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ORIGINAL ARTICLE

Stimulation of adenosine A_1 receptors decreases in vivo dopamine D_1 receptor binding of [^{11}C]SCH23390 in the cat striatum revealed by positron emission tomography

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Abstract It has been previously suggested that activation of adenosine A_1 receptor modulates dopamine D_1 receptor binding in vitro, although the direct mechanism of this interaction in vivo has not yet been demonstrated. Here, we conducted a positron emission tomography (PET) study to demonstrate in vivo the interaction between these receptors. The specific adenosine A_1 receptor agonist N^6-cyclopentyladenosine (CPA) was acutely administered to cats under anesthetized condition. Cats underwent repeated measurement of striatal and cerebellar radioactivity following intravenous injection of dopamine D_1 receptor-specific [^{11}C]SCH23390. The pretreatment with CPA decreased the striatum/cerebellum ratio of the uptake of [^{11}C]SCH23390. Using the cerebellar radioactivity as an input function, kinetic analysis was performed and demonstrated that CPA caused about 40% decrease in the association rate constant. These results suggest that stimulation of adenosine A_1 receptors modulates dopamine D_1 receptor binding in vivo.

Keywords PET · N^6-cyclopentyladenosine · SCH23390 · Receptor · Cat

Introduction

Adenosine plays a role as an endogenous neuromodulator in the central nervous system, and the action is mediated by specific postsynaptic adenosine receptors linked to adenylate cyclase activity [1]. Adenosine receptors have been well characterized and several distinct subtypes have been identified such as A_1, A_{2a}, A_{2b}, and A_3 receptors [2]. A_1 receptors are widely distributed in the hippocampus, dentate gyrus, cerebral cortex, certain thalamic nuclei, caudate-putamen, nucleus accumbens, and granule cell layer of the cerebellum [3], whereas A_{2a} receptors are exclusively localized on postsynaptic areas in the basal ganglia (caudate-putamen, globus pallidus, nucleus accumbens, and olfactory tubercle) [4, 5]. On the other hand, dopamine receptors are richly distributed in the striatum, and are now classified as dopamine D_1-like receptors (D_1 and D_5) and dopamine D_2-like receptors (D_2, D_3, and D_4) [6]. The existence of the postsynaptic interaction between adenosine A_{2a} and dopamine D_2 receptors has been reported using biochemical and behavioral approaches [7–11]. Recent studies have also found evidence for the existence of another specific interaction between adenosine A_1 receptors and dopamine D_1 receptors [12–18]. Although A_1 receptors are more widely distributed in the central nervous system than A_{2a} receptors, in vivo microdialysis and in situ hybridization have revealed that strioentopeduncular neurons are the main locus for A_1–D_1 interaction [12].

The A_1–D_1 interaction in vivo has been suggested by various pharmacological studies [13, 19]; however, little is known concerning the direct mechanism of the in vivo interaction between A_1–D_1 receptors. One approach to demonstrate this is to use the in vivo autoradiographic technique, although this technique requires a lot of animals, is labor intensive, and interanimal variation of data cannot be neglected.

On the other hand, in vivo dopamine D_1 or D_2 receptor mapping in middle-sized animals such as dogs,

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baboons, or monkeys using positron emission tomography (PET) has become available [20–22]. These studies have demonstrated the great potential of PET for investigating in vivo the binding properties of the radioligand to receptors, including the ligand binding kinetics on the basis of a compartment model. In addition, PET enables noninvasive and repetitive dynamic measurement with the use of a minimal number of animals. The effect of neuroleptic or neuropsychotic drugs on the ligand-receptor binding can be evaluated in the same animal, and thus the effect of interanimal variation can be minimized.

Against this background the aim of the present experiment is to demonstrate in vivo the adenosine A_1 receptor-dopamine D_1 receptor interaction in the striatum by repeated PET measurement, using the adenosine A_1 receptor-specific agonist N^6-cyclopentyladenosine (CPA), which modulates in vivo dopamine D_1 receptor-specific [^{11}C]SCH23390 binding in the striatum.

Methods

Materials

[^{11}C]SCH23390 was prepared by ^{11}C-methylation of the desmethyl compound with ^{11}C-methyl iodide [23]. N^6-CPA, an adenosine A_1 receptor agonist, was purchased from Research Biochemical International (RBI, Natick, MA, USA).

