[Frontiers in Bioscience 4071-4096, May 1, 2008]

Potential role of adenosine A_{2A} receptors in the treatment of schizophrenia

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1. ABSTRACT

Schizophrenia is a complex neuropsychiatric disorder characterized by cognitive deficits, and positive and negative symptoms. All antipsychotics currently used in clinical practice are dopamine D_2 receptor antagonists. The idea that adenosine A_{2A} receptor agonists might be of interest for the treatment of schizophrenia derived from studies showing the existence of antagonistic intramembrane interaction between A_{2A} and D_2 receptors. Based on results obtained in animal models, a putative antipsychotic-like profile of A_{2A} agonists was put forward. However, A_{2A} agonists were shown to have detrimental effects in animal models of learning and memory. Moreover, these compounds produce many peripheral side-effects which limits their use in clinical trials. On the other hand, The results concerning the influence of A_{2A} receptor antagonists in animal models used in schizophrenia studies such as locomotor activity and prepulse inhibition are fairly controversial. Some cognitive enhancing properties of A_{2A} receptor antagonists have also been found in rats. Recent results showing the existence of heteromeric A_{2A}/D_3 and A_{2A}/mGlu5 receptor complexes seem to open up new perspectives on the search for novel therapies of schizophrenia.

2. INTRODUCTION

Schizophrenia is a major chronic neuropsychiatric disorder affecting approximately 1% of world population. The evidence from genetic, brain imaging and clinical and pharmacologic studies indicates that schizophrenia is a heterogeneous group of disorders and suggests the lack of a single molecular event which could explain its pathophysiology (1, 2). The etiology of schizophrenia remains still unknown, however, it seems that complex interaction between biological, environmental and genetic factors underlies this disease.

The symptoms of schizophrenia are usually divided into **positive** (hallucinations, delusions, disorganised thoughts and behaviours, incoherence of speech, and inappropriate emotions) and **negative** (social withdrawal, blunting of emotional response, anhedonia). Additionally, impairments of cognitive domains are associated with schizophrenia. The main **cognitive impairments,** which are considered to be a core feature of schizophrenia, include deficits in attention, working memory, verbal learning and memory, and executive functions.

It is generally accepted that blockade of dopamine D_2 receptors plays a key role in antipsychotic actions of neuroleptic drugs (3). The discovery of antagonistic interaction between adenosine A_{2A} and dopamine D_2 receptors in the striatum and nucleus accumbens (*see section 4.3.1.*) had important implications for neuropsychiatric disorders, where dopamine neurotransmission seems to play a crucial role such as schizophrenia. Moreover, since even revised dopamine hypothesis of schizophrenia cannot fully explain its pathophysiology, research has focused on the role of other neurotransmitter systems, such as glutamate, GABA, serotonin, and also adenosine. Some review articles appeared in the last years which suggested that dysfunction of adenosinergic system may contribute to the pathophysiology of schizophrenia (4, 5). Most of the work, however, was done regarding the role of adenosine A_1 receptors in these processes, and much less is known about the involvement of A_{2A} receptors. These receptors seem to be of interest also because of the existence of heteromeric complexes, formed by adenosine A_{2A} receptors with not only adenosine A_1 and dopamine D_2 and D_3 receptors, but also with metabotropic glutamate mGlu5 receptors (*see section 4.3. and 6.1.*). The formation of such heteromeric receptor complexes in the brain increases the alternative strategies for design of novel drugs for the treatment of many disorders. Therefore, A_{2A} receptor agonists, which have behavioural effects in animals that are similar to those produced by atypical antipsychotics, offer a potential novel treatment of schizophrenia. The aim of this article is to review the putative role of adenosine A_{2A} receptors in the pathophysiology and therapy of schizophrenia.

3. ROLE OF DOPAMINERGIC AND GLUTAMATERGIC NEUROTRANSMISSION IN SCHIZOPHRENIA

The role of central dopamine neurotransmission in the pathophysiology and pharmacological treatment of schizophrenia is well documented. Initially, it was postulated that a hyperdopaminergic state in limbic structures was responsible for the expression of psychotic symptoms in schizophrenia (6, 7). This hypothesis was based on experimental observations that antipsychotic drugs served as functional dopamine receptor antagonists, and their clinical efficacy correlated with their potency to block dopamine D_2 receptors (3, 8). These findings together with the observation that administration of psychostimulants, such as amphetamine, which increase dopamine release, induce psychosis and exacerbate positive symptoms of this disorder, substantiate this hypothesis (9). Moreover, recent neuroimaging data from PET and SPECT studies validated the dopamine hypothesis of schizophrenia showing the higher release of dopamine in response to amphetamine challenge in unmedicated schizophrenic patients vs healthy controls (10-13). The degree of dopamine release correlates positively with the severity of positive symptoms and with subsequent response to dopamine blockade. Furthermore, subjects with schizophrenia have a higher fraction of D_2 receptors occupied by endogenous dopamine than normal control subjects (12).

The dopamine hypothesis of schizophrenia has been, however, insufficient to explain all aspects of this disease. The main problem is related to the fact that typical antipsychotics do not improve the "negative" and cognitive symptoms. In addition, many schizophrenic patients do not respond to dopamine antagonist therapy. Furthermore, some studies found that dopamine agonists might ameliorate negative symptoms (7).

The recent hypothesis, which may help to explain the discrepancies outlined above, suggests that psychotic symptoms may results from the disturbed balance between cortical and subcortical dopamine systems. This theory links the appearance of positive symptoms to hyperactivation of dopamine system in subcortical structures, including mesolimbic system. On the other hand, the so-called negative symptoms and cognitive disturbances seem to be due mainly to the hypofunction of cortical (prefrontal cortex) dopamine system (14-16). This suggestion has not been, however, supported by recent study of Kellendonk *et al.* (17) who have used a transgenic mouse model to show that prefrontal cortical function can be impaired by increased expression of dopamine in the striatum. Thus, mice overexpressing D_2 receptors in the striatum developed cognitive impairments in working memory tasks and behavioral flexibility. These cognitive deficits were shown to be related to secondary alterations in the prefrontal cortex such as the increased dopamine tissue content and dopamine turnover, as well as D_2 receptor activation in this structure, mainly associated with working memory (17).

It is known that cortical and subcortical systems are functionally linked via the glutamatergic system. Recently, it has been postulated, based on experimental evidences, that dysfunctional glutamatergic transmission plays a major role in the pathophysiology of schizophrenia.

3.1. Involvement of glutamate N-methyl-D-aspartate (NMDA) receptors in the pathophysiology of schizophrenia

Glutamate, the major excitatory neurotransmitter in the brain, regulates neuronal activity via two types of receptors: ionotropic (NMDA, AMPA, KA) and metabotropic, G-protein-coupled receptors (mGlu) (18, 19). The latter with 8 known subtypes are classified into 3 main groups: group I (comprising subtypes 1 and 5), group II (2 and 3) and group III (4, 6, 7 and 8) mGlu receptors (19). Receptors belonging to group I are coupled to inositol phosphate hydrolysis and are localized mainly postsynaptically (19). Receptors belonging to group II and III, which are negatively linked to adenylate cyclase, are mostly presynaptic, and their activation inhibits glutamate release (19).

NMDA but also non-NMDA glutamatergic receptors have been shown to play an important role in a variety of crucial brain functions, including memory and learning, synaptic and developmental plasticity, sensory information processing, and motor function (19-21).

Results from animal studies support the notion that dysfunction of glutamatergic transmission is involved in the pathophysiology of schizophrenia (1, 20, 22-24). Studies with uncompetitive NMDA receptor antagonists, phencyclidine (PCP) and ketamine, which can induce or mimic positive, negative and cognitive symptoms of schizophrenia, when administered to schizophrenic patients or healthy volunteers, support the involvement of NMDA receptors in schizophrenia (25-27). Moreover, clinical observations showed that atypical neuroleptics, such as clozapine alleviate psychotic symptoms evoked by ketamine (27), whereas combined administration of typical neuroleptics with agonists of glycine site of NMDA receptor, such as glycine or D-serine, alleviates schizophrenic symptoms (28-30). Additionally, alterations in expression of NMDA receptor expression have been found in the cerebral cortex, hippocampus and thalamus of schizophrenic patients (31-34).

Based on the above-mentioned observations and taking into account the existence of glutamatergic/dopaminergic interaction, it has been proposed that dopaminergic hyperactivity in the schizophrenia may be secondary to alteration in glutamatergic transmission, in particular NMDA receptor function (35). According to this view, increasing NMDA receptor activation might be expected to alleviate symptoms of schizophrenia and provide a therapeutic benefit for this disease (1, 20-22, 36).

3.2. The role of metabotropic glutamate mGlu5 receptors in animal models relevant for schizophrenia; interaction with NMDA receptors

Recently, it has been suggested that group I mGlu receptors, particularly mGlu5 receptor, may also contribute to schizophrenia (23, 24). The genetic linkage studies have identified the gene encoding RGS4, a regulatory protein that affects mGlu5 receptor-mediated activation of the G-protein, Gq, as a schizophrenia susceptibility gene (37, 38). Moreover, an increased mGlu5 mRNA level has been found in the prefrontal cortex of schizophrenic patients (39).

The mGlu5 receptors are widely distributed in the CNS, they are abundant in the striatum, nucleus accumbens, hippocampus and cereberal cortex (40, 41). Interestingly, the distribution of mGlu5 and NMDA receptors in several brain regions overlaps and both receptors can be physically connected via the chain of anchoring proteins such as PSD95, GKAP (guanylate-kinase-associated proteins), Shank and Homer proteins (19, 42). Furthermore, positive reciprocal interaction between both receptors has been demonstrated in several brain regions. It is worth mentioning that the mGlu5 receptor has been found to interact directly with adenosine A_{2A} receptors, forming the oligomeric complexes (*see sections 4.3.3 and 6.1.2.)*.

