

Effects of Subanesthetic Ketamine on Regional Cerebral Glucose Metabolism in Humans

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Background: The authors have recently shown with positron emission tomography that subanesthetic doses of racemic ketamine increase cerebral blood flow but do not affect oxygen consumption significantly. In this study, the authors wanted to assess the effects of racemic ketamine on regional glucose metabolic rate (rGMR) in similar conditions to establish whether ketamine truly induces disturbed coupling between cerebral blood flow and metabolism.

Methods: ^{18}F -labeled fluorodeoxyglucose was used as a positron emission tomography tracer to quantify rGMR on 12 brain regions of interest of nine healthy male volunteers at baseline and during a 300-ng/ml ketamine target concentration level. In addition, voxel-based analysis was performed for the relative changes in rGMR using statistical parametric mapping.

Results: The mean \pm SD measured ketamine serum concentration was 326.4 ± 86.3 ng/ml. The mean arterial pressure was slightly increased (maximally by 16.4%) during ketamine infusion ($P < 0.001$). Ketamine increased absolute rGMR significantly in most regions of interest studied. The greatest increases were detected in the thalamus ($14.6 \pm 15.9\%$; $P = 0.029$) and in the frontal ($13.6 \pm 13.1\%$; $P = 0.011$) and parietal cortices ($13.1 \pm 11.2\%$; $P = 0.007$). Absolute rGMR was not decreased anywhere in the brain. The voxel-based analysis revealed relative rGMR increases in the frontal, temporal, and parietal cortices.

Conclusions: Global increases in rGMR seem to parallel ketamine-induced increases in cerebral blood flow detected in the authors' earlier study. Therefore, ketamine-induced disturbance of coupling between cerebral blood flow and metabolism is highly unlikely. The previously observed decrease in oxygen

extraction fraction may be due to nonoxidative glucose metabolism during ketamine-induced increase in glutamate release.

THE noncompetitive *N*-methyl-D-aspartate receptor antagonist ketamine is an anesthetic with a rapid onset and a short duration of action. It is known to produce sympathetic activation by direct central nervous system stimulation, making it an anesthetic devoid of the cardiovascular depression that is often associated with other anesthetics.¹ Because of its unique characteristics, ketamine has been deemed particularly suitable for induction and maintenance of anesthesia in hemodynamically compromised patients.^{1,2} Because ketamine induces only minimal depression on respiration and many of the protective reflexes (such as coughing and swallowing), it can also be used for sedation and analgesia outside the operating room. Its moderate analgesic effects make it the closest thing to a monoanesthetic.^{1,2}

Ketamine has been associated with improved outcome in animals with cerebral damage.^{3,4} The observed neuroprotective effect is attributed to *N*-methyl-D-aspartate receptor antagonism.³⁻⁵ However, because ketamine increases cerebral blood flow (CBF) even in sedative or analgesic doses,^{6,7} its use in patients with increased intracranial pressure or decreased intracranial compliance is not recommended.^{2,8} However, ketamine does not seem to have marked effects on the cerebral metabolic rate of oxygen (CMRO_2).^{7,9} Because some evidence of increased cerebral glucose metabolic rate (GMR) during ketamine administration has been previously presented,¹⁰ ketamine-induced disturbance in coupling between CBF and metabolism, however, seems unlikely.

Our aim was to quantify the effects of subanesthetic ketamine on regional GMR (rGMR) in the human brain *in vivo* using ^{18}F -labeled fluorodeoxyglucose (^{18}F]FDG) and positron emission tomography (PET). We wanted to explore whether ketamine-induced changes in rGMR would differ from the changes in CBF or CMRO_2 observed in our earlier study and thus establish whether ketamine truly induces a disturbance of coupling between CBF and metabolism. We hypothesized that subanesthetic ketamine would induce a global increase in GMR.

