Propofol Anesthesia and Cerebral Blood Flow Changes Elicited by Vibrotactile Stimulation: A Positron Emission Tomography Study

V. BONHOMME,1 P. FISET,1 P. MEURET,1 S. BACKMAN,1 G. PLOURDE,1 T. PAUS,2 M. C. BUSHNELL,1 AND A. C. EVANS2
1Department of Anesthesia and 2Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec H3A 1A2, Canada

Received 22 March 2000; accepted in final form 17 November 2000

Propofol anesthesia and cerebral blood flow changes elicited by vibrotactile stimulation: a positron emission tomography study. J Neurophysiol 85: 1299–1308, 2001. We investigated the effects of the general anesthetic agent propofol on cerebral structures involved in the processing of vibrotactile information. Using positron emission tomography (PET) and the $\text{H}_2^{15}\text{O}$ bolus technique, we measured regional distribution of cerebral blood flow (CBF) in eight healthy human volunteers. They were scanned under five different levels of propofol anesthesia. Using a computer-controlled infusion, the following plasma levels of propofol were achieved: Level 1 (0.5 m$g$/ml), Level 2 (1.5 m$g$/ml), Level 3 (3.5 m$g$/ml), and Level R (Recovery).

METHODS

Subjects

Eight healthy right-handed volunteers [4 males and 4 females between 18 and 29 yr of age (mean ± SD, 23.75 ± 3.92 yr)] participated in this study. All procedures were approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital and were in accordance with the Declaration of Human Rights, Helsinki 1975. Written informed consent was obtained from each subject.

INTRODUCTION

Several functional imaging studies of the human brain have shown that physiological changes of the level of consciousness are often associated with a change in thalamic activity (reviewed in Paus 2000). The loss of consciousness induced by general anesthetic agents in healthy volunteers seems to involve brain structures identical to those involved in the control of the sleep-waking continuum. We have previously shown (Fiset et al. 1999) that propofol, a commonly used intravenous anesthetic agent, decreases in a dose-dependent manner regional cerebral blood flow (rCBF) in several brain regions similar to those observed to have a decrease in rCBF during the slow-wave sleep (Hofle et al. 1997; Maquet et al. 1997) including the thalamus and the brain stem.

The loss of consciousness induced by general anesthesia is accompanied by a gradual decrease of the subject’s ability to perceive his external environment. For example, low doses of propofol suppress proprioception, finger counting, and perception of light touch in conscious patients (Dunnet et al. 1994). It is unclear, however, what are the brain mechanisms mediating such effects. In rats, it has been shown that propofol exerts an action on the processing of sensory information mainly at a cortical level by blocking the monosynaptic activation of cortical cells to thalamo-cortical input (Angel and LeBeau 1992). Nevertheless, propofol also disrupts the pattern of firing of thalamic sensory relay cells; at the doses used in the above study, there was an overall increase in the discharge probability of those cells, albeit of small amplitude (Angel and LeBeau 1992).

In the present study, we investigated the effect of propofol-induced anesthesia on changes in brain activity induced by somatosensory stimulation. We wished to determine whether different levels of anesthesia affect differentially cortical and subcortical regions involved in the processing of vibrotactile input. Considering the effect of propofol on the processing of sensory information in rats, we hypothesized that propofol would first affect the vibration-induced CBF response in the somatosensory cortex and, presumably at a higher dose, in the thalamus.
all subjects. The subjects were recruited through advertisement in a local newspaper and underwent a medical and physical examination before participating in the study. Blood tests were also performed to detect any blood cell or plasma ion abnormalities as well as HIV or hepatitis B. Women were tested for pregnancy no more than 1 wk before the experiment and were requested to use an appropriate contraceptive method. None of the subjects had a history of head trauma or surgery, mental illness, drug addiction, asthma, motion sickness, or previous problems during anesthesia. They had no contraindication for a magnetic resonance imaging (MRI) examination, such as vascular clips or metallic implants. All volunteers received financial compensation for inconvenience and time lost during the experiment.

**Vibrotactile stimulation**

Using a protocol similar to that described by Coghill et al. (1994), vibrotactile stimuli were delivered by an electric vibrator (Daito, Osaka, Japan) operating at a frequency of 110 Hz and with a square stimulating surface of 1 cm². The stimulator was placed on the ventral surface of the subject’s right forearm alternately at one of six different locations (3 × 2 matrix with a between-site distance of 3 cm). During the 3-min scanning period, a total of 18 vibrotactile stimuli were applied, each lasting about 6 s and separated by an interstimulus period of 4 s. This sequence was chosen to minimize habituation that may result from repeated presentation of tactile stimuli at the same location.