Results obtained in mGlu5 knockout mice support the role of these receptors in animal models of schizophrenia. These mice showed sensorimotor gating deficits reflected by impaired prepulse inhibition (PPI) of the acustic startle (43-45); such deficits in PPI are also observed in schizophrenic patients (46). In turn, antagonists of mGlu5 receptors (MPEP, MTEP) given acutely neither enhanced the locomotor activity nor did they affect the PPI (45, 47-50).

Moreover, the NMDA-dependent long-term potentiation (LTP), a cellular mechanism for spatial learning, is reduced in the CA1 and dentate gyrus of the hippocampus of the mGlu5 knockout mice (51, 52). Blockade of mGlu5 receptors has been shown to impair LTP in the CA1 and dentate gyrus of the hippocampus as well as to induce deficits in working memory and reference memory performance (23, 53, 54). Contrarily, Ballard *et al.* (55) and Campbell *et al.* (56) did not find any effect of MPEP per se on cognitive function.

Based on the existing interaction between mGlu5 and NMDA receptors (57-62), antagonists of mGlu5 and NMDA receptors can act in a cooperative manner to produce behavioural impairments. Thus, blockade of mGlu5 receptors has been found to potentiate locomotor activity and stereotypy evoked by PCP or MK-801 in rats and mice (45, 48-50, 63). Moreover, aggravation of learning and memory impairment evoked by PCP and MK801 as well as potentiation of PCP- and MK801-induced PPI disruption have been demonstrated (49, 56). A putative mechanism underlying behavioural effects of mGlu5 and NMDA receptor antagonists may be due to the fact that blockade of mGlu5 receptors enhanced the MK-801-induced firing activity in the prefrontal cortex (PFC) of rats, the structure which is critical for cognitive functions and has high density of mGlu5 receptors (63-67).

In summary, since blockade of mGlu5 receptors potentiates the effects of uncompetitive NMDA receptor antagonists on cognitive and psychotic-like symptoms in animals, it seems reasonable to suggest that mGlu5 receptor agonist/positive modulators may represent a novel approach to antipsychotic drug development. In agreement with this suggestion, recent studies have found that intracerebroventricular administration of the selective mGlu5 receptor agonist, CHPG or systemic injection of CDPPB, the mGluR5 positive modulator, reverse locomotor activity and/or deficit of PPI evoked by amphetamine in rodents (68, 69).

4. ADENOSINE METABOLISM AND RECEPTORS

In the last years, research regarding neuropsychiatric disorders has been focused on the role of other neurotransmitters and neuromodulators, such as GABA, serotonin, acetylcholine and adenosine. Adenosine, an endogenous purine nucleoside present in all mammalian tissues, modulates a variety of important physiological processes. The neuromodulatory role of adenosine in the CNS has been proposed to be exerted mainly through the control of neurotransmitter release (70-72).

Adenosine is formed intracelullarly from degradation of AMP through 5'-nucleotidase, or extracelullarly by the metabolism of released nucleotides

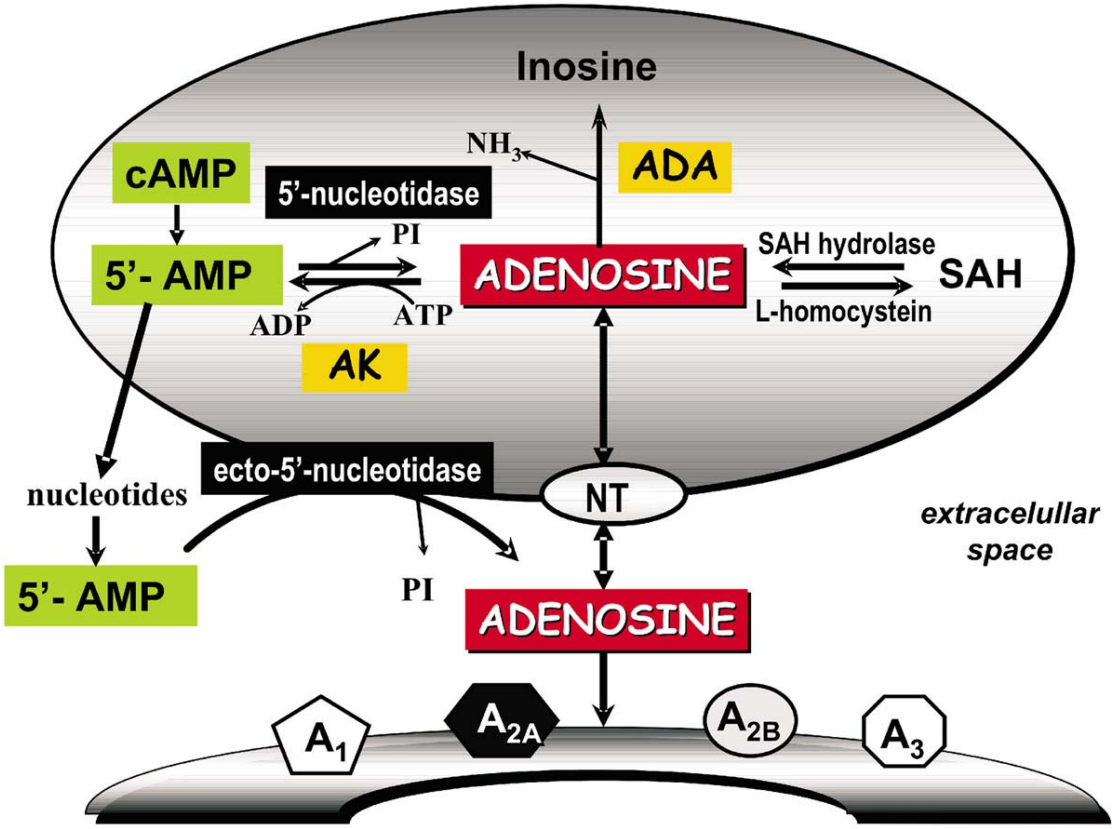

Figure 1. Adenosine metabolism. Adenosine is formed intracelullarly from 5'-AMP by the cytosolic 5'-nucleotidase, or extracelullarly by the metabolism of nucleotides released through the action of ecto-5'-nucleotidase. Hydrolysis of SAH by SAH hydrolase may be another intracellular source of adenosine. Extracellular adenosine is primarily inactivated by uptake through the transporters which are mainly bi-directional, followed by either phosphorylaton to AMP by AK or to a lesser degree, deamination to inosine by ADA. Another possible catabolic pathway, however, of minor significance, is a reversible reaction catalysed by SAH hydrolase, leading to formation of SAH from adenosine and L-homocysteine *(for more details see ref. 73, 74)*. Abbreviations: ADA, adenosine deaminase; AK, adenosine kinase; A_1, A_{2A}, A_{2B} and A_3 – adenosine receptors; NT, nucleoside transporter; SAH, S-adenosylhomocysteine

through the action of ecto-5'-nucleotidase (Figure 1) (73). Hence, its formation depends upon ATP breakdown and synthesis. The main mechanism implicated in adenosine release, facilitated diffusion, involves specialized nucleoside transporters (73). These transporters are mainly bi-directional, and keep the extracellular concentration of adenosine in equilibrium. Hydrolysis of S-adenosylhomocysteine (SAH) by SAH hydrolase (Figure 1), may be another inracellular source of adenosine, however, this pathway does not significantly contribute to adenosine production in the brain (73). Extracellular adenosine is primarily inactivated by uptake across the neuronal cell membrane, followed by either phosphorylaton to AMP by adenosine kinase (AK) or to a lesser degree, deamination to inosine by adenosine deaminase (ADA). Both AMP and inosine are less active than adenosine at the adenosine receptors (73). Another possible catabolic pathway is a reversible reaction catalysed by SAH hydrolyse, leading to formation of SAH from adenosine and L-homocysteine, however, it represents only a minor pathway of adenosine catabolism under basal conditions (Figure 1) (73).

Currently, all four adenosine receptor subtypes (A_1, A_{2A}, A_{2B} and A_3), which belong to the family of G protein-coupled receptors, have been cloned and characterized (Table 1) (74-77). The main intracellular signalling pathways involve the formation of cAMP, with A_1 and A_3 receptors causing (through Gi and Go proteins) inhibition of adenylate cyclase, and A_{2A} and A_{2B} receptors activating it (Table 1) (74-78). Other mechanisms, e.g. voltage-sensitive Ca^{2+} channels, K+ channels and phospholipase C, are also involved in signal transduction by each of the adenosine receptors (Table 1) (74, 75, 77). It has been estimated that under physiological conditions, extracellular levels of adenosine in the rodent CNS range between 30 and 300 nM. These levels are sufficient to stimulate both the higher affinity A_1 and A_{2A} receptors. Under pathological conditions such as hypoxia/ischemia, seizures, adenosine rises markedly to concentrations that can stimulate the lower affinity A_3 and A_{2B} receptors.

