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Cerebral Metabolism during Propofol Anesthesia in Humans Studied with Positron Emission Tomography

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Background: **Although the effects of propofol on cerebral metabolism have been studied in animals, these effects have yet to be directly examined in humans. Consequently, we used positron emission tomography (PET) to demonstrate *in vivo* the regional cerebral metabolic changes that occur in humans during propofol anesthesia.**

Methods: **Six volunteers each underwent two PET scans; one scan assessed awake-baseline metabolism, and the other assessed metabolism during anesthesia with a propofol infusion titrated to the point of unresponsiveness (mean rate ± SD = 7.8 ± 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$). Scans were obtained using the ^{18}fluorodeoxyglucose technique.**

Results: **Awake whole-brain glucose metabolic rates (GMR) averaged 29 ± 8 $\mu moles \cdot 100\ g^{-1} \cdot min^{-1}$ (mean ± SD). Anesthetized whole-brain GMR averaged 13 ± 4 $\mu moles \cdot 100\ g^{-1} \cdot min^{-1}$ (paired *t* test, $P \leq 0.007$). GMR decreased in all measured areas during anesthesia. However, the decrease in GMR was not uniform. Cortical metabolism was depressed 58%, whereas subcortical metabolism was depressed 48% ($P \leq 0.001$). Marked differences within cortical regions also occurred. In the medial and subcortical regions, the largest percent decreases occurred in the left anterior cingulate and the inferior colliculus.**

Conclusion: **Propofol produced a global metabolic depression on the human central nervous system. The metabolic pattern evident during anesthesia was reproducible and differed from that seen in the awake condition. These findings are consistent with those from previous animal studies and suggest PET may be useful for investigating the mechanisms of anesthesia in humans. (Key words: Anesthetics, intravenous: propofol. Brain: cerebral cortex; cerebral metabolic rate. Deoxyglucose: radionuclide imaging. Human. Measurement techniques: tomography, emission-computed.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 27A.

RECENT studies investigating the effects of propofol on whole-brain and regional cerebral glucose metabolism in the rat have shown that propofol causes a dose-dependent, global decrease in whole-brain cerebral glucose metabolic rates ranging from 15% to 55%.[1,2] Additionally, these studies have shown that the regional effects of propofol anesthesia are greater on forebrain structures than on hindbrain structures,[1] and the single largest regional change occurs in a part of the limbic system known as the cingulate cortex.[2] How these data relate to the effects of propofol in humans is not yet known. Generalization of these studies to humans may be inadequate as rats have a comparatively small cerebral cortex, which is devoid of the large cortical association areas characteristic of the human brain. Therefore, to elucidate the effects of propofol in human brain and to establish a background for future studies on the cognitive effects of anesthetics, we have examined the changes in regional cerebral glucose metabolism produced by propofol in volunteers, using the application of positron emission tomography (PET) technology.

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Methods and Materials

The PET Technique

Quantitative imaging of cerebral metabolism with PET uses the same principles as the autoradiography technique developed by Sokoloff *et al.*[3] To study regional cerebral glucose utilization in humans, a positron labeled deoxyglucose tracer is used, such as ^{18}fluorodeoxyglucose (FDG).[4] This tracer is taken up by active brain neurons as if it were glucose. However, once inside a cell, ^{18}fluorodeoxyglucose is phosphorylated by hexokinase to ^{18}fluorodeoxyglucose-6-phosphate, which is not a substrate for glucose transport and cannot be metabolized by phosphohexoseisomerase, the next enzyme in the glucose metabolic pathway. Thus, labeled ^{18}fluorodeoxyglucose-6-phosphate becomes metabolically trapped within the intracellular compartment. The amount of radioactive label that occurs in each discrete part of the brain/body is related to the glucose uptake of that discrete region. The more metabolism occurring in a particular brain region, the more glucose, or tracer, will be taken up.[5]

Although quantitative PET uses the same principles involved in the autoradiography technique, the image is not obtained by dissecting the brain and placing it on film but rather by sampling the radioactivity *in vivo*, while the positrons decay. The placement of a ring of gamma counters around a subject's head (or other body part) allows the location of individual positron decay events to be pinpointed. Computed tomography techniques then are used to reconstruct images that represent the amount of decay activity present in each discrete brain region. These reconstructed images ultimately represent the three dimensional locations (*i.e.*, structure) and the underlying amount of uptake activity (*i.e.*, function) that occur in a particular subject's brain, when a particular tracer is used.

Thus, PET is a functional imaging technique. The pattern of tracer uptake and the PET image will be different depending on what the subject does during the period of tracer uptake. Using FDG, the pattern of metabolic activity will change if the person is, for example, awake or asleep, looking at numbers or letters, speaking words or singing. By contrast, structural imaging, with magnetic resonance imaging or computed tomography, shows the same brain picture irrespective of subject activity.

In this study, the FDG technique was used. Regional glucose utilization may be a more accurate assessment of regional metabolism in the presence of an anesthetic, because anesthetics may directly affect the regional cerebral blood flow/regional cerebral metabolism relationship.[6] The standard FDG technique in humans uses a 32-min uptake period. Uptake of FDG and metabolic trapping of FDG in the brain as FDG-6-phosphate is 80–90% complete at 32 min.[3,5] The actual scanning begins after the 32-min uptake period once the remaining labeled nonphosphorylated FDG has been cleared from the plasma. The eventual images obtained represent the accumulated regional FDG uptake that occurred during the corresponding 32-min uptake period.