**Anesthesia**

Subjects fasted for at least 8 h prior to the induction of anesthesia and were given sodium citrate orally (0.3 M, 30 ml, BDH, Toronto, Ontario, Canada) at their arrival in the positron emission tomography (PET) unit to reduce gastric acidity and the risks associated with an accidental aspiration of the gastric content. Anesthesia was achieved with a computer-controlled intravenous infusion of propofol to obtain constant effect-site (i.e., brain) concentrations. The software controlling the pump (Harvard Apparatus 22) was the Stanpump program developed by Steven L. Shafer and colleagues (Department of Anesthesiology, Stanford University, CA; version 12/06/95), using the pharmacokinetic parameters of Tackley et al. (1989). Propofol was infused through an intravenous catheter placed into the right hand or forearm.

To ensure volunteers’ safety, the following physiological parameters were monitored: 3-lead electrocardiogram (heart rate, HR), oscillometric invasive arterial blood pressure (left radial artery cannulation), and pulse oxymetry (SpO₂). Two certified anesthesiologists were present throughout the experiment, and complete resuscitation equipment was always available. Throughout the study, the subjects breathed an oxygen-enriched air spontaneously through a loosely fitting plastic face-mask. Upper airway obstruction was relieved by gentle chin support if needed. Eyes were covered by pads and ambient noise was attenuated by earplugs. The most comfortable position attainable was sought to avoid painful stimulation related to position.

**Assessment of the level of consciousness and of the perception of vibrotactile stimulation**

The level of consciousness was evaluated clinically throughout the study. Approximately 2 min before each scan, the subject was asked to squeeze the hand of the investigator. She/he was considered conscious if the response to verbal command was clear, and unconscious if there was no response at all. For all volunteers, the response was never ambiguous, i.e., it was either clear or absent. At the end of the experiment, subjects were asked by the experimenter to tell at which level of anesthesia they felt the vibrotactile stimulation. The perception of vibrotactile stimulation was not evaluated during the scans to avoid movements associated with speaking.

**Data acquisition**

PET scans were obtained using a CTI/Siemens HR+, 32-rings, 63-slices tomograph. The H₂¹⁵O bolus technique was used (Raichle et al. 1983). Counts were measured during a 3-min scan after a 10-mCi H₂¹⁵O bolus injection into a vein of the right ventral forearm. To allow for calculation of the absolute values of CBF, arterial blood samples were acquired throughout the scanning period using the catheter placed into the left radial artery.

The data acquisition sequence is summarized in Fig. 1. The desired target concentration of propofol was initially set on the computer controlling the infusion pump using the Stanpump program, which provides an estimate of the plasma and effect-site concentration (i.e.,

![FIG. 1. Sequence of data acquisition.](http://jn.physiology.org/2016.9.01300.F1-c.png)
brain concentration) of propofol in real time (predicted plasma and
effect-site concentrations). Once the predicted effect-site concentra-
tion was equal to the set target concentration, a 5-min equilibration
period ensued to ensure equilibration of concentrations between phar-
macokinetic compartments before clinical assessment of the level of
consciousness. Seven milliliters of blood were then drawn for the
off-line measurement of the plasma concentration of propofol (Plum-
er 1987). The acquisition of the first PET scan began just after that,
with or without vibrotactile stimulation. After a 10-min resting period,
the level of consciousness was assessed again, a blood sample drawn,
and the second bolus of water injected. This scan was accompanied by
vibrotactile stimulation if the first one was not and vice versa.
The order of the scans with or without vibrotactile stimulation was
counterbalanced across subjects but remained constant throughout the
different levels of anesthesia for a given subject.

The sequence of data acquisition described here was followed for
each subject during five different levels of anesthesia. Using the
computer-controlled infusion of propofol, the following plasma levels
of propofol were targeted: Level W (Waking, 0 µg/ml), Level 1 (0.5
µg/ml), Level 2 (1.5 µg/ml), Level 3 (3.5 µg/ml), and Level R
(Recovery, response to verbal command following the end of propofol
infusion). The order of the levels of anesthesia was not randomized to
limit the time spent in the tomograph and the length of anesthesia for
the subject; the subjects always received an increasing concentration of
propofol to avoid delays encountered by the elimination of the drug
from the brain if a decreasing concentration order had been employed.

Throughout the study, systolic arterial blood pressure (SBP), dia-
stolic arterial blood pressure (DBP), and pulse oximetry (SpO₂) were recorded every 5 min for
each subject. The arterial partial pressure in CO₂ (PaCO₂) was mea-
sured for three subjects during Levels W, 1, 2, and 3.

For each subject, high-resolution T1-weighted magnetic resonance
images (MRIs; 160 contiguous sagittal slices, 1-mm thick) were obtained from a Philips Gyroscan ACS (1.5T) in a separate PET count images were reconstructed with a 14-mm Hanning filter
using the data acquired during frame 6 to frame 14 of the 3-min scan
(60 s total). The images were normalized for differences in global
CBF by means of ratio normalization; i.e., the count at each voxel
(3-dimensional image element) was divided by the mean counts
calculated across all brain voxels (Fox et al. 1988). The images were co-registered with individual MRIs (Woods et al. 1993) and
transformed into a standardized stereotaxic space (Talairach and Turnoux
1988) by means of an automated feature-matching algorithm (Collins
et al. 1994).