The inhibitory A_1 receptor, which is present both on neurons and glial cells, is the most abundant adenosine receptor in many regions of the brain. These receptors are

Table 1. Adenosine receptors – classification, signal transduction and localization

	Adenosine Receptors			
	A_1	A_{2A}	A_{2B}	A_3
G-protein coupling	Gi / Go[1]	Gs, Golf	Gs[1]	Gi / Go
Transduction mechanisms	↓ AC[2]; ↓ Ca^{2+} ↑ PLC[3]; ↑ K^+	↑ AC ↑ Ca^{2+}	↑ AC ↑ PLC	↓ AC ↑ Ca^{2+}; ↑ PLC
Distribution	widespread in the brain cortex, hippocampus, striatum, cerebellum, thalamus	restricted in the brain: striatum nucleus accumbens, globus pallidus olfactory tubercle	widespread cecum, colon, bladder, brain, spinal cord, blood vessels, lung, vas deferens, pituitary	widespread – low density in the brain lung, liver, kidney, heart
Agonists	CPA, CCPA, S(-)ENBA, CVT-510	CGS21680, ATL-146e, CVT-3146	LUF5835, NECA (not selective)	IB-MECA, Cl-IB-MECA, CP-608039
Antagonists	DPCPX, KW3902, WRC0571, FK453, FR194921	KW6002, SCH58261, SCH442416, CSC; ZM241385	MRS1754 MRE2029-F20, OSIP-339391	MRS 1220, MRS1523, MRS1334, PSB-11

Adapted from: Dunwiddie and Masino (74), Ralevic and Burnstock (75), Fredholm et al. (77), Jacobson and Gao (193). Abbreviations: [2]AC – adenylate cyclase; [1]Gi, Golf, Gs – G-proteins; [3]PLC – phospholipase C; ↑ stimulation; ↓ inhibition

localized both pre- and postsynaptically. The highest expression of A_1 receptors has been found in the cortex, cerebellum, thalamus and hippocampus (Table 1) (71, 79-81). Moreover, the A_1 receptor mRNA is also present in basal ganglia structures including the striatum, globus pallidus and subthalamic nucleus (71, 82, 83). In turn, A_{2B} receptors are mainly present in peripheral organs such as the bowel, bladder, lung, vas deferens as well as in the spinal cord and brain. (75, 77, 84, 85). In the brain, A_{2B} receptors were found in hippocampal CA1 and CA3 neurons, in the hypothalamus, thalamus, striatum and also in glial cells (Table 1) (74, 75, 77, 84, 85). As for A_3 receptors, their distribution and physiological functions in the brain are still unclear, however, they are known to be widely distributed in peripheral organs (mainly in the testis and lung) (83, 86, 87). A relatively small amount of A_3 receptors and their mRNA were suggested to be present in the rat hippocampus and cerebellum (Table 1) but recent studies have not corroborated their presence in the human hippocampus (86).

4.1. Adenosine A_{2A} receptors and their localization in the brain

The A_{2A} receptor contains seven transmembrane domains and is coupled mostly to Gs and Golf stimulatory proteins, thus being mainly linked to stimulation of adenylyl cyclase (AC) and the protein kinase A (PKA)-dependent signalling cascades (Table 1) (71, 88, 89). The initial binding studies with the selective agonist (^{3}H)CGS21680 showed that A_{2A} receptors are predominantly located in several basal ganglia structures, such as the striatum, nucleus accumbens, globus pallidus and olfactory tubercle, areas that are densely innervated by dopaminergic neurons (Table 1) (90-93). However, studies performed with more sensitive techniques have demonstrated the presence of A_{2A} receptors and corresponding mRNAs, albeit at lower level of expression, in several other brain areas, e.g. the hippocampus, cerebral cortex, extended amygdala, thalamic nuclei, substantia nigra (92). However, some differences were found between human brain and that of other animal species (91, 93, 94). It is noteworthy that A_{2A} receptors are also present on glial cells.

In the striatum, A_{2A} receptors are homogeneously distributed throughout the lateral and medial parts and display dense labelling of the neuropil (92). Studies at the ultrastructural level showed that striatal terminals expressing A_{2A} receptors accounted for 25% of the labelled elements (92, 95). These presynaptic receptors may facilitate both excitatory glutamatergic, and inhibitory GABAergic striatal transmission. However, the majority of A_{2A} receptors were found on postsynaptic elements in the striatum (92, 95), a structure known to be characterized by a high compartmentalization and neurochemical segregation (96, 97). Two distinct GABAergic projection pathways are known to oppositely regulate basal ganglia output. Activation of the direct GABAergic pathway (striatonigral) containing substance P and dynorphin facilitates motor behaviour by disinhibiting cortical and brainstem motor areas, whereas stimulation of the indirect GABAergic pathway (striatopallidal) containing enkephalin, leads to inhibition of motor behaviour (96, 97). In line with this neurochemical segregation, dopamine D_1 receptors are almost exclusively located on the direct pathway whereas D_2 receptors are located together with A_{2A} receptors on the indirect pathway (92, 95, 96, 98, 99).

In the nucleus accumbens (the so-called ventral striatum), A_{2A} receptors followed the same pattern as the dopamine D_2 receptors, and the shell of the nucleus

accumbens displayed a density of adenosine A_{2A} receptors about 40% lower to that in the dorsal striatum (92).

Additionally, the co-expression of adenosine A_{2A} and A_1 receptor mRNAs was found on about 25% of the glutamatergic nerve terminals of the rat hippocampus (100). These results support the previous suggestion that such co-localization may be the basis for the interaction between A_{2A} and A_1 receptors in the control of glutamate release (100-103). It is, however, an open question if such control of glutamate release is also present in other brain areas, such as the cerebral cortex or the striatum, where both receptors are known to be present and co-localized in the same nerve terminals. Functional data revealed that there are also populations of nerve terminals which are only regulated by A_{2A} receptors but not by A_1 receptors, such as GABAergic terminals of the hippocampus (104) and the striatum (105). Thus, the distribution of A_1 and A_{2A} receptors is likely to be heterogeneous in different types of nerve terminals throughout the brain.

4.2. Adenosine A_{2A} receptors and dopamine release

Early *in vitro* studies of the regulation of (^{3}H) dopamine release from striatal slices showed that adenosine (106) and selective agonists of both A_1 and A_{2A} receptors inhibited electrically-evoked (^{3}H) dopamine release (107). The results obtained so far using *in vivo* brain microdialysis on the effects of adenosine A_{2A} agonists and antagonists on dopamine release in the striatum and nucleus accumbens appear conflicting. Thus, the A_{2A} agonists, CGS21680 and CPCA as well as caffeine increased the release of dopamine in the striatum (108-110). In contrast, Okada *et al.* (110-112) reported that A_{2A} agonists and antagonists did not affect striatal dopamine release unless adenosine A_1 receptors had been previously blocked.

Recently, however, Quarta *et al.* (113, 114) showed using *in vivo* microdialysis, that local perfusion of the A_{2A} receptor agonist CGS21680 or A_1 receptor antagonist, CPT, elicited significant increase in extracellular level of dopamine as well as glutamate, in the shell of the nucleus accumbens. In turn, systemic administration or local perfusion of the nonselective adenosine receptor antagonist, caffeine also significantly increased extracellular levels of dopamine and glutamate in this structure (113, 115). The observed effects of caffeine as well as selective A_1 and A_{2A} receptor ligands on the dopamine release seem to be under the stimulatory control of extracellular glutamate and to depend on the activation of NMDA receptors (113, 114, 116). On the basis of the above results, a hypothesis regarding the modulatory role of adenosine on dopamine and glutamate release in both the dorsal and ventral striatum was proposed, taking into account the antagonistic A_1/A_{2A} receptor interaction, by which stimulation of A_1 receptors decreases the effects of A_{2A} receptor stimulation on both dopamine and glutamate release in the striatum (112-114, 117). It was suggested that under basal conditions, when the level of endogenous adenosine was low, its effect on A_1 receptors predominated, which masked the effects produced by A_{2A} receptor stimulation (113, 114). However, under conditions of stronger adenosine release, a sufficiently stronger stimulation of A_{2A} receptors could override the inhibition imposed by A_1 receptors and, thereby inducing both glutamate and dopamine release (113, 114).

In contrast, Aquas *et al.* (118) did not find any effect of caffeine, given intravenously or intraperitoneally, on the dopamine release in all the subdivisions of the nucleus accumbens. Similarly, intravenous administration of selective A_1 and A_{2A} antagonists, DPCPX, and SCH58261, respectively, did not change the dialysate dopamine (118). In the recent work, Quarta *et al.* (113) observed, however, a significant decrease in the extracellular levels of dopamine and glutamate in the shell of the rat nucleus accumbens after acute, systemic administration of A_{2A} antagonist, MSX-3. Moreover, this compound counteracted the release of both dopamine and glutamate induced by systemic administration of caffeine (113). Furthermore, chronic exposure to caffeine in the drinking water resulted in tolerance to the effects of systemic injection of caffeine on extracellular levels of dopamine and glutamate in the nucleus accumbens shell, which may explain its weak, addictive properties and atypical psychostimulant profile (113).

It seems, however, interesting that intravenous administration of caffeine which, according to Aquas *et al.* (118), failed to affect dopamine release in the nucleus accumbens, dose-dependently increased dopamine dialysate concentrations in the medial prefrontal cortex; an effect which might account for the reinforcing psychostimulant properties of this compound (118, 119). Moreover, no changes in dopamine in the prefrontal cortex were seen in rats treated with caffeine for 7 days, when animals became tolerant to its locomotor stimulating effects (118). Furthermore, chronic exposure to caffeine in drinking water resulted in tolerance to the effects of systemic injection of caffeine on extracellular levels of dopamine and glutamate in the nucleus accumbens shell, which may help to explain its weak, addictive properties and atypical psychostimulant profile (113).

4.3. Heteromeric complexes formed by adenosine A_{2A} receptors

A growing body of evidence indicates the existence of G protein-coupled receptor (GPCR) heteromerization. Such heteromers are presently regarded as a molecular basis for the known direct or indirect (via adapter proteins) intramembrane receptor/receptor interactions. Understanding of the biology of the A_{2A} receptor, particularly its molecular interactions with other neurotransmitter receptors, is of great clinical importance since these receptors are molecular targets for numerous therapeutics including antipsychotics and antiparkinsonian ones.

4.3.1. Adenosine A_{2A} and dopamine D_2 heteromers

Evidence for antagonistic interaction between A_{2A}/D_2 receptors within the striatum has been extensively reviewed elsewhere (120-122).