Calculation of absolute glucose metabolic rate values is based on the deoxyglucose kinetic models of Sokoloff developed for autoradiography in animals and modified for humans.[3,4] A primary assumption made by these models is that a near-steady-state level of carbohydrate metabolism exists during the period of tracer uptake. Thus, to ensure steady-state regional metabolism, awake subjects routinely perform a specific repetitive cognitive or behavioral task during the uptake period. In this study, subjects in both the awake and anesthetized conditions passively listened through headphones to a prerecorded audiotape of repeated words. This tape randomly repeated a list of ten words, one word every 5 s for each 32-min uptake period. The ability of subjects to recall the words heard during both awake and anesthetized uptake periods and how such recall correlates to cerebral metabolism will be reported elsewhere.

Experimental Design

After obtaining full institutional review committee approval, six adult right-handed male volunteers gave informed consent, and each underwent two separate PET scan procedures. One scan assessed baseline cerebral metabolism associated with the awake state, while the other scan assessed cerebral metabolism associated with unconsciousness induced by propofol anesthesia.

All subjects were nonsmokers, mean age = 23 ± 4 yr, in excellent medical condition, and classified as ASA physical status 1. Each subject was carefully screened for previous medical or psychiatric history, and each subject was required to pass a urine toxicology examination.

Subjects were asked to avoid caffeine, or any medications, for at least 48 h before each scan. In addition, subjects fasted at least 8 h before each scan session,

and they received oral antacid (Bicitra 30 ml orally) before the scan involving anesthesia.

A minimum of 1 week separated scanning sessions. The order of the scans (awake *vs.* anesthetized) was randomized and counterbalanced to control for any possible order effects. For each scan obtained, those parts of each subject's brain that were the most metabolically active during the uptake period became those most labeled with tracer. Once the tracer is converted to FDG-6-phosphate, it remains intracellular for the additional time necessary to perform each PET scan. Each PET scan image demonstrates the regional cerebral glucose metabolism that occurred during each subject's corresponding uptake period.

Scanning of all subjects began within 20 min from the end of each uptake period. Subjects in the anesthesia group were allowed to emerge from the anesthesia before being placed on the scanner. Between the two groups, the overall time difference from FDG injection to completion of each scanning session was not statistically significant (awake total scan time = 131 ± 15 min *vs.* anesthesia total scan time = 145 ± 6 min).

Anesthetic Procedures

The Brain Imaging Center (Irvine, CA) was equipped with all of the anesthesia equipment and supplies normally present for general anesthesia. The research laboratory was a small sound-shielded room with dim lighting. In addition to having the subjects in a darkened room, the subjects wore blindfolds during both awake and anesthetized uptake periods to minimize any visual input. The headphones that the subjects wore for the audiotape also helped minimize any extemporaneous environmental auditory inputs. Subject monitoring included an electrocardiogram, a noninvasive blood pressure monitor, a pulse oximeter, an end-tidal carbon dioxide monitor, a temperature monitor, and the use of a precordial stethoscope.

Two (or three) intravenous catheters were started (the propofol scan required an additional intravenous catheter). One catheter was for FDG administration and the other for venous blood sampling. Blood samples were taken to quantify the uptake of FDG and to monitor propofol blood levels during the uptake period. FDG brain uptake is quantified using multiple measurements of serum glucose levels and serum radioactivity levels sampled throughout the uptake and scanning periods. These measurements allow calculation of regional glucose metabolic rates based on the well established models of deoxyglucose tracer kinetics.[3,4]

Propofol blood samples were taken at four times: (1) when subjects first lost consciousness; (2) at the start of the uptake period, immediately before FDG injection (which was always at least 12 min after the loss of consciousness); (3) near the midpoint of the uptake period, injection time plus 15 min; and (4) at the end of the 32-min uptake period before stopping the propofol infusion. These propofol samples were taken to document that the propofol blood concentrations evident during the FDG uptake period approached steady-state conditions.

For the awake-baseline scans, the subjects were fasted and were connected to all monitoring equipment as if they were about to have anesthesia. However, the subjects simply lay quiet and still, with their eyes closed and blindfolded, for the 32-min uptake period.

Subjects were connected to a Drager AV anesthesia machine *via* a semicircle breathing system, and 100% inspired oxygen was administered using a soft rubber face mask for at least 3 min before anesthesia was induced. Once subjects were unresponsive, an air/oxygen mixture was used and the inspired oxygen was adjusted to 30%.

