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## Positron Emission Tomography Study of Regional Cerebral Metabolism in Humans during Isoflurane Anesthesia

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## Outline



## Abstract

Background: Although the anesthetic effects of the intravenous anesthetic agent propofol have been studied in the living human brain using brain imaging technology, the nature of the anesthetic state evident in the human brain during inhalational anesthesia remains unknown. To examine this issue, the authors studied the effects of isoflurane anesthesia on human cerebral glucose metabolism using positron emission tomography (PET).

Methods: Five volunteers each underwent two PET scans; one scan assessed awake-baseline metabolism and the other scan assessed metabolism during isoflurane anesthesia titrated to the point of unresponsiveness (means +/- SD; expired = 0.5 +/- 0.1%). Scans were obtained with a GE2048 scanner (4.5-mm resolution-FWHM) using the $^{18}$ fluorodeoxyglucose technique.

## Graphics




Results: Awake whole-brain glucose metabolism averaged 6.9 +/- 1.5 mg [center dot] 100 g sup -1 [center dot] min sup -1 (means +/- SD). Isoflurane reduced whole-brain metabolism 46 +/- 11% to 3.6 +/- 0.3 mg [center dot] 100 g sup -1 [center dot] min sup -1 (P less or equal to 0.005). Regional metabolism decreased fairly uniformly throughout the brain, and no evidence of any regional metabolic increases were found in any brain region for any participant. A region-of-interest analysis showed that the pattern of regional metabolism evident during isoflurane anesthesia was not significantly different from that seen when participants were awake.

Conclusion: These data clarify that the anesthetic state evident in the living human brain during unresponsiveness induced with isoflurane is associated with a global, fairly uniform, whole-brain glucose metabolic reduction of 46 +/- 11%.


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Key words: Anesthetics, inhalational: isoflurane. Brain: cerebral cortex; cerebral glucose utilization; cerebral metabolic rate. Deoxyglucose: radionuclide imaging. Glucose,$^{18}$ Fluorodeoxyglucose. Humans. Measurement techniques: tomography; emission-computed. Positron.


Functional brain imaging technology offers a noninvasive method to investigate the global and regional metabolic effects of various anesthetic agents directly in the living human brain. Previous work with propofol revealed that the anesthetic state induced by propofol is associated with both a global reduction of whole-brain metabolism and some specific changes in regional cerebral metabolic activity. [1]

Until now, the nature of the anesthetic state induced by inhalational anesthesia had not been examined directly in the human brain. Regional cerebral glucose metabolism during inhalational anesthesia has been studied with the autoradiography technique in animal models, but the data regarding the regional metabolic effects of many agents obtained in these previous studies have revealed discrepant results. For example, one study reported that 1.5% isoflurane in the rat increased regional brain glucose metabolism above baseline awake values in several different brain structures. [2] Yet another similar study of isoflurane anesthesia in the rat found that isoflurane only decreased regional cerebral metabolism. [3] Similar discrepancies, regarding the effects of other common anesthetic agents on regional cerebral metabolism, also exist for halothane, [4-6] barbiturates, [7-9] and nitrous oxide. [9-11] Thus a unifying picture of how anesthetic agents effect regional (and global) brain metabolism and produce the anesthetic state has been elusive.

Therefore, to move toward an understanding of what characterizes the anesthetic state in the human brain and to clarify precisely what happens to regional brain metabolism in humans during inhalational anesthesia, we studied the global and regional cerebral glucose metabolic effects of isoflurane anesthesia in volunteers using positron emission tomography (PET).

## Materials and Methods

### Positron Emission Tomography Technique

The methods of quantitative PET imaging and our standard imaging procedures have been described previously. [1,12] Briefly, the study of cerebral glucose metabolism with PET is based on the same principles as the autoradiography technique developed

by Sokoloff and colleagues. [13] To study regional cerebral glucose utilization in humans, a positron-labeled deoxyglucose tracer, such as [18] fluorodeoxyglucose (FDG), is used. [14] This tracer is taken up by active brain neurons as if it were glucose. However, because of its "deoxy" structure and inability to be metabolized, it subsequently becomes metabolically trapped as FDG-6-phosphate within the intracellular compartment. The amount of radioactive label that occurs in each discrete region of the brain is related to the glucose uptake and metabolism of that discrete region. The rate of regional metabolism is driven by the underlying rate of local neuronal activity. [15] The more neuronal activity that occurs in a particular brain region, the more metabolism will increase to support that activity. Because the primary fuel for the brain is glucose, we can assess the relative amount of local functional underlying neuronal activity that occurs in a particular brain region by monitoring how much glucose that particular brain region uses in processing a particular stimulus (or functional state) over time. In essence, the more neuronal activity in a particular region, the more glucose will be used and the more the radioactive label will end up in that particular region of the brain.

