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Effects of anesthesia upon ^{18}F-FDG uptake in rhesus monkey brains

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The kinetics of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in the monkey brain were monitored, and comparisons were made between the conscious state and when under ketamine and pentobarbital anesthesia. Rhesus monkeys were intravenously injected with ^{18}F-FDG and followed by 60 min of PET scanning. In the conscious state, the ^{18}F-FDG concentration reached a plateau 5 min after intravenous injection. Under ketamine anesthesia, the ^{18}F-FDG concentration gradually increased with time in all monitored regions. At 60 min after injection, the concentration in the striatum was about 3.2 times greater than that in the conscious state, and about 4.5 times greater in the cerebral cortex. Under pentobarbital anesthesia, the ^{18}F-FDG concentration in the occipital cortex was slightly lower. These findings demonstrate that ^{18}F-FDG concentration in the monkey brain is significantly affected by anesthesia. The results also imply the existence of a short-term regulation mechanism for hexokinase activity in intact monkey brain.

Key words: ^{18}F-FDG, rhesus monkey, brain, ketamine, pentobarbital, conscious

INTRODUCTION

^{18}F-FDG is a critical tracer for measuring the glucose metabolism in cerebral, myocardial, cancerous or inflammatory tissues.[1–4] Clinically, measurements of the glucose metabolism in the brain are used to diagnose a variety of neural and mental diseases.[5,6] Changes in the glucose metabolism are also used in some experiments as a marker for determining the effectiveness of drugs in rats and other small animals[7–9] as well as humans.[10,11] Because of the significant differences in brain functions between small animals and humans, however, basic research using primates such as monkeys is becoming important to reduce the inter-species gap. While many PET studies have been carried out on anesthetized monkeys to ensure the immobility of the animals,[12,13] it is possible that some of the anesthetics may have significantly changed the kinetics of the tracer.[14–16] In fact, it has been reported that chloral hydrate and barbiturates significantly reduce the cerebral glucose metabolism in rats, and that subanesthetic doses of ketamine can increase the glucose metabolism.[17] In the current study, conscious rhesus monkeys were restrained in the PET scanner to determine the effects of ketamine and pentobarbital anesthesia on cerebral ^{18}F-FDG kinetics.

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MATERIALS AND METHODS

Two male rhesus monkeys (6–9 kg) were used for this study. The monkeys were anesthetized with ketamine (6 mg/kg, i.p.) and restrained in monkey chairs with an acrylic plate attached to their skull beforehand.[18] They were able to move their limbs freely. The head of each monkey was positioned in an animal PET gantry (SHR-2000, Hamamatsu Photonics KK), and ^{18}F-FDG (175–370 MBq) was intravenously injected after complete awakening (about 3 hours after the injection of ketamine). Then PET scans were performed for 60 minutes at a rate of one frame per minute or 5 minutes. Data were collected for seven slices simultaneously with a center-to-center distance of 8.0 mm. Horizontal resolution was 3.5 mm in the center of the field of view. Regions of interest (ROIs)

were drawn on the reconstructed PET images to obtain time-activity curves (TACs). The experiment was repeated with ketamine (5 mg/kg, i.p.) or pentobarbital (25 mg/kg, i.p.) administered once or twice, and ^{18}F-FDG was injected at 5–10 minutes after injection of the anesthetic.

The experiments were conducted with the approval of the Committee on the Safety and Handling Regulations for Laboratory Animal Experiments, NIRS.