Propofol was delivered using a Medfusion infusion pump. A loading bolus of 0.4 $mg \cdot kg^{-1}$ was given, and an infusion was started at an initial rate of 2 $mg \cdot kg^{-1} \cdot h^{-1}$. After the infusion was started, the eyelash reflex was tested every 3 min, and the subjects were asked to open their eyes. The infusion rate was adjusted upward by 2 $mg \cdot kg^{-1} \cdot h^{-1}$ increments every 12 min until the subjects just lost consciousness (this took about 30–60 min).[7] When subjects no longer responded to verbal commands, they were further stimulated by gently touching their shoulders. Loss of consciousness was defined as unresponsiveness to both verbal and tactile stimuli. Once subjects were unresponsive at a particular infusion rate, the rate was set at that level for the remainder of the experiment (mean rate ± SD = 7.8 ± 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$; range 6–10 $mg \cdot kg^{-1} \cdot h^{-1}$).

Before injection of the FDG, an additional 12 min of anesthesia was allowed to ensure that subjects approached a steady level of anesthesia. Once heart rate, blood pressure, and end-tidal values remained stable for at least 5 min (±2%) and the minimum 12-min preinjection period had passed, subjects were given 5 mCi of FDG intravenously over 1 min. The subjects then remained at the same propofol infusion rate for

32 min while the FDG uptake occurred in each subject's brain. After this uptake period, the infusion was stopped, and the subjects were allowed to recover from anesthesia before being taken to the PET scanner.

Subjects did not have their airways instrumented, and they maintained spontaneous ventilation during anesthesia, although on rare occasions, simple assistance (head tilt/jaw thrust) was needed to maintain a patent airway.

Pet Procedures

The PET scans were done after each uptake period using a NeuroEcat scanner. The PET scanner has a single ring with shadow shields and septa to achieve 7.6 mm resolution (full-width-half-maximum) in plane and 9.9 mm resolution in the Z-dimension. For each PET scan session, 9–13 image slices were obtained parallel to the canthomeatal line. Subjects were positioned using laser guidance and scans started at the level of 85% of head height (vertex to canthomeatal line, usually 12–14 cm) and stepped downward in integrals of 10 mm.

In the current paper, where slice levels are indicated, they are expressed as the percentage of head height measured perpendicular to the canthomeatal line, from the line to the highest point on the head. Greater percentages of head height indicate higher, more dorsal, regions (*e.g.*, 100% of head height equals the top of the head).

Scans were transformed into GMR as previously described.[8] Sixteen bilateral (32 total) cortical areas (*i.e.*, gyri) were measured using the cortical peel technique of Buchsbaum as illustrated in Haier.[9,10] Sixty-three bilateral (126 total) subcortical and medial cortical regions-of-interest from our standard analysis templates were located using stereotaxic coordinates derived from a standard neuroanatomic atlas[11] (see Haier[10]). To some extent, scanner resolution limited subcortical structures selected for analysis.

Previous PET studies have found that a large degree of intersubject variability exists in whole-brain GMR values. To make direct comparisons between different subjects, involving any particular brain region-of-interest, it is necessary to take into account this potential difference in whole-brain GMR. This is routinely done for PET studies by dividing the GMR values obtained in each subject's regions-of-interest by that subject's whole-brain mean GMR (for cortical areas) or whole slice mean GMR (for each medial cortical and subcortical region-of-interest). This standardization process then allows for direct comparisons of relative metabolism within specific regions among different subjects.

Propofol Blood Samples

The following procedure[12] was used: 0.5 ml of a precipitating solution (67% Acetonitrile/33% perchloric acid) containing 1 μg of Thymol (internal standard) was added to 0.5 ml of serum samples, and then mixed on a vortex-mixer for 1 min. After centrifugation for 5 min, the supernatant was directly injected into the HPLC system, consisting of a Spherisorb ODS2 C18 reverse phase column (250 $\times$ 4.6 mm). The mobile phase was 670 ml acetonitrile, 330 ml of water, and 0.4 ml of acetic acid (*p*H 4.0) with a flow rate of 1.5 ml $\cdot$ min^{-1}. Propofol was monitored using UV detection at 270 nm. The ratio of propofol to the internal standard was used to construct a standard curve, which was used to calculate the amount of propofol in the test samples.

Statistical Analysis

BMDP was used for all statistical analyses. Differences of the means in whole-brain glucose metabolic rates, regions-of-interest, physiologic variables, and total scan times for the two conditions were compared using paired (two-tailed) *t* tests (Module 3D). Cortical data were analyzed for changes of GMR and relative GMR using a repeated measures analysis of variance (ANOVA Module 4V).

The ANOVA tested the null hypothesis that propofol anesthesia has no effect on cortical metabolism. The ANOVA was set up with the presence or absence of anesthesia as the main condition (on and off anesthesia). The GMR values obtained for each of the different cortical areas were the repeated measures and were nested within the main condition effect.

Using a nested structure allowed the following additional hypotheses to be tested: (1) the effect of propofol does not vary across cerebral hemispheres, (2) the effect of propofol does not vary among the different cortical lobes, and (3) the effect of propofol does not vary among the individual cortical gyri. The repeated measures were organized by hemisphere (left and right), lobe (frontal, temporal, parietal, and occipital), and gyrus (each of the four gyri within each lobe). Using the "structure" option in the BMDP 4V procedure allowed gyri terms to be excluded when they were not nested within lobe or hemisphere.