Statistical analysis of rCBF

Statistical analysis of rCBF was performed using normalized rCBF
of the 8 subjects, scanned 10 times each. Because of excessive
movement or technical problems, the two recovery scans for one
subject, two Level-3 scans for another subject and one Level-3 scan
with vibrotactile stimulation for a third subject were not obtained.
A mean rCBF was calculated for each voxel by dividing the mean CBF difference by its
standard deviation pooled across all brain voxels (Worsley et al.

We assessed the significance of the relationship between the measured plasma concentration of propofol and the normalized rCBF
(i.e., their linear regression) by means of an analysis of covariance,
ANCOVA (Sokal and Rohlf 1981), with subjects and the effect of
vibration as main effects and propofol concentration as a covariate.
The data set consisted of 45 rCBF volumes {[8 volumes × 3
anesthesia levels (Levels 1, 2, and 3) × 2 vibration conditions (ON or
OFF)] − 3 missing volumes}. The parameter of interest was the slope
of the effect of the measured propofol plasma concentration versus
normalized CBF. We first removed the subject effect and the effect of
vibration and then calculated a regression t-statistic map. An estimate
of the slope and its standard deviation were obtained by least-squares
fitting of the model (ANCOVA) at each voxel. A total of 45 values of
covariate was used, corresponding to the 45 volumes in the dataset.
The degrees of freedom of the standard deviation were increased from
34 (45 − 8 − 1) by pooling the standard deviation across all voxels,
so that the distribution of the t-statistic was normal. The resulting
t-statistic map tested whether, at a given voxel, the slope of the regression
was significantly different from zero. Using a similar approach
(ANCOVA), we assessed the interaction between vibrotactile
stimulation and propofol concentration on rCBF at a given voxel.

Cortical activity is highly variable among fully awake subjects,
in the absence of any sedative drug. For that reason, including the scans
recorded at Level W in the regression analysis would have introduced
bias in detecting cortical regions where rCBF is correlated to propofol
concentration. It is the reason why we decided to perform the regression
analysis not including values recorded at Level W. As the plasma
concentrations of propofol were not measured at Level R, because not
reflecting brain concentrations (see comments in the legend of Fig. 5),
we did not include the scans recorded at that level in the regression
analysis as well.

For the subtraction, regression, and interaction t-maps, the presence
of a significant peak was tested by a method based on the three-
dimensional Gaussian random-field theory, which corrects for the
multiple comparisons involved in searching across a volume (Worsley
et al. 1992). In all cases, only peaks located in the gray matter were
taken into account, assuming that any peak in the white matter is a
false positive. Values equal to or exceeding a criterion of t = 3.5 were
considered significant, yielding a false-positive rate of 0.64 in 182
resolution elements (each of which has dimensions 14 × 14 × 14
mm) if the volume of the gray matter is 500 cm³.

To obtain the mean relative CBF of various regions of interest, the
coordinates of significant peaks observed in a t-map served as the
center of a 7-mm radius volume of interest (VOI). The mean relative
CBF value in that VOI was then extracted from each normalized rCBF
volume. The difference in rCBF between the vibration-off condition
and the vibration-on condition was then calculated for each subject at
each level of anesthesia and for each VOI. One-sample t-tests were
performed on these data to determine whether the average difference
in rCBF between the two vibration conditions was significantly dif-
ferent from 0. \( P < 0.05 \) was considered significant.

Calculation of the absolute CBF

The absolute CBF was calculated for the whole brain, the gray
matter, and the white matter, for each scan of each subject. We used
the two-compartment weighted integration method of Ohtah and coll-
eagues (Ohta et al. 1996). Cerebral perfusion maps (K1 maps) were
generated for each 3-min scan of each subject using the sum of the
native PET images across all frames. Mean whole-brain CBF values
were then obtained by averaging the K1 maps.

The mean CBF values in the gray and the white matter were obtained
by masking the K1 maps with standard probabilistic maps of
grey or white matter that were co-registered with each K1 map. A
probability of 0.6 was chosen as a cutoff point for a voxel to be of gray
or of white matter, respectively.
The significance of the differences in absolute CBF was assessed using a three-way ANOVA for related samples, the first factor being anesthesia level (Level W, Level 1, Level 2, Level 3, and Level R), the second factor being the brain volume (whole brain, gray matter, or white matter), and the third one being the vibration condition (OFF or ON). Tukey’s HSD tests were used for post hoc comparisons, and \( P < 0.05 \) was considered significant. Three subjects were displaying missing data and were excluded from this analysis.

**Statistical analysis of the vital signs**

We analyzed the variability of HR, SBP, DBP, MBP, and SpO\(_2\) across conditions using a one-factor within-subjects ANOVA and Tukey’s HSD for post hoc comparisons. A Bonferroni corrected \( P < 0.01 \) was considered significant.

