Adenosine Receptor Ligands and PET Imaging of the CNS

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Contents

Abstract Advances in radiotracer chemistry have resulted in the development of novel molecular imaging probes for adenosine receptors (ARs). With the availability of these molecules, the function of ARs in human pathophysiology as well as the safety and efficacy of approaches to the different AR targets can now be determined. Molecular imaging is a rapidly growing field of research that allows the identification of molecular targets and functional processes in vivo. It is therefore gaining increasing interest as a tool in drug development because it permits the process of evaluating promising therapeutic targets to be stratified. Further, molecular imaging has the potential to evolve into a useful diagnostic tool, particularly for neurological and psychiatric disorders. This chapter focuses on currently available AR

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ligands that are suitable for molecular neuroimaging and describes first applications in healthy subjects and patients using positron emission tomography (PET).

Keywords Adenosine receptors · Brain disorders · Drug development · Molecular imaging · Positron emission tomography · Radioligands · Radiosynthesis

Abbreviations

AMP	Adenosine monophosphate
AR	Adenosine receptor
A_1AR	A_1 adenosine receptor
A_{2A}AR	A_{2A} adenosine receptor
A_{2B}AR	A_{2B} adenosine receptor
A_3AR	A_3 adenosine receptor
AD	Alzheimer's disease
BS–DMPX	(*E*)-8-(3-Bromostyryl)-3,7-dimethyl-1-propargylxanthine
Bq	Becquerel
CNS	Central nervous system
CPFPX	8-Cyclopentyl-3-(3-fluoropropyl)-1-propylxanthine
CSC	(*E*)-8-Chlorostyryl-1,3,7-trimethylxanthine (8-chlorostyrylcaffeine)
D_2R	Dopamine D_2 receptor
DMPX	3,7-Dimethyl-1-propylxanthine
DPCPX	8-Cyclopentyl-1,3-dipropylxanthine
ED_{50}	50% Efficient dose
EPDX	2-Ethyl-8-dicyclopropylmethyl-3-propylxanthine
FDG	2-Deoxy-2-fluoro-D-glucose
[^{18}F]FE@SUPPY	5-(2-[^{18}F]fluoroethyl)-2,4-diethyl-3-(ethylsulfanylcarbonyl)-6-phenylpyridine-5-carboxylate
FR194921	2-(1-Methyl-4-piperidinyl)-6-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-3(2*H*)-pyridazinone
IS–DMPX	(*E*)-3,7-Dimethyl-8-(3-iodostyryl)-1-propargylxanthine
keV	Kiloelectron volt
KF15372	8-Dicyclopropylmethyl-1,3-dipropylxanthine
MPDX	8-Dicyclopropylmethyl-1-methyl-3-propylxanthine
KF17837	(*E*)-8-(3,4-Dimethoxystyryl)-1,3-dipropyl-7-methylxanthine
KF18446 (TMSX)	(*E*)-8-(3,4,5-Trimethoxystyryl)-1,3,7-trimethylxanthine
KF19631	(*E*)-1,3-Diallyl-7-methyl-8-(3,4,5-trimethoxystyryl) xanthine

KF21213	(*E*)-8-(2,3-Dimethyl-4-methoxystyryl)-1,3, 7-trimethylxanthine
KF21652	3-[1-(6,7-Dimethoxyquinazolin-4-yl)piperidin-4-yl]-1, 6-dimethyl-2, 4(*1H*, *3H*)-quinazolinedione
KW-6002 (istradefylline)	(*E*)1,3-Diethyl-8-(3,4-dimethoxystyryl)-7-methylxanthine
PET	Positron emission tomography
PD	Parkinson's disease
SCH442416	5-Amino-7-(3-(4-methoxyphenyl)propyl)-2-(2-furyl)-pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine
SCH 58261	7-(2-Phenylethyl)-5-amino-2-(2-furyl)-pyrazolo [4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine
SPECT	Single-photon emission computed tomography
SUV	Standard uptake value
Sv	Sievert

1 Introduction

Adenosine contributes to many physiological processes, particularly in excitable tissues such as the heart and brain. In the brain, adenosine acts as a neuromodulator and seems to have an inhibitory net effect on neuronal tissue (Dunwiddie and Masino 2001). It participates in the autoregulation of cerebral blood flow (Berne et al. 1981; Dirnagl et al. 1994), functions as a retrograde synaptic messenger (Brundege and Dunwiddie 1997), and is involved in the induction and maintenance of sleep and the regulation of arousal (Elmenhorst et al. 2007b; Porkka-Heiskanen 1999; Portas et al. 1997). Given the broad range of adenosine involvement in physiological and pathophysiological processes, numerous agonists and antagonists of adenosine receptors (ARs) are presently under evaluation in order to explore their therapeutic and diagnostic potential.

Molecular imaging is a means to get access to these processes in vivo in the human body. It will, therefore, aid in stratifying the process of evaluating promising therapeutic compounds from bench to market, and it has also the potential to evolve into a useful diagnostic tool of adenosine-related diseases, particularly, neurodegenerative disorders [e.g., Parkinson's disease (PD) and Alzheimer's disease (AD)], and brain pathologies including epilepsy, ischemia, and sleep disorders (Jacobson and Gao 2006). This chapter will primarily focus on AR-related ligands suitable for molecular neuroimaging, and their research and clinical applications using positron emission tomography (PET).

Adenosine exerts its physiological actions through four subtypes of G-protein-coupled receptor ARs (A_1, A_{2A}, A_{2B}, and A_3) (Fredholm et al. 1997, 2001; Olah and Stiles 2000). The A_1 adenosine receptor (A_1AR) is densely and heterogeneously expressed in the brain. High densities occur in thalamus and basal ganglia, as well as in neocortical and allocortical regions. A_1AR density is low in cerebellum,

midbrain, and brain stem (Chaudhuri et al. 1998; Deckert et al. 1998; Fastbom et al. 1986; Glass et al. 1996; Schindler et al. 2001; Svenningsson et al. 1997). Pre- and postsynaptic A_1ARs mediate the depressant, sedative, and anticonvulsant effects of cerebral adenosine. A_1ARs are involved in the pathology of seizure disorders (Franklin et al. 1989; Moraidis and Bingmann 1994) and are reduced in cerebral inflammatory diseases (Johnston et al. 2001). In AD there are reports of regional losses of A_1AR binding sites (Deckert et al. 1998; Jaarsma et al. 1991; Schubert et al. 2001; Ulas et al. 1993) and local increases of A_1AR immunoreactivity (Albasanz et al. 2008; Angulo et al. 2003), which could reflect a specific regional and stage-related pattern of cerebral A_1AR involvement in AD. Therefore, evidence is accumulating that cerebral A_1ARs are potential targets for diagnostic imaging and therapeutic interventions in these diseases (Abbracchio and Cattabeni 1999; Fukumitsu et al. 2008; Ribeiro et al. 2003; Schubert et al. 1997).