A significant "condition" F value demonstrates that the overall effect of propofol on cortical metabolism is statistically significant. A significant "condition by

hemisphere" effect demonstrates whether the effect of propofol varies by hemisphere. A significant "condition by lobe" effect demonstrates whether the effect of propofol varies by lobe. Finally, a significant "condition by gyrus within lobe" effect demonstrates whether the effect of propofol varies by gyrus within each lobe.

The cortical ANOVA analysis was performed twice, once on the cortical GMR data and once on the relative GMR cortical data. To explore which areas contributed to the significance of the cortical ANOVA, *post hoc* testing was applied using a paired Student's *t* test (two-tailed). Although each pixel in a PET image can be correlated to neighboring pixels, data from each region-of-interest were treated as independent variables for these exploratory analyses. Results showing $P \leq 0.05$ are noted with the usual caution demanded by a small sample and multiple comparisons.

Results

Propofol significantly decreased regional metabolism in all brain areas studied (fig. 1). Awake whole-brain GMR averaged 29 ± 8 μmoles · 100 g^{-1} · min^{-1} (mean ± SD). Anesthetized whole-brain GMR averaged 13 ± 4 μmoles · 100 g^{-1} · min^{-1} (two-tailed paired *t* test, $P \leq 0.007$). The magnitude of this 55% metabolic reduction caused by propofol can be appreciated by referring to figure 2. This image shows the PET scan data obtained in one representative subject whose whole-brain metabolic reduction during propofol anesthesia equaled 57%. Although this subject's metabolic pattern is representative of the group mean, the individual variation in the percent decrease of whole-brain metabolism that was evident during anesthesia ranged from 35% to 72% across the six subjects.

Propofol did not uniformly depress metabolism throughout the brain, some regions were affected more than others. The differential effect of propofol is evident by examination of the relative GMR data (fig. 3). Relative metabolism was significantly lower in the frontal, parietal, and occipital lobes during the anesthesia condition as compared to the awake condition.

The pattern of metabolic reduction caused by propofol was reproducible among the subjects (fig. 4). Figure 4 shows how relative metabolism changed within the cortical lobes for each subject. The figure shows that metabolic changes induced by propofol were similar in five of the six subjects. In subject number six, the changes seen in the parietal lobe were less than those seen in the other subjects. Additionally, for subject 6 relative metabolism in the temporal lobes decreased.

Regional Analysis of GMR

Cortical. Glucose metabolic rates decreased in all measured cortical areas under anesthesia (table 1). The

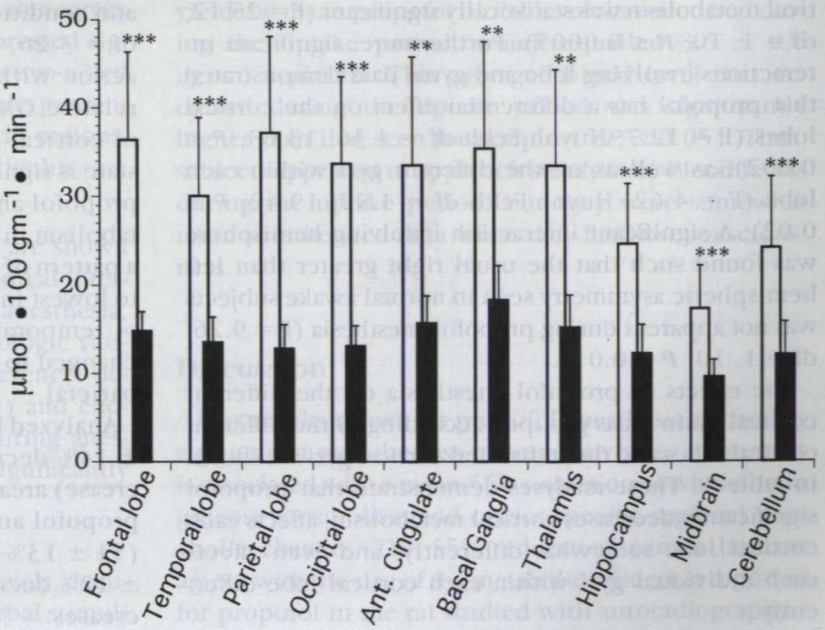

Fig. 1. Regional cerebral glucose metabolism (μmoles · 100 g^{-1} · min^{-1}) during awake (light bars) and anesthetized (dark bars) conditions. The results are mean ± SD (n = 6). **$P \leq 0.01$. ***$P \leq 0.005$.