Materials and Methods

Subjects and Study Design

The study protocol was approved by the Ethical Committee of the Hospital District of Varsinais-Suomi (Turku, Finland). After giving written informed consent, nine healthy (American Society of Anesthesiologists physical

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status class D), nonsmoking, right-handed male volunteers aged 22–29 yr with body mass index of $23.8 \pm 2.4 \text{ kg/m}^2$ (mean \pm SD, hereinafter presented similarly) were recruited in this open, nonrandomized study. All nine subjects underwent a detailed prestudy examination, including laboratory investigations and 12-lead electrocardiography. They confirmed having no history of drug allergies or ongoing medications. Subjects refrained from using alcohol or any medication for 48 h and fasted at least 6 h before the PET scans.

^{18}F -labeled fluorodeoxyglucose was used as a PET tracer to assess rGMR at baseline (no drug) and during 300 ng/ml pseudo-steady state concentration level of ketamine. Because of the long half-life of ^{18}F (110 min), the two PET scans were performed on separate days. The first rGMR assessment was performed without the drug, and the second was performed during ketamine infusion approximately 2 weeks later.

Administration of the Study Treatment and Monitoring

The left radial artery and two large veins in the right forearm were cannulated for blood sampling and for the administration of acetated Ringer's and 0.9% NaCl solutions (50 ml/h), ketamine, and ^{18}F FDG. The subjects were connected to a monitor (Datex AS/3; Datex-Ohmeda Division, Instrumentarium Corp, Helsinki, Finland) recording the electrocardiogram, noninvasive blood pressure, heart rate, respiratory rate, peripheral oxygen saturation, and end-tidal carbon dioxide (ETCO_2). The vital signs and individual values of ETCO_2 were recorded every 5–10 min throughout the study. Oral breathing instructions were given to keep subjects' ETCO_2 values at the baseline level.

Subjects received no premedication. Ketamine was administered as a continuous intravenous target-controlled infusion using the Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA) connected to a portable computer running Stanpump software $\S\S$ (Prof. Steven L. Shafer, M.D., Department of Anesthesia, Stanford University, Stanford, CA).^{11,12} The ketamine target serum concentration level was set to 300 ng/ml based on our previous study.⁷ After commencing the infusion, a 15-min stabilization period was allowed to pass before the PET scan. At the end of the second scan before the ketamine infusion was terminated, a 5-ml arterial blood sample was collected for determination of serum ketamine concentration. Serum was immediately separated and kept frozen at -70°C until analyzed with high-performance liquid chromatography (Yhtyneet laboratorio, Helsinki, Finland).¹³

PET Assessment

^{18}F was manufactured locally with cyclotron MGC-20 (D.V. Efemov Institute, St. Petersburg, Russia). For assessment of rGMR, ^{18}F FDG (2- ^{18}F fluoro-2-deoxy-D-glucose) was produced with automatic apparatus using a modified aminopolyether-supported nucleophilic substitution method.¹⁴ Radiochemical purity of ^{18}F FDG exceeded 95%, and at the end of synthesis, the specific activity surpassed $74 \text{ GBq}/\mu\text{mol}$ (2 Ci/ μmol).

All PET studies were performed in a quiet, dimly lit room. Head movement was minimized with a plastic head holder. ^{18}F FDG (111 MBq) was administered as a 20-s bolus injection followed by a 60-min dynamic three-dimensional tissue activity image acquisition consisting of 25 frames (one 30-s frame, ten 15-s frames, two 30-s frames, one 1-min frame, and eleven 5-min frames). Descriptions of the PET scanner and image reconstruction are given in our previous article.¹⁵ Starting immediately after the tracer injection, 22 arterial samples were drawn for plasma activity determination (13 samples within the first 3 min followed by a sample at 4, 6, 10, 15, 20, 30, 40, 50, and 60 min after the tracer injection). Activity was measured using an automated cross calibrated well counter (Wizard 1480; Wallac, Turku, Finland). Additional arterial samples were obtained for plasma glucose concentration measurement before the tracer injection and 30 and 60 min after the beginning of the scan. The mean of these three measurements was used in data analysis.

