



Review

Allosteric Interactions between Adenosine A_{2A} and Dopamine D₂ Receptors in Heteromeric Complexes: Biochemical and Pharmacological Characteristics, and Opportunities for PET Imaging

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Abstract: Adenosine and dopamine interact antagonistically in living mammals. These interactions are mediated via adenosine A_{2A} and dopamine D₂ receptors (R). Stimulation of A_{2A}R inhibits and blockade of A_{2A}R enhances D₂R-mediated locomotor activation and goal-directed behavior in rodents. In striatal membrane preparations, adenosine decreases both the affinity and the signal transduction of D₂R via its interaction with A_{2A}R. Reciprocal A_{2A}R/D₂R interactions occur mainly in striatopallidal GABAergic medium spiny neurons (MSNs) of the indirect pathway that are involved in motor control, and in striatal astrocytes. In the nucleus accumbens, they also take place in MSNs involved in reward-related behavior. A_{2A}R and D₂R co-aggregate, co-internalize, and co-desensitize. They are at very close distance in biomembranes and form heteromers. Antagonistic interactions between adenosine and dopamine are (at least partially) caused by allosteric receptor–receptor interactions within A_{2A}R/D₂R heteromeric complexes. Such interactions may be exploited in novel strategies for the treatment of Parkinson’s disease, schizophrenia, substance abuse, and perhaps also attention deficit-hyperactivity disorder. Little is known about shifting A_{2A}R/D₂R heteromer/homodimer equilibria in the brain. Positron emission tomography with suitable ligands may provide in vivo information about receptor crosstalk in the living organism. Some experimental approaches, and strategies for the design of novel imaging agents (e.g., heterobivalent ligands) are proposed in this review.

Keywords: adenosine A_{2A} receptor; dopamine D₂ receptor; heteromers; allosteric interaction; receptor–receptor interactions; striatum; GABAergic enkephalinergic neuron



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1. Introduction

Adenosine, a purine nucleoside, plays several behavioral and physiological roles throughout the central nervous system (CNS). Adenosine is generated in the living brain from adenine nucleotides such as adenosine triphosphate (ATP) and adenosine monophosphate (AMP). A much less important, other source of adenosine is S-adenosylhomocysteine, that originates from S-adenosylmethionine after physiological transmethylation [1]. Increased firing of neurons is associated with increased consumption of ATP, nucleotide dephosphorylation, and increases of intracellular adenosine levels (Figure 1). Since equilibrative nucleoside transporters are present in neuronal membranes, the extracellular levels of adenosine will also increase under such conditions. Thus, extracellular adenosine concentrations fluctuate, depending on neuronal activity.

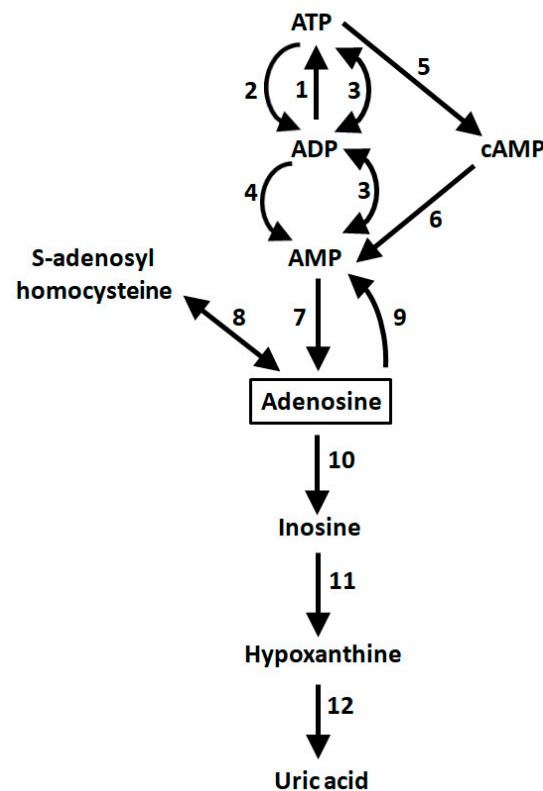


Figure 1. Metabolic pathways involved in the formation and removal of adenosine. 1 = Oxidative phosphorylation (and creatine kinase), 2 = Energy-consuming processes, 3 = Adenylate kinase, 4 = Apyrase, 5 = Adenylate cyclase, 6 = Phosphodiesterase, 7 = 5'-Nucleotidase, 8 = S-adenosyl homocysteine hydrolase, 9 = Adenosine kinase, 10 = Adenosine deaminase, 11 = Purine phosphorylase, 12 = Xanthine oxidase. ATP = adenosine 5'-triphosphate, ADP = adenosine 5'-diphosphate, AMP = adenosine 5'-monophosphate, cAMP = 3',5'-cyclic adenosine monophosphate.

Extracellular adenosine levels in the mammalian brain range from 20 to 250 nM [2–7]. Extracellular adenosine can bind to four subtypes of adenosine receptors, called A_1 , A_{2A} , A_{2B} and A_3 , which belong to the P1 receptor family. A_1 and A_{2A} receptors have a high affinity for adenosine (10–100 nM range), whereas A_{2B} and A_3 receptors are only activated when extracellular adenosine reach very high (micromolar) levels, after tissue damage (e.g., inflammation, hypoxia, ischemia, brain injury). Physiological levels of adenosine will stimulate the A_1 and A_{2A} receptors. It is unlikely that adenosine exerts major physiological functions via A_{2B} and A_3 receptors in the brain, since physiological levels of adenosine are too low to activate these proteins, and A_{2B} and A_3 receptors are mainly expressed in peripheral organs rather than in the CNS [8–13].

A_1 receptors (A_1R) are coupled to G_i proteins. Stimulation of these receptors by adenosine causes a decrease in cAMP levels through an inhibitory effect on adenylate cyclase. A_{2A} receptors (A_{2AR}) are coupled to an excitatory G_s protein. Stimulation of A_{2AR} results in an increase of cAMP levels and activation of protein kinase A [8–13].

2. Antagonistic Interactions between Adenosine and Dopamine

2.1. Living Animals

Interactions between adenosine and dopamine in living animals were already observed in 1974. Adenosine antagonists (caffeine and theophyllamine) were then reported to enhance the action of dopamine agonists such as apomorphine, bromocriptine and L-DOPA (stimulation of rotation behavior) in the 6-hydroxydopamine hemiparkinson model of rats [14]. In later studies using reserpinized (i.e., dopamine-depleted) mice, the action of bromocriptine was found to be inhibited by adenosine agonists (L-PIA, NECA)

and this inhibition could be reversed by the adenosine antagonists caffeine, paraxanthine, and theophylline. Since the non-subtype-selective agonist 5'-(N-ethyl)carboxamido-adenosine (NECA) was considerably more potent than the A₁-selective agonist N⁶-phenylisopropyladenosine (L-PIA), A_{2A} rather than A₁ receptors seem to be involved in the inhibition of the locomotor response to dopaminergic stimulation [15,16]. Central administration of the adenosine A_{2A}R agonist 2-[p-(2-carboxyethyl)phenethylamino]-5'-N-ethylcarboxamido-adenosine (CGS21680) was shown to induce catalepsy in the rat, and this effect was counteracted by systemic administration of the adenosine antagonist theophylline or the dopamine D₂ agonist 5,6,7,8-Tetrahydro-6-(2-propen-1-yl)-4H-thiazolo[4,5-d]azepin-2-amine dihydrochloride (BHT-920) [17]. The dopamine D₂R antagonist haloperidol induces catalepsy and Parkinsonian symptoms in rats and mice. Such symptoms can be reversed by treating rats with the non-selective adenosine antagonist caffeine or the selective A_{2A}R antagonist SCH58261 [18] and are significantly reduced in A_{2A}R knockout mice [19]. Haloperidol-induced motor impairments in monkeys (catalepsy, extrapyramidal syndrome) are counteracted by the A_{2A}R antagonists SCH-412348, istradefylline, and caffeine [20].

As A_{2A} receptors are known to be located mainly in the striatum, in postsynaptic locations on dendrites and dendritic spines [21,22] and, to a lesser extent (25%), on nerve endings [23,24]. These findings suggest the existence of postsynaptic interactions between adenosine and dopamine receptors, probably the A_{2A} and D₂ subtypes. Stimulation of A_{2A} receptors results in inhibition, and blockade of A_{2A} receptors in enhancement of D₂-receptor mediated locomotor activation.

Stimulation of A_{2A}R in the nucleus accumbens of rats by local infusion of CGS21680 produced behavioral effects similar to those induced by local dopamine depletion (i.e., decreased lever pressing for preferred food and substantially increased consumption of the less preferred but freely accessible chow) [25]. On the other hand, decreases of lever pressing for preferred (high carbohydrate) food caused by the D₂R antagonist eticlopride could be partially reversed by treating rats with the A_{2A}R antagonist MSX-3 [26]. Similar decreases induced by the D₂R antagonist haloperidol could be reversed by the A_{2A}R-subtype-selective antagonist istradefylline or the non-subtype selective AR antagonist caffeine [27]. Thus, antagonistic interactions between A_{2A}R and D₂R occur not only in the dorsal striatum where they control locomotor activity, but also in the nucleus accumbens (ventral striatum) where they affect goal-directed behavior.

2.2. Membrane Preparations

Antagonistic interactions between A_{2A} and D₂ receptors could also be observed *in vitro*, in membrane preparations from rat striatum. Administration of the adenosine A_{2A} receptor (A_{2A}R) agonist CGS21680 resulted in a significant, 40% increase of the K_d (i.e., a loss of the affinity) of dopamine D₂ receptors to the agonist L-(-)-N-[³H]propylnorapomorphine without changing the B_{max} (i.e., the number of D₂ receptors) [28]. However, the K_d and B_{max} for binding of the dopamine D₂ antagonist [³H]raclopride were not affected [28]. The effect of CGS21680 on D₂R affinity was most pronounced at concentrations similar to the K_d for binding of CGS21680 to A_{2A}R. At very high, saturating doses of CGS21680 (300 nM), the effect of the agonist was reduced, probably because such high doses cause a desensitization of A_{2A}R [28]. In striatal membrane preparations of adult (as opposed to young) rats, CGS21680 reduced not only the affinity of D₂ receptors for agonists, but also the fraction of D₂ receptors in the high-affinity state. Thus, A_{2A}R stimulation may inhibit the motor responses induced by dopamine receptor agonists by decreasing both the affinity and the signal transduction of D₂ receptors [29,30]. Adenosine appears to regulate the properties of D₂R via its interaction with A_{2A}R. Direct receptor–receptor interactions in striatal membranes were suggested as a potential mechanism involved in this pharmacological crosstalk between A_{2A}R and D₂R [28,31,32].