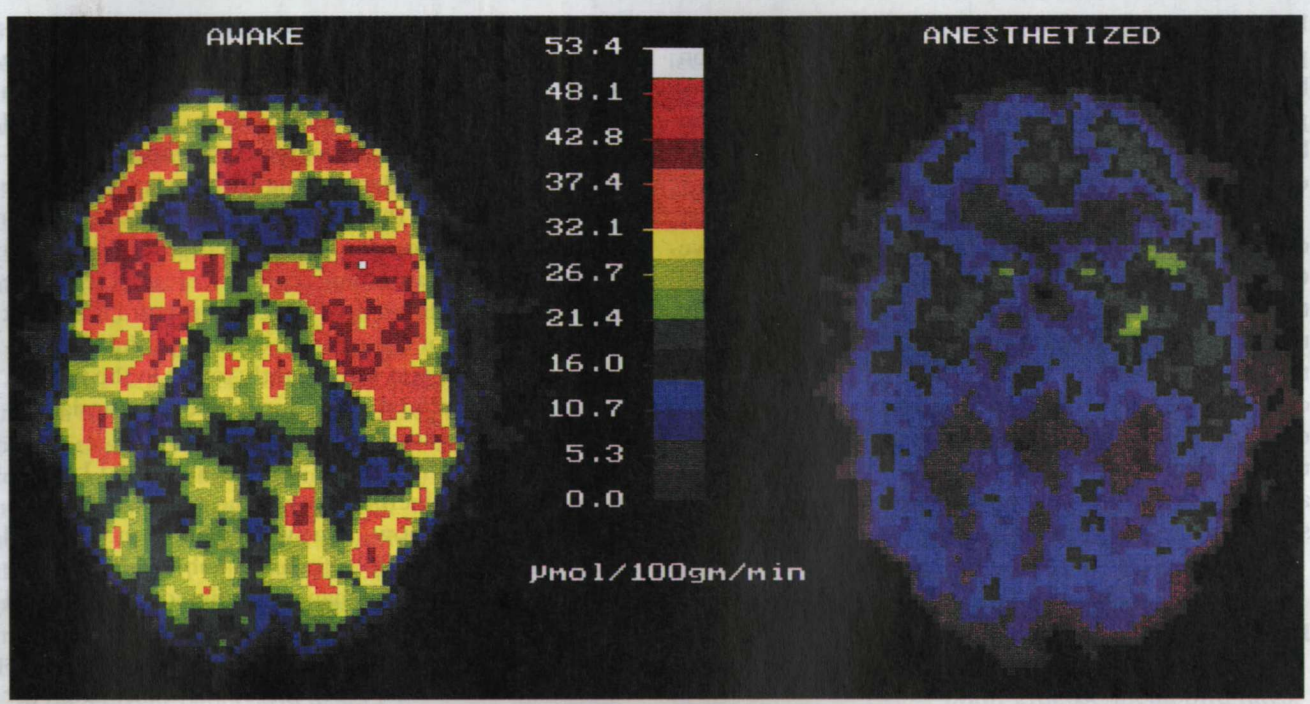

Fig. 2. PET images of regional cerebral glucose metabolism (μmoles · 100 g^{-1} · min^{-1}). The image shows a comparison within a single subject of glucose metabolism measurements obtained in both the awake and the anesthetized conditions. This representative subject's overall whole-brain metabolic reduction was 57%. The horizontal slices are at the level of the caudate (41% head height above the canthomeatal line). In each slice, the front of the brain is at the top of the picture and the left side of the image is the left side of the brain.

overall percent decrease of metabolism that occurred over the entire cortex averaged 58 ± 12%. The ANOVA demonstrated that the overall effect of propofol on cortical metabolism was statistically significant ($F = 25.12$, df = 1, 10; $P \leq 0.0005$). Furthermore, significant interactions involving lobe and gyrus data demonstrated that propofol has a differential effect on the cortical lobes ($F = 12.7$, Huynh-Feldt df = 1.36, 13.63; $P \leq 0.002$), as well as on the different gyri within each lobe ($F = 4.62$, Huynh-Feldt df = 1.92, 19.42; $P \leq 0.02$). A significant interaction involving hemisphere was found such that the usual right greater than left hemispheric asymmetry seen in normal awake subjects was not apparent during propofol anesthesia ($F = 9.26$, df = 1, 10; $P \leq 0.01$).

The effects of propofol anesthesia on the different cortical brain areas grouped according to the different cortical lobes and the individual cortical gyri are shown in table 1. These analyses demonstrate that propofol significantly decreases cortical metabolism, affects each cortical lobe somewhat differently, and even affects each individual gyri within each cortical lobe differently.

The relative GMR cortical data also showed significant interactions involving condition by lobe ($F = 16.98$, Huynh-Feldt df = 1.89, 18.91; $P \leq 0.0001$) and condition by lobe by gyri ($F = 6.09$, Huynh-Feldt df = 3.26, 32.64; $P \leq 0.002$). No significant interaction with hemisphere was seen ($F = 1.58$). The relative GMR analyses demonstrate that the pattern of cortical glucose utilization present in the awake state is significantly different from that evident during propofol anesthesia. In the awake state, cortical metabolism in the different cortical lobes demonstrated a pattern of regional metabolism ranging from highest to lowest in the order of parietal > frontal > occipital > temporal. In the anesthetized state, the order changed to that of frontal > temporal > occipital > parietal.

Analyzed by cortical gyri, the parietal superior (65 ± 14% decrease) and angular gyrus (64 ± 13% decrease) areas had the largest percent decreases during propofol anesthesia, whereas the temporal superior (51 ± 13% decrease) and the temporal inferior (52 ± 12% decrease) areas had the smallest percent decreases.