Data Analysis

The subject's dynamic tracer activity acquisition images (dynamic ^{18}F FDG image) were first computed into parametric rGMR images using tracer kinetic modeling and plasma activity data (see the next paragraph).¹⁶ Individual magnetic resonance images acquired in a separate session with a 1.5-T scanner (Siemens Magnetom SP63, Erlangen, Germany) were then coregistered separately for both parametric (baseline and 300 ng/ml ketamine) images of the subject using Statistical Parametric Mapping (SPM) software (version 99; Wellcome Department of Cognitive Neurology, University College London, England).¹⁷ Individual regions of interest (ROIs) were drawn to the planes of the coregistered magnetic resonance images using Imadeus 1.0 (Forima Inc., Turku, Finland) to bilaterally outline the frontal (on 14 or 15 image planes), parietal (5 planes), temporal (8 or 9 planes), and occipital (4 planes) gray matter; the anterior (7 or 8 planes) and the posterior cingulate (2–4 planes); the insula (3 planes); the thalamus (2 or 3 planes); the caudate (3 or 4 planes); the putamen (3 or 4 planes); and the cerebellum (3 planes). The whole-brain GMR was determined by drawing a single ROI (on 3 planes superior to the lateral ventricles) outlining all brain tissue inside the skull. ROIs were then transferred to the cor-

$\S\S$ Stanpump software. Available at: <http://anesthesia.stanford.edu/pkpd>. Accessed March 24, 2004.

responding planes of the dynamic [^{18}F]FDG images to obtain time-activity curves for each structure.

For the kinetic modeling, the influx constant of [^{18}F]FDG (K_i) was determined from time activity data using a graphical analysis based on the assumption of irreversible trapping of the tracer.¹⁶ The equilibrium of the tracer plasma and tissue concentrations is achieved as the plot becomes linear approximately 10 min after [^{18}F]FDG injection. rGMR was determined using K_i , plasma glucose concentration (C_{glu}), and the lumped constant according to equation 1.¹⁸

$$\text{rGMR} = \frac{K_i \times C_{\text{glu}}}{\text{Lumped Constant}} \quad (1)$$

The lumped constant is necessary for correcting the differences in the transport and the phosphorylation velocities between [^{18}F]FDG and glucose. A lumped constant value of 0.52 was used in the analysis.¹⁹ It was assumed in this study that ketamine has no effect on this constant. The average brain tissue density (1.04 g/ml) was used to convert the values of absolute rGMR into $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$.

Statistical Analysis of ROI and Monitoring Data

Quantitative rGMR and physiologic variables were analyzed with repeated-measures analysis of variance having the treatment (no drug/ketamine) as the within factor. The subjects were treated as a random effect. To exclude significant differences between the hemispheres in the rGMR changes induced by ketamine, the repeated-measures analysis of variance was also used for models with two within factors: side (left/right) and treatment (no drug/ketamine). Statistical analyses were conducted with SAS (version 8.2; SAS Institute Inc., Cary, NC). A two-sided P value of less than 0.05 was considered statistically significant. Data are presented as mean \pm SD if not otherwise stated.

Relative Voxel-based Analysis with SPM

Statistical Parametric Mapping software¹⁷ running under MATLAB (MATLAB 6.5; The MathWorks, Inc., Natick, MA) was used for the voxel-based statistical analysis of the quantitative parametric rGMR images. The SPM preprocessing was performed as described in our previous article.¹⁵ The images were smoothed using an isotropic Gaussian filter of 12 mm full width at half maximum. SPM was used to analyze the relative changes in rGMR to detect the most significant changes in rGMR. This was accomplished by scaling the rGMR values proportionally to global mean (global normalization with proportional scaling). It is emphasized that during a

