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ORIGINAL ARTICLE

Vasodilatory effect of adenosine triphosphate does not change cerebral blood flow: a PET study with ^{15}O-water

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Abstract
Objective Adenosine triphosphate (ATP) is the parent compound of adenosine and well known as a powerful vasodilator. To investigate the effect of ATP on cerebral blood flow (CBF) and cerebral vessels, ^{15}O-water positron emission tomography (PET) studies were performed to evaluate changes in CBF and blood volume before and after ATP administration.
Methods Ten healthy young volunteers underwent ^{15}O-water PET scans under the conditions of baseline, 3 and 1 min after ATP continuous infusion. CBF values in cortical regions of the bilateral middle cerebral arteries and basal ganglia were obtained for each subject. Statistical parametric mapping (SPM) was applied for analysis of regional changes. Physiologic parameters, such as blood gas and blood pressure were also measured.
Results Cortical CBF showed no significant change after continuous infusion of ATP compared with the baseline. Dilatation of major vessels induced by ATP was visualized on SPM analysis. Heart rates increased and mean blood pressure decreased during ATP administration while blood gas data showed no changes between the different conditions.
Conclusions Intravenous ATP administration caused dilatation of major cerebral vessels but no significant change in CBF under normoventilation and decrease in systemic blood pressure, indicating that this no change in CBF under vasodilatory effect of ATP may be caused by cerebral microvascular autoregulation.

Keywords ATP · Cerebral blood flow · Vasodilation · Cerebral autoregulation · Statistical parametric mapping

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Introduction

Adenosine triphosphate (ATP) is a well-known vasodilator for the skeletal and myocardial blood vessels [1, 2]. It is the parent compound of adenosine [3], and being widely used for measurement of coronary flow reserve [4]. ATP has a short plasma half-life (<20 s) and is rapidly metabolized to adenosine diphosphate (ADP), followed by adenosine monophosphate (AMP), adenosine and finally allantoin [5]. Adenosine, the metabolic product of ATP, plays a role of maintaining vasodilation in the coronary and skeletal arteries [6], as well as an endogenous vasodilator for the cerebral blood flow (CBF) regulation [7]. This effect may be linked to the stimulation of adenylate cyclase and a subsequent increase in smooth muscle cyclic AMP, which is mediated through an adenosine A2 receptor [8]. The vasodilatory effect of ATP is mainly dependent on its degradation to adenosine, yet the direct stimulation of adenosine receptors by ATP itself was also reported [5].

Intravascular administration of adenosine induced cerebral vasodilation in rabbits and baboons but did not work in cats and dogs [9–13]. In human studies, adenosine

administration increases CBF by cerebral vasodilation under normoventilation [14, 15], which was assumed to be counteracted by hyperventilation [14]. Dipyridamole increases effects of adenosine and causes a significant decrease in CBF, although this effect is considered to be caused by hyperventilation [16]. Adenosine, dipyridamole and ATP are all used as a pharmacologic stressor for myocardial perfusion studies, and ATP is also used for treatment of intracranial diseases, such as aftereffects of head injury and Meniere's disease. To our knowledge, however, it has not been investigated whether intravenous ATP administration provides vasodilation of the human cerebral arteries and causing a change in CBF. The purpose of this study was to investigate effects of the intravenous injection of ATP on CBF as well as the cerebral arteries in human. We studied changes in CBF after ATP administration using positron emission tomography (PET) and ^{15}O-labeled water. The same procedure of ATP administration for examination of coronary flow reserve was applied in this study to evaluate cerebrovascular reaction during myocardial SPECT studies.