The interaction and coexpression of A_{2A} adenosine receptors (A_{2A}ARs) and D_2 dopamine receptors (D_2Rs) in medium-sized cells of the striatum have drawn attention to the therapeutic potentials of A_{2A}AR antagonists. Treatment with these compounds alleviates symptoms in PD and seems to decelerate the neurodegenerative process (Xu et al. 2005). Given the importance of A_1ARs and A_{2A}ARs in brain physiology and pathology, they were the first AR subtypes to be successfully visualized in the human brain in vivo (Bauer et al. 2003; Fukumitsu et al. 2003, 2005; Ishiwata et al. 2005a; Mishina et al. 2007).

Adenosine A_{2B} receptors (A_{2B}ARs) and A_3 receptors (A_3ARs) seem to be primarily activated under pathological conditions, such as ischemia and various types of cancer. For both AR subtypes, there is currently no radiotracer that has successfully been applied in the human brain.

Molecular imaging methods, such as PET and single-photon emission computed tomography (SPECT), are characterized by a high sensitivity that allows the visualization of receptors of neurotransmitters and neuromodulators (e.g., adenosine; i.e., ARs) in vivo with excellent temporal and reasonable spatial resolution, respectively. PET is based on the imaging of radiopharmaceuticals labeled with positron-emitting radionuclides such as ^{11}C, ^{15}O, and ^{18}F, and on measuring the annihilation radiation using a coincidence technique. Two 511 keV γ-rays are emitted at ∼180° as a result of the collision between a positron emitted from a radionuclide and a nearby electron. The two 511 keV γ-rays are detected by external coincidence circuits. Importantly, the nanomolar amount of mass for the radionuclide that is injected intravenously is too small to affect the steady state of the biochemical process under investigation. Therefore, the advantage of PET is its ability to measure low-density binding sites without perturbing the biochemistry of the system. Besides, PET can determine the pharmacokinetics of labeled drugs and assess the effects of drugs on metabolism in vivo in a quantitative manner. Because only very low amounts of the radiolabeled drug have to be administered (far below toxicity levels) human studies can be carried out even before the drug is entered in Phase I clinical trials. Such studies can provide cost-effective predictive toxicology data and information on the metabolism and mode of action of drugs. Especially valuable is the contribution of PET to bridge the gap between molecular biology/pathophysiology and the design

of new drugs. Regarding ARs, there are several reports of successful visualizations of A_1ARs, A_{2A}ARs (in humans and different animal species), and recently A_3ARs (in the rat) using PET, which clearly demonstrate the feasibility of these powerful modalities to further enhance the role of radiotracer studies in drug-effect monitoring. However, so far, all of these applications are of an experimental nature and have not yet reached the arena of clinical diagnostic use.

This chapter provides an overview of the current status regarding the development of both PET radioligands for mapping ARs and new lead compounds for potential PET radioligands. It also summarizes preclinical and clinical results that have so far been obtained by molecular imaging of ARs.

2 Development of PET Radioligands

For the last two decades, ARs have been extensively studied biologically and pharmacologically, and advancements in the synthesis and screening of a large number of compounds have resulted in the identification of selective ligands with high affinity and high specific binding for each receptor subtype. Since 1995, several PET ligands with xanthine-type structures, which are expected to penetrate the blood–brain barrier, have been proposed for mapping A_1ARs (Furuta et al. 1996; Holschbach et al. 1998; Ishiwata et al. 1995; Noguchi et al. 1997) and A_{2A}ARs (Hirani et al. 2001; Ishiwata et al. 1996, 2000a, b, d, 2003a; Marian et al. 1999; Noguchi et al. 1998; Stone-Elander et al. 1997; Wang et al. 2000) in the central nervous system (CNS). Later, nonxanthine-type ligands were also developed (Matsuya et al. 2005; Todde et al. 2000). Among them, at least five PET ligands for A_1AR and A_{2A}AR subtypes have been applied to clinical studies (Fig. 1) (Bauer

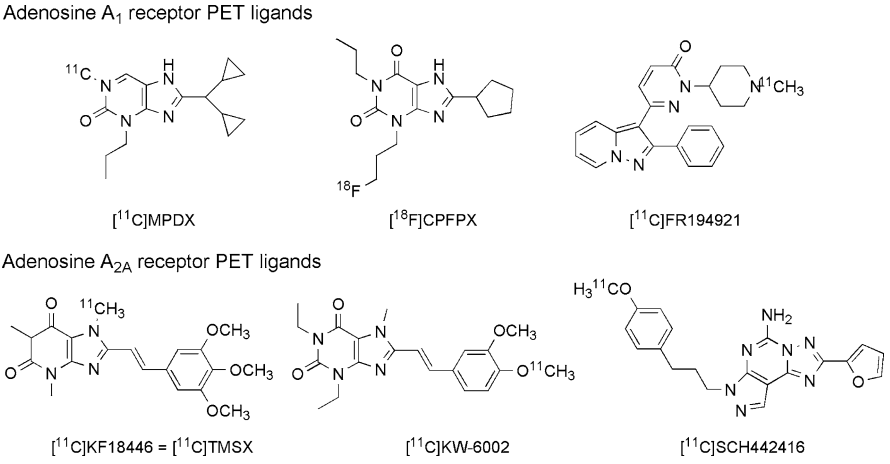

Fig. 1 Representative PET ligands for mapping adenosine A_1 receptors (A_1ARs) and adenosine A_{2A} receptors (A_{2A}ARs). All ligands except for [^{11}C]FR194921 have been used clinically, but only preliminary results have been published for [^{11}C]SCH442416

et al. 2003; Fukumitsu et al. 2003; Hunter 2006; Ishiwata et al. 2005a). On the other hand, PET ligands for the A_3AR subtype (Wadsak et al. 2008) and the adenosine uptake site (Ishiwata et al. 2001; Mathews et al. 2005) are limited, and no PET ligand for the A_{2B}AR subtype has been reported until now. Early works on the development of PET ligands have been described (Holschbach and Olsson 2002; Ishiwata et al. 2002c; Suzuki and Ishiwata 1998), and recent advances in the development of PET ligands and medicinal chemistry, including candidates for this purpose, have been reviewed (Ishiwata et al. 2008).