**RESULTS**

**Propofol concentrations**

The plasma propofol concentrations were as follows (mean \( \pm \) SD, 7 subjects): 0.55 \( \pm \) 0.14 for Level 1, 1.52 \( \pm \) 0.25 for Level 2, and 3.45 \( \pm \) 0.61 for Level 3. For technical reasons, plasma concentrations of propofol were not available for one subject at all levels and were not measured for all subjects at Level R (see comments in the legend of Fig. 5). We used the mean measured plasma concentration of propofol to replace the missing values at Levels 1, 2, and 3 for further analysis. The mean and median absolute errors on propofol plasma concentrations in the seven remaining subjects were 3.4 and 1.0% of the values predicted by the Stanpump program, respectively. The correlation between the predicted propofol plasma concentration and the measured propofol plasma concentration was excellent (\( r = 0.97 \)).

**Evaluation of the level of consciousness**

All volunteers were conscious but mildly sedated at Level 1. They responded clearly to verbal commands and reported being slightly drowsy. At Level 2, all subjects were moderately sedated, having a slurred speech and responding slower but still clearly to verbal commands. At Level 3, all subjects were unconscious, i.e., they were not responding to verbal commands at all. At the end of the experiment, all subjects remembered clearly having felt the vibrotactile stimulation during Levels W, 1, and R, but not during Levels 2 and 3.

**Vital signs**

The means \( \pm \) SD of the vital signs for the eight volunteers across the levels of anesthesia are shown in Fig. 2. The vibrotactile stimulation did not affect the values observed at each level of anesthesia. There was a significant decrease in SBP, MBP, and DBP at Level 3 compared with all other levels (\( P < 0.01 \)). There was no significant change in HR or SpO\(_2\) across levels, although the tendency was toward an increase from Level W to Level 3 for HR. The PaCO\(_2\) (in mmHg) measured in three subjects during Levels W, 1, 2, and 3 increased from 42.7 \( \pm \) 3.1 at Level W, 43.9 \( \pm \) 5.84 at Level 1, and 46.33 \( \pm \) 4.33 at Level 2 to 51.1 \( \pm \) 8.84 at Level 3 (means \( \pm \) SD; Fig. 3). Significant upper airway obstruction in three subjects during Level 3 necessitated chin holding to facilitate spontaneous respiration.

**CBF**

The mean absolute whole-brain, gray-matter and white-matter CBF at each level of anesthesia is summarized in Fig. 3 (\( n = 5 \)). A three-way ANOVA for related samples performed on these data revealed a significant main effect of brain volume (\( F_{2,8} = 145.35, P < 0.0001 \)) and anesthesia level (\( F_{4,16} = 4.5, P < 0.05 \)). Post hoc pair-wise comparisons revealed that CBF was significantly higher in the gray matter than in the whole brain and in the white matter (\( P < 0.01 \)). CBF was also higher in the whole brain than in the white matter (\( P < 0.05 \)). It increased significantly from Level 2 to Level 3 (\( P < 0.05 \)) and decreased significantly from Level 3 to Level R (\( P < 0.05 \)). Interaction between brain volume and anesthesia level was not significant (\( F_{8,32} = 1.18, P = 0.34 \)).

**FIG. 2.** Mean \( \pm \) SD of the vital signs for the 8 volunteers across the levels of anesthesia. SBP, systolic arterial blood pressure; MBP, mean arterial blood pressure; DBP, diastolic arterial blood pressure; HR, heart rate; SpO\(_2\), peripheral saturation in oxygen; vib.on, vibration-ON; vib.off, vibration-OFF. Blood pressures are expressed in mmHg, heart rate in beats/min, and peripheral saturation in oxygen in %. * Significant decrease in SBP, MBP, and DBP at Level 3 compared with all other levels (\( P < 0.01 \)).
rCBF

MAIN EFFECT OF PROPFOLO. A regression t-statistic map is presented in Fig. 4A, and the significant peaks determined from this analysis are shown in Table 1. A negative correlation between the measured plasma concentration of propofol and rCBF was observed in the thalamus, the left and right precuneus, the left and right posterior cingulate gyrus, the left and right angular gyrus, the left superior parietal lobe, and several regions in the prefrontal cortex. Positive correlation was found in the cerebellar vermis, the left cerebellar lobe, the left post-central gyrus, and the left gyrus rectus.

MAIN EFFECT OF VIBRATORY STIMULATION. Representative slices of subtraction t-statistic maps (vibration-on minus vibration-off) at Levels W, 1, 2, and 3 are shown in Fig. 4B. As summarized in Table 2, vibratory stimulation of the right forearm during waking (Level W) induced an increase in relative CBF in several regions, including the left thalamus, the left primary somatosensory cortex (S1), the left and right secondary somatosensory cortex (S2), and the left superior frontal gyrus (midline). Vibratory stimulation led to rCBF decreases in the left and the right cuneus, the left and the right lingual gyrus, the left fusiform gyrus, and the left middle occipital gyrus.