2.3. Intact Cells

Antagonistic interactions between A_{2A} and D₂ receptors were also demonstrated in intact cells. In a mouse fibroblast cell line stably transfected with A_{2A}R and D₂R, the D₂R agonist quinpirole induced a concentration-dependent increase in intracellular (cytosolic) free calcium. This response was completely blocked if cells were pretreated with haloperidol. CGS21680 by itself did not affect intracellular calcium levels (even when it was administered at high dose), but CGS21680 strongly counteracted the response of [Ca²⁺]_i to quinpirole [33]. Similar observations were made in SH-SY5Y (human neuroblastoma) cells that were transfected with human D₂R [34]. The effect of CGS21680 was shown to be related to a two- to three-fold decrease of the affinity of the D₂R in the cells to dopamine receptor agonists [34,35]. A similar three- to four-fold increase of the K_D of dopamine at high-affinity D₂R sites after administration of CGS21680 was noted in Chinese hamster ovary (CHO) cells that were co-transfected with A_{2A} and D₂ receptors [36]. In such cells, CGS21680 decreased the affinity of D₂ receptors for [³H]dopamine but not the number of dopamine binding sites [37]. Since A_{2A}R stimulation increases, but D₂R stimulation decreases, the intracellular formation of cyclic AMP, A_{2A}R, and D₂R may interact not only at the membrane level but also at the second messenger level. The experiments in CHO cells suggested that the latter interaction may be quantitatively the most important [36].

In initial cell experiments, A_{2A}R agonists were shown to decrease the affinity of D₂R for agonists. In later experiments, interactions in the opposite direction were also demonstrated. D₂R activation by quinpirole resulted in a less rapid and reduced binding of the fluorescent A_{2A}R agonist MRS5424 to HEK293 cells, which expressed both A_{2A} and D₂ receptors [38]. Similar decreases of A_{2A}R agonist binding were observed when the cells were treated with D₂R agonists in clinical use, such as pramipexole, rotigotine, and apomorphine [39]. On the other hand, chronic D₂R blockade by haloperidol increased both the affinity and the responsiveness of the A_{2A}R to the agonist NECA in CHO cells that expressed both A_{2A} and D₂ receptors [40].

In CHO cells transiently transfected with A_{2A}R and D₂R, both the A_{2A}R agonist CGS21680 and the AR antagonist caffeine caused a decrease of the affinity of the D₂R for radioligands, not only the D₂R agonist [³H]quinpirole but also the D₂R antagonist [³H]raclopride. Yet, CGS21680 and caffeine canceled out each other's effect on D₂R affinity when they were administered together [41]. These apparently paradoxical findings led to a novel hypothesis concerning the structural basis of adenosine–dopamine receptor interactions, which is described in Section 5 of this review.

2.4. Brain Slices

Antagonistic interactions between A_{2A} and D₂ receptors could also be demonstrated in cryostat sections of rat and human brain. CGS21680 significantly increased the IC₅₀ values of competition between the D_{2/3}R ligand [¹²⁵I]iodosulpiride and dopamine in the striatal region of such preparations [42].

3. Regional, Cellular, and Subcellular Distribution of A_{2A} and D₂ Receptors

The antagonistic interactions of A_{2A} and D₂ receptors that were observed in rat striatal membranes [28–30] suggested that the A_{2A} and D₂ receptor genes are co-expressed by some cells in the mammalian brain.

3.1. Regional Distribution

Both in the rodent and human brain, A_{2A}R mRNA [43–48] and A_{2A}R protein [24,49–56] are mainly located in the striatum (caudate-putamen) and nucleus accumbens. In monkeys, A_{2A}R immunoreactivity is mainly present in striatum and nucleus accumbens, but can also be detected in the substantia nigra, an area showing very low A_{2A}R density in rats. This finding indicates that there may be species differences between rodents and primates concerning the regional distribution of A_{2A}R [57].

Caudate, putamen and nucleus accumbens express also high numbers of dopamine D₂R [58–62]. The distribution of D₂R in the rodent brain is very similar to that of A_{2A}R mRNA, although D₂R is also present in the substantia nigra and piriform cortex [63].

3.2. Cellular Distribution

The majority (more than 95%) of the neurons in the striatum are medium spiny neurons (MSNs; i.e., medium-sized neurons (diameter 12–15 μm in rodents) with large and extensive dendritic trees) [64]. MSNs in the dorsal striatum can be divided in two subtypes [65,66]. Both subtypes use gamma-aminobutyric acid (GABA) as neurotransmitter, but the subtypes have different projection patterns and they express different receptors and neuropeptides. Some MSNs send direct (monosynaptic) projections to the substantia nigra and the globus pallidus internus. Based on this projection pattern, this subtype is said to form part of the “direct pathway” (Figure 2). MSNs of the direct pathway express dopamine D1R and the peptide dynorphin (together with substance P). Other MSNs are indirectly linked to the substantia nigra and the globus pallidus internus, via the globus pallidus externus and the subthalamic nucleus. Because of this distinctive projection pattern, they are said to form part of the “indirect pathway” (Figure 2). MSNs of the indirect pathway express dopamine D₂R and the peptide enkephalin [63,67,68] (reviewed in [69]).

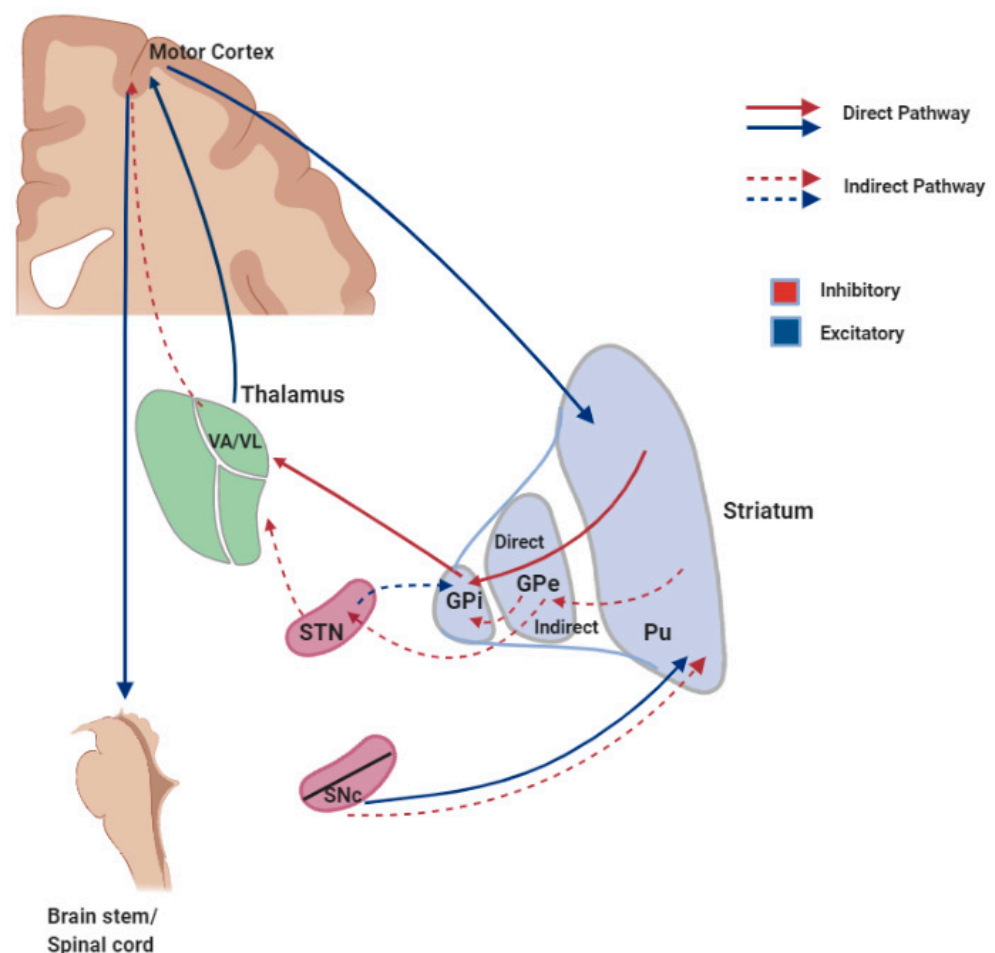


Figure 2. Schematic drawing of the direct and indirect pathways for motor control. Solid and faded lines represent direct and indirect pathways, respectively. Blue lines represent excitatory connections and red lines represent inhibitory connections. Pu = putamen, Gpe = globus pallidus externus, Gpi = globus pallidus internus, STN = subthalamic nucleus, SNc = substantia nigra pars compacta, VA/VL = ventral anterior/ventral lateral thalamic nucleus. Created with BioRender.com.

In early publications, the A_{2A}R (at that time still called RDC8) was shown to be present in medium-sized but not in large neurons of the dog and rat striatum [70]. In contrast to A_{2A}R, dopamine D₂R mRNA is present both in medium-sized and large neurons [71]. Later studies employed double in situ hybridization [43,44,47,72,73] and double-labeling immunohistochemistry [52] to determine the phenotype of A_{2A}R-containing neurons in dorsal and ventral striatum. In the ventral striatum, a population of neurons expresses the gene for the A_{2A}R, but not for preproenkephalin. This sub-population is absent in the dorsal striatum. In the dorsal striatum, 95–96% of the A_{2A}R mRNA is co-expressed with D₂R mRNA. Only a few neurons expressing 3–6% of the A_{2A}R mRNA co-express dopamine D₁R or substance P mRNAs. In the ventral striatum, most A_{2A}R mRNA (89–92%) co-localizes with preproenkephalin A mRNA, and the vast majority (93–95%) with D₂R mRNA [74]. Adenosine A_{2A} receptors were shown to co-localize with enkephalin and dopamine D₂R, but not with dopamine D₁R, substance P or somatostatin. These data were interpreted as evidence for a preferential expression of A_{2A}R in striatopallidal GABAergic MSNs of the indirect pathway, cells which also express D₂R [44,72,75]. Microdialysis experiments in intact freely moving rats supported this hypothesis. In these experiments, adenosine and dopamine agonists and antagonists were infused in the striatum, either alone or in combination, and the effect on the release of GABA was measured in the ipsilateral globus pallidus [76].

MSNs from the indirect pathway are the main, but not the only, cells in the striatum that co-express A_{2A} and D₂ receptors. Striatal astrocytes also express both proteins [77–80] and receptor–receptor interactions between A_{2A}R and D₂R have been demonstrated in glia. Administration of the D₂R agonist quinpirole to rat striatal astrocytes inhibits the 4-aminopyridine-provoked release of glutamate. The A_{2A}R agonist CGS21680 alone did not affect glutamate release but reduced the D₂R-mediated inhibiting effect of quinpirole [81]. A third class of cells in the striatum which express both A_{2A}R and D₂R are cholinergic interneurons [82].