2.1 Adenosine A_1 Receptor Ligands

In Table 1, in vitro and in vivo properties of A_1AR PET ligands are summarized. Xanthine derivatives such as 8-dicyclopropylmethyl-1,3-dipropylxanthine (KF15372) (Shimada et al. 1991; Suzuki et al. 1992) and 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) (Bruns et al. 1987; Lohse et al. 1987) are selected as leading compounds for PET ligands. [^{3}H]DPCPX has been used in vitro as a radioligand with high affinity and selectivity for the A_1AR (Deckert et al. 1998; Jaarsma et al. 1991; Svenningsson et al. 1997; Ulas et al. 1993). Both compounds have two propyl groups, each of which can potentially be labeled with ^{11}C (half-life of 20.4 min). Ishiwata et al. prepared [^{11}C]KF15372 and its [^{11}C]ethyl and [^{11}C]methyl derivatives (2-[^{11}C]ethyl-8-dicyclopropylmethyl-3-propylxanthine ([^{11}C]EPDX) and 8-dicyclopropylmethyl-1-[^{11}C]methyl-3-propylxanthine ([^{11}C]MPDX), respectively) (Furuta et al. 1996; Ishiwata et al. 1995; Noguchi et al. 1997). [^{11}C]MPDX (Fig. 1) showed a slightly lower affinity for A_1ARs than [^{11}C]KF15372; however, [^{11}C]MPDX was selected for further investigations among the three ligands because of a high radiochemical yield and easy penetration through the blood–brain barrier. Later, Holschbach et al. examined a series of DPCPX analogs and found several candidates containing fluorine or iodine (Holschbach et al. 1998). The selected ligand was [^{18}F]8-cyclopentyl-3-(3-fluoropropyl)-1-propylxanthine ([^{18}F]CPFPX) (Fig. 1) (^{18}F, half-life of 110 min), in which a [^{18}F]fluoropropyl group was incorporated into DPCPX instead of ^{11}C labeling a propyl group (Holschbach et al. 2002). This substitution greatly enhanced the affinity and selectivity for A_1ARs. Radioiodine-labeled ligands may be used for PET (^{124}I, half-life of 4.18 days) and SPECT (^{123}I, half-life of 13.3 h). Recently, nonxanthine-type pyrazolpyridine compounds were proposed for A_1AR ligands (Kuroda et al. 2001; Maemoto et al. 2004), and Matsuya et al. prepared [^{11}C]2-(1-methyl-4-piperidinyl)-6-(2-phenylpyrazolo [1,5-*a*]pyridin-3-yl)-3(2*H*)-pyridazinone ([^{11}C]FR194921) (Fig. 1) (Matsuya et al. 2005).

Among five ligands, [^{18}F]CPFPX shows the highest affinity and selectivity in vitro as well as high uptake and specific binding in vivo (Table 1). In mice, the brain uptake was rapid and remained constant for 40 min after injection, followed by a gradual decrease because of high affinity, suggesting that a long PET scan covering

Table 1 PET ligands for the A_1 adenosine receptor (A_1AR)

	In vitro studies				In vivo studies		
	Affinity (K_i nM)		Selectivity		Uptake[a] (cerebral		
	A_1	A_{2A}	A_{2A}/A_1	Reference	cortex) (SUV)	Specific binding[b] (%)	Reference
DPCPX	6.4	590	92	Shimada et al. (1991); Suzuki et al. (1992)			
[^{11}C]KF15372	3.0	430	143	Shimada et al. (1991); Suzuki et al. (1992)	0.43 (m, 15 min)	57 (m, 15 min)[d]	Noguchi et al. (1997)
[^{11}C]EPDX	1.7	>100	>59	Noguchi et al. (1997)	0.66 (m, 15 min)	47 (m, 15 min)[d]	Noguchi et al. (1997)
[^{11}C]MPDX	4.2	>100	>24	Noguchi et al. (1997)	0.54 (m, 15 min)	43 (m, 15 min)[d]	Noguchi et al. (1997)
						61–64 (r, 15 min)[e, c]	Wang et al. (2003)
[^{18}F]CPFPX	0.183			Holschbach et al. (1998)			
	0.63–1.37 (K_d)	812–940 (K_d)	>700	Holschbach et al. (2002)	0.88 (m, 40 min)	70–80 (m, 10–40 min)[e,f]	Holschbach et al. (2002)
[^{11}C]FR194921	2.91	>100	>34	Matsuya et al. (2005); Maemoto et al. (2004)	0.3 (r, 30 min)	50 (r, 30 min)[e]	Matsuya et al. (2005)

[a]Uptake was normalized as the standardized uptake value [SUV, (tissue activity/total injected activity) × (gram body weight/gram tissue weight)], assuming the body weights of rats and mice were 300 g and 35 g, respectively. In the parentheses, "r" and "m" express the uptakes in the brain of rats and mice, respectively, which were killed at the indicated time after injection of the tracer. The tissue uptake was measured by the tissue dissection method, except in one case (marked by [c]), where it was measured by ex vivo autoradiography

[b]The reduced percentages of the uptake by blockade with injection of selective appropriate adenosine A_1 receptor ligand together with the tracer[d] or before[e] or after[f] injection of the tracer

the pseudoequilibrium state of the ligand–receptor binding may be preferable. The other ligands showed reasonable brain uptake and specific binding due to the affinity in vitro and the liphophilicity.

Xanthine derivatives are unstable in relation to peripheral metabolism. Percentages of the unchanged form in rodent plasma were <30% for both [^{11}C]MPDX and [^{18}F]CPFPX 30 min postinjection, whereas [^{11}C]FR194921 was much more stable (87% at 60 min) (Bier et al. 2006; Matsuya et al. 2005; Noguchi et al. 1997). The metabolic pathway of [^{18}F]CPFPX was extensively investigated (Bier et al. 2006), and Matusch et al. (2006) identified that cytochrome P-450 1A2 catalyzed the metabolism of it. Later [^{11}C]MPDX was confirmed to be much more stable in human plasma (75% was unchanged at 60 min) (Fukumitsu et al. 2005), while [^{18}F]CPFPX was metabolized faster in humans (Bauer et al. 2003).