INTERACTION BETWEEN THE EFFECT OF PROPFOLO AND THE EFFECT OF VIBRATION. We did not find any significant peak in the interaction t-statistic map. However, as illustrated in Fig. 4B, the vibration-induced CBF response in the primary somatosensory cortex and in the thalamus differed across the different levels of anesthesia. At Level 1, there was no significant positive peak in the subtraction map, although we observed t-values of 2.86 and 3.22 in the thalamus and left S2, respectively. At Level 2, we found a significant positive peak in the thalamus (t = 5.47). At Level 3, no significant peaks were observed either in the somatosensory cortex or in the thalamus. Furthermore, as illustrated in Fig. 5, the analysis of rCBF in selected VOIs led to the same conclusion. Figure 5 illustrates the difference in rCBF between the vibration-on condition and the vibration-off condition at each level of anesthesia in a 7-mm radius VOI centered at the coordinates of the thalamic, S1, and S2 peaks obtained in the subtraction map at a given anesthesia level. If no peak was observed for a given VOI at a given anesthesia level, the coordinates of the peak observed at Level W were used. Statistical analysis of those data (1-sample t-tests) is reported in the legend of Fig. 5. It revealed that, during propofol administration, at Level 2 in the thalamus and at Level 1 in left S2, rCBF remained significantly higher when vibration was applied than when it was not. This is not true in left S1 and right S2.

Vibration-induced deactivations observed at Level W disappeared at the other levels except for peaks in the medial frontal gyrus at Levels 1 and 2 (x = 10.72 and −5.36; y = −26.32 and −26.32; z = 63.00 and 63.00; t = −3.69 and −3.52, respectively) and in the right cuneus at Level 2 (x = 8.04; y = −71.04; z = 19.50; and t = −3.64). No significant deactivation was observed at Level 3.

DISCUSSION

The main findings of the present study can be summarized as follows. First, propofol tended to reduce the absolute global CBF as its concentration increased, except for the deepest level of anesthesia, where we observed an increase in CBF. Second, propofol reduced in a dose-dependent manner normalized rCBF in specific brain regions including the thalamus and several cortical regions. Third, propofol affected the vibration-induced increases in rCBF differentially in cortical and subcortical regions.

Rationale for choosing propofol

Propofol is a commonly used general anesthetic agent with relatively pure hypnotic properties (White 1997). The development of computer-driven administration systems, such as the one used in the present study, allows targeting of precise brain concentrations of the anesthetic agent (Shafer 1993). Several animal studies have investigated the central effects of propofol and suggested that its anesthetic effects may result at least
partially from an inhibition of thalamocortical transfer of information (for a review, see Yaksh et al. 1998). Nevertheless, little is known about its effect on the functioning human brain. We recently observed a dose-dependent reduction in thalamic activity by propofol, suggesting that propofol might reduce thalamo-cortical information transfer in humans (Fiset et al. 1999). Further studies are needed to determine whether other general anesthetic agents have similar effects on thalamocortical sensory transfer as does propofol.

**Effect of propofol on the absolute CBF**

Propofol is known to reduce the cerebral metabolic rate of $O_2$ (CMRO$_2$) and CBF in animals (Enlund et al. 1997) as well as in humans (Newman et al. 1995). It has been suggested that anesthetic agents can interfere with normal metabolism-flow coupling in the brain (Jezzard et al. 1997), but several human and animal studies have provided strong evidence against this notion for propofol (Enlund et al. 1997; Newman et al. 1995).

In our previous study (Fiset et al. 1999), the infusion of propofol targeted to reach a plasma concentration of 3 $\mu$g/ml reduced the mean whole-brain CBF by 22%. In the present study, we observed an initial (nonsignificant) decrease of the mean whole-brain CBF from the awake baseline state (Level W) to the moderately sedated state (Level 2). Surprisingly, as propofol concentration further increased and subjects progressively lost consciousness (Level 3), this decrease was followed by the return of CBF values to values close to baseline or even higher. At Level 3, all subjects were unresponsive to verbal
commands, three of them needed chin holding to support ventilation, and the PaCO₂ measured in three volunteers substantially increased by approximately 20% at Level 3 compared with Level W (Fig. 3). This increase in PaCO₂ is related to the central depression of ventilation by propofol and to the obstruction of the upper airway associated with the reduced muscle tone (pharynx, tongue, jaw) observed during propofol anesthesia (Fragen and Avram 1992). An increase in PaCO₂ is

Table 1. Negative and positive covariations between normalized CBF and the measured plasma concentration of propofol