Animals

Five male cats (ICO CAT, IFFA CREDO, Lyon, France) of 1–2 years weighing 2.5–3.5 kg were used. The cats were anesthetized by initial induction using ketamine (25–50 mg/kg i.m.) followed by continuous inhalation with isoflurane. During the experiment the isoflurane concentration was kept at 2.0%. The animals were mechanically ventilated to maintain the end-tidal carbon dioxide at approximately 3.0%. The body temperature was kept at 37.0°C with a heating lamp and thermo-controller. These physiological conditions were continuously monitored during the experiment. The anesthetized animal was positioned in a holder made of polyacrylate, a modification of a stereotaxic holder for physiological experiments (Hamamatsu Photonics, Hamamatsu, Japan).

The present animal study was approved by the Animal Care and Use Committee of the National Institute for Longevity Sciences.

PET imaging in cats

Three of the five cats underwent repeated measurements under two conditions, control and CPA treatment. Two of the five cats underwent one measurement in each condition. Totally four measurements on each control an d CPA treatment were carried out. The successive PET scanning was performed as described earlier [24]. Briefly, the SHR-2000 PET camera (Hamamatsu Photonics) was used and provided a set of seven-slice images at 6.5 mm intervals axially, and transaxial image spatial resolution was 3.0 mm full-width at half-maximum [25]. With axial bed motion, 14-slice images at 3.25 mm intervals were obtained. Transmission data were acquired with a rotating ^{68}Ge/^{68}Ga rod source. Subsequently two emission scans were repeated in a day in the same animal at the same position. [^{11}C]SCH 23390 (200–300 MBq) was injected into the cats through a cannula inserted into a forearm vein. Simultaneously, the first emission scan was started (baseline). The second emission scan was started after the radioactivity was negligible. The interval between each scan was approximately 3 h. CPA (1 mg/kg) was intravenously administered 30 min prior to the start of the second scan. Data were dynamically acquired for 64 min (2 min × 32 frames) in which the first 60 min scanning was used for the kinetic analysis.

Data analysis

After the measurement, tomographic images were reconstructed using a Butterworth filter with a cutoff frequency of 144 cycles/cm. To measure the radioactivity in the striatum and the cerebellum, the regions of interest (ROIs) were determined on each slice of the reconstructed images with the aid of the published atlas of the cat brain [26]. Two of the 43 coronal cross-sectional drawings on the atlas including striatal and cerebellar regions, axially 26 mm apart, were selected. The striatal PET image was determined so that 1 of the 14 coronal PET images included bilateral hot spots (each spot was approximately 2–3 mm in diameter), which anatomically corresponded to the striatal region. Although no hot spots were observed in the later phase images (30–60 min after tracer injection), the cerebellar PET image was determined with the aid of early phase images (0–10 min) since the approximate location of the cerebellum can be determined by the whole brain images reflected in the early phase images. The axial distance between the striatal and cerebellar slices thus obtained was 8 slices apart, which showed good agreement with the distance obtained from the brain atlas. Then circular ROIs determined on the atlas were superimposed on the corresponding striatal and cerebellar PET images (see "Results" section).

The PET signal was calibrated to Bq/ml, and the tissue uptake of tracer was evaluated by the differential uptake ratio (DUR) calculated by the following equation:

$$\mathrm{DUR} = \frac{\text{tissue radioactivity (MBq/ml)}}{\text{injected dosage (MBq)/body weight (g)}}$$

From the DUR as a function of time, we obtained a measure of specific binding by using the ratio of striatal to cerebellar uptake. The tissue uptake was calculated as the area under the curve (AUC) by the trapezoidal rule, over a 30–60-min period after the administering of tracer.

The most convenient techniques for quantitative in vivo dopamine receptor binding, at present, are based on a two-parameter compartment model using the cerebellum as an indirect input function [27, 28]. The kinetic parameters were calculated according to the model which can be written by the following equation:

$$\mathrm{d}C_{\mathrm{b}}(t)/\mathrm{d}t = k_3 C_{\mathrm{ce}}(t) - k_4 C_{\mathrm{b}}(t),$$

where C_{b} is the radioactivity of receptor-bound compartment, C_{ce} the radioactivity of free/nonspecific compartment (identical to the cerebellar radioactivity). k_3 is the rate constant from the free/nonspecific ligand to the receptor-bound ligand compartment, which is proportional to the bimolecular association rate (k_{on}) and the number of receptors (B_{max}). k_4 is the rate constant from the receptor-bound ligand compartment to the free/nonspecific ligand compartment, which is equivalent to the dissociation rate from the receptors (k_{off}). The cerebellar uptake was used for the reference of free/nonspecific compartment, and the difference between the striatal uptake and cerebellar uptake was used for the receptor-bound compartment. The optimal values of k_3 and k_4 were obtained by using a non-linear least-squares method.