In this study, we used the FDG technique. It stands to reason that, in the presence of an anesthetic, the assessment of regional cerebral glucose utilization is a more accurate assessment of regional brain metabolism than are estimates of brain metabolism derived from changes in regional cerebral blood flow data because anesthetics may directly affect the regional cerebral blood flow-regional cerebral metabolism relationship. [16] The FDG technique in humans uses a 32-45-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. [17] The eventual PET scan images obtained represent the accumulated regional FDG uptake that occurred during the corresponding uptake period. Glucose metabolic rate values (mg [center dot] 100 g sup -1 [center dot] min sup -1) were calculated using the deoxyglucose kinetic models of Sokoloff developed for autoradiography in animals and modified for humans. [13,14,17]

## Experimental Design

After obtaining full institutional review committee approval, five 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, whereas the other scan assessed cerebral metabolism associated with unconsciousness induced by isoflurane anesthesia. A minimum of 1 week separated scanning sessions.

## Participants

All participants, whose mean age was 24 +/- 3 yr, were nonsmokers, in excellent medical condition, and each was classified as American Society of Anesthesiologists physical status 1. All were screened carefully and found to have no evidence of previous psychiatric history or significant medical problems. Participants were asked to avoid caffeine and all other medications for at least 48 h before each scan. In addition, they fasted at least 8 h before each scan session and they received oral antacid (30 ml Bicitra [Baker Norton Pharmaceuticals, Miami, FL] orally) before the scan involving anesthesia.

An overview of the labeling and scanning sequence is discussed briefly below. Subjects were brought into a small sound-shielded room and placed on a gurney. After Bicitra was given, intravenous access was obtained, monitors were placed, and participants underwent a slow, careful inhalational induction of isoflurane anesthesia. Once the participants' conditions

were stable under anesthesia, the radioactive tracer FDG was injected and they remained at the same level of anesthesia for the next 32 min. During this period, the FDG tracer was taken up by active brain cells and converted to FDG-6-phosphate. Once the FDG was metabolized to FDG-6-phosphate it became trapped intracellularly. Because of this "trapping," the functional brain state evident during the uptake period essentially became fixed in time; this is analogous to exposing the film on a camera by snapping the shutter. After the brain was labeled with the positron-emitting tracer, the isoflurane was discontinued. Participants were allowed to emerge from the anesthetic and regain awareness before being taken to the PET scanner. Once in the scanner, the data representing the pattern of regional cerebral metabolism evident during the just-completed uptake period were collected; this is analogous to developing the film in the camera that had just been exposed. Participants continued to recover from the anesthetic while they were in the PET scanner.

The anesthesia scans always preceded the awake baseline scans. For the baseline condition, a similar labeling and scanning sequence, as outlined above, was followed. Scanning of all participants began within 20 min from the end of each uptake period for both the awake and anesthetized conditions. The time between injection of the FDG and the start of each scan itself was standardized across conditions to ensure that it was similar in length for all participants. Participants in both the awake and anesthetized conditions passively listened through headphones to a prerecorded audiotape of repeated words. Participants' ability to recall the words heard during anesthesia and how such recall correlates with cerebral metabolism will be reported in another publication.

## Anesthetic Procedures

The research laboratory was a small sound-shielded room with dim lighting. The participants wore blindfolds during both awake and anesthetized uptake periods to minimize any visual input. The headphones that the participants wore for the audiotape also helped minimize any extemporaneous environmental auditory inputs. Participant 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 intravenous catheters were inserted. One catheter was for FDG administration and the other for venous blood sampling. Blood samples were taken to quantify the uptake of FDG (see Phelps et al. [17]). For the awake-baseline scans, the participants were fasted and lay on a gurney as if they were about to have anesthesia. However, they simply lay quiet and still, with their eyes closed and blindfolded, while they listened to the audiotape for the 32-min uptake period.

For the anesthesia condition, subjects were connected to a Drager AV anesthesia machine (North American Drager, Telford, PA) 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 the participants were unresponsive, an air-oxygen mixture was used and the inspired oxygen level was adjusted to 30%.

