated with pharmacophore modeling. *Chemico-Biological Interactions*. 2016;**254**:93-101

[69] Anighoro A, Bajorath J. Binding mode similarity measures for ranking of docking poses: A case study on the adenosine A_{2A} receptor. *Journal of Computer-Aided Molecular Design*. 2016. DOI: 10.1007/s10822-016-9918-z

[70] Yang X et al. A covalent antagonist for the human adenosine A_{2A} receptor. *Purinergic Signal*. 2017. DOI: 10.1007/s11302-016-9549-9

[71] Jaiteh M et al. Docking screens for dual inhibitors of disparate drug targets for Parkinson's disease. *Journal of Medicinal Chemistry*. 2018. DOI: 10.1021/acs.jmedchem.8b00204

[72] Sabbadin D et al. Bridging molecular docking to membrane molecular dynamics to investigate GPCR-ligand recognition: The human A_{2A} adenosine receptor as a key study. *Journal of Chemical Information and Modeling*. 2013. DOI: 10.1021/ci400532b

[73] Caliman AD, Swift SE, Wang Y, Miao Y, McCammon JA. Investigation of the conformational dynamics of the apo A_{2A} adenosine receptor. *Protein Science*. 2015. DOI: 10.1002/pro.2681

[74] Basu S et al. Design, synthesis of novel, potent, selective, orally bioavailable adenosine A_{2A} receptor antagonists and their biological evaluation. *Journal of Medicinal Chemistry*. 2017. DOI: 10.1021/acs.jmedchem.6b01584

[75] Guo D et al. Binding kinetics of ZM241385 derivatives at the human adenosine A_{2A} receptor. *ChemMedChem*. 2014. DOI: 10.1002/cmdc.201300474