3.3. Subcellular Location

In bright field photomicrographs of coronal sections of rat striatum, A_{2A}R protein was detected on the cell bodies of GABA/enkephalin striatopallidal neurons [73]. Using immuno-electron microscopy, A_{2A}Rs were mainly detected on dendrites, to a lesser extent on axon terminals, soma and astrocytic processes [23,24,52]. Subcellular fractionation experiments using the radioligand [³H]SCH58261 suggested that A_{2A}R in the striatum of the rat are not enriched in synaptosomes [22]. In dendrites and soma, A_{2A}R were shown to be present not only on the plasmalemma, but also throughout the cytoplasm and around intracellular membranous structures [23]. The predominantly postsynaptic location of A_{2A}Rs (on dendrites and dendritic spines) was interpreted as evidence for an important function of these receptors in modulating the excitatory glutamatergic input to the striatum [24].

D₂ receptor immunoreactivity was detected by immunocytochemistry and electron microscopy in rat basal ganglia. Subcellular experiments using fusion protein antibodies depicted predominant localization of D₂ in spiny dendrites and spine heads within the neutrophil of the striatum. The receptors were also located in submembranous sites of dendritic shafts and dendritic spines [83].

4. A_{2A}R and D₂R Co-Aggregate, Co-Internalize and Co-Desensitize

Interactions between A_{2A} and D₂ receptors were found to affect not only the signaling but also the intracellular trafficking of the two proteins. The human neuroblastoma cell line SH-SY5Y constitutively expresses A_{2A} receptors. In a groundbreaking article [84], SH-SY5Y cells were transfected with D₂ receptors, and incubated with fluorescein-conjugated anti-A_{2A}R (green fluorescence) and rhodamine-conjugated anti-D₂R antibodies (red fluorescence). Receptor trafficking in the cells could then be monitored with confocal laser microscopy. In untreated cells, A_{2A}R and D₂R were shown to be generally at close distance

(<100 nm) but rather uniformly distributed in the plasma membrane. When the cells were treated with either CGS21680 (100 nM) or quinpirole (10 μ M) for 3 h, the distribution of the receptors in the plasma membrane became less uniform and significant co-aggregates were formed (yellow hotspots). When the same doses of the A_{2A}R and D₂R agonist were administered together for 3 h, the total intensity of the fluorescence signals was decreased, suggesting that co-aggregation of the A_{2A}R and D₂R was followed by co-internalization. This effect was dose-dependent, both the co-aggregation and the signal loss being stronger after treatment with 200 nM CGS21680 plus 50 μ M quinpirole than with 100 nM CGS21680 plus 10 μ M quinpirole. In cells lacking D₂R, quinpirole did not cause any aggregation or internalization of the A_{2A}R. Prolonged (3 h) administration of either 1 μ M of CGS21680 or 1 μ M of quinpirole to cells expressing both A_{2A}R and D₂R resulted in desensitization of their A_{2A} receptors (decrease of the cAMP response to A_{2A}R stimulation), but desensitization of the D₂R occurred only when both agonists were simultaneously administered [84]. When A_{2A}R in the cells were immunoprecipitated with A_{2A}R antibodies, Western blots indicated that the D₂R was co-precipitated and that three glycosylated forms of the D₂R were present in the precipitate [84]. Thus, A_{2A}R and D₂R were shown to co-aggregate, co-internalize, co-desensitize, and co-precipitate in the presence of D₂R and A_{2A}R agonists.

Computer-assisted analysis of dual-channel fluorescence laser microscopy images indicated co-localization, co-aggregation and co-internalization of A_{2A}R and D₂R also in Chinese hamster ovary (CHO) cells [85,86]. In the CHO cell experiments, the effect of receptor stimulation was examined at different time intervals (3, 15 and 24 h) after administration of quinpirole. Co-aggregation of A_{2A}R and D₂R was observed after 3 h, and the co-aggregates internalized after 15 h. A return to the plasma membrane was detected after 24 h. In contrast to treatment with quinpirole, treatment of CHO cells with the D₂R antagonist raclopride did not decrease but increased the fluorescence signal of both A_{2A}R and D₂R, indicating that a D₂R antagonist reduced the internalization of the two receptors [86].

Similar microscopy techniques suggested that A_{2A} and D₂ receptors form a macro-complex with caveolin-1 that internalizes when cells are treated with an A_{2A} and a D₂ agonist. Thus, caveolin-1 may play a role in the process of co-internalization [87]. Later experiments using bioluminescence resonance energy transfer (BRET) indicated that A_{2A} and D₂ receptors also form a macrocomplex with β -arrestin2, A_{2A}R agonists promoting (and A_{2A}R antagonists reducing) the D₂R agonist-induced recruitment of β -arrestin2 by the D₂R protomer and subsequent co-internalization [88,89].

The D₂R agonist 3-(3,4-dimethylphenyl)-1-(2-piperidin-1-yl)ethyl-piperidine was shown to reduce the affinity and functional responsiveness of A_{2A}R to agonists. In addition, this D₂R agonist induced co-internalization of the A_{2A}R and D₂R proteins [90].

5. A_{2A}R and D₂R Are at Very Close Distance in Biomembranes and Form Heteromers

At the end of the twentieth and beginning of the twenty-first century, several biophysical techniques, such as atomic force microscopy (AFM), bimolecular fluorescence complementation (BiFC), fluorescence resonance energy transfer (FRET), bioluminescence resonance energy transfer (BRET), in situ proximity ligation assay (PLA), and AlphaScreen technology, were developed that allow the detection of spatial proximity of protein molecules, and such techniques have also been applied to A_{2A} and D₂ receptors [85,91–100]. The results of these techniques and the observed co-aggregation, co-internalization and co-immuno-precipitation of A_{2A}R and D₂R indicate that both receptors are at very close distance in biological membranes (<10 nm) and form heteromers. Molecular biology experiments have provided insight in the mechanisms and atomic interactions that are involved in heteromer formation.

Using BRET technology, Japanese authors demonstrated that A_{2A}R form homomers and also heteromers with D₂R in living HEK293T cells. A_{2A} and D₂ receptors were fused to either an energy donor (Renilla luciferase) or an energy acceptor (modified green fluorescent protein) without affecting the ligand binding affinity, subcellular distribution or

co-immunoprecipitation of the two receptor proteins [101]. BRET and FRET techniques were also applied to quantify $A_{2A}R/D_2R$ heteromers in receptor co-transfected cells, including cells that were transfected with modified D_2 receptors: Chimeric proteins in which part of the D_2 receptor protein was replaced by the corresponding part of the D_1 receptor protein. Such experiments, and molecular modeling studies, suggested that heteromerization between $A_{2A}R$ and D_2R depends on interaction of the third intracellular loop of the D_2R with the C-terminal tail of the $A_{2A}R$ [102,103]. Transmembrane domains of the D_2R , particularly the fifth transmembrane domain, also appeared to play a role [37]. A comprehensive molecular model of the $A_{2A}R/D_2R$ heteromer was developed [104].

Triplet homologies in $A_{2A}R$ and D_2R (e.g., alanine-alanine-arginine) have been proposed to guide the heteromer partners and to clasp them together [105]. “Pull-down” assays are *in vitro* methods to identify and determine physical interactions between two proteins. Using such techniques and mass spectrometry, a strong electrostatic interaction was demonstrated between negatively charged motifs (aspartic/phosphorylated serine residues) in the C-terminal tail of the $A_{2A}R$ and a positively charged (arginine-rich) epitope in the third intracellular loop of the D_2R [106]. This electrostatic interaction was shown to possess an amazing stability, comparable to the stability of a covalent bond [107]. The importance of the serine residue in the C-terminal tail of the $A_{2A}R$ for $A_{2A}R$ - D_2R receptor-receptor interaction was proven by mutation studies. A point mutation (change of serine 374 to alanine) reduced the formation of A_{2A}/D_2 heteromers and the allosteric modulation of D_2R by $A_{2A}R$ agonists and antagonists [108]. Additional mutation of two aspartate residues (401–402 to alanine) in the C-terminal tail of the $A_{2A}R$ reduced the heteromer formation even further and completely abolished the allosteric modulation of D_2R by A_{2A} ligands [109]. The importance of transmembrane domains of the D_2R for heteromer formation was proven by administering synthetic peptides corresponding to the structure of the fourth and fifth transmembrane domain of the D_2R . Such peptides reduced the ability of $A_{2A}R$ and D_2R to form heteromers [109]. BRET techniques also demonstrated that calmodulin (CaM) interacts with the C-terminal tail of the $A_{2A}R$ and provided evidence for the formation of CaM- $A_{2A}R$ - D_2R oligomeric complexes [110].

Japanese investigators created a single-polypeptide chain $A_{2A}R/D_2R$ heteromer by fusing the C-terminus of the $A_{2A}R$ to the N-terminus of the D_2R via a type II transmembrane protein. The resulting synthetic heterodimer showed similar specific binding of $A_{2A}R$ and D_2R ligands and functional coupling to G-proteins as the original wild-type receptors [111].

A very interesting study used BiFC to demonstrate the presence of receptor oligomers in CAD cells, a differentiated neuronal cell model. Prolonged treatment of the cells with the D_2R agonist quinpirole led to internalization of D_2R/D_2R oligomers and $A_{2A}R/D_2R$ heteromers and decreased the relative number of $A_{2A}R/D_2R$ heteromers compared to $A_{2A}R/A_{2A}R$ oligomers. This effect of quinpirole was reversed by D_2R antagonists (spiperone, sulpiride), and prolonged treatment of the cells with either a D_2R antagonist or the $A_{2A}R$ agonist MECA resulted in a significant increase of the relative number of $A_{2A}R/D_2R$ heteromers compared to $A_{2A}R/A_{2A}R$ oligomers. Changes of the heteromer:oligomer ratio were not equivalent to the changes of total $A_{2A}R$ and D_2R numbers in the cells. Thus, drug treatment appeared to modulate G-protein-coupled receptor oligomerization [112].

Investigators from Taiwan demonstrated that both $A_{2A}R$ and D_2R are substrates for sialyltransferases (e.g., St8sia3) in the mouse striatum. If sialylation is reduced (as in St8sia3 knockout mice), a larger fraction of both receptors moves to lipid rafts and a greater number of D_2R form heteromers with $A_{2A}R$. Thus, sialylation may be a mechanism counteracting heteromer formation and shifting the homomer/heteromer equilibrium in the living brain [113]. Treatment of mice with an $A_{2A}R$ antagonist (SCH58261) causes a dose-dependent increase of locomotor activity. This response is much lower in St8sia3-knockout animals than in wild-type mice [113]. On the other hand, treatment of mice with a D_2R antagonist (L741626) results in a dose-dependent reduction of their locomotor activity, and St8sia3-knockout animals are more sensitive to this effect of a D_2R antagonist than their wild-type counterparts [113]. Alterations of the $A_{2A}R/D_2R$ homomer/heteromer

equilibrium in the striatum thus appear to be associated with altered responses of the animals to adenosine and dopamine receptor blockade.