Isoflurane was delivered into the breathing system using a standard vaporizer. End-tidal expired concentrations were monitored on a Poet II gas analyzer (Criticare Systems, Milwaukee, WI). Participants 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. Induction proceeded in a slow and deliberate step-wise manner to ensure that each participant would tolerate the isoflurane and undergo the induction without difficulty. The anesthetic agent was increased in 0.1% (expired) increments (i.e., 0.1%, 0.2%, 0.3%, and so on) approximately every 10-15 min until a stable percent expired isoflurane concentration was obtained at each targeted incremental step (i.e., the expired isoflurane concentration did not vary from the targeted incremental step for at least 4 min). Participants expired each incremental level of isoflurane for a minimum of 4 min before proceeding to the next higher step. Induction in this manner was well tolerated by all participants, although it took more than 1 h to achieve the desired anesthetic end-point before brain metabolic activity was measured. The anesthetic level was thus titrated to that which rendered participants just unresponsive to verbal or tactile stimulation. As they approached unresponsiveness, the eyelash reflex was tested every 3 min and they were asked to open their eyes until they no longer followed commands. When participants 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 loss of consciousness had occurred, an additional 12 min of anesthesia time was allowed to ensure that the brain anesthetic partial pressure was constant. In addition, the period of glucose metabolism measurement (i.e., injection of the FDG) only occurred after heart rate, blood pressure, and end-tidal carbon dioxide values remained stable for at least 5 min (+/- 2%) and the minimum 12-min preinjection period had passed. Once stable under the targeted level of isoflurane anesthesia, the participants were given 5 mCi FDG intravenously over a period of 1 min. The expired isoflurane concentration then remained constant for the subsequent 32-min period when the audiotape was played. After this uptake period, the isoflurane was discontinued and the participants were allowed to emerge from anesthesia before being taken to the PET scanner. After the discontinuation of the isoflurane, the participants opened their eyes at 6 +/- 2 min (means +/- SD), and they moved to the scanner with assistance at 14 +/- 2 min.

## Positron Emission Tomography Procedures

The PET scans were done after each uptake period using a GE 2048 head-dedicated scanner (GE/Scanditronix, Stockholm, Sweden). Two sets of 15 image planes, resulting in 30 PET images across the whole brain, were obtained for each participant. The PET scanner has a resolution of 4.5 mm (full-width-half-maximum) in plane and 6 mm axially. Scans were obtained relative to the canthomeatal line. Participants were positioned using laser guidance, and a thermosetting plastic face mask was used to hold each participant's head stationary while images were acquired. In vivo attenuation correction was obtained by previous transmission scanning using a (sup 68 Ge/sup 68 Ga) rod source.

Scans were transformed into glucose metabolic rates (GMR) as previously described. [18] Regions of interest were identified using stereotaxic coordinates derived from a standard neuroanatomic atlas. [19] Regions selected and analyses are comparable to our earlier propofol study, [1] but the isoflurane data were collected using a newer higher resolution scanner with updated software. Thus identical analyses between the two studies are not possible. [20] Nonetheless, regional anesthetic-induced "percent changes" from baseline are directly comparable between the studies. With the updated scanner software used, the units of absolute glucose metabolism are reported in milligrams of glucose per 100 g of tissue per minute rather than in micromoles. The sagittal image reconstruction (Figure 1) was rendered using BrainImage software (Kennedy Krieger

Institute, Baltimore, MD). [21]

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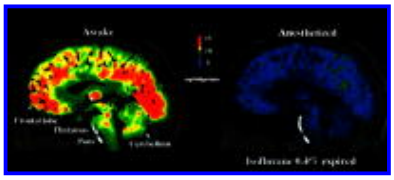

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Figure 1. Regional brain metabolism during isoflurane anesthesia. These positron emission tomography/magnetic resonance coregistered images show data from one representative participant whose whole-brain metabolic reduction during isoflurane anesthesia was at the group mean of 46%. The left image represents the person's awake baseline resting brain metabolic state. The right image represents this same man's brain metabolism during isoflurane anesthesia. He became unresponsive at 0.4% expired isoflurane concentration. The figure illustrates both the magnitude of the metabolic reduction and its uniformity throughout the brain. The sagittal images of regional metabolism are quantitative and placed on the same scale of glucose utilization (mg [center dot] 100 g sup -1 [center dot] min sup -1) according to the color scale bar. Comparing each participant's scan during anesthesia with their baseline scans revealed that isoflurane does not increase metabolism in any regions of the human brain. The underlying magnetic resonance image was obtained using the SPGR sequence with repetition time of 24 ms, echo time of 5 ms, and flip angle of 40 degrees for contiguous 1.2-mm-thick axial slices.