All analysis procedures were performed on a workstation with an image analysis software Dr.View version 4.0 (Asahi Kasei Joho System, Tokyo, Japan). After the analysis, mean and SD of all data were calculated. The significant difference between the groups was evaluated by Student's t test.

Results

The effect of intravenous injection of CPA (1 mg/kg) on the brain uptake of the dopamine D_1 receptor-specific [^{11}C]SCH 23390 in vivo was evaluated by consecutive PET studies. As shown in Fig. 1, the striatal uptake of [^{11}C]SCH 23390 decreased by the pretreatment with CPA, although no changes were observed in the cerebellar uptake. The ROIs were superimposed on the PET images, and the striatal and cerebellar uptakes were calculated. The time–activity curves of the striatum and cerebellum following intravenous injection of [^{11}C]SCH 23390 were shown in Fig. 2. CPA caused a decrease in the striatal uptake at all times after the injection of the tracer, whereas no significant changes were observed in

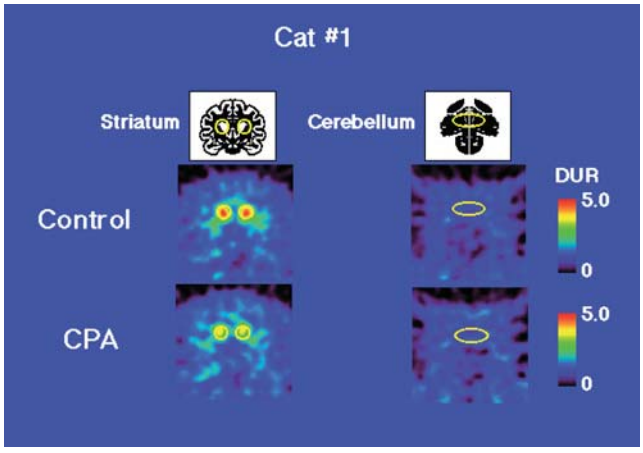

Fig. 1 Regional distribution of [^{11}C]SCH 23390 in the cat brain (average of 30–60 min). The uppermost two cross-sectional drawings including striatal and cerebellar regions, axially 26 mm apart, were selected from the cat brain atlas, and the next *two rows* illustrate positron emission tomography (PET) images at these sites. *Upper row* shows the distribution of [^{11}C]SCH 23390 (control), and *lower row* shows the distribution of [^{11}C]SCH 23390 after the pretreatment with cyclopentyladenosine (CPA, 1 mg/kg i.v.). The tissue uptake was evaluated by the differential uptake ratio (DUR) calculated by the equation described in the text

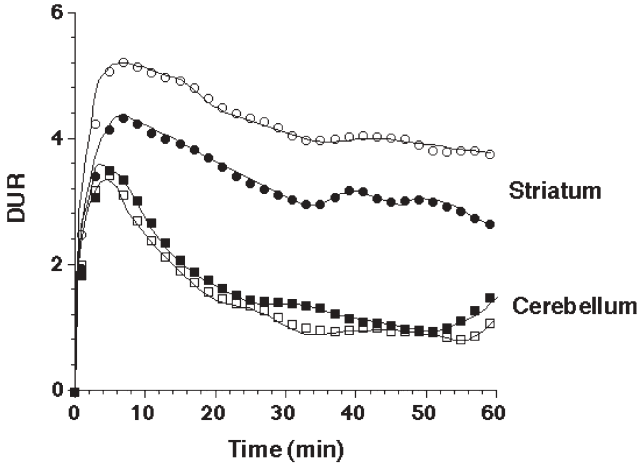

Fig. 2 Time–activity curves of the striatum and cerebellum following intravenous injection with [^{11}C]SCH 23390. All data were obtained from the same cat, according to the regions of interests determined on each slice of the PET images with the aid of the atlas as shown in Fig. 1. *Open symbol*, control; *closed symbol*, CPA treated (1 mg/kg i.v.)