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>t</th>
<th>Change in Relative CBF*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative covariation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus (midline)</td>
<td>7</td>
<td>0.00</td>
<td>−72.16</td>
<td>39.00</td>
<td>−10.53</td>
<td>−16.93 ± 7.49</td>
</tr>
<tr>
<td>Cingulate gyrus (posterior, midline)</td>
<td>7</td>
<td>0.00</td>
<td>−52.12</td>
<td>30.00</td>
<td>−10.16</td>
<td>−15.70 ± 6.98</td>
</tr>
<tr>
<td>Cingulate gyrus (posterior, midline)</td>
<td>31</td>
<td>0.00</td>
<td>−34.92</td>
<td>36.00</td>
<td>−9.22</td>
<td>−14.47 ± 5.04</td>
</tr>
<tr>
<td>Right angular gyrus</td>
<td>40</td>
<td>44.22</td>
<td>−52.12</td>
<td>48.00</td>
<td>−6.64</td>
<td>−10.66 ± 6.51</td>
</tr>
<tr>
<td>Thalamus (midline)</td>
<td></td>
<td>4.02</td>
<td>−14.28</td>
<td>7.5</td>
<td>−6.60</td>
<td>−11.03 ± 10.23</td>
</tr>
<tr>
<td>Left superior parietal lobule</td>
<td>7</td>
<td>−33.50</td>
<td>−65.88</td>
<td>48.00</td>
<td>−5.45</td>
<td>−9.02 ± 5.7</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>46</td>
<td>45.56</td>
<td>45.92</td>
<td>3.00</td>
<td>−5.04</td>
<td>−9.35 ± 4.93</td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>10</td>
<td>36.18</td>
<td>51.08</td>
<td>21.00</td>
<td>−4.91</td>
<td>−8.03 ± 6.6</td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>10</td>
<td>−33.50</td>
<td>56.24</td>
<td>4.50</td>
<td>−4.82</td>
<td>−8.05 ± 4.6</td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>10</td>
<td>−42.88</td>
<td>40.76</td>
<td>18.00</td>
<td>−4.52</td>
<td>−8.68 ± 4.88</td>
</tr>
<tr>
<td>Medial frontal gyrus (midline)</td>
<td>8</td>
<td>0.00</td>
<td>35.60</td>
<td>39.00</td>
<td>−4.41</td>
<td>−7.9 ± 7.99</td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>8</td>
<td>−30.82</td>
<td>27.00</td>
<td>46.50</td>
<td>−4.37</td>
<td>−7.52 ± 6.52</td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>8</td>
<td>37.52</td>
<td>20.12</td>
<td>46.50</td>
<td>−4.21</td>
<td>−7.91 ± 8.34</td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>9</td>
<td>−28.14</td>
<td>44.20</td>
<td>36.00</td>
<td>−4.06</td>
<td>−6.78 ± 5.08</td>
</tr>
<tr>
<td>Medial frontal gyrus (midline)</td>
<td>10</td>
<td>1.34</td>
<td>54.52</td>
<td>4.50</td>
<td>−4.03</td>
<td>−6.87 ± 6.71</td>
</tr>
<tr>
<td>Left angular gyrus</td>
<td>39</td>
<td>−46.90</td>
<td>−62.44</td>
<td>37.50</td>
<td>−4.02</td>
<td>−6.64 ± 5.58</td>
</tr>
<tr>
<td>Left lingual gyrus</td>
<td>8</td>
<td>−42.88</td>
<td>18.40</td>
<td>43.50</td>
<td>−3.85</td>
<td>−7.13 ± 6.04</td>
</tr>
<tr>
<td>Left angular gyrus</td>
<td>40</td>
<td>−52.26</td>
<td>−41.80</td>
<td>43.50</td>
<td>−3.76</td>
<td>−6.6 ± 6.8</td>
</tr>
<tr>
<td><strong>Positive covariation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum (midline)</td>
<td></td>
<td>2.68</td>
<td>−50.40</td>
<td>−12.00</td>
<td>8.78</td>
<td>13.11 ± 5.57</td>
</tr>
<tr>
<td>Left cerebellar lobe</td>
<td></td>
<td>−14.74</td>
<td>−46.06</td>
<td>12.00</td>
<td>8.12</td>
<td>13.44 ± 9.11</td>
</tr>
<tr>
<td>Left postcentral gyrus</td>
<td>40</td>
<td>−50.92</td>
<td>−9.12</td>
<td>24.00</td>
<td>5.25</td>
<td>6.65 ± 4.21</td>
</tr>
<tr>
<td>Left gyrus rectus</td>
<td>11</td>
<td>−4.02</td>
<td>23.56</td>
<td>−22.50</td>
<td>3.74</td>
<td>5.43 ± 7.69</td>
</tr>
</tbody>
</table>

Values in last column are means ± SD. Brain regions with significant negative and positive covariations between normalized regional cerebral blood flow (rCBF) and the measured plasma concentration of propofol. BA, tentative Brodmann’s cytoarchitectonic areas approximated according to the Talairach and Tournoux atlas (Talairach and Tournoux 1988). The coordinates are expressed in millimeters. * Changes in relative CBF are calculated as follows: the mean relative CBF value of a 7 mm volume of interest centered at the listed coordinates is extracted from the normalized positron emission tomography volume of each subject during Level 1, vibration-on or -off. The 16 resulting values are then averaged.