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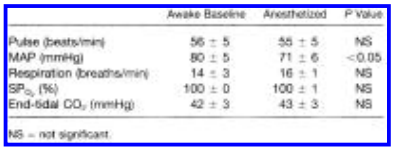
## Statistical Analysis

Differences of the means in whole-brain GMRs, various regions of interest for both GMR and relative GMR (GMR within a region of interest divided by whole-slice GMR), and physiologic variables were compared using paired (two-tailed) t tests. Calculations of relative GMR normalize for individual variations in whole-brain GMR between participants and conditions. Relative GMR was used to determine if the pattern of metabolic activity changed significantly within the brain during isoflurane anesthesia.

Data from each region of interest were treated as independent variables and are reported uncorrected for multiple comparisons. Results showing P less or equal to 0.05 are noted with the usual caveats demanded by a small sample and multiple comparisons. The multiple comparison problem in PET data analysis is a complex one, and no one method for dealing with this dilemma is yet accepted as a superior standard. Thus one common convention for addressing the multiple comparison problem is to simply report the various levels of probability values obtained for whatever comparison is made. This approach implies that a comparison with a probability value of 0.001 is more likely to represent a more robust finding than is a comparison with a value of 0.05, and thus it also implies that caution should be used when evaluating comparisons with probability values in the range of 0.05. For this study, we followed the common PET convention of reporting the various significance levels of the probability values obtained uncorrected for multiple comparisons so that other researchers can compare their results to ours for all brain areas.

## Results

The expired end-tidal isoflurane concentration that rendered the participants unresponsive to verbal or tactile stimulation ranged from 0.4% to 0.6% and averaged (+/- SD) 0.5 +/- 0.1%. Table 1 shows changes in the physiologic variables produced by this level of isoflurane anesthesia. Even though no participant required clinical intervention for any physiologic changes during anesthesia, the group-averaged evaluation of the physiologic variables does show that a statistically significant difference occurred in mean blood pressure (P less or equal to 0.05). The mean (+/- SD) blood pressure decreased from 80 +/- 5 mmHg at baseline to 71 +/- 6 mmHg during isoflurane anesthesia. Other variables did not change significantly during anesthesia.



| | Awake Baseline | Anesthetized | P Value |
|---|---|---|---|
| Pulse (beats/min) | 56 ± 5 | 55 ± 5 | NS |
| MAP (mmHg) | 80 ± 5 | 71 ± 6 | <0.05 |
| Respiration (breaths/min) | 14 ± 3 | 16 ± 1 | NS |
| $SP_{O_2}$ (%) | 100 ± 0 | 100 ± 1 | NS |
| End-tidal $CO_2$ (mmHg) | 42 ± 3 | 43 ± 3 | NS |

NS = not significant.

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Table 1. Physiologic Variables

Awake whole-brain Glucose Metabolic Rates (GMR) averaged 6.9 +/- 1.5 mg [center dot] 100 g sup -1 [center dot] min sup -1 (mean +/- SD). Isoflurane anesthesia significantly reduced whole-brain GMR to an average of 3.6 +/- 0.3 mg [center dot] 100 g sup -1 [center dot] min sup -1 (two-tailed paired t test; P less or equal to 0.005). The magnitude of this mean 46 +/- 11% metabolic reduction caused by isoflurane anesthesia can be appreciated by referring to Figure 1. This image shows the PET scan data obtained in one representative participant whose whole-brain metabolic reduction during isoflurane anesthesia equaled the group mean of 46% (this person also had magnetic resonance scanning). The figure shows a sagittal PET/magnetic resonance coregistered image in which the regional brain glucose metabolic data are plotted on the participant's magnetic resonance scan using a color-coded scale representing the metabolic pattern evident for both the awake and the anesthetized conditions. The rate of glucose metabolism in a particular brain area can be determined by noting the color in a particular region of interest and then finding that corresponding color on the color scale bar. For example, most of the activity within the "awake" brain is in the range of the yellows and reds and thus has regional metabolic rate values around 10-15 mg [center dot] 100 g sup - [center dot] min sup -1. In the "anesthetized" brain, however, the colors are in the range of the purples and blues and thus have values of approximately 3-8 mg [center dot] 100 g sup - [center dot] min sup -1 of glucose utilization. Because these PET images are quantified and placed on the same color scale bar, it can be seen that the amount of metabolism (a reflection of the underlying neuronal activity) occurring in an isoflurane-anesthetized brain is dramatically less than that of an awake brain. Although this participant's metabolic pattern is representative of the group mean, the individual variation in the percent decrease of whole-brain metabolism that was evident during isoflurane anesthesia ranged from 29% to 55% for the five participants.