D₂R-agonists can inhibit the 4-aminopyridine-provoked glutamate release in rat striatal astrocytes. Modulation of this inhibition with CGS21680 was shown to depend on the formation of A_{2A}R/D₂R heteromers, whereas the synthetic peptide VLRRRRKRVN abolished the effect of CGS21680 [81,114]. VLRRRRKRVN binds to the region of the D₂R that is involved in electrostatic interaction with the A_{2A}R and thus blocks the formation of A_{2A}R-D₂R heteromers [106].

Using fluorescent PLA and time-resolved FRET, A_{2A}R/D₂R complexes were detected in the striatum of rodents [94,115–117], monkeys [118], and humans [119]. Such complexes could also be demonstrated and quantified in postmortem brain tissue from patients with Parkinson's disease and healthy control subjects, using AlphaScreen technology [97].

A_{2A}R/D₂R heteromers are now considered to be receptor heterotetramers, consisting of an A_{2A}R homodimer and a D₂R homodimer, each coupled to its own G-protein (Gs and Gi, respectively). Adenylate cyclase subtype AC5 also forms part of this multi-protein complex [41,120–125]. The heterotetramer model can explain the apparently paradoxical effects of A_{2A}R agonists and antagonists on D₂R ligand binding in CHO cells that were described in Section 2.3 of this review. Occupancy of the A_{2A}R homodimer by either an agonist or an antagonist (at high dose) causes a conformational change in the heterotetramer, resulting in decreased function of the D₂R protomer in the complex. However, when one of the two adenosine binding sites in the A_{2A}R homodimer is occupied by an agonist and the other is simultaneously occupied by an antagonist, the conformational change does not occur [41].

6. Pharmacological Consequences of A_{2A}/D₂ Heteromer Formation

Receptors can form heteromers if certain basic criteria are met. These include: (a) The individual receptors that can form a heteromeric complex (protomers) must co-localize (i.e., be present in the same membrane domains, at very close distance from each other) and physically interact; (b) formed receptor complexes must exhibit distinct properties which differ from those of the individual, isolated protomers; and (c) chemical compounds that bind selectively to the heteromers should alter the properties or functions of the heteromers [126].

A_{2A}R and D₂R meet all these criteria. Biophysical and molecular biology techniques have demonstrated that these receptors co-localize and physically interact, both in cells and in mammalian tissues (see above, Section 5). Synthetic peptides that interact with the receptor domains involved in heteromer formation affect the electrostatic interactions between the protomers and alter the response of cells to certain drugs (Section 5). In addition, within A_{2A}R/D₂R heterotetramers, various receptor–receptor interactions are possible [125]:

(i) “Canonical interaction”. The agonist-activated Gi-coupled receptor in the complex (i.e., the D₂R) will inhibit the activation of adenylate cyclase AC5 by the Gs-coupled receptor (i.e., the A_{2A}R) [36]. The Ras GTPase domain of the subunits of the Gs and Gi proteins will interact with the C2 and C1 catalytic domains of adenylate cyclase AC5. The receptor partners in the complex can modulate each other's downstream signaling cascade [36].

(ii) “Allosteric interaction”. Allosterism is defined as communication between distant sites in a protein (or protein complex) in which energy associated with ligand binding or conformational change at one site is transferred to other, remote sites of the protein (or protein complex) resulting in changes of the kinetic or conformational properties of these sites. When a ligand binds to one of the receptors in an A_{2A}R-D₂R complex, the conformation of the complex (quaternary structure of the heterotetramer) is altered, resulting in different binding and signaling properties of the other receptor proteins in the complex [41,121,127–129]. When an A_{2A}R ligand (either an agonist or an antagonist) binds to the A_{2A}R homodimer in the complex, the affinity and signaling efficacy of D₂R agonists is decreased. On the other hand, when a D₂R agonist binds to the D₂R heteromer in the complex, the binding of A_{2A}R agonists is suppressed. Such allosteric effects between

A_{2A}R and D₂R have been demonstrated in isolated biomembranes, intact cells, brain slices, and living animals (see above, Section 2).

(iii) “Formation of new modulatory sites”. When different receptor proteins associate to form a heteromer, novel binding sites may be created that are not present in the isolated receptors. Ligands specific to the receptor complex as such may exist [130] and, if discovered, may be used to specifically modulate the complex when it is present [131] (see also Section 11.3).

(iv) “Higher order interaction”. A_{2A}R/D₂R heterotetramers may become part of higher order heteromers, so-called “receptor mosaics” [132]. Such interactions may, for example, involve the metabotropic glutamate receptor 5 (mGluR5) [133,134] or the sigma-1 receptor [117,135–137]. The presence or absence of such additional partners in a higher-order heteromer changes the strength of A_{2A}R-D₂R allosteric interactions and alters the response of the A_{2A} and D₂ protomers to adenosine or dopamine. Since an unknown (and variable) number of additional proteins may bind to A_{2A}R and D₂R, the term “heteroreceptor complexes” is used in recent literature rather than A_{2A}/D₂R heterotetramers [138].

Thus, A_{2A}R/D₂R heterotetramers have a distinct pharmacology and distinct functions which differ from those of the individual constituent receptors [139].

7. A_{2A}/D₂ Interactions and Parkinson’s Disease

Upper motor neurons in the motor regions of the cortex initiate movements, such as continuous postural control, body locomotion, orientation towards sensory stimuli, and orofacial behavior. The activity of lower motor neurons in the spinal cord is coordinated by the upper motor neurons. These lower motor neurons directly or indirectly innervate skeletal muscle fibers [140].

In movement control, there is also a close cooperation of regions in the cortex with the basal ganglia [65,141] (Figure 2). Neurons that belong to the basal ganglia regulate the activity of the upper motor neurons although they do not directly project to them. The major nuclei that comprise the basal ganglia are: The striatum, the globus pallidus (GP), the substantia nigra (SN), and the subthalamic nucleus (STN) [142] (Figure 2). In the rodent brain, the striatum is a single nucleus whereas in primates, it is divided into caudate nucleus and putamen [143]. The basal ganglia receive input from areas of the cerebral cortex and their output is directed towards the thalamus, from where there is a transient excitation back to the motor regions in the cortex (Figure 2). MSNs in the striatum are known to be involved in movement control.

Activation of GABAergic MSNs of the “direct pathway” results in inhibition of the globus pallidus internus (GPi), for GABA is an inhibitory neurotransmitter. Since the GPi is connected to the thalamus via another GABAergic projection, inhibition of the GPi causes disinhibition of the thalamus. Because the thalamus contains excitatory neurons that project to the cortex, activation of the direct pathway results in facilitation of motor activity [140] (Figure 2).

In the “indirect pathway”, GABAergic MSNs project from the striatum to the globus pallidus externus (GPe). A second GABAergic projection runs from the GPe to the subthalamic nucleus (STN) and an excitatory glutamatergic projection connects the STN to the GPi. Activation of the indirect pathway therefore results in disinhibition of the STN and activation of the GPi. This activation of the GPi causes inhibition of the thalamus and reduced activity of the excitatory neurons that run from the thalamus to the cortex. Thus, activation of the indirect pathway results in suppression of motor activity. Although this description of the indirect pathway is probably a gross over-simplification [144], the concept is still widely used as a basis for research and therapy.

Normal movements require a delicate, coordinated balance of activity in the direct and indirect pathways [65]. The healthy brain contains dopaminergic neurons in the substantia nigra pars compacta that project to the striatum. Dopamine from these neurons stimulates the MSNs from the direct pathway via D1R and inhibits the MSNs from the indirect pathway via D2R. Both actions of dopamine facilitate motor activity. Loss of dopaminergic

neurons from the brain, as occurs in Parkinson's disease, will result in a decreased activity of the direct pathway, an increased activity of the indirect pathway and impaired motor control, particularly hypokinesia.

Since loss of dopamine results in overactivity of the indirect pathway, A_{2A}R antagonists have been proposed as therapeutic drugs for the treatment of Parkinson's disease [75,145–149]. Such drugs may restore the disturbed balance between the indirect and direct pathways and may increase the effect of endogenous dopamine, L-DOPA and specific D₂ agonists, at least in the early stages of Parkinson's disease [150,151]. A_{2A}R antagonists may bind to the A_{2A}R protomer in A_{2A}R-D₂R heteromeric complexes and increase the affinity of the D₂R protomer for dopamine, its coupling to the G-protein and its signaling. In accordance with this hypothesis, perfusion measurements with MRI and pulsed arterial spin labeling have proven that the A_{2A}R antagonist tozadenant inhibits (i.e., suppresses the overactivity of) the indirect pathway in the brain of Parkinson's patients [152].

A_{2A}R antagonists have been shown to be beneficial in various animal models of PD (e.g., D₂R knockout mice [153], 6-OHDA-lesioned rats [154,155] and mice [156], rats with pharmacological D₂R blockade [157], MPTP-treated marmosets [158], and MPTP-treated monkeys [159]). Since locomotor abnormalities in D₂R knockout mice were rescued by the blockade of A_{2A}R, not all actions of A_{2A}R are related to the formation of A_{2A}R-D₂R heteromers. Apparently, striatal neuronal activity can also be regulated by A_{2A}R via a dopamine D₂R-independent pathway [152].

Many clinical studies have been performed to explore the effect of adenosine antagonists in Parkinson patients. These studies involved the non-subtype selective adenosine antagonists theophylline [160–162] and caffeine [163], and the A_{2A}R-antagonists istradefylline [164–174] and tozadenant [175]. In a single study, theophylline was reported to have no significant effect, probably because group sizes were too small to reach adequate statistical power [162], but in two other studies, the drug caused mild improvement of the objective and subjective symptoms of disability and did not worsen dyskinesia [160,161]. Caffeine temporarily improved freezing of gait in Parkinson's patients with symptoms of total immobility, but not in subjects who suffered from episodes of trembling with incapacity to any further movement [163]. Istradefylline as monotherapy was reported to not improve motor symptoms in early PD [169], but as adjunct therapy was shown to potentiate and prolong the action of L-DOPA. In the presence of istradefylline, lower doses of L-DOPA could be given to the patients and the severity of dyskinesia and resting tremor were reduced [164]. Several studies reported a reduction in "off" time (i.e., the time intervals in which disease symptoms return) when patients were given istradefylline [165–168,170,171] or tozadenant [175] in combination with L-DOPA, and this beneficial effect was not associated with any increase of dyskinesia [168]. Other symptoms of Parkinson's disease, such as daytime sleepiness [172], gait disturbance, freezing of gait, and postural instability [174], were also improved by istradefylline. As a consequence of these positive findings, istradefylline is now a registered drug for treatment of Parkinson's disease, both in Japan [176] and in the U.S. [177].