Table 2. Vibration-related changes in rCBF

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>t</th>
<th>Change in Relative CBF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left postcentral gyrus (S1)</td>
<td>1−2</td>
<td>−36.18</td>
<td>−36.64</td>
<td>58.50</td>
<td>5.51</td>
<td>7.25 ± 6.01</td>
</tr>
<tr>
<td>Left inferior parietal lobule (S2)</td>
<td>40</td>
<td>−56.28</td>
<td>−29.76</td>
<td>28.50</td>
<td>5.43</td>
<td>6.96 ± 4.43</td>
</tr>
<tr>
<td>Left inferior parietal lobule (S2)</td>
<td>40</td>
<td>−45.56</td>
<td>−28.04</td>
<td>22.50</td>
<td>5.09</td>
<td>6.38 ± 3.34</td>
</tr>
<tr>
<td>Left precentral gyrus</td>
<td>40</td>
<td>−45.56</td>
<td>−0.52</td>
<td>10.50</td>
<td>4.99</td>
<td>4.86 ± 4.39</td>
</tr>
<tr>
<td>Right inferior parietal lobule (S2)</td>
<td>40</td>
<td>54.94</td>
<td>−31.48</td>
<td>27.00</td>
<td>4.99</td>
<td>6.12 ± 5.62</td>
</tr>
<tr>
<td>Left thalamus</td>
<td></td>
<td>−8.04</td>
<td>−14.28</td>
<td>12.00</td>
<td>4.43</td>
<td>5.02 ± 9.56</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>40</td>
<td>−10.72</td>
<td>21.16</td>
<td>10.50</td>
<td>4.36</td>
<td>4.85 ± 8.26</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td></td>
<td>1.34</td>
<td>21.84</td>
<td>52.50</td>
<td>3.63</td>
<td>3.04 ± 5.62</td>
</tr>
<tr>
<td>Right cuneus</td>
<td>19</td>
<td>9.38</td>
<td>−79.64</td>
<td>36.00</td>
<td>−4.52</td>
<td>−9.24 ± 2.27</td>
</tr>
<tr>
<td>Left lingual gyrus</td>
<td>17</td>
<td>−13.40</td>
<td>−88.24</td>
<td>1.50</td>
<td>−4.98</td>
<td>−8.20 ± 5.86</td>
</tr>
<tr>
<td>Left cuneus</td>
<td>18</td>
<td>−12.06</td>
<td>−84.80</td>
<td>18.00</td>
<td>−4.06</td>
<td>−8.62 ± 6.42</td>
</tr>
<tr>
<td>Left lingual gyrus</td>
<td>18</td>
<td>−14.74</td>
<td>−76.20</td>
<td>−6.00</td>
<td>−3.97</td>
<td>−7.87 ± 7.04</td>
</tr>
<tr>
<td>Left fusiform gyrus</td>
<td>19</td>
<td>−17.42</td>
<td>−53.84</td>
<td>−7.50</td>
<td>−3.72</td>
<td>−7.81 ± 5.32</td>
</tr>
<tr>
<td>Left middle occipital gyrus</td>
<td>19</td>
<td>−26.80</td>
<td>−88.24</td>
<td>16.50</td>
<td>−3.70</td>
<td>−7.51 ± 5.39</td>
</tr>
<tr>
<td>Right lingual gyrus</td>
<td>18</td>
<td>18.76</td>
<td>−74.48</td>
<td>1.50</td>
<td>−3.58</td>
<td>−6.71 ± 4.83</td>
</tr>
<tr>
<td>Left middle occipital gyrus</td>
<td>18</td>
<td>−37.52</td>
<td>−83.08</td>
<td>0.00</td>
<td>−3.57</td>
<td>−7.06 ± 6.84</td>
</tr>
<tr>
<td>Right cuneus</td>
<td>19</td>
<td>24.12</td>
<td>−71.04</td>
<td>37.50</td>
<td>−3.51</td>
<td>−7.63 ± 4.30</td>
</tr>
</tbody>
</table>

Values in last column are means ± SD. Vibration-related changes in regional cerebral blood flow (rCBF). BA, Brodmann’s cytoarchitectonic areas approximated according to the Talairach and Tournoux atlas (Talairach and Tournoux 1988). The coordinates are expressed in millimeters. S1, primary somatosensory cortex; S2, secondary somatosensory cortex. Negative r values indicate that blood flow was lower during the vibration condition than during the control condition. * Changes in relative CBF are calculated as follows: the mean relative CBF value of a 7 mm volume of interest centered at the listed coordinates is extracted from the normalized positron emission tomography volume of each subject during Level W, vibration-on. This value is then subtracted from a similar value obtained at Level W, vibration-off. The 8 resulting values are then averaged.
known to cause cerebral vasodilatation, leading to an increase in CBF and cerebral blood volume (Brust 1991). Propofol does not affect cerebrovascular reactivity to CO2 (Stephan et al. 1987), and it preserves the autoregulatory response to variations in arterial blood pressure (Strebel et al. 1995). It is therefore likely that the observed evolution of the mean whole brain CBF in our study results from opposite effects of propofol and PaCO2, the effect of propofol being antagonized by the effect of CO2 at Level 3. Although the arterial blood pressure was significantly lower at Level 3 than at the other levels, it probably did not affect CBF, as the autoregulatory response to variations in arterial blood pressure was probably preserved. In our previous study (Fiset et al. 1999), mean end-tidal PCO2 increased only by 10%, probably because the highest concentration of propofol reached (3 μg/ml) was lower than the concentration reached in the present study (3.5 μg/ml).