RESULTS

Ketamine induced a state of sedation and stuporous behavior with an absence of eye closure. The monkeys' behavior returned to a normal arousal state around 3 hours after injection. Pentobarbital induced deep anesthesia with their eyes closed. Figure 1 shows integrated images of ^{18}F-FDG kinetics measured in the conscious state and under ketamine and pentobarbital anesthesia. Figure 2 shows typical TACs for the striatum, frontal lobe, occipital lobe, and cerebellum. In the conscious state, the ^{18}F-FDG concentration in all areas of the brain reached the maximum level 5 min after uptake, and the ^{18}F-FDG level remained almost the same until the end of the 60-min period. The ^{18}F-FDG concentration was highest in the occipital lobe and striatum, and lowest in the cerebellum. Under pentobarbital, the concentration of ^{18}F-FDG in the occipital cortex was slightly lower than when the animals were conscious. Reproducibility of ^{18}F-FDG kinetics under pentobarbital anesthesia was not good. Out of the total 11 measurements made under pentobarbital anesthesia, 3 showed a peak followed by a gradual decrease in the ^{18}F-FDG concentration while in the remaining 8 the concentration level showed a plateau. On the other hand, ketamine significantly increased ^{18}F-FDG concentrations in all regions. Table 1 shows the average ^{18}F-FDG concentration levels and standard deviations for each brain region with the animals conscious, ketamine-anesthetized, and pentobarbital-anesthetized. The ^{18}F-FDG concentration was significantly higher in all regions when the animals were ketamine-anesthetized. When the animals were pentobarbital-anesthetized, only the occipital lobe showed significantly lower ^{18}F-FDG concentrations than in the conscious state.

DISCUSSION

^{18}F-FDG is an extremely useful radiotracer for quantitative assessment of regional brain metabolism in small animals including mice and rats, and humans. Recently, small animal PET imaging systems such as Micro-PET have been used widely for this purpose,[16,19,20] but the use of anesthetics affects the measurements. Several recent studies have used glucose metabolism as indices to analyze a subject's response patterns to various drugs that affect the central nervous system. Duncan et al. reported that the increases in the brain glucose metabolism induced by small dosages of MK-801 and ketamine are completely inhibited by clozapine (an atypical antipsychotic drug), but not by haloperidol (a typical antipsychotic drug).[17,21] Potkin et al. studied the effect of clozapine on the dopamine D_1 receptor genotypes (commonly associated with schizophrenics) in relation to the clinical response to clozapine.[22] Pharmacological actions of many psychotropic drugs vary greatly between rodents and primates. For this reason, it is important to use monkeys as test subjects for these kinds of pharmacological perturbation studies.

In the current study, our ^{18}F-FDG PET scans of conscious monkeys yielded relatively clear images. However, quantitative analysis of the glucose metabolism was not possible, as arterial blood was not sampled this time. To reduce invasiveness, it will be necessary to develop an alternative to arterial blood sampling, such as using the ^{18}F-FDG concentration in the carotid arteries as an input function.

Under ketamine anesthesia, the increase in the ^{18}F-FDG concentration in the brain was sustained throughout the 60-min PET monitoring period. The largest increase

Table 1 ^{18}F-FDG concentration (nCi/cc/m*l*)
t = 60 min

Status	Conscious n = 3 [monkey A n = 1 monkey B n = 2]	Ketamine n = 6 [monkey A n = 3 monkey B n = 3]	Pentobarbital n = 11 [monkey A n = 5 monkey B n = 6]
Region	Mean ± SD	Mean ± SD	Mean ± SD
Cerebellum	215 ± 20	482 ± 48***	245 ± 66
Striatum	305 ± 31	640 ± 183*	252 ± 96
Frontal cortex	255 ± 30	603 ± 81***	236 ± 63
Occipital cortex	298 ± 22	529 ± 96**	213 ± 57*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$ vs. Conscious