Table 1. Summary of Hemodynamic and Respiratory Values at Baseline and during 300 ng/ml Target Concentration of Ketamine

Parameter	No Drug	300 ng/ml	P Value
Ketamine concentration, ng/ml	—	326.4 \pm 86.3	NA
Mean arterial blood pressure, mmHg	93.8 \pm 6.8	109.0 \pm 6.1	< 0.001
Heart rate, beats/min	60.8 \pm 12.1	77.8 \pm 16.4	< 0.001
Respiratory rate, breaths/min	14.5 \pm 1.5	14.7 \pm 1.2	NS
Peripheral oxygen saturation, %	98.1 \pm 0.9	99.0 \pm 0.8	0.015
End-tidal carbon dioxide, mmHg	41.8 \pm 2.6	39.9 \pm 4.2	NS

Statistically significant differences between the ketamine target concentration level and baseline are shown. Values are given as group mean \pm SD.

NA = not applicable; NS = not significant.

global absolute increase (as in this study), the relative decreases may actually represent the areas of the smallest increase. Biologic implication of the smallest rGMR increase may be considered questionable, and to avoid confusion, the areas of relative rGMR decrease were not visualized.

Subtraction analysis with T contrasts was used to test ketamine-induced differences between the conditions at cluster level.^{7,20} The changes were considered significant at $P < 0.05$ (corrected for multiple comparisons). For visualization of the relative changes, the height threshold was set to $T = 2.90$, and the extend threshold was set to 400 voxels.

The Montreal Neurological Institute (McGill University, Montreal, Quebec, Canada) coordinates received from the statistical analysis were converted to Talairach coordinates²¹ using mni2tal conversion software (MRC Cognition and Brain Sciences Unit, Cambridge, England).||| For the localization, Talairach Daemon Software (University of Texas Health Science Center at San Antonio, San Antonio, TX)## was used.²²

Results

The mean \pm SD measured ketamine serum concentration was 326.4 \pm 86.3 ng/ml. All volunteers experienced distinct ketamine-induced subjective effects but remained conscious, responsive, and cooperative during the assessments. Altered body image (six of nine), visual hallucinations (five of nine), sensation of moving or floating (three of nine), and disturbances in the concept of time (three of nine) were most often reported.

The baseline ETCO_2 varied between 30.2 and 44.7 mmHg. There was no statistically significant difference in the mean ETCO_2 between the scans. The mean arterial pressure was increased by 16.4% ($P < 0.001$) and heart rate was increased by 28.3% ($P < 0.001$) during the ketamine infusion (table 1). Measured mean plasma glucose con-

||| Brett M, 1999. Available at: <http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.html>. Accessed March 24, 2004.

Lancaster *et al.* 2000. Available at: <http://ric.uthscsa.edu/research/body.html>. Accessed March 24, 2004.

Table 2. Absolute Regional Glucose Metabolic Rate ($\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) Values of Region-of-interest-defined Structures at Baseline and during 300 ng/ml Target Concentration of Ketamine

Region	No Drug	300 ng/ml	P Value
Anterior cingulate	29.79 \pm 3.52	32.32 \pm 2.77	0.035
Posterior cingulate	39.66 \pm 4.60	42.84 \pm 4.50	0.032
Frontal cortex	36.15 \pm 2.97	40.87 \pm 3.77	0.011
Occipital cortex	30.60 \pm 2.68	32.76 \pm 3.67	NS
Parietal cortex	33.60 \pm 2.60	37.92 \pm 3.67	0.007
Temporal cortex	32.18 \pm 2.93	35.31 \pm 4.23	NS
Caudate	36.97 \pm 3.62	40.36 \pm 3.61	0.039
Putamen	39.36 \pm 4.38	41.82 \pm 4.83	NS
Thalamus	37.40 \pm 3.82	42.67 \pm 5.95	0.029
Cerebellum	28.53 \pm 3.41	31.59 \pm 4.05	0.026
Insula	30.74 \pm 2.54	32.51 \pm 4.47	NS
Whole brain	29.58 \pm 2.56	33.02 \pm 3.61	0.012

Statistically significant differences between the ketamine target concentration level and baseline are shown. Values are given as group mean \pm SD.