A few years ago the first evidence was presented in neuronal and fibroblast cell lines that adenosine A_{2A} and dopamine D_2 receptors form functional heteromeric

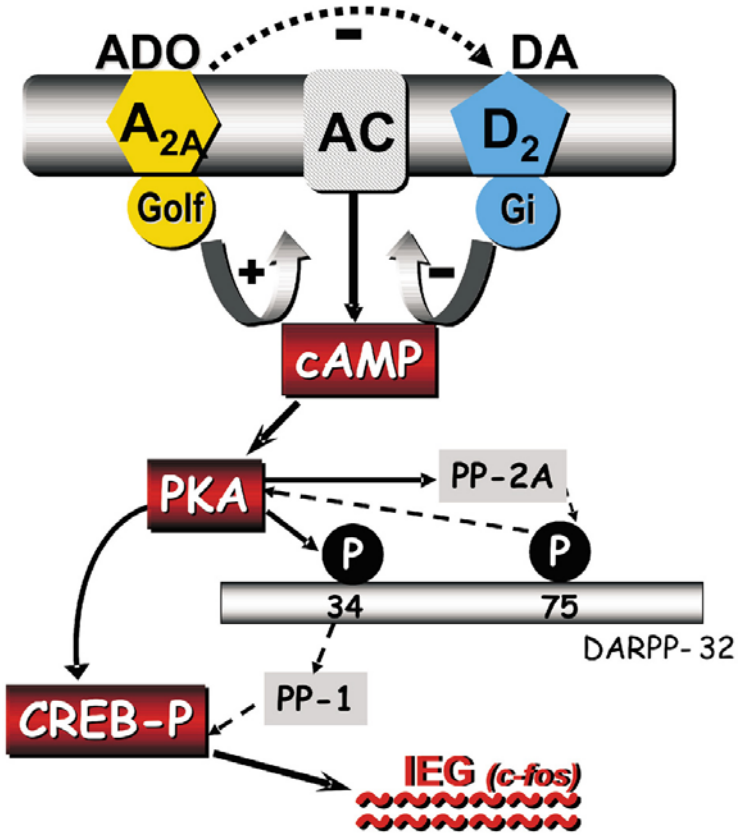

Figure 2. Schematic representation of the interaction between adenosine A_{2A} and dopamine D_2 receptors in the striatum.Stimulation of A_{2A} receptors decreases the affinity of D_2 receptors for dopamine and influences in the opposite manner the adenylyl cyclase, namely activation of A_{2A} receptors through Gs protein enhances the AC and cAMP production while stimulation of D_2 through Gi proteins inhibits it; the A_{2A}/D_2 interaction has been also found at the level of DARPP-32 protein which is abundantly expressed in striatal projection neurons; thus stimulation of A_{2A} receptors increases the phosphorylation of DARPP-32 protein at the Thr34 (threonine residue 34) which converts this protein into a potent inhibitor of PP-1; blockade of A_{2A} receptors decreases the effect of D_2 antagonist on DARPP-32 phosphorylation and at the same time, increases the phosphorylation of this protein at Thr75 (threonine residue 75), which converts DARPP-32 protein into an inhibitor of PKA; PKA regulates the state of phosphorylation of various substrate proteins, including DARPP-32 and CREB (*see ref. 120-122 and 135*); Abbreviations: AC, adenylyl cyclase; ADO, adenosine; A_{2A}, adenosine A_{2A} receptor; DA, dopamine; D_2, dopamine D_2 receptor; DARPP-32, dopamine- and cAMP-regulated phosphoprotein of relative molecular mass 32 kDA; Gi, inhibitory G-protein, Golf, stimulatory G-protein; PKA, protein kinase A; CREB, the cAMP response element-binding protein; IEG, immediate early genes; PP-1, protein phosphatase-1; PP-2A, protein phosphatase-2A; broken arrows, inhibitory effect; **(+)** stimulation; **(-)** inhibition

complexes, which undergo coaggregation, cointernalization, and codesensitization on D_2 or A_{2A} agonist treatment (120, 122-124). Direct evidence for A_{2A}/D_2 heteromers in addition to A_{2A} homomeric complexes within the plasma membrane came from fluorescent and bioluminescent resonance energy transfer (FRET and BRET) analyses (124). Such a heteromer represents one of the possible molecular mechanisms for the functional antagonism between A_{2A}/D_2 receptors, demonstrated earlier at different levels, including the receptor and second messenger levels (Figure 2).

Numerous biochemical and behavioural studies provided evidences for the existence of distinct negative interaction between adenosine A_{2A} and dopamine D_2 receptors, located on the same GABAergic neurons in the dorsal striatum, which allows both dopamine and adenosine to modulate the activity of output pathways (120-122). Evidence indicates that such A_{2A}/D_2 heteromeric receptor complexes also exist in the ventral striatopallidal GABA pathway, mainly originating in the ventral striatum (nucleus accumbens), and known to be a target for antipsychotic drugs that are D_2 receptor antagonists (121).

Biochemical studies showed that stimulation of A_{2A} receptors decreased the high-affinity binding of (^{3}H)-dopamine to striatal D_2 but not D_1 receptors, and also reduced D_2 coupling to Gi protein (125-130). Adenosine A_{2A} receptor agonists are even more effective in reducing the binding of D_2 receptor agonist in the nucleus accumbens than in the striatum (128, 131). Moreover, stimulation of A_{2A} receptors elicits effects opposite to D_2

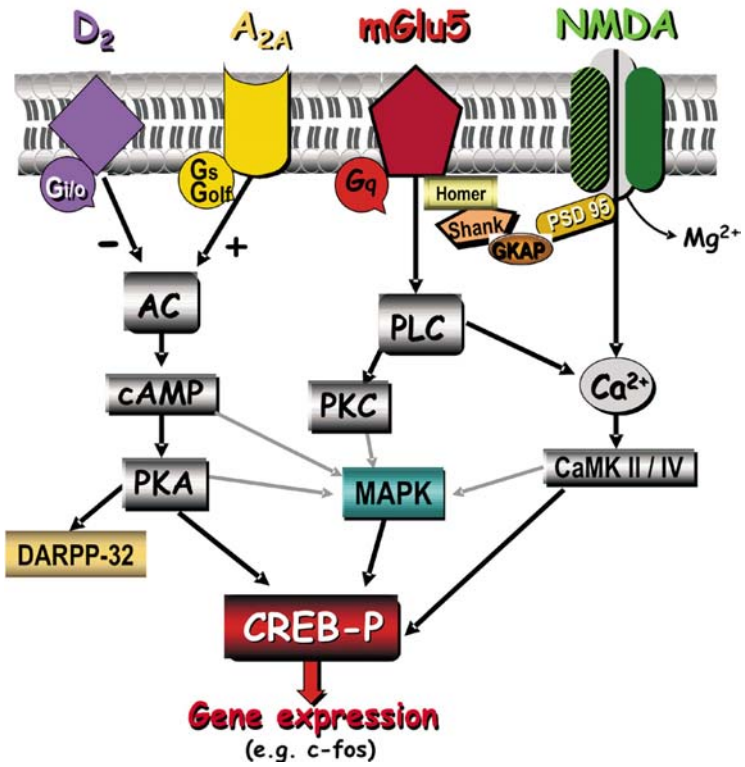

Figure 3. Interaction between the dopamine D_2, adenosine A_{2A} and metabotropic glutamate mGlu5 receptors**.** Adenosine A_{2A} and dopamine D_2 receptors interact antagonistically at the intramembrane level and at the adenylyl cyclase level (*see Figure 2*); metabotropic glutamate mGlu5 and adenosine A_{2A} receptors act synergistically to counteract the D_2 dopamine receptor signaling in striatopallidal neurons; synergistic interaction between A_{2A} and mGlu5 receptors was demonstrated at the level of c-fos expression, MAP kinases and phosphorylation of DARPP-32 protein. Note that mGlu5 receptors are physically linked with NMDA receptors by a chain of anchoring proteins and the NMDA receptors act synergistically with both mGlu5 and A_{2A} receptors to counteract D_2 receptor signalling; (*for further explanation see Figure 2 legend, section 4.3. and 6.2.2. in the text and ref. 19, 120*). Abbreviations: AC, adenylyl cyclase; Ca^{2+}, calcium ions; CaMK II/IV, calcium/calmodulin–dependent protein kinase type II/IV; cAMP, cyclic AMP; CREB, cAMP response element-binding protein; K^+, potassium channel; DARPP-32, dopamine and cAMP-regulated phosphoprotein; Gi, Go, inhibitory G-proteins, Gq, Gs, Golf, stimulatory G-proteins; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; **(+)** stimulation; **(-)** inhibition.

receptor activation at the level of second messenger systems, DARPP-32 phosphorylation and early gene expression (Figure 2) (132-135).

4.3.2 Adenosine A_{2A} and dopamine D_3 heteromers

It is well known that many antipsychotic drugs, such as haloperidol, clozapine or olanzapine, block both dopamine D_2 and D_3 receptors, and that D_3 receptors are preferentially expressed in the ventral striatum (136, 137). Therefore it has been suggested that the particularly strong interaction between adenosine and dopamine receptors found in the ventral vs. dorsal striatum (121, 131) may be explained by the existence of A_{2A}/D_3 heteromeric receptor complexes. In line with the latter assumption, a recent study by Torvinen *et al.* (138) has shown using the FRET analysis that in cell lines cotransfected with A_{2A} and D_3 receptors, both these receptors form the heteromeric complexes. Similarly to A_{2A}/D_2 interaction, activation of A_{2A} receptors reduced the affinity of the high-affinity agonist binding state of the D_3 receptor for (^{3}H)-dopamine (139, 140). Both A_{2A} and D_3 receptors seem to interact also at the G-protein coupling. However, the possible existence of A_{2A}/D_3 heteromers in the ventral striatopallidal GABA neurons and their functional interactions in the nucleus accumbens remains to be clarified. Furthermore, a similar kind of interaction may exist between A_{2A} and another subtype of dopamine D_2-class of receptors, the D_4 receptor (121, 141).

4.3.3 Heteromeric complexes formed by A_{2A} and metabotropic glutamate mGlu5 receptors

The morphological findings strongly suggest that besides adenosine A_{2A} and D_2 receptors, metabotropic glutamate mGlu5 receptors also are co-localized at the same e.g. GABAergic striatal output neurons and in glutamatergic nerve terminals in the striatum (142, 143) and form heteromeric complexes with A_{2A} receptors. This co-localization gives a morphological frame for the existence of multiple A_{2A}/D_2/mGlu5 receptor interactions (Figure 3). Moreover, the interdependence of these three

receptors suggests that such receptor complexes might integrate multiple signals converging on striatopallidal GABAergic neurons.