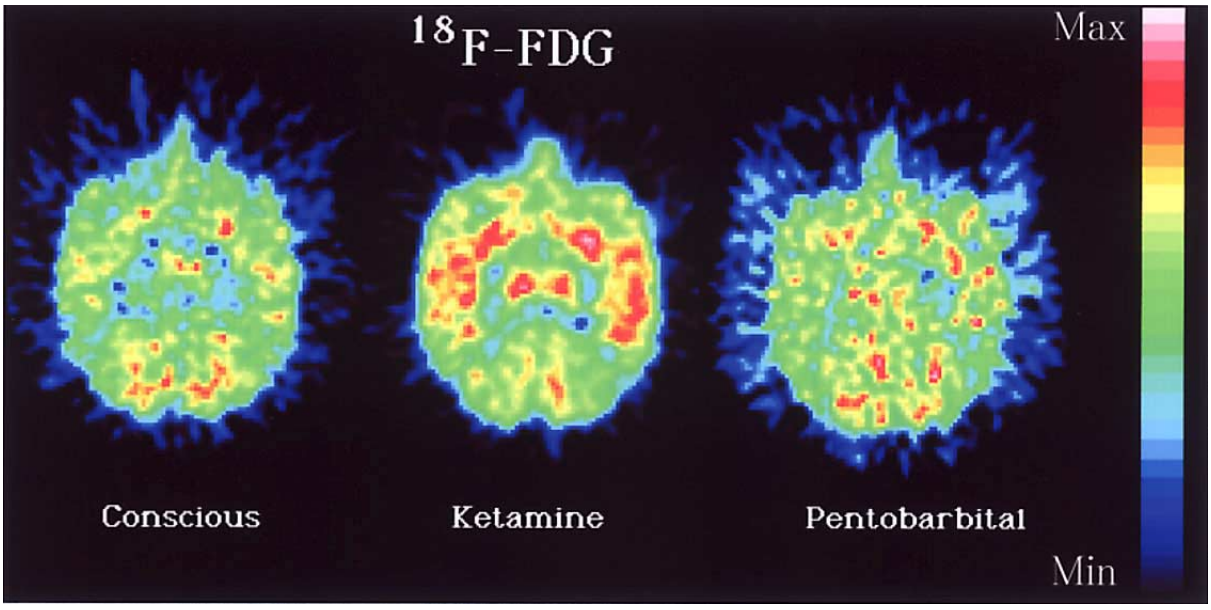

Fig. 1 PET images of ^{18}F-FDG in the same monkey brain under conscious, ketamine-anesthetized, and pentobarbital-anesthetized state. Data were collected for 60 min after the injection of ^{18}F-FDG, and summation images were obtained. The color bar shows relative values of ^{18}F-FDG concentration in the respective image.