8. A_{2A}R-D₂R Interactions and Schizophrenia

Schizophrenia is thought to be associated with an overactivity of dopamine neurons in the ventral tegmental area of the brain, resulting in increased D₂R signaling in the nucleus accumbens [178]. As explained above (Sections 2.1 and 3.1), A_{2A}R and D₂R are present not only in the dorsal striatum, but also in the nucleus accumbens. Powerful antagonistic interactions between both receptors occur in this area of the brain and could be detected both in receptor binding studies and in microdialysis experiments. Administration of CGS21680 resulted in a reduced efficacy of dopamine to displace [¹²⁵I]iodosulpiride from D₂R in the nucleus accumbens. Infusion of the A_{2A}R agonist CGS21680 in the nucleus accumbens had the same effect as infusion of the D₂R antagonist raclopride (i.e., increasing the extracellular levels of GABA in the ipsilateral ventral globus pallidus),

and the stimulation of GABA release by an A_{2A}R agonist and a D₂R antagonist were found to be synergistic [179].

According to several hypotheses, altered levels of extracellular adenosine and adenosine receptors are involved in the pathophysiology of schizophrenia [180–182]. In accordance with such hypotheses, A_{2A}R were found to be upregulated in the striatum [183,184] and hippocampus [185] of chronic schizophrenics (although this upregulation could also be a consequence of the antipsychotic treatment that the patients received). A Chinese study reported significant associations between single nucleotide polymorphisms of the A_{2A}R gene and schizophrenia in the northern Chinese Han population [186].

Since D₂R of the ventral striatopallidal neurons are implied in the antipsychotic effects of neuroleptics [187], A_{2A}R agonists, either alone or in combination with D₂R antagonists, have been proposed as potential anti-schizophrenic drugs [179]. The ventral striatopallidal GABA pathway is considered as an anti-reward pathway which is over-activated in schizophrenia due to increased activation of its D₂R [188]. The antagonistic A_{2A}R-D₂R interactions in the nucleus accumbens, which presumably occur within receptor heteromers, could be exploited to reduce the activity of the D₂R protomer in the heteroreceptor complex [151,189]. In support of this idea, CGS21680 was shown to act as an atypical antipsychotic drug in rodent models of schizophrenia (phencyclidine, amphetamine) [190] and also in monkeys [191].

Some findings in humans have suggested that stimulation of A_{2A}R may be beneficial in the treatment of psychosis. Dipyridamole, a nucleoside transport inhibitor that increases the extracellular levels of adenosine, has been tested as an add-on therapy in the treatment of schizophrenics. Combined treatment with haloperidol and dipyridamole (16 patients) was found to be significantly better than treatment with haloperidol and placebo (14 patients) in reducing positive and general psychopathology symptoms as well as PANNS scores [192]. Administration of allopurinol, a drug which blocks the degradation of purines and increases the levels of adenosine and inosine in the brain, resulted in clinical improvement in two poorly responsive schizophrenic patients [193].

Chronic treatment of rodents with clozapine, an atypical antipsychotic which is more effective than classical antipsychotics in some patients, was found to increase the activity of the enzyme ecto-5'-nucleotidase in the striatum, whereas chronic treatment with haloperidol did not have this effect [194]. These preclinical data suggest that clozapine treatment, in contrast to treatment with typical antipsychotics, is associated with increases of the levels of extracellular adenosine in the brain and with stimulation of A_{2A}R.

9. A_{2A}R-D₂R Interactions and Treatment of Drug Addiction

According to a common hypothesis of reward-related behavior, the nucleus accumbens exerts tonic inhibitory effects on downstream structures in the brain. When MSNs in the nucleus accumbens are inhibited (e.g., by stimulation of dopamine D₂R), these downstream structures are excited and an endogenous brake on reward-related behavior is released [195]. Addictive drugs are believed to be rewarding and reinforcing due to their effects on the dopamine reward pathway. They enhance dopamine release as is, for example, the case with nicotine, or they inhibit the reuptake of dopamine as does cocaine, or they act themselves as agonists at D₂R [196].

Physiologically-relevant rewarding stimuli cause a release of dopamine in the shell of the nucleus accumbens, and this response is subject to habituation when the stimuli are repeatedly administered. Thus, the amount of dopamine that is released by a rewarding non-drug stimulus decreases as a result of repeated exposure to that stimulus. However, the dopamine response in the nucleus accumbens to addictive drugs is not prone to habituation but rather to sensitization, meaning that the amount of dopamine that is released by the drug increases as a result of repeated drug exposure.

Animal experiments in which rats with electrodes implanted in the medial forebrain bundle were trained to rotate a wheel in order to receive a rewarding electrical current

have indicated that A_{2A}R agonists elevate current reward thresholds (i.e., inhibit central reward processes) [197]. This observation suggests that A_{2A}R modulate reward.

Studies in animal models of cocaine addiction have indicated that stimulation or blockade of A_{2A}R has a significant impact on cocaine use. Administration of the non-subtype selective adenosine receptor antagonist caffeine to rats facilitates cocaine self-administration [198,199], whereas an A_{2A}R agonist, like CGS21680 or NECA, suppresses the tendency of animals to take cocaine [200,201]. Adenosine receptor agonists appear to suppress cocaine intake by an interaction with A_{2A}R in the nucleus accumbens, since microinjections of CGS21680 in the nucleus accumbens, but not in the prefrontal cortex, dose-dependently decrease cocaine self-administration [202]. Microinjections of a synthetic TM5 peptide (which interacts with the fifth transmembrane domain of the A_{2A}R and disrupts A_{2A}/D₂ heterotetramers), completely counteracted the inhibitory effect of CGS21680 on cocaine intake [203]. In contrast to this striking impact of a TM5 peptide, microinjections of a TM2 peptide (which disrupts A_{2A}/A_{2A} homodimers but not A_{2A}/D₂ heterotetramers) did not counteract the effect of CGS21680 on cocaine self-administration [204]. These results suggest that the beneficial actions of CGS21680 in animal models of cocaine abuse are mediated by the triggering of an allosteric inhibition of D₂ protomer signaling in A_{2A}R-D₂R heteromeric complexes.

The development of cocaine sensitization is enhanced when rats are treated with the A_{2A}R antagonist MSX-3 but is reduced when they are treated with the A_{2A}R agonist CGS21680 or the D₂R antagonist raclopride [205]. Administration of CGS21680 (0.25 to 0.5 mg/kg) to rats decreases the acquisition and expression of conditioned place preference induced by cocaine [206] or amphetamines [207].

In the treatment of substance abuse, relapse or drug-seeking behavior after a period of abstinence is a very serious problem. Thus, the finding that CGS21680 dose-dependently inhibits cocaine-induced reinstatement in rats after a period of drug abstinence of at least one week [201,208] is of great interest. On the other hand, A_{2A}R antagonists (MSX-3, istradefylline, SCH58261, CGS15943), when administered systemically or by microinjections in the nucleus accumbens, promote cocaine-seeking behavior [202,209–211]. The impact of A_{2A}R antagonists appears to be dependent on the question whether postsynaptic or presynaptic A_{2A}R are blocked. Istradefylline is a postsynaptic A_{2A}R antagonist, whereas SCH442416 blocks mainly presynaptic A_{2A}R [212]. Postsynaptic blocking was found to enhance whereas presynaptic blocking reduced reinstatement of cocaine seeking [211,213]. The different antagonist affinities of pre- and postsynaptic A_{2A}R may be due to the fact that presynaptic A_{2A}R form heteromers with adenosine A₁R, whereas postsynaptic A_{2A}R interact with dopamine D₂R.

Prolonged cocaine self-administration in rats is associated with a significant upregulation of A_{2A}R in the nucleus accumbens [214,215]. After seven days of cocaine withdrawal, A_{2A}R numbers in this area of the brain return to normal. This upregulation has been interpreted as a compensatory mechanism to counteract cocaine-induced increases in D₂R signaling [214]. Mice that were prenatally exposed to cocaine showed an upregulation of D₂R function and a downregulation of adenosine transporter function, consistent with increased levels of extracellular adenosine and more stimulation of A_{2A}R [216]. Thus, cocaine exposure both prenatally and in later life, has direct effects on the dopamine and modulatory adenosine systems.

Cocaine is known to also increase the density of sigma-1R in the nucleus accumbens [217] and to cause trafficking of intracellular sigma-1R to the plasma membrane, where they can interact with D₂R [135,218]. In fact, cocaine self-administration has been reported to increase the number of A_{2A}R-D₂R and D₂R-sigma-1R heteromers in the nucleus accumbens shell [117]. These data can also be interpreted as the formation of A_{2A}R-D₂R-sigma-1R heteromeric complexes in response to cocaine, the addition of the sigma-1R to the complex resulting in increased strength of antagonistic A_{2A}R-D₂R interactions [136,137,219,220].

BRET experiments in HEK-293T cells that were co-transfected with A_{2A}R and D₂R demonstrated that cocaine induces a concentration-dependent transient decrease of D₂R

homodimers and A_{2A}R/D₂R heteromers, but not of A_{2A}R homodimers, via a specific interaction with the D₂R. In co-transfected CHO cells, cocaine was found to cause an increase of the affinity of D₂R for dopamine and increased coupling of D₂R to G-proteins by changing the conformation of the receptor protein [221].

Based on such findings (and many others, which are extensively reviewed in [196]), it has been postulated that stimulation of A_{2A}R could be a possible strategy to treat drug addiction [201,222–224]. A_{2A}R antagonists that preferentially block presynaptic A_{2A}R may also offer therapeutic benefits.

10. A_{2A}R-D₂R Interactions and Attention Deficit Hyperactivity Disorder

Attention-deficit hyperactivity disorder (ADHD) is a disorder of human behavior that involves dysfunctions of sustained attention, behavioral hyperactivity and impulsivity. ADHD seems to be characterized by reduced functioning of the dopaminergic reward pathway [225,226]. Oral methylphenidate, an inhibitor of noradrenaline and dopamine reuptake, is often prescribed as a therapeutic drug to treat ADHD.

A study that was published in 2000 reported that apart from several genes of the noradrenergic system, polymorphisms of the A_{2A}R gene are significantly associated with human ADHD [227]. A later Swedish study confirmed that the A_{2A}R gene may indeed be involved in ADHD traits [228]. In rodent models of ADHD, A_{2A}R were found to be upregulated in various brain regions [229,230] and adenosine A_{2A}R antagonists were shown to have beneficial effects, such as improvement of short-term object-recognition ability, attention and memory function [230,231] and improved development of frontal cortical neurons [232].