Functional heteromeric complexes between A_{2A} and mGlu5 receptors have been demonstrated in HEK-293 cells using co-immunoprecipitation studies and in rat striatal membrane preparations (144). Unlike the functionally antagonistic interactions between A_{2A} and dopamine D_2, D_3 receptors, the A_{2A}/mGlu5 receptor interaction may account for the synergism found after combined agonist or antagonists treatments, demonstrated at both biochemical and behavioural levels (142, 144-149). Co-stimulation of A_{2A} and mGlu5 receptors synergistically modulates the binding characteristics of D_2 receptors in striatal membrane preparations as well as on cell lines expressing the receptors (140, 145) and the quinpirole-induced turning behaviour in 6-OHDA-lesioned rats (145, 146). A strong functional synergistic interaction at the level of extracellular signal-regulated kinase (ERK1/2) phosphorylation and dopamine- and cAMP-regulated DARPP-32 phosphoprotein, as well as at the level of immediate early gene (c-*fos*) expression in HEK-293 cells, transiently co-transfected with A_{2A} and mGlu5 receptors was found after their co-activation (Figure 3) (144, 147). Therefore, it seems that a major biochemical site of integration responsible for the synergistic interaction between A_{2A} and mGlu5 receptors might be at the mitogen-activated protein kinase (MAPK) level (Figure 3). However, the lack of synergistic interaction between A_{2A} and mGlu5 receptors at the level of second messenger (cAMP and (Ca^{2+})i) was also seen by Ferre *et al.* (144).

4.3.4 Heteromeric complexes formed by adenosine A_{2A} and A_1 receptors

Very recently, heteromeric complexes between adenosine A_1 and A_{2A} receptors have been discovered by co-immunoprecipitation, BRET and FRET techniques in co-transfected cells (150). Radioligand-binding experiments in co-transfected cells and rat striatum showed that a main biochemical characteristic of the A_1/A_{2A} receptor heteromer is the ability of A_{2A} receptor activation to reduce the affinity of the A_1 receptor for agonists (150). Interestingly, the same is not true for the activation of the A_1 receptors, which does not alter the binding characteristic of A_{2A} receptor (150). The ability of A_{2A} receptors to control A_1 receptors in such heteromers was further confirmed functionally, showing, upon formation of heteromers, the significant reduction in the A_1-induced intracellular calcium peak, obtained by preincubation with a selective A_{2A} receptor agonist (150).

At present, however, it is still an open question whether the formation of such A_1/A_{2A} receptor heteromers might play a physiological role in native brain preparations. This question is of major relevance since the involvement of GPCR heteromers in pathophysiological processes in the CNS remains still unknown, despite substantial evidence for their presence in native brain preparations. Recently, Ciruela *et al.* (2006) proposed that A_1/A_{2A} receptor heteromers might exert a fine-tuning modulation of glutamatergic neurotransmission in the striatum. This hypothesis was based on the well-known opposite role of A_1 and A_{2A} receptors in the regulation of glutamate release in the striatum and hippocampus, where both receptors are present on presynaptic terminals (102, 103, 113). Since it is already known that glutamatergic terminals in the striatum establish synaptic contacts with the dendritic spines of the GABAergic efferent neurons, such heteromeric complexes may also control the activity of output neurons of this structure. Furthermore, it has been shown that A_1/A_{2A} heteromers constitute a unique target for caffeine and that chronic caffeine treatment leads to modifications in the function of the A_1/A_{2A} receptor heteromer that could underlie the strong tolerance to the psychomotor effects of caffeine, the most widely used psychoactive compound in the world (89, 150).

5. ADENOSINE A_{2A} RECEPTORS IN SCHIZOPHRENIA

The discovery of A_{2A}/D_2 interaction in the dorsal and ventral striatum has important implications for neuropsychiatric disorders, where dopamine neurotransmission seems to play a crucial role. Moreover, the dopamine hypothesis of schizophrenia cannot fully explain its pathophysiology. Therefore, recent research has focused on the role of other neurotransmitter systems such as glutamate, GABA, serotonin, and also adenosine dysfunction of the latter has been recently suggested by Lara *et al.* (4, 5) to contribute to the pathophysiology of schizophrenia.

Based on the the dopamine hypothesis of schizophrenia Ferre *et al.* (131, 151) and Rimondini *et al.* (152) proposed that adenosine A_{2A} receptor agonists may constitute the novel class of antipsychotic drugs by decreasing the D_2 receptor signalling via an A_{2A}/D_2 intramembrane interaction in the ventral striatopallidal GABA system described earlier (*see section 4.3.1.*). Recently, this suggestion was strengthened by the studies showing the existence of heteromeric complexes between adenosine A_{2A} and dopamine receptors, including D_2, D_3 receptors (see section 4.3.). However, it should be kept in mind, that also other mechanisms than direct A_{2A}/D_2 interaction. e.g. the influence on GABA and glutamate release from presynaptic sites, may contribute to effects of adenosine agonists and antagonists (78, 153-156). Moroever, some evidence indicates that A_{2A} receptors can operate independently of dopamine D_2 receptors since e.g. in D_2 receptor knockout mice blockade of A_{2A} receptors could rescue locomotor deficits and reverse the altered enkephalin and substance P expression caused by the absence of D_2 receptors (157, 158).

An involvement of adenosine A_{2A} receptors in schizophrenia is also supported by data from genetic and *postmortem* experiments. Thus, the gene encoding A_{2A} receptor is localized on the chromosome 22 which includes two potential schizophrenia –related loci on 22q11.2 and 22q12-13 (159). In turn, Ottoni *et al.* (160) found an association of A_{2A} receptors polymorphism and negative symptoms. Contrarily, the studies of Deckert *et al.* (1161) and Hong *et al.* (162) failed to find an association between

A_{2A} receptors and schizophrenia. Of interest, however, is the fact that the G-protein coupled to A_{2A} receptor, Golf, which is mainly expressed in the nucleus accumbens and striatum, is a candidate gene for schizophrenia (163). Moreover, the Golf knockout mice showed a reduced locomotor activation by caffeine and amphetamine compared to wilde type mice (164).

Likewise, *postmortem* studies support the role of A_{2A} receptors in the pathophysiology of schizophrenia by showing an increased binding of (^{3}H)-CGS21680 in the putamen and caudate of schizophrenic patients (165). Such a statistically significant increase in the specific binding was observed in two groups of schizophrenic patients: (1) "off-drug" individuals who had received no antipsychotics for more than 40 days before death, and (2) "on-drug" patients who had been treated with antipsychotics almost until death. Furthermore, an increased number (Bmax) of A_{2A} receptors and their increased affinity (Kd) in the post mortem striatum of schizophrenic patients were reported by Deckert *et al.* (166); however, those authors also observed a correlation with the dose of previous antipsychotic medication. Therefore, it seems plausible that the observed up-regulation of A_{2A} receptors in schizophrenia may be due to the antipsychotic treatment rather than the disease itself, since similar increase in the number of A_{2A} receptors were seen e.g. after chronic haloperidol treatment in the rat striatum (167).

Studies on animals carried out in the last years delivered premises that suggested the role of adenosine A_{2A} receptors in the pathophysiology of schizophrenia and also in the effect of antipsychotic drugs, which are mainly D_2 receptors antagonists. The following evidences were among the first:

(1) Adenosine A_{2A} receptors in the brain are mainly located in dopaminergic structures, such as the striatum, nucleus accumbens, olfactory tubercle, together with dopamine D_2 receptors (*see section 4.1*) (91-94, 99).

(2) The interaction between both subtypes A_{2A} and D_2 occurs not only in the dorsal but also in the ventral parts of the striatum i.e. nucleus accumbens, a structure that is thought by some researchers to be important for the antipsychotic action of neuroleptics (131, 168). Both dorsal and ventral striatum are components of anatomically and functionally differentiated circuitry (131, 169, 170), and the functional role of dopamine is different in both parts of the striatum (171). Therefore, drugs that antagonize ventral D_2 receptor function via an action on GABAergic striatopallidal efferents may have efficacy in managing positive symptoms of schizophrenia.

(3) Adenosine A_{2A} agonists evoke behavioural effects in animals similar to those observed after administration of dopamine D_2 receptor antagonists *(see below)*.

(4) Caffeine, a psychoactive drug most commonly consumed in coffee, tea, cocoa beverages, chocolate and soft drinks, is a non-selective adenosine antagonist. It has been suggested that schizophrenic patients have a higher-than-average intake of caffeine, but the findings are inconsistent in this respect (172-177). A recent study by Gurpegui *et al.* (178), showed that daily caffeine intake was less frequent in schizophrenic patients than in controls, but among caffeine consumers, a heavy caffeine intake (>200 mg/day) was significantly more frequent in schizophrenics than in controls. Additionally, some earlier reports showed that high intakes of caffeine can produce psychoses in healthy subjects (176, 179) and may worsen psychotic symptoms in schizophrenic patients (180-182). However, given that caffeine is the most widely used substance in the world, it appears that caffeine-induced psychoses are extremely rare. Moreover, Hughes *et al.* (176) suggested that caffeine elimination from patients with schizophrenia did not appear to make them better or worse. In line with this opinion, it was shown that switching from caffeinated to decaffeinated beverages had no effect on schizophrenic symptoms (173, 175, 183). Likewise, Gurpegui *et al.* (174) found no relation between caffeine intake and schizophrenic symptomatology. However, since De Freitas *et al.* (181) showed that a switch to decaffeinated coffee was associated with a decrease in hostility and suspiciousness, and was reversed when regular coffee was reintroduced, the possibility of a relationship between caffeine intake and schizophrenia symptomatology cannot be completely ruled out. In addition, caffeine was shown to ameliorate the negative symptoms, e.g. it improved mood and decreased withdrawal and was found to improve extrapyramidal symptoms of neuroleptics (180). Interestingly, a high dose of caffeine did not increase anxiety scores in schizophrenic patients (176).