Materials and methods

PET procedure

Ten healthy young male volunteers (age range: 20 to 31 years, mean: 24.0 ± 3.7 years) participated in this study. The study received approval of our institutional review board and written informed consent was obtained from all subjects. All subjects were restricted caffeine and other methylxanthine containing foods or beverages for at least 12 h before the study. They underwent ^{15}O-water PET scans with a whole body PET scanner (ADVANCE, GE Medical Systems, Milwaukee, WI, USA), which permits simultaneous acquisition of 35 image slices in a two-dimensional acquisition mode with inter-slice spacing of 4.25 mm [17]. Performance tests showed the intrinsic resolution of the scanner to be 4.6 to 5.7 mm in the trans-axial direction and 4.0 to 5.3 mm in the axial direction. A transmission scan was performed using ^{68}Ge/^{68}Ga for attenuation correction in each subject before tracer administration. PET data were reconstructed using a Hanning filter with 6.0 mm full width at half maximum (FWHM) in the trans-axial direction.

The subjects were positioned properly on the PET table with an arterial line in the right arm and two venous lines in the left arm. A bolus injection of 740 MBq $H_2^{15}O$ was given intravenously from one of the venous lines for each 2-min PET scan. The arterial blood was drawn using a mini pump (Perista mini-pump, Atto, Tokyo, Japan) with a rate of 7 mL/min for the first 90 s, followed by manual sampling of 0.5 mL blood at 90, 105 and 120 s. Radioactivity in the arterial blood drawn by the mini pump was counted continuously using an automatic radioactive counter (Apollo Mec., Kobe, Japan). The arterial radioactivity concentration was calibrated by that of manually obtained arterial blood. Decay of radioactivity from PET and blood data was corrected to the starting point of each scan. Dispersion for the external tube in the arterial radioactivity curve was corrected with a double-exponential dispersion function. CBF images were calculated from the PET data and arterial blood curves by means of the autoradiographic method [18].

Four sequential $H_2^{15}O$-PET scans with 10-min intervals were performed in each subject (Fig. 1). The first and third scans were baseline condition without ATP administration. The second and fourth scans were performed during the continuous injection of ATP using the other venous line different from that for ^{15}O-water administration. The injection rate of ATP was 0.16 mg/kg/min which is a common dose used for myocardial perfusion studies. The ATP injection continued during the 2-min PET scan. Since ATP is administered continuously for 5 min and perfusion tracer is injected at 3 min from the beginning to evaluate flow reserve in myocardial perfusion studies, the second scan was started at 3 min after the beginning of continuous ATP infusion. To evaluate the earlier effect of ATP administration, the fourth scan was started at 1 min after

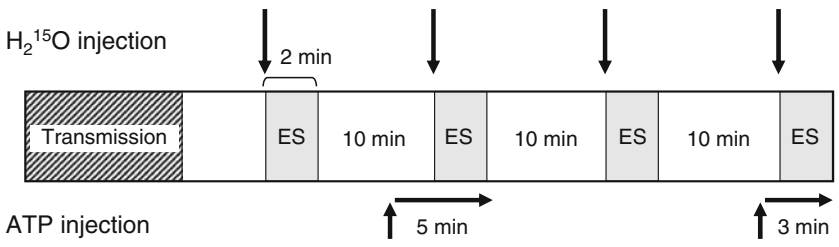

Fig. 1 Diagram of PET scans and timings of $H_2^{15}O$ and ATP injections (*vertical arrows*). Transmission scan was performed for 10 min, followed by four emission scans (ES) with $H_2^{15}O$ injection. At the second scan, ATP injection was started 3 min before the start of emission scan and continued for 5 min (*horizontal arrow*). At the fourth scan, ATP injection was started 1 min before the start of emission scan

the beginning of ATP administration. Several physiologic parameters, such as blood gas (P_aCO_2, P_aO_2), blood pressure and heart rate were also measured.

Data analysis and statistics

Subjects underwent a high-resolution MRI scan (192 slices, 1.6-mm thick, 0.8-mm pitch) using a Signa Excite scanner (3.0T, GE Medical System, Milwaukee, WI). Before drawing regions of interest (ROIs), CBF images were co-registered to the individual MRI image using an automatic procedure [19]. Multiple circular ROIs of 10 mm in diameter were placed in the cortical territories of bilateral middle cerebral arteries using the co-registered individual MRI (12 ROIs/slice $\times$ 5 slices $=$ 60 ROIs). Twelve ROIs in the same size were also placed in the bilateral basal ganglia using two or three corresponding slices. The regional CBF values were averaged for the cortex and the basal ganglia in each subject. Cerebral vascular resistance (CVR) was also calculated by dividing the mean blood pressure (MBP) with CBF (i.e. CVR $=$ MBP/CBF). The MBP was calculated from the equation of MBP $=$ (2DBP $+$ SBP)/2, where DBP and SBP are diastolic and systolic blood pressure, respectively.