However, the evaluation of PET ligands at a single or a limited number of time points after injection, as shown in Table 1, was not adequate when comparing several ligands. Dynamic PET studies in monkeys or cats were carried out for [^{11}C]KF15372 (Wakabayashi et al. 2000), [^{11}C]MPDX (Ishiwata et al. 2002a; Shimada et al. 2002) and [^{11}C]FR194921 (Matsuya et al. 2005). Although [^{11}C]KF15372 and [^{11}C]FR194921 have similar affinities in vitro, the brain kinetics were considerably different in monkeys. [^{11}C]KF15372 accumulated and reached a maximum at 10 min followed by a gradual decrease, while [^{11}C]FR194921 accumulated over 60 min. In the time frame of a PET scan using a ^{11}C-labeled tracer (60–90 min), [^{11}C]KF15372 showed preferable brain kinetics for quantitative evaluation of the ligand–receptor binding, while the affinity of [^{11}C]FR194921 may be too high. Compared with [^{11}C]KF15372, [^{11}C]MPDX showed a faster brain clearance in monkeys and cats, but quantitative evaluation of A_1ARs in the cat brain was nevertheless successfully performed by PET.

The other radioligands labeled with positron emitters are 5′-*N*-(2-[^{18}F]fluoroethyl)-carboxamidoadenosine and 5′-(methyl[^{75}Se]seleno)-N^6-cyclopentyladenosine (^{75}Se, half-life of 7.1 h) (Lehel et al. 2000; Blum et al. 2004). Although the biological evaluation of these tracers has not been reported, they may be suitable ligands for peripheral organs but not for the CNS, if available for PET studies; however, 5′-*N*-(2-[^{18}F]fluoroethyl)-carboxamidoadenosine may not be a selective ligand for A_1ARs (Lehel et al. 2000).

2.2 *Adenosine A_{2A} Receptor Ligands*

Considering 3,7-dimethyl-1-propylxanthine (DMPX) as a lead for A_{2A}AR-selective antagonists (Seale et al. 1988), Shimada et al. have discovered that xanthines with the styryl group in the 8 position have selective A_{2A}AR antagonistic properties (Nonaka et al. 1994; Shimada et al. 1992). Later, Müller et al. also introduced brominated and chlorinated styryl groups in the 8 position of DMPX to produce A_{2A}AR-selectivity (Müller et al. 1997, 1998). The representative compound (*E*)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine (KF17837) has been used for pharmacological and neurochemical studies as a selective antagonist for

A_{2A}ARs (Correa et al. 2004; Hayaishi 1999; Koga et al. 2000). So far KF17837 and seven other derivatives have been labeled with ^{11}C, and these radiotracers were investigated as potential PET ligands (Ishiwata et al. 1996, 2000a, b; Noguchi et al. 1998; Stone-Elander et al. 1997; Wang et al. 2000) (Table 2). [^{11}C](*E*)-8-(3-Bromostyryl)-3,7-dimethyl-1-propargylxanthine ([^{11}C]BS-DMPX) and [^{11}C](*E*)-3,7-dimethyl-8-(3-iodostyryl)-1-propargylxanthine ([^{11}C]IS-DMPX) (Ishiwata et al. 2000d) can potentially be labeled with radiolabeled bromines (^{75}Br, $t_{1/2} = 1.7$ h or ^{76}Br, $t_{1/2} = 16.1$ h) and iodines (^{124}I, half-life of 4.18 days, and ^{123}I, half-life of 13.3 h), respectively, for PET or SPECT. Most of these studies were done by Ishiwata et al. in collaboration with Kyowa Hakko Kogyo Co., Ltd. (Tokyo, Japan). Later, Kyowa Hakko Kogyo chose the selective A_{2A}AR antagonist (*E*)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methylxanthine (KW-6002), known as istradefylline, for clinical evaluation as an antiPD agent (Bara-Jimenez et al. 2003; Hauser et al. 2003) after an experimental study of [^{11}C]KW-6002 (Fig. 1) (Hirani et al. 2001). It was noted that photoisomerization occurred in the styryl group at the 8 positions of xanthine-type A_2AR-selective ligands such as (*E*)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine ([^{11}C]KF18446), later designated [^{11}C]TMSX) (Fig. 1) (Ishiwata et al. 2003b; Nonaka et al. 1993). Consequently, all procedures in PET studies were carried out under dim light until injection and also during plasma metabolite analysis.

Besides xanthine derivatives, a number of nonxanthine heterocycles have also been synthesized as A_{2A}AR antagonists. 7-(2-Phenylethyl)-5-amino-2-(2-furyl)-pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (SCH 58261) is a representative ligand with a high and selective affinity for the A_2AR (Zocchi et al. 1996a, b); however, it does not have an appropriate synthon for labeling with positron emitters. Todde et al. used 5-amino-7-(3-(4-methoxyphenyl)propyl)-2-(2-furyl)-pyrazolo [4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (SCH442416) with its 4-methoxyphenylpropyl group, and prepared [^{11}C]SCH442416 (Fig. 1) by *O*-[^{11}C]methylation (Todde et al. 2000).

Table 2 summarizes the in vitro and in vivo properties of A_{2A}AR PET ligands. The highest affinity for A_{2A}ARs was found in SCH442416, followed by KF17837, KW-6002, and (*E*)-8-(2,3-dimethyl-4-methoxystyryl)-1,3,7-trimethylxanthine (KF21213). SCH442416, KF21213 and IS–DMPX showed superior A_{2A}AR selectivity. (*E*)-1,3-Diallyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthine (KF19631), TMSX, (*E*)-8-chlorostyryl)-1,3,7-trimethylxanthine (8-chlorostyrylcaffeine, CSC), and BS–DMPX showed moderate selectivity, but their affinities for the A_1ARs were too low to bind in vivo. In evaluation studies in rodents, all radioligands showed A_2AR-selective uptake in the striatum where the expression of A_{2A}ARs is high; however, specific binding was also observed in the cerebral cortex as well as cerebellum to a certain extent for most radioligands except for [^{11}C]KF21213. Thus, the highest A_{2A}AR selectivity in vivo was observed in [^{11}C]KF21213, followed by [^{11}C]SCH442416 and [^{11}C]TMSX, when evaluated based on the uptake ratio of receptor-rich striatum to receptor-poor cerebellum.