5.1. The effects of adenosine A_{2A} agonists in animal models relevant to schizophrenia

Stimulation of A_{2A} receptors was shown to reduce the psychomotor stimulating effects of dopamine receptor agonists such as amphetamine, including stereotypies at doses failing to evoke catalepsy (131, 152, 184). Moreover, A_{2A} agonist, CGS21680 was shown to block conditioned avoidance responding in rats and to be effective, similarly to haloperidol and raclopride, in the apomorphine-induced climbing mouse assay (185, 186). Systemic administration of CGS21680 was also shown to counteract apomorphine-induced stereotypies and quinpirole-induced yawning but not grooming induced by the selective D1 agonist, SKF38393 (187), which supported the potential antipsychotic-like effect of this compound. Furthermore, *in vivo* microdialysis studies showed that co-infusion of A_{2A} receptor agonist and D_2 receptor antagonist into the nucleus accumbens at ineffective concentrations, produced a significant increase in the level of extracellular GABA in the ventral pallidum (131, 151). In addition, systemic, intrastriatal or intraaccumbal administration of CGS21680, a selective A_{2A} receptor agonist, to rodents reduced spontaneous locomotor activity, and at higher doses, induced catalepsy (152, 186, 188-191).

Taking into account the results, showing an increased dopamine release in the nucleus accumbens shell after stimulation of A_{2A} receptors, it is rather difficult to explain these reversing effects of CGS21680 on the amphetamine-induced locomotor activity and stereotypy. In schizophrenia as well as after injection of amphetamine, which serves as an animal model relevant to this disease, dopamine release in subcortical structures was demonstrated to increase (13, 192). Therefore, after the administration of both, amphetamine and A_{2A} agonists, rather an additive, stimulant effect on the behaviour should be seen. It should be, however, mentioned that effects of A_{2A} receptor stimulation on dopamine and glutamate release seem to depend also on the basal level of adenosine and the existence of antagonistic interaction with A_1 receptors (*see also sections 4.2. and 4.3.4.*). Moreover, an action of CGS21680 compounds also on the A_1 receptors cannot be fully excluded, since the affinity of this compound for A_{2A} receptors is about 10 times higher than to A_1 receptor (193). Furthermore, an action of A_{2A} receptor stimulation on the dopamine transporter (DAT) cannot be rejected since some changes in the binding to DAT as well as in the DAT mRNA level were found in A_{2A} knockout mice (194). In order to solve this problem, further studies are needed. However, a postsynaptic mechanism, involving antagonistic interaction between A_{2A} and D_2 receptors can help to explain the attenuation of amphetamine-induced effects by CGS21680 as this compound was shown to reduce the affinity of D_2 receptors for dopamine in the nucleus accumbens (128).

The antipsychotic-like profile of CGS21680 compound was also confirmed in non-human primates, Cebus appella monkeys (195). In those monkey a reversal of apomorphine-induced psychosis-like symptoms was observed at doses that did not elicit extrapyramidal side-effects (195). All the above mentioned results suggests that A_{2A} agonists show the behavioural profile of antipsychotic drugs. However, it is unclear whether they possess so-called "atypical" antipsychotic profile. Studies of Kafka and Corbett (186) and Hauber and Munkle (191) suggested a profile of A_{2A} agonists similar to classic D_2 receptor antagonists rather than atypical neuroleptics since in behavioural studies they induce effects similar to those produced by D_2 antagonists (e.g. catalepsy). On the other hand, atypical profile of A_{2A} agonists was suggested by the following data:

(1) A stronger antagonistic A_{2A}/D_2 interaction was observed in the ventral striatum, as in the presence of CGS21680, dopamine exhibited lower efficacy in displacing the radiolabelled D_2 receptor antagonist from the rat ventral striatum, especially in the nucleus accumbens (131, 151).

(2) Studies of Rimondini *et al.* (152) showed that the ED_{50} of CGS21680 for inducing catalepsy was more than 10-times higher than the ED_{50} for depressing exploratory activity in rats treated systemically.

(3) A selective increase in the expression of the immediate early gene, c-fos, in the shell of the nucleus accumbens, which is a part of the ventral striatum, but not in the dorsolateral striatum, was found after the systemic administration of the selective adenosine A_{2A} agonists, CGS21680 and HE-NECA (133). The observed effects in the nucleus accumbens shell were counteracted by the selective A_{2A} receptor antagonist, SCH58261 and by stimulation of D_2/D_3 receptors by quinpirole (133). In line with these results is the antagonism of clozapine-induced Fos-like immunoreactivity by blockade of A_{2A} receptors with SCH58261 in all subdivisions of the nucleus accumbens (196), which additionally suggests the contribution of A_{2A} receptors to the therapeutic effects of antipsychotics.

Adenosine A_{2A} receptor agonists were also shown to counteract many effects of NMDA receptor antagonists such as PCP, ketamine and MK-801 in animals. In particular, the stimulation of A_{2A} receptors was shown to reverse ketamine- and MK-801-induced motor activity in mice (197, 198). CGS21680 antagonizes also the locomotor stimulatory action of PCP at doses lower, than that, necessary to reduce the amphetamine-induced hyperactivity in rats (152). Similar effects have been observed after administration of atypical neuroleptics (199). Since the effects of NMDA antagonists are considered to be a pharmacological model of schizophrenia, the interaction between adenosine and the glutamatergic system may have therapeutic implications.

Previously it has been suggested that „atypical" antipsychotic drugs including clozapine, olanzapine, seroquel or remoxiprid, in contrast to classic neuroleptics such as haloperidol, reversed the effects of PCP in the prepulse inhibition (PPI) of the startle reflex, an animal model relevant to schizophrenia (200-204). Moreover, the deficit in PPI induced by PCP was reversed by stimulation of adenosine A_{2A} receptors by CGS21680 at doses, devoid of motor side-effects (205, 206). Thus, CGS21680 was without effect on catalepsy, muscle rigidity and rotarod performance in rats, as well as on the proenkephaline mRNA expression in the striatum, estimated by *in situ* hybridization (206).

The putative mechanism by which adenosine A_{2A} receptor stimulation reverses the effects of PCP and other uncompetitive NMDA receptor antagonists has not been satisfactorily elucidated as yet. Nevertheless, it is known that mesolimbic dopamine neurotransmission is involved in these effects and that PCP stimulates dopamine neurotransmission, particularly within the nucleus accumbens (207-209). Therefore, it might be suggested that CGS21680 attenuates the PCP effect by inhibiting dopamine transmission via antagonistic A_{2A}/D_2 interaction. However, the blockade of dopamine D_2 receptors by neuroleptics does not influence the PCP effect in this model (200, 202, 204). Also, Sills *et al.* (205) did not observe any influence of CGS21680 given systemically on the apomorphine- and amphetamine-induced deficits in PPI in rats which do not support this hypothesis. Another plausible explanation is based on the existence of similar or synergistic effects of NMDA and A_{2A} receptors at the cellular level. It is already known that both these receptors are involved in the haloperidol-induced early gene c-fos

expression in the striatum (210). According to Nash and Brotchie (211), both NMDA and A_{2A} receptors share a common second messenger signalling pathway within the striatum, since the stimulation of either NMDA or A_{2A} receptors leads to increases in cAMP levels via activation of the same adenylyl cyclase. Therefore, it seems that stimulation of adenosine A_{2A} receptors may counteract the effects induced by PCP-mediated NMDA receptor blockade, including the reversal of PCP-induced PPI impairment.

All the above-mentioned results support the hypothesis of antipsychotic profile of A_{2A} receptor agonists, qualitatively similar to dopamine antagonists. However, it should be mentioned that many of the above-described effects of A_{2A} agonists were also shared by adenosine A_1 receptor agonists. Nevertheless, whereas A_{2A} agonists display a clear separation between doses inducing catalepsy and motor incoordination, A_1 agonists induce ataxia and sedation at similar doses. Finally, despite the promising results obtained in experimental animals, A_{2A} receptor agonists such as CGS21680 are known to induce a marked hypotension, and tachycardia, which limits the clinical development of these compounds (212).

5.2. The effects of adenosine A_{2A} antagonists in animal models of schizophrenia

Similarly to amphetamine and NMDA receptor antagonists, caffeine and theophylline were shown to produce psychomotor stimulant effects by enhancing locomotor activity and schedule-controlled behaviour, which was reversed by antipsychotics (131, 213-216). However, it should be keep in mind, that only low doses of caffeine increase motor activity in mice and rats, while higher doses are depressant and inhibit it (119, 217, 218). These high doses of caffeine can also produce conditioned place aversion in rodents (219). The psychostimulant effect of caffeine was shown to be mediated by antagonism at both adenosine A_1 and A_{2A} receptor levels (220-222), whereas adenosine A_{2A} receptors seem to play a fundamental role in caffeine-mediated motor behaviour (223, 224). Moreover, methylxanthines potentiate the motor behaviour induced by direct and indirect dopamine agonists and block the effects of dopamine D_2 antagonists (225-227). In contrast, caffeine given for seven days was shown to abolish the hyperlocomotion and cognitive deficits induced by MK-801, without influencing the amphetamine-induced locomotor activity in rats (228).

The results regarding the locomotion, obtained in studies with selective A_{2A} antagonists are rather controversial. Namely, increased locomotor activity was shown after systemic or intraaccumbal (into the core but not shell part) injection of selective adenosine A_{2A} antagonists, like SCH58261, KF17837, KW6002 (229-233). Furthermore, locomotor activity produced by subthreshold dose of ketamine or dizocilpine in mice, was potentiated by selective adenosine A_{2A} antagonists and by theophylline (197, 198). SCH58261 increased, besides basal locomotion, also the apomorphine-induced motor stimulation, with no signs of tolerance after repeated treatment (234). In contrast, Kuzmin *et al.* (221) did not observe any influence of A_{2A} receptor blockade by SCH58261 on motor activity in mice habituated to the test environment. However, combined administration of SCH58261 and A_1 receptor antagonist, DPCPX, produced stimulation of motility and locomotion, comparable to the effect of caffeine. However, the rearing counts were not significantly influenced either by SCH58261 or caffeine. Moreover, blockade of A_{2A} receptors with KF17837 did not significantly increase the locomotor activity, measured in an open-field, but it completely reversed the suppression of locomotion induced by haloperidol and increased rearnig behaviour in these haloperidol-treated rats, supporting the existence of A_{2A}/D_2 interaction (235). Additionally, results derived from studies in A_{2A} knockout mice showed reduced locomotor activity compared to control, wilde-type mice, measured in an open-field or actometers (236, 237).