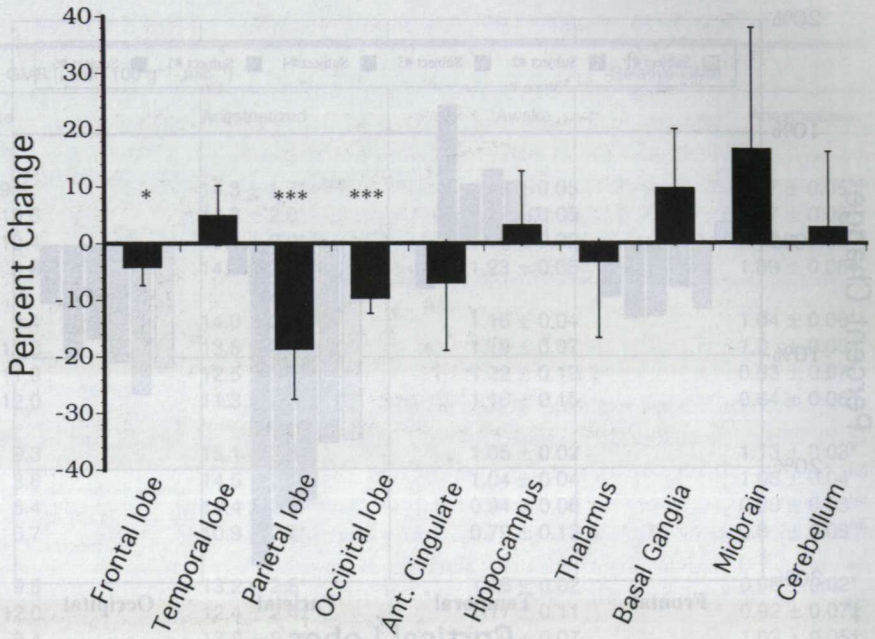

Fig. 3. Relative changes in the pattern of regional cerebral glucose metabolism (relative percent change in each area) from the awake condition to the anesthetized condition. The results are mean ± SD (n = 6). *$P \leq 0.05$. **$P \leq 0.01$. ***$P \leq 0.005$.

Medial Cortical Regions-of-Interest. GMR decreased in all medial cortical regions-of-interest under anesthesia. The largest single percent change (64 ± 16% decrease) for medial cortical regions-of-interest occurred in the left anterior cingulate slice level 34% of head height.

Subcortical Regions-of-Interest. GMR decreased in all subcortical regions of interest. The overall average percent change for subcortical regions-of-interest was 48 ± 16%, which is less than that seen in the cortex (58%). Thus, cortical metabolism was depressed significantly more than subcortical metabolism (two-tailed paired *t* test; $P \leq 0.001$). The largest single percent change (59 ± 13% decrease) for subcortical regions-of-interest occurred in the left inferior colliculus.

Physiologic Data

The changes in the physiologic variables are shown in table 2. Although no subject required clinical intervention for any physiologic changes during anesthesia, the group-averaged evaluation of the physiologic variables shows that statistically significant differences occurred in mean blood pressure ($P \leq 0.05$) and end-tidal carbon dioxide values ($P \leq 0.05$) during anesthesia. Other variables did not change significantly during anesthesia.

Propofol Blood Concentrations

Group analysis of the propofol blood levels documented that the loss of responsiveness to verbal stimuli first occurred at an average blood level of 2.7 ± 0.3 $\mu g \cdot ml^{-1}$ plasma (sample 1). No significant differences were found in the means of the samples taken during the start of the uptake period (sample 2 = 3.8 ± 1.2 $\mu g \cdot ml^{-1}$ plasma), the midpoint of the uptake period (sample 3 = 3.1 ± 0.8 $\mu g \cdot ml^{-1}$ plasma), and the end of the uptake period (sample 4 = 3.6 ± 0.8 $\mu g \cdot ml^{-1}$ plasma). Because there was no difference between samples 2, 3, and 4, these samples were averaged to yield the mean propofol blood level that occurred during the uptake period, which equalled 3.5 ± 0.6 $\mu g \cdot ml^{-1}$ plasma. This averaged blood level that occurred during the uptake period was significantly higher than that seen for sample 1 ($P \leq 0.05$). Thus, subjects appeared to approach steady-state blood levels during the uptake period, but they were somewhat more anesthetized than when they first lost consciousness.

Discussion

Our results show that propofol anesthesia titrated to a point just past the loss of responsiveness in humans is associated with a mean 55% reduction of whole-brain glucose metabolism and causes specific regional metabolic changes. The 55% reduction seen in humans agrees with the size of the metabolic reduction reported for propofol in the rat studied with autoradiography.[1]