NS = not significant.

centrations did not differ significantly between the scans.

Absolute rGMR: ROI Analysis

The mean baseline rGMR was 28.5–39.7 $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ in the studied regions. There were no statistically significant differences between the hemispheres in any of the regions, and no significant side-by-treatment interactions were observed. Ketamine increased rGMR significantly in most ROIs studied. The greatest increases were detected in the thalamus (14.6 \pm 15.9%; $P = 0.029$) and the frontal (13.6 \pm 13.1%; $P =$

0.011) and parietal cortices (13.1 \pm 11.2%; $P = 0.007$), and lesser increases were detected in the cerebellum (11.2 \pm 12.4%; $P = 0.026$), the caudate (9.8 \pm 12.1%; $P = 0.039$), the anterior cingulate (9.2 \pm 10.5%; $P = 0.035$), and the posterior cingulate (8.5 \pm 10.2%; $P = 0.032$). Whole brain GMR was increased by 11.9 \pm 10.9% ($P = 0.012$) (table 2 and figs. 1 and 2). rGMR was not decreased in any of the regions studied.

Regional GMR increases correlated positively (correlation coefficient ranging from 0.69 to 0.86) with the measured ketamine serum concentrations in the frontal ($P = 0.019$), parietal ($P = 0.011$), temporal ($P = 0.014$), and posterior cingulate ($P = 0.034$) cortices; the thalamus ($P = 0.038$); the caudate ($P = 0.003$); the putamen ($P = 0.012$); the insula ($P = 0.021$); the cerebellum ($P = 0.009$); and the whole brain ($P = 0.018$).

Relative rGMR: SPM Analysis

The clusters of the relative rGMR increase were detected in the frontal, temporal, and parietal cortices (fig. 3). Clusters of the relative rGMR decreases extended to the claustrum, the cerebellum, the lentiform nucleus, the head of caudate, the insula, and the temporal cortex. The stereotactic coordinates for the relative changes in rGMR are presented on the ANESTHESIOLOGY Web site at <http://www.anesthesiology.org>.

Discussion

Continuous target-controlled infusion of ketamine aiming at a subanesthetic serum concentration level of