A large study involving 1239 human subjects reported an association between the rs2298383 TT genotype of the A_{2A}R and anxiety disorders in ADHD. No association with the D₂R genotype was detected, but a significant, positive gene-gene interaction effect between A_{2A}R and D₂R on the presence of anxiety disorders was noted [233]. This synergistic effect between the A_{2A}R and D₂R genes suggests that A_{2A}R-D₂R heteromers could be explored as a possible target in the treatment of ADHD.

11. PET Imaging of Adenosine–Dopamine Interactions

Positron emission tomography (PET) is a minimally invasive imaging technique that allows quantitative assessment of the interaction of radioactive ligands with receptors, enzymes, or transporters in the living brain. Since PET makes it possible to study such interactions repeatedly in experimental animals and humans, this imaging modality may be employed to acquire information about adenosine–dopamine interactions in the healthy human brain, their alterations in disease, and the impact of treatment. Radioligands for adenosine A_{2A} and dopamine D₂ receptors are currently available (see Tables 1 and 2, and [234–238] for an overview). However, until now the number of PET studies aiming to demonstrate A_{2A}/D₂ interactions have been very limited.

Based on findings acquired with other techniques and reported in the literature, three classes of PET studies concerning adenosine–dopamine interactions appear possible:

Table 1. Overview of ligands for positron emission tomography (PET) imaging of A_{2A} receptors.

Ligand (Alphabetic Order)	Animal Study		Human Study	Comments
	Animal Model	Reference		
[¹¹ C]CSC	Rodent	[239]		
DMPX analogues	Rodent	[240]		
[¹⁸ F]FDA-PP ₁ [¹⁸ F]FDA-PP ₂				Agonists, no in vivo data [241]
[¹⁸ F]FESCH (=[¹⁸ F]MRS5425)	Rodent	[242–245]		
[¹¹ C]Istradefylline (=[¹¹ C]KW6002)	Rodent	[246,247]	[247]	Extrastriatal off-target binding
[¹¹ C]KF17837	Rodent Monkey	[248–250] [251]		High non-specific binding
[¹¹ C]TMSX (=[¹¹ C]KF18446)	Rodent	[252–257]	[257–270]	
[¹¹ C]KF21213	Rodent	[271]		
[¹⁸ F]MNI-444	Monkey	[272,273]	[274]	
[¹¹ C]Preladenant	Rodent Monkey	[275–278] [279]	[280,281]	
[¹¹ C]SCH442416	Rodent Monkey	[282,283] [282,284]	[285,286]	

CSC = 8-(3-Chlorostyryl)caffeine, DMPX = 3,7-Dimethyl-1-propargylxanthine, TMSX = [7-methyl-11C]-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine. Other compounds are numbered by the producing institutions or pharmaceutical companies.

Table 2. Overview of ligands for positron emission tomography (PET) imaging of dopamine D_{2/3} receptors.

Ligand (Alphabetic Order)	Rodent, Pig or Cat Study	Monkey or Baboon Study	Human Study	Comments
[¹⁸ F]Benperidol		[287,288]		
[¹⁸ F]DMFP	[289–291]		[292,293]	Longer half-life than [¹¹ C]raclopride
N-Ethyl-[¹¹ C]-eticlopride		[294]		
[¹¹ C]Fallypride		[295]	[296]	
[¹⁸ F]Fallypride	[291,297–299]	[297,300–304]	[305–311]	High-affinity, visualizes also extrastriatal D ₂ R, numerous studies *
[¹⁸ F]FCP		[312]		
[¹⁸ F]FEBF	[313]			
[¹⁸ F]FESP	[314,315]	[314–316]	[314,317]	
[¹¹ C]FLB457	[318]	[319,320]	[296,321–328]	High-affinity, visualizes also extrastriatal D ₂ R, numerous studies *
[¹¹ C]FLB524		[329]	[329]	
5-[¹⁸ F]FPE		[330]		

Table 2. Cont.

Ligand (Alpha-Betic Order)	Rodent, Pig or Cat Study	Monkey or Baboon Study	Human Study	Comments
[¹⁸ F]FPSP	[315,331]	[315,331]	[331]	
[¹⁸ F]Haloperidol	[332,333]	[334]		Binds also to sigmaR
[¹⁸ F]MABN	[335]	[336]		
[¹⁸ F]MBP	[335]	[312,336]		Binds also to rho1
Methyl-[¹¹ C]-eticlopride		[294]		
[¹¹ C]MNPA	[337]	[338,339]	[340]	Agonist ligand
[¹¹ C]Nemonapride	[341–343]			Binds also to sigmaR
[¹¹ C]NMSP	[341,344,345]		[346–349]	
[¹⁸ F]NMSP	[350]	[336,350]	[351]	
[¹¹ C]NPA	[352,353]	[352,354,355]	[356–358]	Agonist ligand
[¹¹ C]PPHT	[359,360]	[359]		Agonist ligand
[¹¹ C]Raclopride	[361,362]	[363–367]	[368–379]	Moderate affinity, visualizes mainly striatal D ₂ R, numerous studies *
[¹⁸ F]Spiperone		[287]		
[¹¹ C]SV-III-130		[380]		Partial agonist ligand
[¹¹ C]ZYY339	[359,360]	[359]		Agonist ligand

* Only a small selection of the available publications is cited for this radioligand. DMFP = Desmethoxyfallypride, FCP = Fluoroclobo-pride, FEBF = Fluorethyl-2,3-dihydrobenzofuran, FESP = Fluoroethyl- spiperone, FPE = Fluoropropyl-epidepride, FPSP = Fluoropropyl-spiperone, MABN = 2,3-dimethoxy-N-[9-(4-fluorobenzyl) -9-azabicyclo[3.3.1]nonan-3beta-yl]benzamide, MBP = 2,3-dimethoxy-N-[1-(4-fluorobenzyl)piperidin4yl]benzamide, MNPA = Methoxy-N-n-propylnorapomorphine, NMSP = N-methyl-spiperone, NPA = N-n-propylnorapomorphine, PPHT = (+/-)-2-(N-phenethyl-N-propyl)amino-5-hydroxytetralin. Other compounds are numbered by the producing institutions or pharmaceutical companies.

11.1. Pharmacological Challenge Studies

In these studies, subjects are scanned twice with a radioligand for adenosine A_{2A}R or dopamine D₂R, first at baseline (or after administration of a placebo) and then at follow-up, after a pharmacological challenge with a drug that binds to the other receptor system (a dopaminergic drug in the case of A_{2A}R imaging, and a purinergic drug in the case of D₂R imaging). Three investigations that used PET imaging have shown that this experimental set-up allows the detection of adenosine–dopamine interactions in the brain of living mammals.

In the first study [242], the radiotracer [¹⁸F]MRS5425, an analogue of the A_{2A}R antagonist SCH442416, was used to image A_{2A}R in the brain of rats that had been unilaterally lesioned with 6-hydroxydopamine. In this animal model of Parkinson's disease, the authors observed an increased binding of the tracer in the ipsilateral (lesioned) striatum with respect to the contralateral (healthy) striatum. The increase of [¹⁸F]MRS5425 in the lesioned hemisphere suggests that loss of dopaminergic neurons can cause upregulation of postsynaptic D₂ and A_{2A} receptors, and binding of the PET ligand [¹⁸F]MRS5425 may be used as a biomarker to monitor Parkinson's disease. Some animals were subsequently treated with the dopamine D₂R agonist, quinpirole. A significant (15–20%) decrease of the striatal uptake of [¹⁸F]MRS5425 was observed after acute administration of quinpirole. The decreased binding of the A_{2A}R ligand after a dopaminergic challenge indicates that interactions between D₂R and A_{2A}R can be monitored in living animals with PET [242].

In the second study [381], healthy human subjects with low levels of daily caffeine intake received oral caffeine (300 mg) and the impact of this challenge on the dopaminergic system was assessed by measuring changes of the binding of [¹¹C]raclopride to D₂R in

the brain. A small but significant increase in the binding potential of [^{11}C]raclopride was detected in the putamen and ventral striatum (5 to 6%), but not in the caudate nucleus. The rise in the ventral striatum was associated with an increase of alertness caused by caffeine [381]. In an earlier study, which involved administration of 200 mg of oral caffeine to eight human subjects with higher levels of daily caffeine intake, a trend towards increased [^{11}C]raclopride binding in the ventral striatum was also noted, but this did not reach statistical significance [382].

In the third study (which was performed in our own institution), anesthetized healthy rats received either the $A_{2A}R$ agonist CGS21680 (1 mg/kg, i.p.), the $A_{2A}R$ antagonist istradefylline (1 mg/kg, i.p.) or vehicle (saline) and the impact of these challenges on the dopaminergic system was assessed by PET imaging, using full kinetic modeling of the cerebral uptake of the radioligand [^{11}C]raclopride. Significant decreases of [^{11}C]raclopride binding potential were detected, which were strong (>50%) after intraperitoneal administration of CGS21680 and moderate (30%) after administration of istradefylline [383].

However, these studies also highlighted the complexity of interactions in the living brain and difficulties in pinpointing the exact mechanisms underlying the observed changes. Altered binding potentials in PET imaging may indicate: (i) An altered size of the total receptor population (i.e., altered expression of the receptor gene). (ii) An altered affinity of existing receptors for the radioligand (which may be due to allosteric receptor–receptor interactions within heteromeric complexes). Both $A_{2A}R$ agonists (like CGS21680) and $A_{2A}R$ antagonists (like istradefylline) can allosterically decrease the affinity of the D_2R protomer for agonists and antagonists [41,129]. (iii) Increases or decreases of the fraction of internalized receptors (since, in most cases only receptors on the cell surface will bind the radioligand). The adenosine $A_{2A}R$ agonist CGS21680 promotes the recruitment of β -arrestin2 to the D_2R protomers in an A_{2A}/D_2 heteromer complex and causes subsequent co-internalization of A_{2A} and D_2 receptors [84,88], a process in which caveolin-1 is involved [87]. (iv) Increases or decreases of the extracellular concentration of the endogenous neurotransmitter or neuromodulator (which competes with the radioligand for binding to a limited number of receptor sites). Selective adenosine $A_{2A}R$ antagonists may increase the release of dopamine [384] and may also inhibit the enzyme monoamine oxidase B and thus raise the levels of extracellular dopamine [385]. The first mechanism (altered gene expression) is unlikely as an explanation for the observed changes of [^{11}C]raclopride binding potential, since the PET studies employed an acute drug challenge and measured radioligand binding shortly after the challenge. The increased binding potential of [^{11}C]raclopride that was noticed in the ventral striatum after administration of caffeine cannot reflect a decrease of extracellular dopamine, since increased alertness was noticed under these conditions. Increased alertness is normally related to augmented release of dopamine in the striatum, whereas reductions of extracellular dopamine are accompanied by increased tiredness and sleepiness [381]. Thus, the increase of [^{11}C]raclopride binding after caffeine intake may reflect an altered affinity of D_2R for the radioligand or a reduced internalization of D_2R in the presence of caffeine.