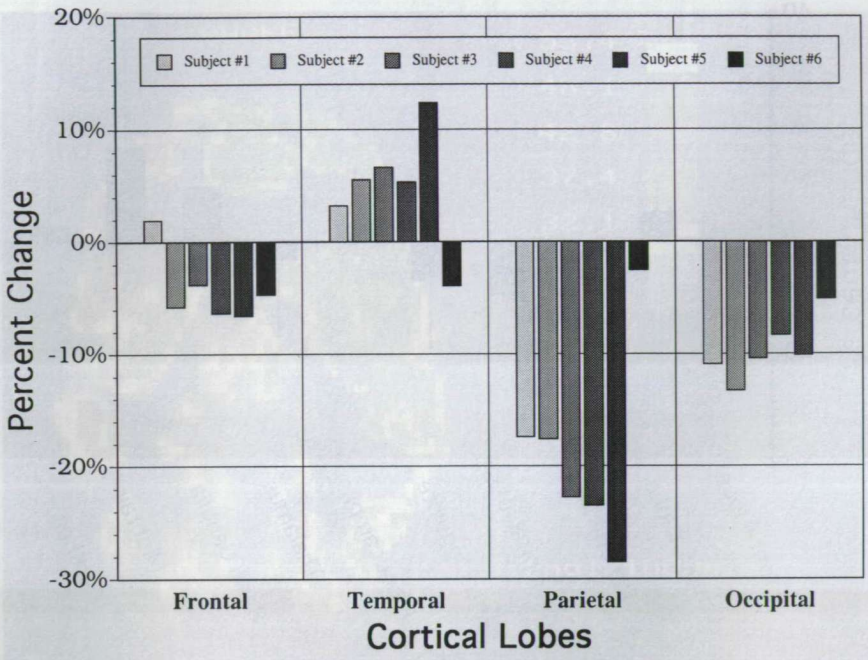

Fig. 4. Relative cortical metabolism data for the six subjects. The figure shows the relative percent change from the awake condition to the anesthetized condition for each subject in each cortical lobe. It can be seen that the metabolic changes induced by propofol anesthesia are reproducible and fairly consistent across the subjects.

The magnitude of this metabolic reduction is larger than the 18–36% reduction of whole-brain glucose metabolism reported in the baboon,[13] and it is in contrast to one report in humans that failed to show any change in whole-brain glucose metabolism during a propofol infusion.[14] However, we believe that a 55% metabolic reduction during anesthesia is not an unreasonable figure, as one might logically think the metabolic reduction associated with the anesthetic state would be greater than the reduction seen with sleep and less than that seen with coma. Indeed, non-REM sleep in humans is known to cause a 23% reduction in whole-brain glucose metabolism,[9] and coma is known to cause a 60% reduction.[15]

It is doubtful that the physiologic changes seen in our subjects during anesthesia significantly affected our results. The decrease in blood pressure seen in our subjects during anesthesia remained within the limits of cerebral autoregulation, and it has been shown that artificially increasing blood pressure during propofol anesthesia does not change overall cerebral blood flow in the primate.[13] A review of the prior animal studies investigating the influence of hypercarbia on cerebral glucose metabolism suggests the increased end-tidal carbon dioxide seen during anesthesia might have increased the apparent magnitude of propofol's effects in this study.[2,16] However, the average end-tidal carbon dioxide value during anesthesia increased only 6 mmHg from baseline. A change of this magnitude probably could not have affected our results by more than 10% if at all.

When propofol is administered as a fixed-rate infusion, the time taken to reach a stable blood concentration exceeds 1 h.[17] Because our subjects were at the same infusion rate before FDG injection for approximately 20–30 min, it is probable that steady-state blood levels were not reached in this study before the start of the FDG uptake period. However, because we found no statistically significant differences between the samples taken at the start of the FDG uptake period, the midpoint of the uptake period, and the end of the uptake period, we believe our subjects reasonably approximated a steady-state metabolic condition for the purposes of FDG uptake.

The mean propofol infusion rate during the FDG uptake period was 7.8 ± 1.5 mg · kg^{-1} · h^{-1}. This infusion rate corresponded to a mean propofol blood level during the FDG uptake period of 3.5 ± 0.6 μg · ml^{-1} plasma. This blood level is higher than the 2.97 ± 1 μg · ml^{-1} plasma that has been reported to be adequate for nonmajor surgery in humans when nitrous oxide and meperidine are also used, yet it is lower than the 4.05 ± 1 μg · ml^{-1} plasma that is required for major surgery.[18] In addition, the blood level is close to the 3.4 μg · ml^{-1} plasma value reported as the EC_{50} for loss of consciousness in female patients.[7] Together, these