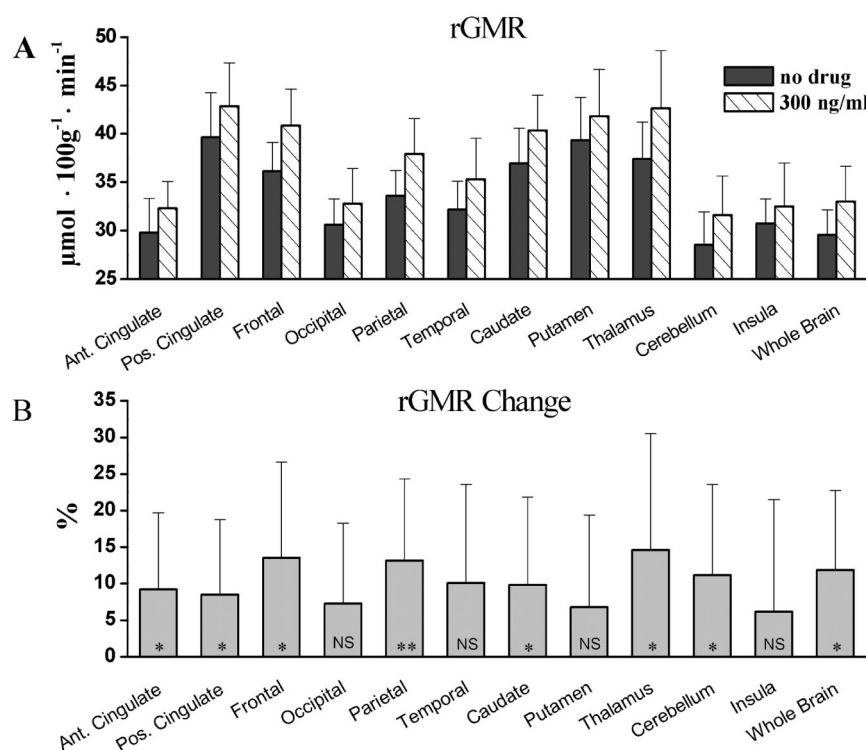
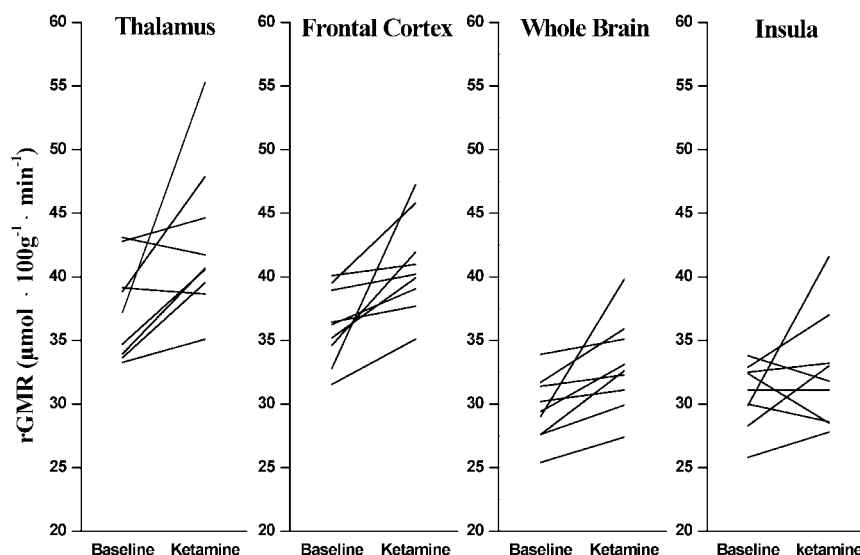


Fig. 1. (A) Absolute values of regional glucose metabolic rate (rGMR; $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) of region of interest-defined structures at baseline and during ketamine target concentration level of 300 ng/ml, shown as group mean \pm SD. **(B)** Ketamine-induced percent changes of rGMR, shown as group mean \pm SD. * $P < 0.05$, ** $P < 0.01$. Ant. = anterior; NS = not significant; Pos. = posterior.

Fig. 2. Absolute values of regional glucose metabolic rate (rGMR; $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) of all nine subjects shown at baseline and during 300 ng/ml ketamine target concentration level in the thalamus, frontal cortex, whole brain, and insula. Changes in the insula were not statistically significant.