Besides locomotion, both caffeine given at low doses, and the selective A_{2A} receptor antagonist were shown to potentiate the amphetamine-induced stereotypy (184) and to elicit the place preference in rats (219, 222, 230). The latter effect was seen at doses increasing the dopamine overflow in the nucleus accumbens (230).

Studies on the influence of caffeine and theophylline, on the responses of sensorimotor gating, such as the P50 evoked potential and prepulse inhibition, produced conflicting results. In humans, theophylline was shown to impair sensory gating measured with the P50 paradigm in healthy volunteers, resembling the findings in schizophrenic patients (238). However, caffeine did not influence the PPI in normal control subjects who were the minimal or heavy coffee drinkers (239). In accordance with these observations, Flaten and Elden (240) described the lack of effect of caffeine on startle magnitude or PPI in relatively heavy caffeine drinkers.

In rats, caffeine did not affect significantly the PPI, but decreased the startle amplitude (241). Koch and Hauber (242) in a subsequent study found that theophylline at a dose which had no intrinsic effect, potentiated the disruption to PPI, caused by a submaximal dose of apomorphine. This effect was suggested to be mediated rather by A_1 receptors since co-administration of A_1, but not A_{2A} selective agonist, abolished the effect of theophylline (242). The lack of effect of A_{2A} blockade on the PPI has been confirmed in studies using the selective A_{2A} receptor antagonist, KW6002 (243). This compound was inactive in PPI across a wide range of doses when given alone and had no effect on the disruption of PPI induced by the D_2 receptor agonist, pergolide (243). However, a disruption of prepulse inhibition of the startle reflex was observed by Nagel *et al.* (231) after bilateral intraaccumbal infusion of selective A_{2A} antagonist, MSX-3. Additionally, the A_{2A} knockout mice showed reduced PPI and startle habituation (244).

5.3. Behavioural sensitization induced by psychostimulants

Behavioural sensitization, which is known to develop after repeated administration of psychostimulants such as amphetamine, may represent the neural adaptation

underlying some features of psychosis and addiction in humans (66, 245-247). Amphetamine was also shown to induce sensitization in rodents (247) and in non-human primates (248, 249). Indeed, sensitization of dopaminergic functions has been proposed to be a core pathophysiological process leading to schizophrenia since it produces neurochemical and behavioural characteristics seen in some schizophrenics (66, 250, 251). Thus, reduced prepulse inhibition of the acoustic startle reflex and profound, long-lasting impairment in working memory were found in amphetamine-sensitized animals (66, 251). Although the mechanisms underlying the process of sensitization are not fully understood as yet, evidence suggests engagement of dopaminergic neurotransmission (245).

Recently, the important role of A_{2A} receptors in the development of amphetamine-induced sensitization was also shown in mice lacking A_{2A} receptors but with preserved dopamine innervation and receptors (252). These mice showed attenuated response to amphetamine and cocaine but not to selective dopamine D1 or D_2 agonists (252). Furthermore, results derived from experiments with A_{2A} knockout mice, including a forebrain-specific conditional (Cre/loxP system) knockouts, suggest a critical role for these receptors in the development of amphetamine-induced behavioural sensitization (232, 252). These results together with the existing and well described A_{2A}/D_2 receptor heteromerization, have been suggested to open new directions in the understanding and treatment of schizophrenia (120, 246).

Besides amphetamine, subchronic caffeine given intermittently in low doses also was shown to produce behavioural sensitization to the motor stimulant effects induced by dopamine agonists in rats (227, 253-257). The caffeine-induced sensitization was associated with reduced levels of A_{2A} receptors and early-gene zif268 mRNAs in enkephaline-positive neurons in the striatum and nucleus accumbens (257). Therefore, these results support the previous suggestions regarding the involvement of A_{2A} receptors in the adaptive changes, which produce behavioural sensitization to amphetamine and caffeine.

5.4. Adenosine A_{2A} receptors and cognitive processes

While positive and negative symptoms of schizophrenia have long been considered as the hallmark of schizophrenia, recent clinical studies emphasized cognitive dysfunction as a primary features of this disorder, because they are detectable even before the onset of psychosis (66, 258, 259). Cognitive impairments are found across most domains (e.g., attention, working memory, verbal fluency, processing speed, executive functions, verbal memory) in the vast majority of schizophrenic patients. These deficits may become more marked in later life and are an important treatment target, because such deficits are the best predictor of a patient's level of interpersonal skills, occupational functioning, and self care (258).

It has already been suggested that adenosine plays an important modulatory role in learning and memory processes by regulating synaptic transmission, neuronal excitability and synaptic plasticity including such processes as hippocampal long-term potentiation (LTP) and long-term depression (LTD) (260-264), which presumably underlie certain forms of learning and memory (265-267). Previous studies have demonstrated that adenosine receptor agonists, mainly of A_1 type, disrupt learning and memory in rats and mice (268-270) while antagonists, either non-selective or selective, facilitate learning and memory in the passive avoidance task (271-274), the step-down inhibitory avoidance task (273) and the water maze task (275, 276). However, the specific role of A_{2A} receptors in learning and memory is still unclear, with A_1 receptors apparently having a more dominant role (274, 276).

Recently, however, new data supporting the role of A_{2A} receptors in these processes have been published, namely acute stimulation of A_{2A} receptors disrupted, and blockade of A_{2A} receptors enhanced the short-term social memory in rats (277). A similar improvement in social memory was found after acute caffeine administration (277). In line with these findings, infusion of A_{2A} receptor antagonist, ZM241385 directly into the posterior cingulate cortex did not affect retrieval of inhibitory avoidance long-term memory. On the contrary, stimulation of A_{2A} receptors after infusion of CGS21680 into the posterior cingulate cortex induced an amnesic effect at all doses tested, which was blocked by co-infusion of A_{2A} antagonist (278). Additionally, facilitative effects with regard to reference memory were found by Hauber and Bareiss (276) after chronic theophylline in rats. Furthermore, recent results obtained by Prediger *et al.* (279) supported the role of A_{2A} receptors in learning and memory processes showing reversal by caffeine and ZM241385 of social memory impairment in spontaneously hypertensive rats. These compounds were also shown to reverse the age-related deficits in olfactory discrimination and short-term social memory in rats (280). All the above-mentioned results together with the data obtained by Wang *et al.* (281), showing an improvement of spatial recognition memory, measured in the Y-maze in mice lacking A_{2A} receptors, support the cognitive enhancing effects of adenosine A_{2A} receptor blockade.

However, much less is known regarding the role of A_{2A} receptors in animal models of working memory. Adenosine A_{2A} antagonists were shown to reverse the detrimental effect induced by MK-801 in a model of working memory in mice (282). On the other hand, Hooper *et al.* (283) did not show any effect of A_2 stimulation on spontaneous alternation, a model of working memory in mice. However, in a very recent study Gimenez-Llort *et al.* (284) showed for the first time deficits in working memory in the new transgenic rat strain, with overexpression of the human A_{2A} receptors. The authors used a set of behavioural tests for spatial reference and working memory and also found that these memory deficits were correlated with increased levels of A_{2A} mRNA and A_{2A} receptor protein, as well as of increased A_{2A} receptor binding function, especially in regions of the cerebral cortex, including the prefronatal cortex, a key region in the functional neural networks of working memory and its deficits (15). The A_{2A} receptor overexpression found in other structures such as

the parietal cortex, hippocampus, basal ganglia, and thalamus, regions also known to be involved in working memory deficits (66, 285), could be of relevance for this deficits. On the other hand, a significant down-regulation of D_2 and mGlu5 receptors found in the striatum of these transgenic rats may suggest involvement of this structure in mediating alterations in working memory. Such down-regulation of D_2 and mGlu5 receptors was suggested to be related to the selective ability of A_{2A} receptors to form heteromeric complexes with both these receptors (89, 123, 124, 144). On the basis of these results and existing adenosine/dopamine interactions, Gimenez-Llort and coworkers (284) suggested that these transgenic rats, overexpressing adenosine A_{2A} receptors could provide an useful animal model for some cognitive disruptions at the level of prefrontal cortex.

6. SUMMARY AND PERSPECTIVES

The idea that adenosine A_{2A} receptors may be of interest for the treatment of schizophrenia has been founded on the studies showing the antagonistic interaction between adenosine A_{2A} and dopamine D_2 receptors and from the subsequent findings that both the receptors may form heteromeric complexes. Based on this intramembrane A_{2A}/D_2 interaction, some suggestions have been put forward about A_{2A} agonists as putative antipsychotic drugs since the enhancement of A_{2A} receptor activity could be relevant for the treatment of schizophrenia, where inhibition of dopamine D_2 action may be beneficial. In line with this suggestion, an involvement of A_{2A} receptors in the antipsychotic effects of neuroleptics such as clozapine and haloperidol was found. However, A_{2A} agonists were shown to have amnesic effects in animal models of learning and memory, which does not support this previous suggestion. Moreover, it remains unclear whether A_{2A} receptor agonists possess a sufficient safety margin or whether their hypotensive effects or extrapyramidal side-effects would limit their therapeutic utility as antipsychotic agents. In addition, some peripheral adverse effects were also observed which, at present, limit their use in the clinical trials.