The data in Figure 1 are displayed in a sagittal reconstruction to emphasize the extent of the generalized uniform metabolic reduction seen during isoflurane anesthesia. Each participant had this same type of generalized global metabolic reduction. No evidence of any regional metabolic increases were found in any brain regions, for any participant, during isoflurane anesthesia.

Isoflurane significantly decreased regional metabolism in all brain areas studied (Figure 2). Regional metabolism decreased in a fairly uniform manner in all brain areas during anesthesia. The minor regional variability seen in Figure 2 might suggest that some brain regions were affected more than others during isoflurane anesthesia. However, the regional variability in responsiveness to isoflurane was not statistically significant for any of the regions examined.

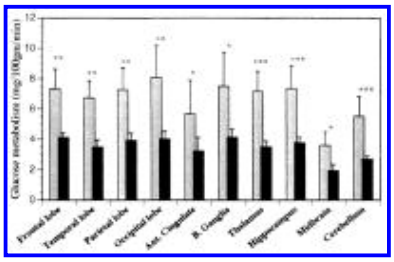

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Figure 2. Regional cerebral glucose metabolism (mg [center dot] 100 g sup -1 [center dot] min sup -1) during the awake (light bars) baseline condition and during isoflurane anesthesia (dark bars). The results are means +/- SD (n = 5). *P less or equal to 0.05; **P less or equal to 0.01; ***P less or equal to 0.005.

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The uniformity of the metabolic reduction during isoflurane anesthesia was also investigated by assessing the regional percentage changes of relative glucose metabolic rates that occurred during anesthesia compared with the baseline awake state. Using relative GMR data normalized out the global effect of the anesthetic agent on regional metabolism and allowed us to show further that no significant shifts in relative metabolism occurred during isoflurane anesthesia. Figure 3 shows where the limited amount of regional variability occurred in relative glucose metabolism between conditions.

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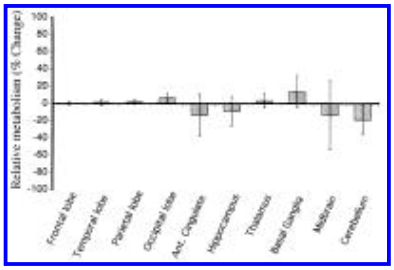

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Figure 3. Relative changes in the pattern of regional cerebral glucose metabolism (relative percentage change in each area) from the awake condition to the anesthetized condition. The figure shows that no significant changes in relative regional metabolism occurred during isoflurane anesthesia, a finding that emphasizes the uniformity of the metabolic reduction caused by isoflurane. Results are means +/- SD) (n = 5).

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## Discussion

Our results show that isoflurane anesthesia titrated to a point just past the loss of responsiveness in humans is, on average, associated with a 46% reduction of whole-brain glucose metabolism. Furthermore, the whole-brain metabolic reduction produced by isoflurane appears to be fairly uniform throughout the brain. However, two important considerations should be noted before concluding that isoflurane's effects on cerebral metabolism are truly uniform throughout the brain. Even though statistically significant changes in relative metabolism did not occur with the persons we studied, this is a relatively small sample (n = 5). A power analysis suggests that a sample of this size has an 80% power to detect a 30% change in regional relative metabolism with a significance level of 0.05 (two-tailed). Given the magnitude of the changes isoflurane produced in regional relative metabolism and the amount of variability present in the data, a sample size of about 20 would be required before a type II error might realistically be avoided on this issue. Therefore, even though our data suggest that isoflurane anesthesia does not result in significant shifts of regional relative metabolism, the possibility that isoflurane can produce regional metabolic shifts should not be ruled out conclusively.