Changes in CBF were compared among the four conditions by the repeated measures analysis of variance (ANOVA). Physiologic values of blood pressure, heart rate and CVR were also compared between baseline and post-ATP conditions by the repeated measures ANOVA with a post-hoc paired t test. Because blood gas data were measured only twice at the first baseline and at the end of the second scan with ATP administration, the difference between the two conditions were analyzed by a paired t test. A probability value of <0.05 was considered to indicate a statistically significant difference. Bonferroni correction for multiple comparison was applied to the threshold probability value to keep an overall $\alpha = 0.05$ when testing multiple null hypotheses. The CBF data were also analyzed using statistical parametric mapping (SPM) [20, 21]. Two pairs of baseline and post-ATP conditions were compared with SPM, i.e. the first versus the second conditions and the third and the fourth conditions. In brief, the t test was applied pixel-by-pixel to compare the regional differences in CBF among the different conditions. Comparison was performed between baseline and post-ATP conditions. The t value for each pixel was then converted to a normal standard distribution (z-value), independent of the degree of freedom from error, constituting a statistical parametric map [21]. In the SPM analysis, each CBF image was smoothed using a Gaussian filter (12 mm FWHM) and the pixel values were normalized so that the global mean of CBF should be 50 mL/min/100 g. Analysis of covariance (ANCOVA) was used for evaluation of regional difference [20]. To identify the regions showing significant differences, the height threshold (u) and the extent threshold (k) were set at $p = 0.001$ and $k = 100$, respectively [22].

Results

Table 1 shows the mean of CBF, blood pressure, heart rate and CVR in different conditions in all subjects. Cortical CBF values showed no significant difference even after intravenous ATP administration (54.0 $\pm$ 5.4 and 54.0 $\pm$ 6.1 mL/100 g/min) compared to the baseline condition (56.0 $\pm$ 5.8 and 56.1 $\pm$ 5.4 mL/100 g/min) although the ATP injection tended to induce a slight decrease ($p = 0.743$, repeated measures ANOVA). CBF values in the bilateral basal ganglia regions were 59.0 $\pm$ 4.6 and 57.4 $\pm$ 5.9 at baseline, 58.1 $\pm$ 5.6 and 57.0 $\pm$ 6.2 (mL/100 g/min) at 3 and 1 min

Table 1 Changes in cerebral blood flow and physiological data

Parameters	3 min Post-ATP			1 min Post-ATP		
	Baseline[a]	Post-ATP	p-value*	Baseline[a]	Post-ATP	p-value*
CBF (mL/min/100 g)	56.0 $\pm$ 5.8	54.0 $\pm$ 5.4	ns	56.0 $\pm$ 5.5	54.0 $\pm$ 6.1	ns
MBP (mmHg)	84.3 $\pm$ 5.7	78.8 $\pm$ 6.9	<0.01	84.7 $\pm$ 6.1	79.3 $\pm$ 5.9	<0.005
SBP (mmHg)	122 $\pm$ 11	123 $\pm$ 14	ns	123 $\pm$ 10	123 $\pm$ 11	ns
DBP (mmHg)	65.8 $\pm$ 5.1	56.6 $\pm$ 5.3	<0.001	65.8 $\pm$ 5.6	57.6 $\pm$ 5.2	<0.001
HR (per min)	62.3 $\pm$ 8.5	81.8 $\pm$ 9.1	<0.001	61.7 $\pm$ 7.5	82.3 $\pm$ 11.3	<0.001
CVR	1.54 $\pm$ 0.22	1.48 $\pm$ 0.23	ns	1.52 $\pm$ 0.23	1.48 $\pm$ 0.18	ns