Compared with A_1AR receptor ligands, a slow peripheral degradation of two xanthine compounds was confirmed in the metabolite analysis in plasma;

Table 2 PET ligands for the A_{2A} adenosine receptor ($A_{2A}AR$)

	In vitro studies				In vivo studies			
	Affinity (K_i)		Selectivity		Striatal uptake[a]	Selectivity[b]		
	A_1	A_{2A}	A_1/A_{2A}	References	(SUV)	(Str/Cer)	Specific binding[c] (%)	References
DMPX	12,000	8,600	1.4	Shimada et al. (1991); Suzuki et al. (1992)				
[^{11}C]KF17837	62	1.0	62	Nonaka et al. (1994)	0.82(m, 15 min)	2.0 (m, 60 min) 1.2 (r, 15 min)[d]	43 (m, 15)[e]	Noguchi et al. (1998)
[^{11}C]KF19631	860	3.5	250	Ishiwata et al. (2002c)	0.33 (m, 15 min)	1.2 (m, 60 min) 1.2 (r, 15 min)[d]	31 (m, 15)[e]	Ishiwata et al. (2000a)
[^{11}C]KF18446 = [^{11}C]TMSX	1,600	5.9	270	Ishiwata et al. (2000a)	1.54 (m, 15 min) 1.68 (r, 15 min)	2.8 (m, 15 min)	72 (m, 15)[e]	Ishiwata et al. (2000a)
[^{11}C]CSC	28,000	54	520	Nonaka et al. (1994)	ND	ND	ND	
[^{11}C]BS–DMPX	2,300	7.7	300	Ishiwata et al. (2000d)	0.90 (m, 15 min)	1.2 (m, 60 min)	51 (m, 15)[e]	Ishiwata et al. (2000d)
[^{11}C]IS–DMPX	>10,000	8.9	>1,100	Ishiwata et al. (2000d)	0.70 (m, 15 min)	1.2 (m, 60 min)	17[ns] (m, 15)[e]	Ishiwata et al. (2000d)
[^{11}C]KF21213	>10,000	3.0	>3,300	Wang et al. (2000)	1.40 (m, 15 min)	10.5 (m, 60 min)	69 (m, 15)[e]	Wang et al. (2000)

[^{11}C]KW-6002	150	2.2	68	Nonaka et al. (1994)	2.9 (r, 15 min)	1.1 (r, 75 min)	88 (r, 75)[f]	Hirani et al. (2001)
SCH-58261	121	2.3	53	Zocchi et al. (1996a)				
[^{11}C]SCH442416	1,800	0.50	3,630	Todde et al. (2000)	1.15 (r, 15 min)	4.6 (r, 15 min)	ND	Todde et al. (2000)
					ca. 1 (r, 15 min)	4.97 (r, 15 min)	31–86 (r, 15)[f]	Moresco et al. (2005)

[a]Uptake was normalized as the standardized uptake value [SUV, (tissue activity/total injected activity) × (gram body weight/gram tissue weight)], assuming the body weights of rats and mice were 300 g and 35 g, respectively. In the parentheses, "r" and "m" express the uptakes in rat and mouse brain, respectively, which were killed at the indicated time after injection of the tracer. The tissue uptake was measured by the tissue dissection method, except in some cases (marked by [d]), where it was measured by ex vivo autoradiography

[b]Selectivity was determined as the uptake ratio of striatum to cerebellum (Str/Cer). This concept is based on the finding that the striatum is rich in A_{2A}ARs, while the expression of A_{2A}ARs is low or negligible in the cerebellum

[c]Reduced percentages of uptake by the blockade with injection of selective appropriate A_{2A}AR ligand together with the tracer[e] or before[f] injection of the tracer

ND, not determined; *ns*, no significance (control versus blocked animals)

percentages of the unchanged form were 81% for [^{11}C]TMSX at 30 min in mice (Ishiwata et al. 2000a) and 66% for [^{11}C]KW-6002 at 45 min in rats (Hirani et al. 2001). [^{11}C]SCH442416 was slightly unstable: 40% was unchanged at 30 min in rats (Todde et al. 2000). Later, [^{11}C]TMSX was confirmed to be much more stable in human plasma (>90% of the unchanged form at 60 min) (Mishina et al. 2007).

Dynamic PET studies in monkeys were carried out for [^{11}C]KF17837, [^{11}C]TMSX and [^{11}C]SCH442416. The striatal uptake of [^{11}C]TMSX was approximately tenfold higher at 5–10 min compared with [^{11}C]KF17837, and the uptake ratios of striatum to cortex and striatum to cerebellum for [^{11}C]TMSX were slightly higher than those for [^{11}C]KF17837 (Ishiwata et al. 2000a). A slightly lower affinity of [^{11}C]TMSX resulted in a faster clearance of the radioligand from the striatum compared to [^{11}C]KF17837. Because it exhibited the highest affinity among the three ligands, [^{11}C]SCH442416 showed more preferable brain kinetics for quantitative evaluating the ligand–receptor binding (Moresco et al. 2005). Although [^{11}C]KF21213 showed the most preferable properties in rodents, in a preliminary PET study using monkeys [^{11}C]TMSX showed better brain kinetics than [^{11}C]KF21213 (Ishiwata et al. 2005b).

Most studies of radioligands have focused on ARs in the CNS. On the other hand, Ishiwata et al. demonstrated that xanthine-type ligands can be applicable to studies on peripheral A_{2A}ARs (Ishiwata et al. 1997, 2003a, 2004). In rodents, specific binding of [^{11}C]TMSX was observed in the muscle and heart. Swimming exercise caused fluctuations in [^{11}C]TMSX-receptor binding in these tissues, and the specific binding of [^{11}C]TMSX to these tissues was also preliminarily demonstrated clinically (Ishiwata et al. 2004). Furthermore, the [^{11}C]TMSX-receptor binding in the cardiac and skeletal muscles was greater in endurance-trained men than in untrained men (Mizuno et al. 2005).

2.3 *Adenosine A_3 Receptor Ligands*

Recently, Wadsak et al. (2008) reported on the synthesis of 5-(2-[^{18}F]fluoroethyl)-2,4-diethyl-3-(ethylsulfanylcarbonyl)-6-phenylpyridine-5-carboxylate ([^{18}F]FE@SUPPY) for the A_3AR and a preliminary evaluation. The tracer was taken up in the rat brain at intermediate levels and bound to rat brain slices in vitro; however, further in vivo studies are essential for the evaluation of its specificity and selectivity.

2.4 *Ligands for the Adenosine Uptake Site*

[1-Methyl-^{11}C]-3-[1-(6,7-dimethoxyquinazolin-4-yl)piperidin-4-yl]-1,6-dimethyl-2,4(*1H*, *3H*)-quinazolinedione ([^{11}C]KF21652), with a K_i value of 13 nM, was prepared by *N*-[^{11}C]methylation (Ishiwata et al. 2001). The brain uptake of [^{11}C]KF21562 was very low in vivo, probably because of its relatively high

lipophilicity (log*P* 3.6), although in vitro autoradiography showed specific binding to adenosine uptake sites to a certain extent (less than 25% of total binding). Peripherally, only the liver showed carrier-saturable uptake. The compound is not a suitable PET ligand.