Furthermore, the time resolution with PET and the autoradiography technique is limited by the kinetics involved with glucose uptake, distribution, and metabolism. Thus the images obtained do not represent the regional metabolic activity

that occurs at the precise moment when consciousness is lost during the induction of isoflurane anesthesia, but rather the near steady-state effects of isoflurane evident at only this one particular dose. The initial distribution of isoflurane throughout the brain may not be as uniform as suggested by these data. Thus it is possible that the metabolic effects of isoflurane evident in the brain at the precise moment when consciousness is lost could be much less uniform than what is suggested by our PET data.

Our results could potentially be affected by several variables that might alter cerebral blood flow physiology and hence delivery of the FDG tracer substance to the brain. Of most concern would be the possibility that CBF was dramatically changed by the anesthetic agent itself, by changes in blood pressure, or by changes in arterial carbon dioxide content.

We will address these concerns in order. First, inhalational anesthetic agents do tend to increase CBF in an agent- and dose-dependent manner. Halothane is thought to have the most effect on CBF and isoflurane the least effect. [22,23] However, isoflurane's effects on CBF are relatively minimal. In fact, even in doses as high as 1 minimum alveolar concentration (MAC), CBF is essentially unaltered. [23,24] Thus, at the low dose of isoflurane used in this study, no significant changes in CBF would have occurred. Second, although it is true that our participants did demonstrate a statistically significant decrease in blood pressure, the absolute level of the change was really fairly minimal and certainly well within the limits of cerebral autoregulation. Thus the small change in blood pressure evident during this study probably did not affect CBF and was inconsequential. Third, at the low dose of isoflurane studied, essentially no changes were evident in respirations or end-tidal carbon dioxide levels. Therefore there is no evidence that arterial carbon dioxide pressure changed enough to significantly affect CBF. Therefore it seems reasonable to conclude that the physiologic changes evident in our participants during anesthesia did not significantly affect tile present results.

The magnitude of the 46% glucose metabolic reduction seen during this low-dose isoflurane anesthesia corresponds reasonably well with the magnitude of the 51% reduction in cerebral oxygen metabolism ($CMRO_2$) reported for humans at 1 MAC of isoflurane anesthesia. [25] Comparing the magnitude of the $CMRO_2$ results with the present glucose metabolic data is reassuring that the order of magnitude of the effect reported here is probably reasonable. However, glucose metabolic data are not directly comparable with $CMRO_2$ data because the $CMRO_2$ data represent calculated values based partially on CBF responses, which can vary depending on the inhalational agent being studied.

The magnitude of the metabolic reduction seen during isoflurane anesthesia in humans corresponds fairly well with the overall magnitude of the metabolic reductions seen with isoflurane in the rat studied with the autoradiography technique. In our human data, 0.5% (expired) isoflurane anesthesia reduced cortical metabolism by 45% of awake baseline values and reduced whole-brain metabolism by 46%. Ori and coworkers [2] found that 1.5% isoflurane decreased regional glucose utilization across the cortical regions they examined by an average of 44%. In addition, Maekawa and colleagues [3] found that isoflurane between 1.5 and 2 MAC decreased regional cerebral glucose metabolism values by 50-70% of baseline awake levels. Thus, some consistency is noted across species in the effects of isoflurane on cerebral metabolism. However, the data are not completely consistent across species because the magnitude of the cortical metabolic reduction seen in humans at only 0.5% expired isoflurane was comparable to that seen in the rat at 1.5% isoflurane. This suggests that human brains may be more sensitive to the metabolic reduction effects of isoflurane than are rat brains, or that rat brains are more resistant

to isoflurane's effects.

Additional inconsistencies between the human and rat data exist. Ori and coworkers [2] found that isoflurane increased regional metabolism in areas of the extrapyramidal motor system and parts of the limbic system. Specifically, in Ori's study, metabolism was increased above baseline in the substantia nigra pars compacta (+43%), CA3 field of the dorsal hippocampus (+27%), medial habenula (+86%), the interpeduncular nucleus (+31%), and the fasciculus retroflexus (+119%). In contrast, Maekawa and colleagues [3] did not find any isoflurane-induced increases of metabolism in any of these rat brain areas, although they did find that some of these regions were resistant to the metabolic suppression effects of the isoflurane. Our human regional cerebral metabolic findings are more supportive of Maekawa's than Ori's findings, because we also found that isoflurane did not increase regional cerebral metabolism in any brain areas.