The PET studies mentioned above [242,381–383] indicate that adenosine–dopamine receptor interactions can be visualized and quantified in the brain of living mammals, but various mechanisms or a combination of mechanisms may be involved and may cause the observed changes.

Other PET studies have indicated that antagonistic effects between adenosine A_{2A} and dopamine D_2 receptors at the MSNs of the striatum occur at physiological levels of receptor occupancy in the living brain. The D_2R antagonist haloperidol is widely used as an antipsychotic, but can induce extrapyramidal symptoms (i.e., movement disorders, such as catalepsy (rigidity, muscle stiffness, fixed posture)). In non-human primates, the duration of the cataleptic posture induced by haloperidol (0.03 mg/kg, i.m.) was reduced when animals were treated with the $A_{2A}R$ antagonist ASP5854 (0.1 mg/kg, oral). A PET study with the $A_{2A}R$ ligand [^{11}C]SCH442416 showed that the anti-cataleptic effect of ASP5854 (0.1 mg/kg, oral) was reached at an $A_{2A}R$ occupancy of 85% [284].

In Parkinson's patients treated with dopaminergic medication (and rodents with 6-OHDA induced hemiparkinsonism), A_{2A}R were found to be upregulated if dyskinesia was present, but not when dyskinesia was absent [56,262,278,285]. This finding indicates that adenosine–dopamine interactions are clinically relevant and A_{2A}R antagonists may be applied as therapeutic drugs [386].

11.2. Studies with Bivalent Radioligands

As discussed above, PET imaging with a suitable radioligand for adenosine A_{2A} or dopamine D₂ receptors may be used to gain information on adenosine–dopamine interactions. Changes of radioligand binding to one protomer after a pharmacological challenge to the other protomer can be monitored with PET. The magnitude of these changes may be proportional to the relative abundance of A_{2A}/D₂R heterotetramers and/or the strength of the A_{2A}R–D₂R interaction, which could be altered by disease or after a successful treatment.

Another approach to visualize and quantify A_{2A}R/D₂R heterotetramers is the use of radiolabeled bivalent ligands for PET imaging, so-called “bivalent probes”. In early attempts to target receptor homodimers, the orthosteric sites of two homodimer partners were bridged by a ligand consisting of two identical pharmacophores connected by a short linker. A similar approach could be tried to target heteromers. The two receptor partners in a heteromer may be bridged by a ligand consisting of two different pharmacophores (appropriately designed for each individual heteromer partner) connected via a short spacer. In this way, the ligand can bind simultaneously to two GPCR receptors if these receptors are closely together (i.e., within a receptor heteromer). A successful bivalent ligand will bind more avidly (with 10–100 fold greater affinity) to the appropriate receptor heteromer than to the isolated receptor monomers or homodimers.

Some experience with bivalent ligands has been acquired by pharmacochemists. In the past, virtually all therapeutic drugs were designed to target a single protein. The discovery of heteromeric receptors has led to a new interest in the development of mixed action drugs for combination therapies, or drugs which selectively bind to receptor heteromers [138,387]. A heterobivalent ligand combining D₂R agonism with A_{2A}R antagonism could be an effective antiparkinsonian drug and might also be radiolabeled for PET imaging of A_{2A}R/D₂R heteromers [388]. The potential of such mixed-actions drugs has been demonstrated in the opioid system, where successful bivalent analgesics combining μ -agonism with δ -antagonism have been developed [389,390].

The synthesis of A_{2A} antagonist-D₂ agonist heterobivalent drugs was first reported in 2009 [391]. The spacer in these drugs was based on trifunctional amino acids that were combined with PEG-polyamide unit repeats. Various bivalent ligands were constituted by connecting the A_{2A}R antagonist 8-(p-carboxymethoxy)phenyl-1,3 dipropylxanthine (XCC) and the D₂R agonist (+/-)-2-(N-phenethyl-N-propyl)amino-5-hydroxytetralin (PPHT-NH₂) via a Lys-Lys-[PEG/polyamide]*n*-Lys-Glu (*n* = 0–7) linker (Figure 3). In competition radioligand binding experiments using striatal membranes, it was shown that these bivalent ligands could displace specific A_{2A}R and D₂R radioligand binding. The bivalent compounds displaced the specific monovalent ligands [³H]-ZM241385 and [³H]-YM09151-2 only when both A_{2A} and D₂ receptors were expressed in cells. Such displacement could also be observed in striatal tissue, indicating the presence of A_{2A}/D₂ receptor heteromers. This suggests that heterobivalent ligands could potentially serve as PET probes for A_{2A}/D₂ receptor heteromers in native tissues and as pharmacological tools to investigate the properties of A_{2A}R-D₂R heterotetramers. They could also pave the way for the design of heteromer-selective drugs for the treatment of Parkinson's disease.

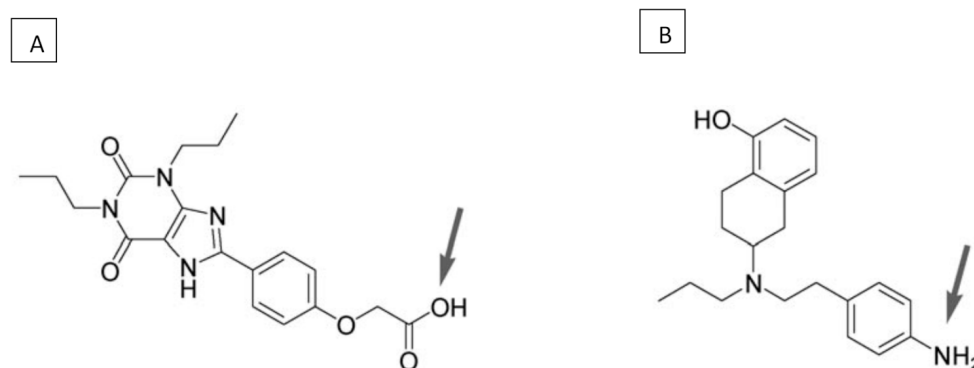


Figure 3. Chemical structures of the A_{2A} antagonist XCC (A) and the D_2 agonist PPHT-NH₂ (B). By attaching a linker to the atomic positions indicated by the arrowheads, a bivalent ligand for $A_{2A}R/D_2R$ heteromers can be created [392].

The distance between the ligand pharmacophores should correspond to the distance of the two binding sites in the receptor heteromer. Thus, the pharmacophore units should be connected with a linker of the appropriate length. Docking experiments predicted that a linker of 26 atoms allows two pharmacophore moieties to bind to the A_{2A}/D_2 heteromer complex. The points of attachment of the linker to the pharmacophore units are another crucial aspect of bivalent ligand design. During the development of a bivalent ligand with $A_{2A}R$ antagonist and D_2R agonist action, it was found that the [COOH] position of the adenosine antagonist XCC and the N-terminal position of dopamine D_2R agonist were most suitable for the attachment of a linker [391]. Another difficulty in the design of bivalent ligands is the fact that the attachment of a linker and a spacer generally results in a reduction in affinity of each pharmacophore for its target. Even if the lead compounds of bivalent ligands have target affinities in the low nanomolar range, the fused ligand with its spacer may have a too low affinity for successful PET imaging [392]. Lead compounds with very high affinities may be required for the design of a successful bivalent probe for PET imaging.

Bivalent ligands also face challenges concerning CNS uptake, metabolism, and excretion. CNS drugs and radioligands for CNS imaging must cross the blood–brain barrier (BBB) in order to be effective. The ability of compounds to penetrate the BBB by passive diffusion is guided by a number of molecular properties: Topological polar surface area (tPSA) should be $<90 \text{ \AA}^2$, hydrogen bond donors (HBDs) < 3 , $c\text{Log } P = 2\text{--}5$, and the molecular weight $<450 \text{ Da}$ [393]. Although some properties of bivalent and heterobivalent drugs may not satisfy these criteria, they may still cross the BBB. The serotonin receptor agonist sumatriptan has a molecular weight of 721 Da (i.e., greater than 450 Da), yet it crosses the BBB and is a successful therapeutic drug [392]. Thus, although the design of a bivalent $A_{2A}R/D_2R$ ligand remains a serious challenge, the problems may be overcome.

Another approach to development of bivalent $A_{2A}R$ - D_2R ligands has been described in the literature [394]. This approach resulted in a new compound, DP-L-A2AANT, that was prepared by amide conjugation of dopamine (DP) to an A_{2A} antagonist (A2AANT) via a succinic spacer (L) (Figure 4). The spacer was bound to the amine group of A2AANT. The fusion compound showed a high $A_{2A}R$ affinity ($K_i 2.07 \pm 0.23 \text{ nM}$ in rat striatum). Although the drug did not exhibit a high affinity towards D_2R and cannot be considered as a suitable candidate for labeling with a positron emitter for PET imaging, it could be a lead compound for the development of antiparkinsonian drugs and PET tracers. Administration of DP-L-A2AANT led to a release of L-A2AANT and dopamine that could be detected in heparinized human whole blood after one and two hours, and DP-L could be detected after 8 h. The bivalent drug may allow prolonged delivery of small amounts of dopamine which are associated with little neuronal toxicity and limited side effects compared to conventional dopaminergic treatments, especially since succinic acid is known to have low toxicity in humans [394].

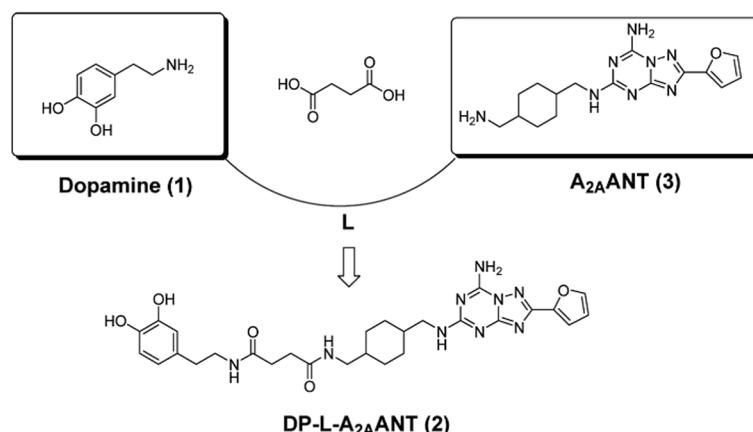


Figure 4. Conjugation of dopamine with the A_{2A} antagonist 7-amino-5-(aminomethyl)-cyclohexylmethyl-amino-2-(2-furyl)-1,2,4-triazolo[1,5-a]-1,3,5-triazine trifluoroacetate via a succinate spacer, to obtain the prodrug DP-L-A_{2A}ANT, a bivalent ligand [394].