Another potential labeled tracer for adenosine uptake sites is [^{11}C]adenosine monophosphate ([^{11}C]AMP) (Mathews et al. 2005). In mice, this tracer was not incorporated in the brain, and the highest uptake was observed in the lung, blood, and heart. The lung uptake was significantly reduced to about 40% by blocking with dipyridamole, a ligand for adenosine uptake sites. The putative value of this ligand needs to be investigated further.

2.5 Radiosynthesis

All ^{11}C-labeled ligands except for [^{11}C]AMP have been synthesized by *N*- or *O*-alkylation with [^{11}C]methyl iodide or [^{11}C]alkyl iodide. Practically speaking, the production of [^{11}C]methyl iodide is much easier than those of [^{11}C]ethyl iodide and [^{11}C]propyl iodide, which were used for the syntheses of [^{11}C]EPDX and [^{11}C]KF15372, respectively, and usually achieved high radiochemical yields of the ligands (Noguchi et al. 1997). [^{11}C]Methyl triflate is a highly reactive alternative to [^{11}C]methyl iodide (Kawamura and Ishiwata 2004). [^{11}C]AMP was produced by reacting [^{11}C]formaldehyde with the corresponding amino-imidazolyl-carboxamide, giving a low radiochemical yield (Mathews et al. 2005).

On the other hand, ^{18}F-labeled ligands were prepared by nucleophilic, cryptate-mediated substitution using ^{18}F anion. In general, ^{18}F-labeled ligands have practical advantages: the specific activity is usually higher than that of ^{11}C-labeled ligands, fluorine-18 provides slightly better resolution of the images, and its longer half-life is more suitable for clinical purposes than that of ^{11}C-labeled tracers. On the other hand, ^{11}C-labeled ligands provide reduced radiation doses for human subjects compared to ^{18}F-labeled ligands. Also, the shorter half-life of ^{11}C can allow successive PET measurements experimentally (Nariai et al. 2003) and clinically (Ishiwata et al. 2005a) on the same day.

3 Experimental Studies

Several studies using experimental animals have demonstrated the usefulness of AR ligands and PET. In the rat model, in which monocular enucleation was performed in order to destroy the anterior visual input, a loss of A_1ARs was detected by ex vivo autoradiography using [^{11}C]MPDX (Kiyosawa et al. 2001). The decrease in presynaptic A_1ARs in the superior colliculus following enucleation was coupled with an upregulation of postsynaptic benzodiazepine receptors (Wang et al. 2003). In an occlusion and reperfusion model of the cat, [^{11}C]MPDX PET was more sensitive

to the detection of severe cerebral ischemic insult than [^{11}C]flumazenil PET when measuring central benzodiazepine receptors (Nariai et al. 2003).

In a glioma-bearing rat model, Bauer et al. found that the binding of [^{18}F]CPFPX was increased in the zone surrounding tumors (136–146% as compared to control brain tissue) due to the upregulation of A_1ARs in activated astrocytes (Bauer et al. 2005; Dehnhardt et al. 2007). Furthermore, in a preliminary study, the same group demonstrated A_1AR occupancy by caffeine in the rat brain by [^{18}F]CPFPX PET (Meyer et al. 2003).

In a Huntington's disease model, induced by intrastriatal injection of quinolinic acid and consecutive degeneration of striatopallidal γ-aminobutyric acid/enkephalin neurons, degeneration of A_{2A}ARs in the lesioned striatum was detected to a similar extent as degeneration of D_2Rs using PET and ex vivo and in vitro autoradiography with [^{11}C]TMSX (Ishiwata et al. 2002b). Another A_{2A}AR ligand, [^{11}C]SCH442416, was applied to the same rat model of Huntington's disease (Moresco et al. 2005), demonstrating that the striatal uptake of [^{11}C]SCH442416 was reduced on the quinolinic acid-lesioned side. Furthermore, an ex vivo autoradiography study showed that [^{11}C]TMSX, but not [^{11}C]raclopride for D_2Rs, was incorporated into the globus pallidus to a lesser extent (the striatum-to-globus pallidus uptake ratio was approximately 0.6), and showed a remarkably reduced uptake in both the striatum and globus pallidus for the lesioned side in the rat model of Huntington's disease (Ishiwata et al. 2000c). These findings suggest that [^{11}C]TMSX is a candidate tracer for imaging the pallidal terminals of striatal projection neurons.

4 Clinical Studies

A large number of selective AR agonists and antagonists have been discovered, and some of them have been taken to the next level and evaluated in Phase I, II, and III clinical trials. So far, no compound has received regulatory approval. The same is true of adenosine and AR-based ligands used as PET tracers, which are under evaluation for diagnostic purposes or as markers to evaluate the efficacy of therapeutics.

4.1 Adenosine A_1 Receptor Imaging

To date, two PET ligands have successfully been applied for the visualization of A_1ARs in the human brain, [^{18}F]CPFPX (Bauer et al. 2003) and [^{11}C]MPDX (Fukumitsu et al. 2003, 2005). A direct comparison of postmortem brain material using autoradiography demonstrated a close correlation between the regional [^{18}F]CPFPX binding potential and the cerebral [^{3}H]CPFPX distribution (Bauer et al. 2003). Consistent with results from [^{3}H]CPFPX autoradiography, high A_1AR

densities were found in the putamen and mediodorsal thalamus using [^{18}F]CPFPX PET. Neocortical areas showed regional differences in [^{18}F]CPFPX binding, with high accumulation in temporal > occipital > parietal > frontal lobes and a lower level of binding in the sensorimotor cortex. Ligand accumulation was low in the cerebellum, midbrain, and brain stem (Bauer et al. 2003; Meyer et al. 2004). The specificity of [^{18}F]CPFPX binding was established in a displacement study using cold CPFPX (Meyer et al. 2006).

The clinical applicability of [^{18}F]CPFPX was assured by test–retest (Elmenhorst et al. 2007a) and dosimetrical studies (Herzog et al. 2008), respectively. The dosimetrical studies showed that an injection of 3×10^8 Bq [^{18}F]CPFPX resulted in an effective dose of 5.3×10^{-3} Sv, which is comparable to other ^{18}F-labeled ligands and thus suitable for clinical applications. Test–retest evaluations were performed in order to study the physiological intrasubject variability of [^{18}F]CPFPX binding. This factor is extremely important for the definition of the normal range of cerebral receptor binding and thus highly accountable for the discriminative power of the method as a diagnostic tool. Elmenhorst et al. (2007a) demonstrated that test–retest variability was low (5.9–13.2% on average) and therefore highly suitable for diagnostic purposes. They also showed that noninvasive quantification (i.e., without the need to take blood samples during the PET scan) is even superior to invasive measurements, which greatly improves the clinical applicability of [^{18}F]CPFPX PET. A series of horizontal planes of the cerebral [^{18}F]CPFPX distribution as well as a three-dimensional reconstruction of the neocortical surface of the brain of a healthy subject are depicted in Fig. 2.