This "no increase" of regional metabolism effect of isoflurane was a consistent finding for all participants. We examined the consistency of this finding by placing each person's awake-baseline scan side by side on the same color scale of glucose metabolism with that particular subject's isoflurane scan. In so doing, it was evident that isoflurane does not increase regional metabolism in any areas of the human brain. This qualitative point can be appreciated by referring again to Figure 1, which shows that there are no areas of the brain where the isoflurane scan has a "hotter" color (color-indicating metabolic rate) than the awake-baseline scan.

It is possible that resolution issues may have contributed to our inability to find any areas of regional metabolic increase during isoflurane anesthesia. Most of the regions where metabolism appeared to increase in Ori's isoflurane study were actually small, and the corresponding structures in the human brain may be below the spatial resolution of PET. However, Ori's hippocampal findings in the rat brain were relatively large, and a similarly sized effect in humans should have been visible in our data. It is unlikely that the high-resolution scanner used in this study would have completely missed such an effect of isoflurane. Therefore, even noting the potential resolution issues involved between the studies, we still conclude that isoflurane titrated to the point of participant unconsciousness does not increase regional metabolism in any areas of the human brain.

It is unclear exactly what is responsible for the differences between the animal and human findings. It is likely a species-related difference because some evidence suggests that certain parts of the rat brain are resistant to the metabolic reduction effects of anesthesia. [3,8] However, the fact that different investigations on the same anesthetic agent in the same species often fail to produce consistent regional metabolic results across studies suggests that other unknown factors might influence the regional metabolic values obtained in animal studies. [2,3]

Our previous propofol study was performed in a manner similar to the present isoflurane study. [1] Volunteers were given propofol anesthesia titrated to the point of unresponsiveness in a manner similar to the present isoflurane study. The PET imaging procedures and data analyses were similar between studies (although the scanner used in the propofol study was an older NeuroECAT scanner). Comparing the present isoflurane results in humans with our previous human propofol findings suggests that some interesting patterns might be emerging.

The magnitude of the global whole-brain metabolic reduction seen with both agents was fairly similar. Isoflurane titrated to the point of participant unresponsiveness reduced whole-brain metabolism 46 +/- 11%, and propofol titrated to a similar clinical end-point reduced whole-brain metabolism 55 +/- 13%. However, the pattern of how global metabolism was reduced by each agent was not identical. Isoflurane reduced cerebral metabolism fairly uniformly throughout the brain, affecting cortical and subcortical structures to a similar extent. Propofol, on the other hand, previously was shown to have more regional variability in its metabolic effects and reduces cortical metabolism significantly more than subcortical metabolism. [1] As this previous observation about propofol might suggest, a comparison between isoflurane's relative cortical and subcortical metabolism and propofol's relative cortical and subcortical metabolism reveals that relative cortical metabolism is depressed significantly more during propofol anesthesia than during isoflurane anesthesia ($P < 0.001$, unmatched t test, two-tailed) and relative subcortical metabolism is significantly higher during propofol anesthesia than during isoflurane anesthesia ($P < 0.05$, unmatched t test, two-tailed).

In summary, the anesthetic state evident during isoflurane anesthesia titrated to the point of unresponsiveness in humans is associated with a fairly uniform global reduction in brain glucose metabolism.

## REFERENCES

1. Alkire MT, Haier RJ, Barker SJ, Shah NK, Wu JC, Kao YJ: Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology 1995; 82:393-403 (discussion 27A). [Context Link]

2. Ori C, Dam M, Pizzolato G, Battistin L, Giron G: Effects of isoflurane anesthesia on local cerebral glucose utilization in the rat. Anesthesiology 1986; 65:152-6. **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

3. Maekawa T, Tommasino C, Shapiro HM, Keifer GJ, Kohlenberger RW: Local cerebral blood flow and glucose utilization during isoflurane anesthesia in the rat. Anesthesiology 1986; 65:144-51. **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

4. Savaki HE, Desban M, Glowinski J, Besson MJ: Local cerebral glucose consumption in the rat. I. Effects of halothane anesthesia. J Comp Neurol 1983; 213:36-45. **ExternalResolverBasic Bibliographic Links** [Context Link]

5. Shapiro HM, Greenberg JH, Reivich M, Ashmead G, Sokoloff L: Local cerebral glucose uptake in awake and halothane-anesthetized primates. Anesthesiology 1978; 48:97-103. **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