Repeated measures ANOVA applied for four conditions showed significant differences among four conditions in MBP ($p < 0.001$), DBP and HR ($p < 0.0001$)

* p-values were calculated by the post-hoc paired t test

MBP mean blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *CVR* cerebral vascular resistance, *ns* not significant

[a] Baselines are the first scan for 3 min post-ATP and the third scan for 1 min post-ATP

after ATP administration, respectively, and there were no significant difference between the conditions. Regarding the physiologic data, heart rate showed significant increases ($p < 0.0001$), whereas MBP showed significant decreases ($p < 0.001$, repeated measures ANOVA) by 6.5% at 3 min ($p < 0.01$, paired t test) and 6.4% at 1 min ($p < 0.005$, paired t test) after the ATP injection compared to the corresponding baseline. Systolic blood pressure did not change, but diastolic blood pressure significantly decreased after ATP administration ($p < 0.001$, paired t test). No changes in CVR were observed in all conditions (Table 1). P_aCO_2 and P_aO_2 did not show any significant changes between pre- and post-ATP administration (Table 2).

Table 2 Changes in blood gas data before and after ATP injection

Parameter	Baseline	Post-ATP (3 min)	p-value*
P_aCO_2	41.4 ± 3.6	39.2 ± 2.1	0.13
P_aO_2	93.7 ± 9.4	96.1 ± 11.7	0.40

* p-values were calculated by paired t test

The SPM analysis did not show any significant regional changes in CBF in the cortical regions, although significant increases were revealed in the basal regions of the brain after the ATP injection (Fig. 2). No regional decrease was observed by the analysis of baseline minus post-ATP subtraction for both 3 and 1 min after injection. Superimposed slice sections showed that the regional differences