The spatial distribution of [^{11}C]MPDX differed significantly from the regional cerebral blood flow measured by PET using [^{15}O]H_2O and the regional cerebral metabolism of glucose evaluated using 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), and was in good agreement with autoradiographic data from other highly specific A_1AR ligands (Fukumitsu et al. 2003). Moreover, this A_1AR radiotracer showed a better metabolic stability than [^{18}F]CPFPX but had a lower affinity to A_1ARs (4.2 nM in comparison to 0.183 nM).

For both tracers, quantitative methods have been developed to measure the A_1AR binding potential in vivo in the human brain (Kimura et al. 2004; Meyer et al. 2005a, b). For clinical applications, noninvasive but fully quantitative methods with significantly shortened scan durations and without blood sampling have been developed (Naganawa et al. 2008; Meyer et al. 2005b).

With respect to the use of AR-based PET tracers in humans to define the role of ARs in neuropathology, only a limited number of clinical studies have been published so far. Boy et al. (2008) reported lower cortical and subcortical A_1AR binding in patients suffering from liver cirrhosis and hepatic encephalopathy in comparison to controls. They concluded that regional cerebral adenosinergic neuromodulation is heterogeneously altered in cirrhotic patients, and that the decrease in cerebral A_1AR binding may further aggravate neurotransmitter imbalance at the synaptic cleft in hepatic encephalopathy.

In a recent study utilizing an A_1AR-based PET tracer, Fukumitsu et al. (2008) reported on changes in A_1ARs in the brains of patients with AD. They applied two

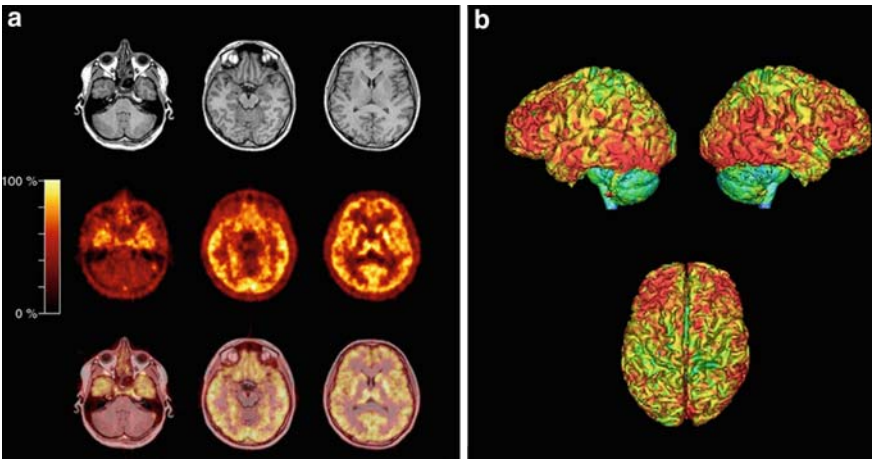

Fig. 2 a–b Distribution of adenosine A_1 receptors (A_1ARs) in the human brain. **a** Serial horizontal MRI (*upper line*) and coregistered PET images (*middle line*) from a healthy subject. Summed data from 5 to 60 min after intravenous injection of [^{18}F]CPFPX are depicted. The fusion images (*bottom line*) show high ligand binding in neocortical areas as well as thalamus and basal ganglia (as indicated by *bright yellow colors*); low binding is found in the cerebellum (depicted by *dark orange colors*). **b** Three-dimensional reconstruction of the brain surface generated from serial planes from the same PET scan as in **a**. Note that A_1ARs are ubiquitously but not homogeneously distributed in the neocortex. There are clusters with high A_1AR binding in prefrontal and temporoparietal cortices (high binding is indicated by *red* and *orange colors*, low binding is indicated by *green* and *cyan colors*)

PET scans with [^{11}C]MPDX and [^{18}F]FDG to the same patients to directly compare A_1ARs and glucose metabolism reflecting neural activity in the brain. There was significantly reduced binding of [^{11}C]MPDX in patients with AD in the temporal and medial temporal cortices and in the thalamus. Thus, the regional pattern of A_1AR changes in AD was different from the well known and previously reported hypometabolic brain regions (temporoparietal cortex and posterior cingulate gyrus), where [^{18}F]FDG uptake was typically decreased in AD. This pilot study was the first study to show with the use of a PET tracer for A_1ARs that A_1ARs are reduced in AD. It clearly demonstrates that A_1AR PET ligands could become valuable tools for the investigation of neurodegenerative disorders like AD.

An interesting example of the scientific potential of A_1AR imaging in neuroscience has been published in a study on the effect of sleep deprivation for 24 h on healthy subjects, which shows promise for clinical applications in sleep disorders (Elmenhorst et al. 2007b). It is currently hypothesized that adenosine is involved in the induction of sleep after prolonged wakefulness. This effect is partially reversed by the application of caffeine, which is a nonselective blocker of ARs. Elmenhorst et al. (2007b) report that the A_1AR is upregulated after 24 h of sleep deprivation in a region-specific pattern in a broad spectrum of brain regions, with a maximum increase in the orbitofrontal cortex. There were no changes in the control group, who had regular sleep. Thus, the study provides in vivo evidence for an A_1AR

contribution to the homeostatic regulation of sleep in humans. Molecular imaging using A_1AR ligands therefore shows significant potential for sleep research and, in the long run, sleep medicine.

These findings are also of importance regarding the role of caffeine as a neurostimulant and nonselective antagonist of adenosine effects at A_1ARs and A_{2A}ARs. Throughout the world, caffeine is the most widely used pharmacological agent; it is present in beverages such as coffee, tea, and soft drinks. As a stimulant, caffeine promotes wakefulness and reduces sleep and sleep propensity (Fredholm et al. 1999; Landolt 2008; Schwierin et al. 1996; Virus et al. 1990; Yanik and Radulovacki 1987). Molecular imaging using adenosine tracers has great potential to provide insights into the regional and temporal modes of caffeine action in the human brain. In vivo A_1AR occupancy by caffeine has so far only been demonstrated in the rat brain by [^{18}F]CPFPX PET (Meyer et al. 2003).