Table 1. Cortical Metabolism

Cortical Region	GMR (μmol · 100 g^{-1} · min^{-1})		Relative GMR	
	Awake	Anesthetized	Awake	Anesthetized
Frontal lobe gyri				
Superior frontal	33.7 ± 9.4	14.3 ± 1.7*	1.08 ± 0.05	1.07 ± 0.05^{NS}
Middle frontal	36.9 ± 10.6	14.3 ± 2.0*	1.17 ± 0.05	1.07 ± 0.05†
Inferior frontal	36.7 ± 10.4	15.8 ± 2.0*	1.16 ± 0.02	1.18 ± 0.05^{NS}
Precentral (motor)	38.5 ± 9.8	14.8 ± 2.7*	1.23 ± 0.05	1.09 ± 0.08†
Parietal lobe gyri				
Postcentral (sensory)	36.4 ± 9.4	14.0 ± 2.7*	1.16 ± 0.04	1.04 ± 0.06*
Supramarginal	37.6 ± 11.3	13.5 ± 2.5*	1.19 ± 0.07	1.0 ± 0.05†
Angular gyrus	38.5 ± 11.8	12.5 ± 2.4*	1.22 ± 0.12	0.93 ± 0.07*
Superior parietal	36.4 ± 12.0	11.3 ± 2.6*	1.16 ± 0.15	0.84 ± 0.06‡
Temporal lobe gyri				
Superior temporal	33.1 ± 9.3	15.1 ± 2.3*	1.05 ± 0.02	1.13 ± 0.03*
Middle temporal	32.9 ± 8.8	14.5 ± 2.4*	1.04 ± 0.04	1.08 ± 0.04^{NS}
Inferior Temporal	29.6 ± 8.4	13.4 ± 2.5*	0.94 ± 0.06	0.99 ± 0.03^{NS}
Posterior temporal	24.7 ± 6.7	10.9 ± 2.7*	0.79 ± 0.13	0.8 ± 0.09^{NS}
Occipital lobe gyri				
Area 19	33.4 ± 9.5	13.2 ± 2.8*	1.06 ± 0.02	0.98 ± 0.02*
Area 17, superior	37 ± 12.0	12.4 ± 2.4‡	1.17 ± 0.11	0.92 ± 0.07‡
Area 17, inferior	34.3 ± 9.4	13.8 ± 2.2*	1.09 ± 0.07	1.03 ± 0.05†
Area 18	30.1 ± 8.0	12.9 ± 2.3*	0.96 ± 0.09	0.96 ± 0.06^{NS}

Values are mean ± SD.

NS = not significant; GMR = glucose metabolic rate.

* $P < 0.005$.

† $P < 0.05$.

‡ $P < 0.01$.

observations suggest our measurements of regional cerebral glucose metabolism were obtained when our subjects were at a clinically relevant depth of anesthesia.

Some of the regional metabolic effects reported to occur with propofol anesthesia in the previous rat autoradiography studies have been confirmed in our human data. Notably, in both rats and humans, it was found that overall metabolism in the cortex was depressed more than overall metabolism in subcortical brain areas.[1] Other metabolic effects noted in the rat data were not found in this study. In a previous rat study, the largest regional effect of propofol occurred in the cingulate cortex.[2] In contrast, our human data showed that metabolism in the cingulate cortex was not depressed to any greater extent than metabolism in other medial cortical brain areas, with one possible exception. One of the largest percent decreases of metabolism occurred in a localized region of the left anterior cingulate cortex visualized on slice level 34% of head height. We are unclear about the significance of this finding. There may be some localized neuronal network in this part of the human cingulate that is uniquely sensitive to propofol anesthesia, or this finding may simply represent some random sampling error in our data. Further investigation is required to clarify this issue.

Figure 3 demonstrates that the pattern of glucose utilization present in the awake state differs from that seen during propofol anesthesia. In other words, propofol not only depresses cerebral metabolism, it also results in marked regional shifts of metabolism. Understanding which of these two effects (*i.e.*, depression *vs.* regional shifts) are more closely related to the anesthetic state

Table 2. Physiologic Variables

	Awake Baseline	Anesthetized
Pulse (beats/min)	62 ± 13	60 ± 6^{NS}
MAP (mmHg)	79 ± 1	64 ± 6*
Respiration (breaths/min)	11 ± 2	17 ± 1*
SP_{O_2} (%)	99 ± 1	98 ± 2^{NS}
End-tidal CO_2 (mmHg)	33 ± 4	39 ± 4*

* $P < 0.05$.

and cognitive effects produced by propofol will require further investigation.

Studies of pentobarbital anesthesia in primates have shown that it also depresses metabolism in all brain areas.[19] However, the exact pattern of how metabolism is depressed with each agent (compared across species) is not identical. Pentobarbital studied in primates, decreased regional cortical metabolism the most in the parietal, frontal, and preoccipital areas. Whereas propofol, in this study, affected regional cerebral metabolism the most in the parietal lobe and the least in the frontal and temporal lobes.

Animal studies of regional cerebral glucose metabolism have demonstrated conclusively that regional metabolic shifts occur during anesthesia.[19] Our data confirm that regional metabolic shifts occur in humans during propofol anesthesia. In addition, what has not been noted previously is that the pattern of metabolic depression is remarkably similar among different individuals (fig. 4). The idea that each anesthetic agent might produce its own characteristic changes in the pattern of cerebral glucose metabolic activity is not new.[6] However, the consistency with which a single agent produces similar metabolic changes within different subjects has not been previously reported. It has not been possible to make this observation using the autoradiography method in animals, as the autoradiography technique requires brain dissection, and thus the same animal has never been studied in both the awake and anesthetized conditions.

Benzodiazepines are thought to produce their effects through their actions on the GABA receptor complex.[20,21] Recent evidence suggests that propofol also may produce its effects *via* a GABA receptor complex mediated mechanism.[22] It has been shown that benzodiazepine receptor density is higher in human cortical brain areas than in subcortical brain areas.[23,24] It may be that the regional differences in receptor densities underlie our finding that significantly more metabolic depression occurred in the cortical brain areas than in the subcortical brain areas during propofol anesthesia (*i.e.*, regional metabolism goes down more in areas with more receptors). It is proposed that a propofol dose-response study might elucidate more clearly the subtle regional metabolic effects of propofol that are associated with the known regional differences in GABA receptor distribution.

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