On the other hand, antagonists of A_{2A} receptors, both selective and nonselective such as caffeine, which are known to produce the antiparkinsonian and neuroprotective effects in Parkinson's disease, failed to produce behavioural effects resembling negative symptoms of schizophrenia, moreover, they showed lack of effects or even some cognitive enhancing properties in animals. Taking into account all the discrepancies discussed above, the usefulness of A_{2A} receptor agonists/antagonists and their limitations, as well as the fact that all results indicating involvement of A_{2A} receptors in schizophrenia stem from animal experiments only, it seems that further studies are ncessary to elucidate their role in the pathophysiology and treatment of schizophrenia.

Finally, it should be mentioned that Lara *et al.* (5) proposed recently a model of adenosine dysfunction in schizophrenia, which takes into consideration the dopamine and glutamate hypothesis. This "two hits" hypothesis, based on the neurobiological role of adenosine in the CNS, suggests that after a transient increase in adenosine release due to perinatal events (such as hypoxia, virus), a decreased adenosinergic activity persists in schizophrenic patients due to partial loss of A_1 receptors (*see* 5). Therefore, the pharmacological treatments enhancing adenosinergic activity, especially through A_1 receptors, might be concordant with this hypothesis, effective for alleviating symptoms of schizophrenia. In line with this suggestion, allopurinol, which may indirectly increase the level of adenosine, was shown to be effective in the clinical trial (286, 287, see 6.1 below).

6. 1. Adenosine in clinical trials for schizophrenia

To date, A_{2A} agonists or antagonists have not been examined in clinical trials. The results of pilot clinical studies indicate the use of substances which can enhance the extracellular level of adenosine. Such treatment – when applied together with neuroleptics - may be of therapeutic value in reducing psychopathological symptoms in schizophrenic patients. A few clinical trials were conducted with the adenosine transporter inhibitor, dipyridamole and inhibitor of purine degradation, allopurinol. When dipyridamole was given together with haloperidol to schizophrenic patients, some beneficial effects on positive symptoms, thought to be due to adenosine–dopamine interactions were seen (288). Moreover, administration of allopurinol as adjunctive therapy to schizophrenic patients, previously resistant to typical antipsychotics, produced the clinically relevant improvement in about half of the patients (289). Similar results were obtained by Brunstein *et al.* (286) who administered allopurinol to patients undergoing antipsychotic treatment and found improvement in 9 out of the 22 patients who completed this study. Response was more pronounced for positive symptoms and responders had shorter illness duration (286). In addition, an independent clinical trial replicated the finding that add-on allopurinol was effective in amelioration positive but not negative symptoms of schizophrenia in acute patients treated with haloperidol (287). No significant central side effects were observed in either study. Despite these promising results, allopurinol should be, however, regarded as a treatment targeting purine metabolism in general rather than directly increasing adenosinergic transmission. Moreover, a recent case report by Gomberg (290) demonstrated a potential for allopurinol to cause a relapse in schizophrenic patients, i.e. recurrence of typical auditory hallucinations and paranoia was observed after one dose of allopurinol in a patient who was stable on clozapine and ziprasidone. In the light of the latter report, patients treated with such compounds should be carefully monitored for the recurrence or worsening of their symptoms. Therefore this fairly theoretical hypothesis of Lara *et al.* (5) needs further studies, since the role of adenosine in schizophrenia is still not well established.

A recent study by Brunstein *et al.* (291) gives support to the hypothesis postulating a dysfunction in adenosinergic activity in schizophrenia, which leads to synaptic adenosinergic deficit, possibly due to receptor modifications or altered metabolism (decreased production or increased degradation). The authors showed an

increased activity of the enzyme adenosine deaminase in the serum of male schizophrenic patients under antipsychotic monotherapy. The observed elevation in serum adenosine deaminase activity may be, however, related to the disease itself (i.e. to altered adenosine metabolism in schizophrenic patients) or to the use of antipsychotics, especially clozapine (291).

In summary, it appears that manipulation of the endogenous level of adenosine may be of greater interest than selective activation of adenosine A_{2A} receptors. Indeed, the above-mentioned results indicate that therapeutics based on adenosine are of interest rather as modulators or enhancers of other more direct compounds, which in consequence leads to their lower doses and less adverse effects.

6.2. Implications of the existence of heteromeric complexes formed by A_{2A} receptors with dopamine and glutamate receptors for the treatment of schizophrenia

Recently, the existence of heteromeric complexes formed by A_{2A} receptors with dopamine D_2-, D_3 receptors and metabotropic glutamate mGlu5 receptors has been demonstrated, which seems to open up a new perspective on the search for novel, alternative therapies of schizophrenia.

6.2.1. Adenosine A_{2A} and dopamine D_3 receptor heteromers

Besides dopamine D_2 receptors, also D_3 receptors have been suggested to be involved in the pathogenesis of schizophrenia (292, 293). The D_3 receptors are known to be mainly localized in limbic structures and several neuroleptics display high affinity for these receptors (293, 294). In accordance with this opinion, Gurevich *et al.* (295) found a significant increase in the density of dopamine D_3 receptors in the ventral striatum of patients with schizophrenia. In addition, a significant decrease in the D_2 /D_3 binding in drug-naive schizophrenic patients in temporal cortex (296) as well as significant reductions in extrastratial (e.g. in the thalamus) D_2 /D_3 receptor availability (297) were also found.

Since D_3 receptors seem to be one of the therapeutic targets for treatment of schizophrenia (292, 293, 298), the existence of such interaction between A_{2A} and D_3 receptors *(see section 4.3.2.)* could provide an alternative therapy. However, the possible existence of A_{2A}/D_3 heteromers in the e.g. ventral striatopallidal GABA neurons, and their functional interactions in the nucleus accumbens remain to be clarified.

6.2.2. Adenosine A_{2A} and mGlu5 receptor heteromers

The existence of heteromeric A_{2A}/mGlu5 receptor complexes seems to play an important modulatory role not only in the dorsal striatum but also in the function of the ventral striatopallidal GABA pathway (146). Accordingly, the combined A_{2A} and mGlu5 receptors activation synergistically elevated extracellular GABA levels in the ventral pallidum after local co-perfusion with A_{2A} and mGlu5 receptor agonists (146). Also behavioural studies have shown that co-administration of A_{2A} and mGlu5 receptor agonists counteracted the PCP-induced motor activity in rats, known to be mediated via D_2 receptor activity, which correlated with synergistic activation of c-Fos immunoreactivity in the nucleus accumbens (144).

Taking into account the important modulatory role of mGlu5 receptors in schizophrenia *(for details see 3.2.)* it might be suggested that combined activation of mGlu5 and A_{2A} receptors may have a substantial antipsychotic action by overcoming the D_2 mediated inhibition of the ventral striatopallidal GABA pathway. By increasing the activity of cortical glutamatergic afferents from the mediodorsal thalamic nucleus to the prefrontal cortex, such treatment may enhance the glutamatergic transmission in the prefrontal cortex and in this way, may counteract the hypofrontality, observed in schizophrenia. However, this suggestion requires further examinations.

7. ACKNOWLEDGEMENT

This study was supported by a statutory fund from the Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland. The author wishes to express her thanks to Dr M. Pietraszek for valuable comments and helpful discussion and to Mrs. E. Smolak, MAs for her valuable help with the linguistic correction of the paper.

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Abbreviations: AC: adenylyl cyclase, ADA: adenosine deaminase, AK: adenosine kinase, AMPA: Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, BRET: bioluminescence resonance energy transfer, CGS21680: 2-(*p*-(2-carbonyl-ethyl)-phenylethylamino)-59-*N*-ethylcarboxamidoadenosine; CHPG, (RS)-2-chloro-5-hydroxyphenylglycine; CPCA, 5'-(N-cyclopropyl)-carboxamido-adenosine; CPT, 8 cyclopenthyl-1,3-dimethylxanthine, DARPP-32: dopamine- and cAMP-regulated phosphoprotein of relative molecular mass 32 kDA, DAT: dopamine transporter, DPCPX: 1,3-dipropyl-8-cyclopentylxanthine, ERK: extracellular signal-regulated kinase, FRET: fluorescent resonance energy transfer, GABA: gamma-aminobutyric acid, GKAP: guanylate kinase-associated protein, GPCR: G-protein-coupled receptors, HE-NECA: 2-hexynyl-5'N-ethylcarboxamidoadenosine, KA: kainic acid, KF17837: 1,2-dipropyl-8-(3,4-dimethoxystyryl)-7-methylxanthine, KW6002: (1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methilxanthine, LTD: long-term depression, LTP: long-term potentiation, MK-801: (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine hydrogen maleate, MPEP: 2-methyl-6-(phenylethynyl)-pyridine, MSX-3: (*E*)-phosphoric acid mono-(3-(8-(2-(3-methoxyphenyl)vinyl)-7-methyl-2,6-dioxo-1-prop-2-ynyl-1,2,6,7-tetrahydropurin-3-yl)propyl) ester disodium salt, MTEP: ((2-methyl-1,3-thiazol-4-yl) ethynyl) pyridine, NMDA: N-methyl-D-aspartate, PCP: phencyclidine, PET: positron emission tomography, PKA: protein kinase A, PPI: prepulse inhibition, PSD95: PSD-95-family proteins also known as membrane-associated guanylate kinases, SAH: S-adenozylhomocysteine, SCH58261: 5-amino-7-(2-phenylethyl)-2 (2-furyl)-pyrazolo(4,3-*e*)-1,2,4-triazolo(1,5-*c*)pyrimidine, SKF38393: 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine, SPECT: single photon emission computed tomography, ZM241385: 4-(2-(7-amino-2-(2-furyl))1,2,4-triazolo(2,3-*a*)(1,3,5)triazin-5-ylamino)ethyl)phenol.

Key Words: Adenosine, Adenosine A_{2A} Receptors, Animal Models, Antipsychotics, Cognitive Processes, Dopamine, Dopamine D_2 Receptors, Glutamate, Heteromeric Receptor Complex, NMDA Receptors, Mglu5 Receptors, Psychostimulants, Schizophrenia, Review

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