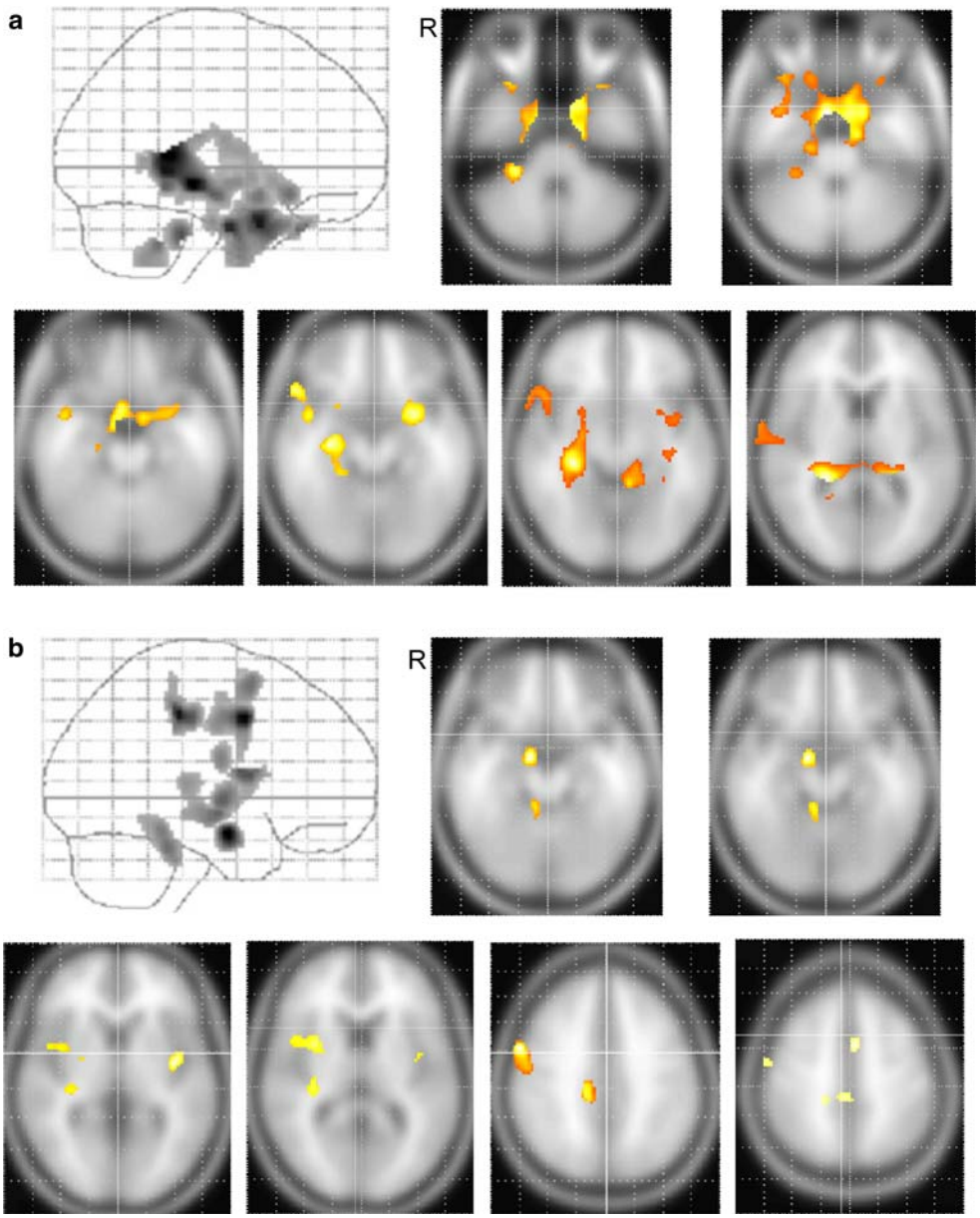

Fig. 2 SPM analysis for regional changes in CBF images with transparent view (*top left*) and overlying on six trans-axial slices. **a** The regions of significant differences between 3 min post-ATP administration and baseline (post-ATP—baseline) correspond to the location of major vessels including the circle of Willis. **b** Similar but lesser differences are demonstrated between 1 min post-ATP and baseline conditions (post-ATP—baseline) representing major vessels compared with the result of 3 min post-ATP. No significant difference was observed from the analysis of baseline—post-ATP. *R* indicates right side of the brain

were corresponding to the major cerebral arteries. Areas of difference were larger at 3 min after continuous ATP administration (Fig. 2a) compared with 1 min post-ATP (Fig. 2b).

Discussion

ATP, the parent compound of adenosine, has been introduced as a pharmacologic stressor for myocardial perfusion studies [4]. In the present study, we tried to evaluate its effects on the human major cerebral vessels and CBF. No increase in cortical CBF, rather a slight non-significant decrease, after the ATP injection was observed, although vasodilatory change at basal major vessels was indicated according to SPM analysis. The relaxation of vascular smooth muscles by the stimulation of the A2 receptors [7, 23] did not change CBF in the cerebral cortices, which goes in line with previous reports studied with adenosine [24, 25]. This no change in CBF despite vasodilation in the major vessels is considered to be caused by systemic hypotension due to vasodilation in peripheral arteries and the cerebral microvascular autoregulation which preserves intracranial perfusion pressure [22]. Vasodilatory change with decrease in systemic blood pressure usually causes reduction of blood flow; however, slight vasodilatory change in major cerebral arteries may induce constriction of arterioles and restore blood flow immediately by the well-known function of microvascular autoregulation [22]. There was no change in CVR between different conditions which supports this assumption.

The effect of ATP on CBF was different from that of acetazolamide which causes an increase in CBF. Administration of acetazolamide is known to induce dilatation of cerebral vessels, but it does not induce a decrease of systemic blood pressure, or rather induces a slight increase, which is considered to provide a CBF increase [26]. Several studies with human subjects or non-human primates reported that the intracarotid injection of adenosine increased CBF [13, 15, 27]. However, their injection method may have caused dilatation of the cerebral vessels only, which did not induce any significant effect on peripheral arteries in the body. They observed no changes in systemic blood pressure, which is different from our results showing decrease in systemic blood pressure induced by intravenous ATP administration. Both MBP and CBF tended to show decrease after ATP administration, although only MBP showed significant decrease. CVR, a ratio of these two parameters, did not change because the effect of the MBP decrease on CVR was weakened by the small decrease in CBF. No change in CVR was assumed to be caused by the physiologic function of autoregulation as mentioned above.