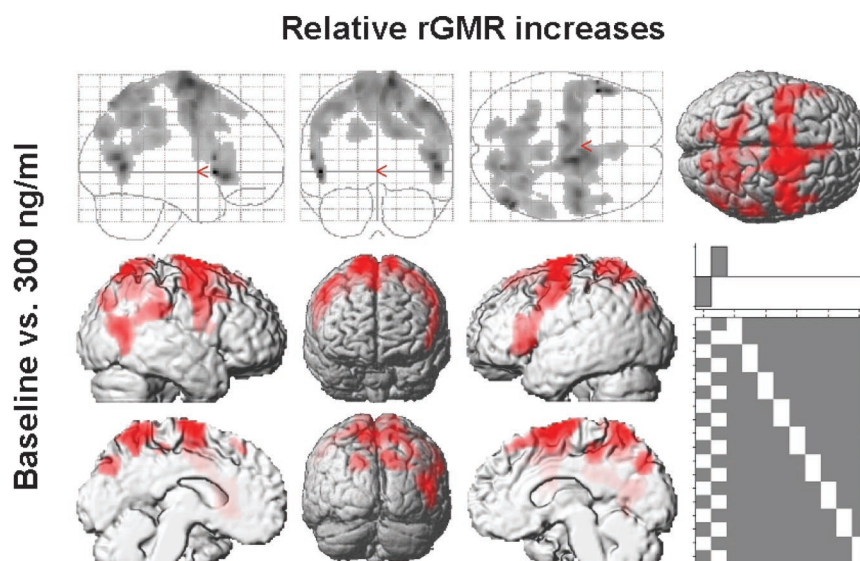


300 ng/ml induced a global increase in rGMR. The greatest absolute increases were detected in the thalamus and the frontal and parietal cortices, followed by lesser increases in the cerebellum, the caudate nucleus, and the cingulate gyrus. rGMR did not decrease anywhere in the brain. During the study, all nine subjects experienced distinct subjective effects by ketamine but remained conscious, spontaneously breathing, and cooperative.

General anesthetic agents such as propofol and isoflurane are known to reduce global cerebral rGMR because decreased cerebral uptake of [^{18}F]FDG has been observed with PET.^{23,24} The metabolic effects of ketamine seem to be unique among anesthetics because 10- to 100-mg/kg bolus doses have been shown to increase glucose metabolism in the limbic system and to decrease GMR in the inferior colliculus of the rat brain.^{25,26} In a recent human PET study, a subanesthetic ketamine infusion ($0.02\text{--}0.03 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) increased rGMR (maximally by 34%) in the anterior cingulate; the insula;

and the frontal, parietal, somatosensory, motor, and temporal cortices in healthy subjects.¹⁰ Similarly to the current study, rGMR was not decreased in any brain region. However, there are a few differences between these two studies. The rGMR increases were generally somewhat smaller, and the increases in the insula and the temporal cortex were not statistically significant in our study. Ketamine-induced changes in GMR may be concentration dependent, as we have recently demonstrated for CBF.⁷ Therefore, the differences in rGMR could, at least partly, be explained by the slightly lower ketamine serum concentration level in the current study ($326.4 \pm 86.3 \text{ ng/ml}$ compared with $557 \pm 254 \text{ ng/ml}$ in the study by Volleweider *et al.*¹⁰) but also by the applied infusion scheme. To our knowledge, the effect of target-controlled ketamine infusion on brain GMR has not been studied previously. The current target concentration level of 300 ng/ml was selected based on our previous study demonstrating marked changes in CBF on con-

Fig. 3. Regions with statistically significant ($P < 0.05$, corrected for multiple comparisons) ketamine-induced (300 ng/ml) relative regional glucose metabolic rate (rGMR) increases (cluster level) are presented in red. The increases are located in the frontal, temporal, and parietal cortices. The stereotactic coordinates are presented on the ANESTHESIOLOGY Web site at <http://www.anesthesiology.org>. For details, see Materials and Methods, Data Analysis, Relative Voxel-based Analysis with SPM.



scious, cooperative subjects.⁷ To date, only few studies have assessed the effects of anesthetic doses of ketamine on cerebral metabolism in humans. One early study has suggested that anesthetic ketamine would not have significant effects on human GMR.⁹ Regional effects of anesthetic doses remain to be studied.