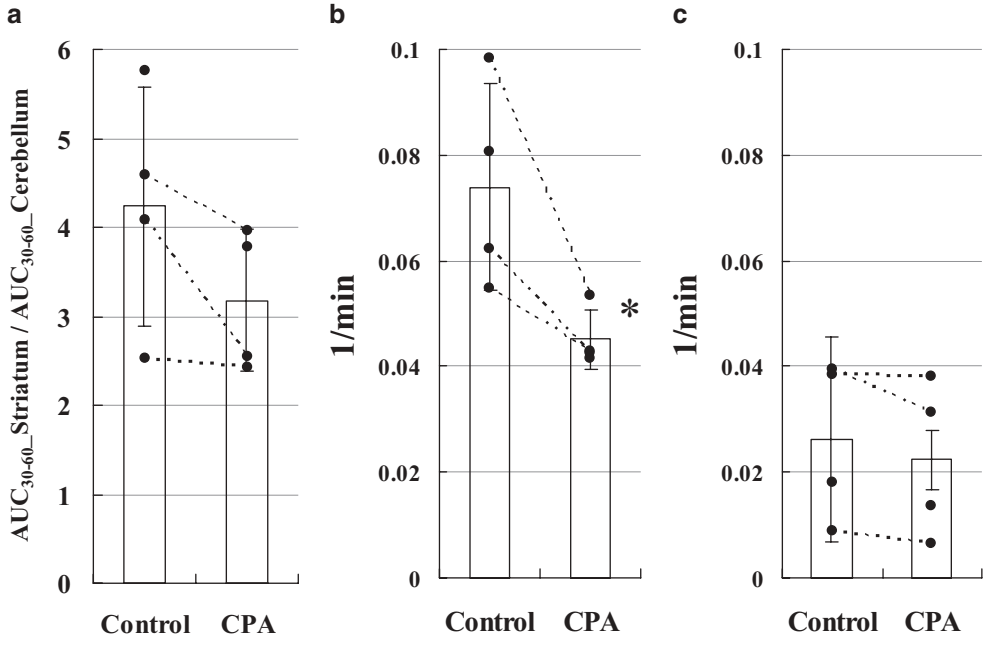

Fig. 3 **a** The ratio of striatal to cerebellar uptake of [^{11}C]SCH 23390 in control and CPA treated groups. Each tissue uptake was calculated as AUC over a 30–60 min period after tracer injection. *Open bar* represents mean ± SD (n = 4) of all observations, and each *dot* denotes individual observation, in which data from the same animal are connected by a *dotted line*. **b** Rate constants k_3, from free/nonspecific ligand to the receptor-bound ligand compartment, calculated according to the two-compartment model as described in the text. **c** Rate constants k_4, from the receptor-bound ligand compartment to the free/nonspecific ligand compartment. Significant differences between control and CPA treated groups were evaluated using Student's t test (*$P < 0.05$)

Table 1 Results of quantitative analyses on each animal

Animals	Treatment	$AUC_{30\,min-60\,min}$ of DUR			Rate constants (min^{-1})	
		Striatum	Cerebellum	Str/cere	k_3	k_4
Cat #1	Control		29.0	4.1	0.098	0.038
	CPA	89.7	35.1	2.6	0.054	0.038
Cat #2	Control	206.9	45.2	4.6	0.055	0.009
	CPA	269.9	68.1	4.0	0.043	0.006
Cat #3	Control	256.4	44.5	5.8	0.081	0.018
Cat #4	CPA	214.5	56.7	3.8	0.042	0.014
Cat #5	Control	193.0	76.4	2.5	0.062	0.040
	CPA	173.6	71.6	2.4	0.042	0.031
Mean	Control	193.7	48.8	4.2	0.074	0.026
	CPA	186.9	57.9	3.2	0.045*	0.022
SD	Control	57.0	19.9	1.3	0.019	0.015
	CPA	75.9	16.5	0.8	0.006	0.015

AUC area under the curve, *DUR* differential uptake ratio, *CPA* cyclopentyladenosine
* $P < 0.05$, significantly different compared with control group by Student's t test

the cerebellar uptake. After the tracer was injected, the striatal uptake decreased by 23% at 45 min. Figure 3 shows the obtained measure of specific binding by the striatum/cerebellum ratio during a 30–60-min period, and the rate constants calculated according to the two-parameter compartment model as described in "Materials and methods" section. CPA caused a decrease in the striatum/cerebellum ratio from 4.2 to 3.2 (24% decrease from control level). The CPA also caused a significant decrease ($P < 0.05$) in k_3 from 0.074 ± 0.019 to 0.045 ± 0.006 1/min (39% decrease from control level). On the other hand, CPA did not cause a significant change in k_4 (from 0.026 ± 0.015 to 0.022 ± 0.015 1/min). The results of quantitative analysis on each animal are summarized in Table 1. The decrease in the striatum/cerebellum ratio as well as k_3 was observed in every individual animal.