4.2 Adenosine A_{2A} Receptor Imaging

With regard to adenosine A_{2A}AR imaging, the most promising clinical application is currently PD. Striatopallidal A_{2A}ARs have been implicated in the modulation of motor functions because they partially antagonize the functions of striatal D_2Rs. Since A_{2A}ARs show a highly enriched distribution in basal ganglia cells and are able to form functional heteromeric complexes with D_2Rs and metabotropic glutamate mGluR5 receptors, A_{2A}ARs are of particular interest with regard to the nondopaminergic modulation of motor behavior (Ferré and Fuxe 1992; Fuxe et al. 1993; Marino et al. 2003). Additional evidence for an adenosinergic contribution to PD comes from epidemiological studies showing that chronic consumption of caffeine, a nonselective AR antagonist, is able to reduce the risk of developing PD (Ascherio et al. 2001; Ross et al. 2000). Given the relevance of A_{2A}ARs in PD, an important advance was made by Ishiwata et al. (2005a), who were able to introduce [^{11}C]TMSX, allowing A_{2A}ARs to be imaged in the living human brain for the first time. The specificity of [^{11}C]TMSX PET was confirmed by theophylline challenge (Ishiwata et al. 2005a), and the cerebral distribution pattern was consistent with previous autoradiographic findings in human postmortem brain. The binding potential was largest in the anterior (1.25) and posterior putamen (1.20), followed by the head of caudate nucleus (1.05) and thalamus (1.03). Low ligand binding was found in the cerebral cortex, particularly in the frontal lobe (0.46). Interestingly, the binding of [^{11}C]TMSX was relatively large in the thalamus in comparison with previous reports for other mammals (Mishina et al. 2007). For clinical purposes, the authors developed a modeling method (Naganawa et al. 2007) and proposed recently a noninvasive method for in vivo receptor quantification (Naganawa et al. 2008). A preliminary application of [^{11}C]TMSX to patients suffering from PD was presented at an international meeting (Mishina et al. 2006). Figure 3 depicts [^{11}C]TMSX PET images of a unilaterally affected patient with early-stage PD and a healthy control subject. [^{11}C]TMSX binding was reduced in the left putamen, which

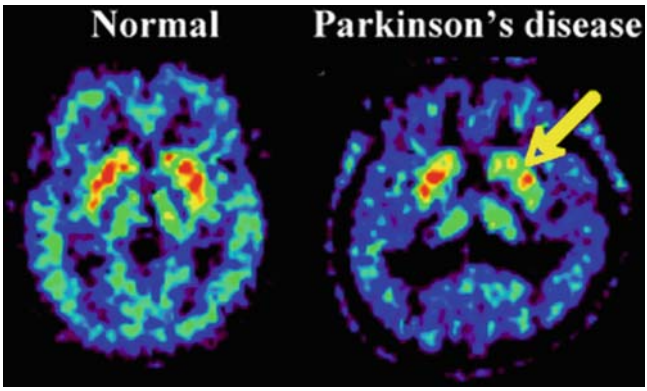

Fig. 3 Distribution of adenosine A_{2A} receptors (A_{2A}ARs) in the human brain: a normal subject (*left*) and a patient with Parkinson's disease (PD) (*right*). The binding potential of [^{11}C]TMSX (Naganawa et al. 2007) in a patient with early-stage PD (*right*) was lower in the putamen of the left hemisphere (*arrow*), which was consistent with more severe clinical symptoms on the right body side. In contrast, the binding of [^{11}C]raclopride to dopamine D_2 receptors (D_2Rs) was slightly increased in the left putamen (Mishina et al. 2006). See text for comments on the findings of this PET study in humans

is contralateral to the primarily affected body side, while binding of [^{11}C]raclopride to D_2Rs was slightly increased. Upregulation of D_2Rs most likely reflects a postsynaptic compensation to impaired presynaptic dopamine release. Simultaneous downregulation of A_{2A}ARs and upregulation of D_2Rs is therefore likely to reflect an imbalance of adenosinergic and dopaminergic transmission at the postsynaptic site as a consequence of PD pathophysiology. This study suggests that PET imaging with A_{2A}AR-selective radiotracer PET ligands may be used to monitor the natural history and progression of PD in both animal models of PD and humans with PD, and may serve as guide for therapy with A_{2A}AR antagonists in patients with PD. Moreover, PET imaging with A_{2A}AR-selective radiotracer PET ligands may be used to stratify patients for recruitment into clinical trials (i.e., patients with early versus later stages of PD), in order to determine the safety and efficacy of A_{2A}AR antagonists in this patient population.

The above mentioned development of the selective A_{2A}AR antagonist istradefylline (KW-6002) as a nondopaminergic drug for PD (Kase et al. 2003) is another good example of the usefulness of PET imaging in the process of drug development. In a study of healthy subjects, seven groups received doses of cold istradefylline ranging from 0 to 40 mg per day for 14 days (Brooks et al. 2008). Thereafter, ^{11}C-labeled istradefylline ([^{11}C]KW-6002) and PET were applied in order to determine the binding potential of [^{11}C]KW-6002. Estimates of the striatal binding potential were used to derive saturation kinetics in the presence of cold KW-6002, assuming that nonspecific binding was constant across subjects and the binding potential was proportional to the concentration of available A_{2A}AR binding sites.

Brain [^{11}C]KW-6002 uptake was well characterized by a two-tissue compartmental model with a blood volume term, and the 50% efficient dose (ED_{50}) of cold KW-6002 was 0.5 mg in the striatum. The study revealed that over 90% receptor occupancy was achieved with daily oral doses of greater than 5 mg.

5 Conclusion

Both basic neuroscience and clinical research have established substantial evidence for an important role of adenosine and its receptors in the pathophysiology of the brain. Molecular in vivo imaging of ARs in the human brain is therefore an attractive means to study the role of adenosine, its receptor subtypes and their alterations under disease conditions in patients suffering from neurologic and psychiatric disorders, sleep disorders, and perhaps drug addiction. The first two high-affinity and subtype-selective AR ligands dedicated for use in PET, [^{18}F]CPFPX and [^{11}C]MPDX permit quantitative measurements of A_1ARs in the living human brain. The clinically important A_{2A}AR has been made accessible through the use of [^{11}C]TMSX and [^{11}C]KW-6002, a radiolabeled drug. Reports on human applications are currently focused on A_1ARs and A_{2A}ARs, reflecting current understanding of their specific implications in cerebral neuropathology and their potential as neuroprotective targets. Regarding A_{2B}ARs and A_3ARs, their relatively low densities and their disease-specific appearance make it more challenging to assess them in vivo. However, given that it is now clear that adenosine plays a greater role in the pathophysiology of neurological and psychiatric disorders than previously thought, and the systematic and intensive search that is now underway for ligands with high affinity and selectivity, the molecular imaging of ARs will become an increasingly important tool in clinically oriented research.

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