Preservation of ion gradients across the cellular membranes is the major energy consumer in the brain. Most of this energy is derived from oxidative metabolism of glucose.²⁷ Eighty to ninety percent of the cortical glucose consumption is due to energy demands of glutamatergic neurons, the dominant excitatory neurotransmitter system in the brain.²⁸ Although ketamine inhibits the effects of glutamate on *N*-methyl-D-aspartate receptors,³ it has also been shown to concomitantly induce the release of glutamate.²⁹ The mechanism for ketamine-induced glutamate release, however, is unclear. Racemic ketamine might disrupt the tonic autoinhibition of glutamate release *via* inhibition of presynaptic glutamate receptors,^{2,29–31} but disrupted γ -aminobutyric acid-mediated inhibition of glutamate release has also been suggested.^{29,32,33} The released glutamate must be removed from the synaptic cleft not only to terminate its neurotransmitter effects, but also to prevent extracellular glutamate from reaching excitotoxic concentrations.³⁴ Astrocytes have been suggested to be primarily responsible for this glucose-consuming uptake of glutamate.²⁸ Indeed, tight coupling (approximately 1:1) of cerebral glucose metabolism and the cycling of glutamate between the neurons and the astrocytes has been demonstrated.³⁵ Although the mechanism behind ketamine-induced increase in rGMR is not known, it is tempting to suggest that glutamate release is probably closely involved.

Positron emission tomography studies performed more than a decade ago have challenged the classic paradigm of neuronal activation \approx cerebral metabolism \approx CBF because increases in CBF and GMR seem to exceed the changes in CMRO₂ during focal neuronal activation and cause a decrease in the oxygen-to-glucose index (OGI).^{36,37} In our previous PET study, ketamine increased rCBF without concomitant changes in CMRO₂, insinuating disturbed coupling between CBF and metabolism.⁷ Because rGMR was increased by ketamine in similar conditions in the current study, the disturbance in coupling seems highly unlikely. Interestingly, the effects of subanesthetic ketamine seem to resemble those seen during focal neuronal activation. As an explanation to the activation-induced decrease in OGI, it has been postulated that astrocytes respond to increased glutamate release by nonoxidative glucose metabolism and lactate production (*i.e.*, glycolysis) to quickly meet the energy requirements needed for glutamate uptake and normalization of the ionic milieu.^{34,38–40} However, OGI would be decreased only if the increase in GMR would exceed the increase in CMRO₂. This would ensue if part of the created lactate were effluxed into the circulation

and oxidized outside the brain, as has been theorized previously.⁴¹ Although there is evidence of lactate transport to other tissues for oxidation,^{38,42} the theory of lactate efflux has been questioned because it would lead to wasteful use of glucose in the brain.³⁸ Nevertheless, ketamine has been shown to increase brain lactate concentration in rats.⁴³

Because neuronal activity *per se* cannot be unambiguously quantified, the functional brain imaging is based on the assumption that changes in CBF reflect concomitant changes in cerebral metabolism and neuronal signaling.⁴⁴ However, during anesthesia with volatile anesthetics, disturbed coupling between CBF and metabolism may occur, as recently demonstrated during sevoflurane and nitrous oxide anesthesia.¹⁵ Therefore, it seems that neurofunctional effects of anesthetics cannot always be unequivocally evaluated using only CBF measurements. Concomitant CMRO₂ assessment may provide additional information, but according to our own previous results⁷ and the current results, CMRO₂ may not always detect drug-induced changes in cerebral metabolism. A direct comparison of the current changes in GMR and the CBF changes reported previously⁷ was impossible because the study subjects and the measured ketamine concentrations were different. For the same reason, we could not determine individual OGI values. However, the global increase in rGMR combined to unchanged CMRO₂ observed previously⁷ suggests that OGI would be decreased by subanesthetic ketamine. Ideally, it would be preferable to assess all three, *i.e.*, rCBF, regional CMRO₂, and rGMR, concomitantly when studying the effects of anesthetics on brain homeostasis. However, because of the longer half-life of ¹⁸F (110 *vs.* 2 min for ¹⁵O), the baseline [¹⁸F]FDG scan must be performed in a separate study session.

We conclude that subanesthetic ketamine produces a widespread increase in glucose metabolism in the brain, refuting the earlier suspicion of ketamine-induced disturbance in coupling between CBF and metabolism. The previously observed decrease in oxygen extraction fraction may be due to nonoxidative glucose metabolism during ketamine-induced increase in glutamate release.

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