6. Crosby G, Atlas S: Local spinal cord glucose utilization in conscious and halothane-anaesthetized rats. Can J Anaesth 1988; 35:359-63. **ExternalResolverBasic Bibliographic Links** [Context Link]

7. Crane PD, Braun LD, Cornford EM, Cremer JE, Glass JM, Oldendorf WH: Dose dependent reduction of glucose utilization by pentobarbital in rat brain. Stroke 1978; 9:12-8. **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

8. Hodes JE, Soncrant TT, Larson DM, Carlson SG, Rapoport SI: Selective changes in local cerebral glucose utilization induced by phenobarbital in the rat. Anesthesiology 1985; 63:633-9. **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

9. Sakabe T, Tsutsui T, Maekawa T, Ishikawa T, Takeshita H: Local cerebral glucose utilization during nitrous oxide and pentobarbital anesthesia in rats. Anesthesiology 1985; 63:262-6. **Ovid Full Text ExternalResolverBasic Bibliographic**

**Links** [Context Link]

10. Cole DJ, Shapiro HM: Different 1.2 MAC combinations of nitrous oxide-enflurane cause unique cerebral and spinal cord metabolic responses in the rat. Anesthesiology 1989; 70:787-92. **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

11. Ingvar M, Siesjo BK: Effect of nitrous oxide on local cerebral glucose utilization in rats. J Cereb Blood Flow Metab 1982; 2:481-6. **ExternalResolverBasic Bibliographic Links** [Context Link]

12. Haier RJ, Siegel BJ, MacLachlan A, Soderling E, Lottenberg S, Buchsbaum MS: Regional glucose metabolic changes after learning a complex visuospatial/motor task: A positron emission tomographic study. Brain Res 1992; 570:134-43. **ExternalResolverBasic Bibliographic Links** [Context Link]

13. Sokoloff L, Reivich M, Kennedy C, Des RM, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M: The [14C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 1977; 28:897-916. **ExternalResolverBasic Bibliographic Links** [Context Link]

14. Huang SC, Phelps ME, Hoffman EJ, Sideris K, Selin CJ, Kuhl DE: Noninvasive determination of local cerebral metabolic rate of glucose in man. Am J Physiol 1980; 238:E69-82. **ExternalResolverBasic Bibliographic Links** [Context Link]

15. Sokoloff L: Relationships among local functional activity, energy metabolism, and blood flow in the central nervous system. Fed Proc 1981; 40:2311-6. **ExternalResolverBasic Bibliographic Links** [Context Link]

16. Michenfelder JD: Anesthesia and the Brain. New York, Churchill Livingstone, 1988, pp 36-41. [Context Link]

17. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE: Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: Validation of method. Ann Neurol 1979; 6:371-88. **ExternalResolverBasic Bibliographic Links** [Context Link]

18. Buchsbaum MS, DeLisi LE, Holcomb HH, Cappelletti J, King AC, Johnson J, Hazlett E, Dowling ZS, Post RM, Morihisa J: Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. Arch Gen Psychiatry 1984; 41:1159-66. [Context Link]

19. Matsui T, Hirano A: An Atlas of Human Brain for Computerized Tomography. Tokyo, Igaku-Shoin, 1978. [Context Link]

20. Grady CL: Quantitative comparison of measurements of cerebral glucose metabolic rate made with two positron cameras. J Cereb Blood Flow Metab 1991; 11:A57-63. **ExternalResolverBasic Bibliographic Links** [Context Link]

21. Reiss AL, Hennessey JG, Subramanium B, Beach LS, Rubin MA: BrainImage version 2.0. Balitmore: Kennedy Krieger Institute, 1996. [Context Link]

22. Barash PG, Cullen BF, Stoelting RK: Clinical Anesthesia. Philadelphia, JB Lippincott, 1992, p 444. [Context Link]

23. Todd MM, Drummond JC: A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. Anesthesiology 1984; 60:276-82. **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

24. Eger EI. II: Isoflurane: A review. Anesthesiology 1981; 55:559. **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

25. Olsen KS, Henriksen L, Dige-Petersen H, Chraemmer-Jorgensen B, Rosenorn J: Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam-fentanyl or isoflurane anaesthesia. Br J Anaesth 1992; 69:263-

Ovid: Positron Emission Tomography Study of Regional Cerebral Metabolism in Humans during Isoflurane Anesthesia.

8. **ExternalResolverBasic Bibliographic Links** [Context Link]

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