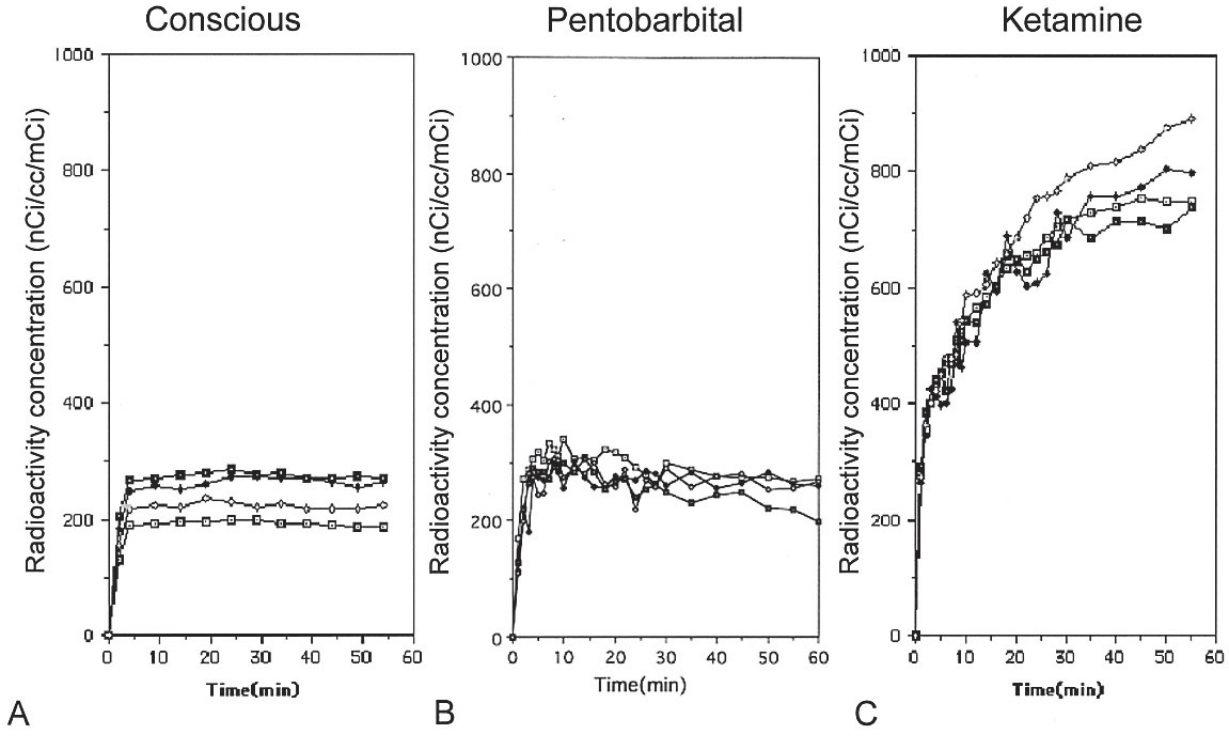

Fig. 2 The time activity curve of ^{18}F-FDG concentration in various brain regions under conscious (A), pentobarbital-anesthetized (B) and ketamine-anesthetized (C) state. ^{18}F-FDG concentration was determined by cross calibration of the PET camera: it is expressed as nCi/cc/injected mCi of ^{18}F-FDG. □: Cerebellum, ◆: Striatum, ■: Occipital cortex, ◇: Frontal cortex

was in the frontal cortex region, with an ^{18}F-FDG concentration about 4.5 times higher than when the subjects were conscious. While no kinetic analysis is possible because the input function was not measured, it is surmised that the ^{18}F-FDG accumulation in the brain was accelerated by enhancement of the hexokinase-mediated phosphorylation process. The ^{18}F-FDG kinetics of the soft tissues in the head was observed to decrease with time after ^{18}F-FDG injection, in a manner similar to that in the conscious state.

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist[23] which causes symptoms of schizophrenia, both positive (hallucination and delusion) and negative, when administered to humans. For this reason, the effects of ketamine are attracting attention as a model of the pathophysiology of schizophrenia.[24] In the future, we intend to examine alterations in the glucose metabolism caused by small dosages of ketamine and the suppression of increases in the glucose metabolism by clozapine.

Under pentobarbital anesthesia, the differences in ^{18}F-FDG concentration among the various brain regions were relatively small, which probably reflects the overall decline in brain neural activity. In some cases under pentobarbital anesthesia, the ^{18}F-FDG concentration peaked about 5 min after the administration and decreased over time, whereas, in other cases the concentration remained relatively flat and stagnant. The peaking and subsequent decrease in ^{18}F-FDG concentration suggests significant suppression of the hexokinase-mediated phosphorylation process. The known mechanisms for regulation of hexokinase activity are product inhibition by glucose-6-phosphate[25] and translocation of hexokinase.[26] However, it remains unclear what mechanism alters hexokinase activity in the brain under pentobarbital anesthesia or ketamine anesthesia.

In conclusion, we determined that anesthetic drugs considerably influence the concentration and kinetics of ^{18}F-FDG in the monkey brain: ketamine and pentobarbital have opposite effects. The short-term regulation mechanism for hexokinase activity is responsible for these effects. Future studies should measure the input function of ^{18}F-FDG through arterial blood sampling or other methods to elucidate the increase in the glucose metabolism resulting from the use of ketamine and its suppression by anti-schizophrenic drugs.

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