The SPM analysis showed significant difference in the basal regions corresponding to the major cerebral arteries including the circle of Willis, although ATP administration did not induce regional CBF changes in the cerebral cortices. ATP causes generalized peripheral vasodilation which includes the major arteries of the brain. The autoradiographic method for CBF calculation using $H_2^{15}O$ shows effects of vascular radioactivity on CBF images [28], and thus, SPM analysis shows regional changes not only for CBF, but also for the vascular radioactivity due to changes in regional blood volume. Elimination of early phase of PET data may have reduced this effect [28]. However, a single 2-min frame was employed for PET acquisition in the present study because of the limitation of ATP administration time (5 min or shorter), which prevented diminishing effects of vascular radioactivity. Direct measurement of vascular volume would be ideal to evaluate vasodilatory change although we could not apply the two-compartment analysis in this study because the short scan time of 2 min is not enough length for the analysis. In the present study, however, SPM analysis for assessment of changes in intravascular radioactivity, which reflects increase in blood volume, was able to visualize the ATP effect on the cerebral vessels as the increase in radioactivity in the basal region. No significant change in cortical CBF in quantitative values and the relative increase in major vascular regions visualized by SPM indicated the vasodilatory effect of ATP without change in CBF. The extent threshold of 100 cluster voxels was applied in this study because effect of a drug on CBF and cerebral vessels were evaluated, and thus, small change in extent should be removed. A larger extent threshold could be applied, but the regions of significant change was not significantly different when $k = 200$ was applied.

Ito et al. [16] reported that dipyridamole, which increases interstitial adenosine by inhibiting degradation of endogenous adenosine, caused significant decreases in CBF and P_aCO_2. They assumed that hyperventilation induced by dipyridamole caused CBF reduction, rather than a direct effect of the drug on the cerebral arteries. Sollevi et al. [14] reported that intravenous administration of adenosine at a dose of 0.2–0.5 mg/kg/min induced an increase in mean CBF by 23–85% and decrease in mean CVR by 43–65% in patients with normoventilation, and that this effect was counteracted by hyperventilation observed in one patient. In the present study, we administered ATP with a clinical dose for coronary stress (0.16 mg/kg/min), which was lower than the previous studies used for adenosine. This lower dose of ATP did not cause hyperventilation and all subjects in our study showed no changes in P_aCO_2 during ATP administration. A longer ATP administration caused changes in broader areas (Fig. 2), indicating that the longer stimulation of ATP induces the greater effect on large cerebral vessels.

For measurement of coronary flow reserve with ATP, myocardial blood flow tracers are usually administered at 3 min after the beginning of constant infusion of ATP as the protocol of the second condition in the present study. Thus, the timing of the tracer injection is considered to be appropriate to evaluate vasodilatory effect and flow reserve in myocardial SPECT studies.

There were reports of cerebrovascular accidents caused by an intracranial vascular steal phenomenon during dipyridamole stress tests for the study of coronary flow reserve [29, 30]. The vasodilatory effect of ATP also induced systemic hypotension during continuous infusion, however, the fact that the CBF was stable during ATP administration indicates that ATP can be safely and adequately be used for coronary examinations with fewer side effects, which is clinically important although all side effects are well-tolerated and resolved spontaneously within a few minutes after discontinuation [3]. The age difference between younger healthy volunteers who participated in this study and the patients who have cardiovascular diseases and the need for further studies on coronary flow reserve might be some of possible limitations. However, the result of this study showed that no change in CBF presumably due to cerebral autoregulation which is a basic physiologic function that should be preserved in older people as well.

Conclusion

Our results indicate that intravenous ATP administration does not produce any significant change in cortical CBF although the vasodilatory effect on the major cerebral arteries was observed. This result was presumably caused by decrease in systemic blood pressure and microvascular autoregulation in the brain. The findings support safety and usefulness of ATP in clinical use for myocardial perfusion studies or therapeutic managements.

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