The potent A_{2A}R antagonist ZM 241385 and the D₂R agonist ropinirole are considered to have favorable properties for the design of bivalent therapeutic drugs. These classic ligands were used in 2015 to synthesize a novel series of compounds [395] (Figure 5). A cyclic linker between the A_{2A} and D₂ pharmacophores could be used to increase the structural rigidity of a bivalent ligand. Generally, triazine-linker based members of the family showed a 4-fold decrease in A_{2A} inhibitory potency compared to the parent A_{2A}R antagonist and maintained their functional potency towards the D₂R. Non-cyclic dual acting ligands showed a 28- to 54-fold reduction in their A_{2A}R inhibitory potency. Many of the developed compounds passed preliminary BBB permeability tests. However, the in vivo brain uptake kinetics of these dual acting ligands should still be determined [395].

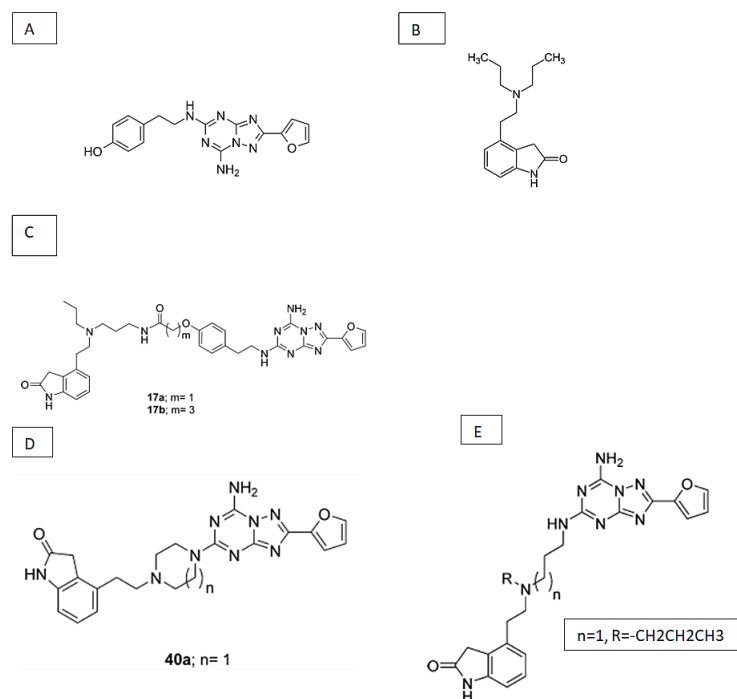


Figure 5. Conjugation of the adenosine A_{2A}R antagonist ZM241385 (A) and the dopamine D₂ agonist ropinirole (B) to form a heterobivalent ligand (C). Dual action drugs can be prepared by using cyclic (D) or non-cyclic (E) spacers, and the latter may contain an ionizable tertiary amine [395].

In conclusion, although the development of bivalent radioligands for PET imaging of A_{2A}R/D₂R heterotetramers will be a major challenge, the design of such compounds may prove to be possible.

11.3. Studies with Radiolabeled Heteromer-Specific Allosteric Modulators

Experiments in which the impact of homocysteine on A_{2A}R-D₂R heteromers was examined have suggested that heteromer-specific allosteric modulators may exist [131,220,396,397]. In CHO cells that express both A_{2A}R and D₂R, homocysteine reduces the internalization of A_{2A}R-D₂R complexes after stimulation of the D₂R [396]. Homocysteine was shown to form a non-covalent complex with an arginine-rich epitope involved in heteromer formation but did not disrupt or prevent the formation of A_{2A}R-D₂R heteromers in co-transfected HEK cells [396]. In striatal astrocytes, homocysteine reduces the D₂R-mediated inhibition of glutamate release but does not affect the A_{2A}R-mediated antagonism of this D₂R effect [397]. These data have been interpreted as evidence that homocysteine binds to A_{2A}R-D₂R heteromers and modulates the allosteric energy transmission between A_{2A}R and D₂R in a heteromer complex [220].

Labeling homocysteine with a positron emitter is definitely not a viable strategy to develop a heteromer-specific radioligand for PET imaging, but if other substances can be identified which bind to specific pockets in the A_{2A}R-D₂R interface within a heteromer without disrupting or preventing heteromer formation, such substances could be used as lead compounds to develop heteromer-specific imaging agents or therapeutic drugs.

11.4. Other Opportunities for PET Imaging

PET may not only be used to visualize and quantify A_{2A}R-D₂R heterotetramers or to determine the strength of receptor-receptor interactions within heteromeric complexes, but also to assess the physiological consequences of pharmacological targeting of A_{2A}R-D₂R heteromers. Regional changes of cerebral glucose metabolism after administration of a heterobivalent drug may be measured with the PET tracer [¹⁸F]fluorodeoxyglucose (FDG), and regional changes of cerebral perfusion can be measured with flow tracers and PET or single photon emission computed tomography (SPECT), or with functional magnetic resonance imaging (fMRI). In animal models of Parkinson's disease, A_{2A}R antagonists have been found to not only improve motor function, but also to be neuroprotective [398–403]. The neuroprotective actions of such drugs, drug combinations or heterobivalent drugs may be assessed with PET imaging (e.g., by visualizing dopaminergic nerve endings with dopamine transporter ligands such as [¹¹C]PE2I or [¹⁸F]-FE-PE2I, or by visualizing neuroinflammation with radiolabeled TSPO ligands, in longitudinal studies. An exciting final possibility is to compare changes of the binding of a radioligand for presynaptic A_{2A} receptors, such as [¹¹C]SCH442416, with changes of the binding of a radioligand for postsynaptic A_{2A} receptors in disease models (although [¹¹C]KW6002 = istradefylline is probably not ideal for this purpose).

12. Conclusions

Understanding the complexities of A_{2A}/D₂ interactions is important in unravelling basal ganglia physiology. Initial observation of antagonistic interactions between adenosine and dopamine in membrane preparations, intact cells and living animals was followed by proof of direct interactions between A_{2A} and D₂ receptors supplied by various biophysical techniques and demonstration of the molecular mechanisms involved in these protein-protein interactions. Such biochemical and biophysical findings facilitated further studies of basal ganglia disorders.

Several neurodegenerative and neuropsychiatric disorders are associated with a dysregulation of corticostriatal and nigrostriatal afferents that leads to aberrant neurotransmission. Membrane interactions between adenosine A_{2A}R and dopamine D₂R are an important aspect of striatal function and appear to be altered in Parkinson's disease, schizophrenia, substance abuse, and ADHD. A_{2A}R and D₂R have been proposed as therapeutic targets.

Decreasing A_{2A} signaling by selective A_{2A} antagonists may result in a recovery of GPe activity in Parkinson's disease, thereby reinstating the thalamocortical motor stimulatory activity. A_{2A} agonists, either alone or in combination with D₂R antagonists, have been proposed for the treatment of schizophrenia. Such combination treatments reduce over-activity of the D₂R protomer in the A_{2A}/D₂ receptor complex. Drugs that are known to increase the levels of extracellular adenosine (such as nucleoside transport inhibitors, inhibitors of purine degradation and antipsychotics increasing the activity of the enzyme 5'-nucleotidase) may be used as a replacement for A_{2A} agonists in A_{2A}R-D₂R based combination therapies. Stimulation of A_{2A}R has also been postulated as a possible strategy to treat substance abuse, in particular addiction to cocaine. A_{2A}R antagonists, on the other hand, could have a beneficial effect in combination therapies for ADHD. Thus, heteromers of A_{2A}R and D₂R are potential targets for the treatment of several human disorders.

PET imaging may provide significant *in vivo* information that leads to greater understanding of the role of A_{2A}R/D₂R heteromers in the physiology of the healthy and diseased brain. PET studies with radioligands for A_{2A}R or D₂R before and after a pharmacological challenge to the other protomer in the A_{2A}R-D₂R complex may be used to assess the strength of A_{2A}/D₂ receptor interactions. Bivalent ligands that bind simultaneously to A_{2A} and D₂ receptors if the receptor proteins are at close proximity may be used as molecular probes to assess the regional abundance of A_{2A}R-D₂R heteromers. The physiological consequences of pharmacological targeting of A_{2A}R-D₂R heteromers in patients can be assessed by PET imaging with tracers visualizing cerebral energy metabolism, cerebral perfusion, neuroinflammation, or dopamine transporter expression.

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Abbreviations

A2AR	Adenosine A2A receptor
ADHD	Attention deficit hyperactivity disorder
AlphaScreen	Amplified luminescent proximity homogeneous assay screen (based on luminescent oxygen channeling immunoassay)
BBB	Blood–brain barrier
BHT-920	5,6,7,8-Tetrahydro-6-(2-propen-1-yl)-4H-thiazolo[4,5-d]azepin-2-amine dihydrochloride
BiFC	Bimolecular fluorescence complementation
BRET	Bioluminescence resonance energy transfer
CGS21680	2-[p-(2-carboxyethyl)phenethylamino]-5'-N-ethylcarboxamido-adenosine
CNS	Central nervous system
CSC	8-(3-Chlorostyryl)caffeine
D2R	Dopamine D2 receptor
DMFP	Desmethoxyfallypride
DMPX	3,7-Dimethyl-1-propargylxanthine
FCP	Fluoroclebopride
FEBF	Fluorethyl-2,3-dihydrobenzofuran
FESP	Fluoroethyl-spiperone
FPE	Fluoropropyl-epidepride

FPSP	Fluoropropyl-spiperone
FRET	Fluorescence resonance energy transfer
MABN	2,3-dimethoxy-N-[9-(4-fluorobenzyl)-9-azabicyclo[3.3.1]nonan-3beta-yl]benzamide
MBP	2,3-dimethoxy-N-[1-(4-fluorobenzyl)piperidin-4-yl]benzamide
MNPA	Methoxy-N-n-propylnorapomorphine
MSN	Medium spiny neuron
MECA	5'-(N-methyl)carboxamido-adenosine
NECA	5'-(N-ethyl)carboxamido-adenosine
NMSP	N-methyl-spiperone
NPA	N-n-propylnorapomorphine
PANNS	Positive and Negative Syndrome Scale
PIA	N6-R-phenylisopropyladenosine
PPHT	(+/-)-2-(N-phenethyl-N-propyl)amino-5-hydroxytetralin
TMSX	[7-methyl- ¹¹ C]-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine
XCC	8-(p-carboxymethoxy)phenyl-1,3 dipropylxanthine

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