A significant decrease in k_3 was observed between control and CPA-treated groups ($P = 0.034$, by Student's t test).

Discussion

The intravenous injection of CPA (1 mg/kg) into cats significantly decreased the striatal uptake of [^{11}C]SCH 23390, whereas no changes were observed in the cerebellar uptake. The specific binding of [^{11}C]SCH 23390, estimated by the striatal uptake minus the cerebellar uptake, was thus decreased by CPA. This decrease in dopamine D_1 receptor binding of [^{11}C]SCH 23390 in the striatum in vivo shows the same tendency as the evidence revealed by in vitro biochemical studies in which CPA decreased the affinity of dopamine D_1 receptors for the specific D_1 antagonist [^{125}I]SCH 23982 in both the nucleus accumbens and medial prefrontal cortex of the rat brain [14]. CGS21680, an adenosine A_2 receptor agonist, also decreased dopamine D2-specific [^{125}I]iodosurpiride binding in vivo [29]. These results suggest that stimulation of adenosine receptors in vivo causes a decrease in the binding characteristics of dopamine receptors in the striatum.

The precise biological mechanism of the in vivo A_1–D_1 interaction remains unclear; however, the mechanism can be speculated from many previous biochemical studies regarding the interaction. Recent in vivo microdialysis, studies have revealed that striatal infusion of CPA counteracts the effect of striatal infusion of D_1 agonist SKF 38393 on the extracellular gamma-aminobutyric acid (GABA) levels of entopeduncular nucleus, together with the result that A_1 receptor mRNA expression could be less than 20% of the striatal neurons containing D_1 receptor mRNA [9]. These receptor subtypes are expected to be colocalized and functionally linked on GABAergic neurons of the striatonigral and strioentopeduncular pathways. Electroneurochemical studies using tissue slices have demonstrated that A_1–D_1 seems to be important in modulating GABA release in limbic regions (ventral pallidum and nucleus accumbens) but not basal ganglia [18]. In mammalian cells stably cotransfected with A_1 receptor and D_1 receptor cDNAs, CPA induced inhibition of dopamine-induced cAMP accumulation [15]. In addition, combined pretreatment with SKF 38393 (D_1 agonist) and R-PIA (A_1 agonist) but not either one alone, reduced the D_1 agonist-induced accumulation of cAMP [17]. A recent study using A_1 knockout mice has revealed modification of glutamatergic and dopaminergic neurotransmission [30]. The molecular basis of this interaction is postulated to be heteromerization on the basis of the receptor subtype specific interactions between the different types of homomers of G protein-coupled receptor (GPCR) [31, 32]. On the basis of this evidence, synergistic A_1–D_1 interaction could take place not only at the level of intramembrane but also at the level of the second messenger.

Recent pharmacological and physiological studies on the A_1–D_1 interaction have found that the interaction regulates various functions, such as oral dyskinesia [13], rotational behavior [33], electroencephalography (EEG) arousal [34], cocaine-seeking behavior [35], antinociception [36], and motor activity but not prepulse inhibition [37] or rapid tolerance to ethanol [38]. These changes are expected to be owing to the changes in in vivo receptor binding demonstrated here, which are essential for the underlying biological mechanism. It remains unclear whether the change in association rate constant (k_3) of [^{11}C]SCH 23390 by acute treatment with CPA is attributable to changes in the bimolecular association rate (k_{on}) as well as the number of receptors (B_{max}), because the present results were obtained by using only tracer amounts of SCH 23390 throughout the experiment. In vivo saturation studies will be needed to clarify whether the change in k_3 is resulting from the change in k_{on} or B_{max}.

Despite the lack of spatial resolution in a PET camera, PET is a prominent tool in that consecutive dynamic measurements can be performed and thus the effect of acute drug treatment can be evaluated in the same animal, a series of dynamic data can be obtained by one scanning, and the kinetic parameters can be assessed using a minimal number of animals. Furthermore, the investigation of in vivo adenosine receptor–dopamine receptor interaction using PET can offer insights into new therapeutic areas for basal ganglia disorders such as Parkinson's disease and Huntington's disease [39–41].

Conclusions

The present studies have demonstrated the in vivo adenosine A_1–dopamine D_1 interactions in the cat brain by means of PET. CPA has altered in vivo kinetics of [^{11}C]SCH 23390-dopamine D_1 receptor binding via stimulation of adenosine A_1 receptors which may functionally interact with dopamine D_1 receptors in the striatum.

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