Effects of propofol on rCBF

The infusion of propofol reduced rCBF in brain regions identical to those described in our previous study (Fiset et al. 1999) except for several additional peaks in the frontal cortex observed in the present study. This could be related to the fact that the propofol concentrations used were lower in that study than in the present one. We therefore confirm our previous findings and provide further evidence in support of the region-specific, rather than global, mode of action for this general anesthetic.

The brain regions where propofol concentration and rCBF were positively correlated are the cerebellum, the left postcentral gyrus, and the orbitofrontal cortex. In our previous study (Fiset et al. 1999), we observed a similar trend in the cerebellum, the medial frontal gyrus, and the left temporal lobe. Discussion about the functional significance of the positive correlation between rCBF and propofol concentration can be found in Fiset et al.’s paper. Although we were not able to randomize or counterbalance the order in which increasing doses of propofol were delivered to each subject, the distribution of brain regions where rCBF is significantly correlated with the measured plasma concentration of propofol is unlike that observed in PET studies examining nonspecific effects of time on rCBF. For example, Ath-
Eugenia C. Vila and colleagues demonstrated a nonspecific rCBF increase with time in large confluent regions of both frontal lobes and a nonspecific decrease with time in posterior regions of the left and right temporal lobe (Athwal et al. 1998).

Effects of propofol on vibration-induced rCBF changes

During waking, we observed a robust vibration-induced increase in rCBF in the left (contralateral) primary somatosensory cortex, the left and the right secondary somatosensory cortex, and in the thalamus, a finding consistent with previous studies (Coghill et al. 1994).

In the voxel-based analysis, we did not find a significant interaction between the effect of anaesthesia level and the effect of vibration. This lack of significant interaction can be related to slight changes of the coordinates of peak vibration-related activity from one anaesthesia level to the other. For this reason, we performed the VOI-based analysis, using the coordinates of the thalamic, the primary, and the secondary somatosensory cortex peaks observed at each level of anaesthesia in the subtraction maps. This analysis confirmed that vibration was still able to induce a significant increase in left S2 rCBF at Level 1 and in thalamic rCBF at Level 2. Based on both the voxel-based subtraction analysis and the VOI-based analysis, the vibration-induced increase in rCBF disappears only at Level 3 in the thalamus. It is still present at Level 1 ($t = 2.86$, highly significant at Level 2 ($t = 5.47$), and absent at Level 3. On the contrary, the vibration-induced increase in rCBF of the left S1 observed at Level W is not present at Levels 1, 2, or 3. Thus the blood-flow response observed at Level W was attenuated first in the primary somatosensory cortex and then in the thalamus.

In rats, propofol alters the transmission of sensory information primarily by acting on cortical cells and by blocking the monosynaptic activation of cortical cells by thalamo-cortical input. It also disrupts the pattern of firing of thalamic sensory relay cells. Unlike other general anesthetic agents that affect the ascending transmission of sensory information both by activating corticothalamic inhibitory mechanisms and by reducing the thalamo-cortical transfer of information through the thalamic relay nuclei, propofol increases the discharge probability of the thalamic relay cells, although the amplitude of discharge is reduced (Angel and LeBeau 1992). The fact that the cortical activation observed in our study disappears at lower doses than the thalamic activation is consistent with these observations and those of Ergenzinger et al., who have demonstrated that chronic and acute suppression of neuronal activity in the primary sensory cortex of primates increases the receptive field size in the ventroposterior thalamus (Ergenzinger et al. 1998).

As long as the volunteers remained conscious, there was still a thalamic activation by vibrotactile stimulation. This activation disappeared only at higher concentrations of propofol, when subjects were unconscious. Subjects clearly perceived vibrotactile stimulation at Levels W and 1, but it was less evident at Level 2. At least, they did not remember having perceived it at that level. As cortical inhibition by propofol alters sensory perception without altering consciousness, it seems that consciousness is lost only when the concentration of propofol is high enough to reduce sufficiently the thalamic activation induced by external stimulation.

Vibration-induced deactivations observed at Level W disappeared at the other levels except for poorly significant peaks in the medial frontal gyrus at Levels 1 and 2 and in the right cuneus at Level 2. No significant deactivation was observed at Level 3. As hypothesized by Coghill et al. (1994), decreased rCBF may indicate areas that exhibit increased activation during the control condition or may indicate a real reduction in activity. A decrease in rCBF is unlikely to be related to a local inhibitory process, since the release of inhibitory neurotransmitters is considered an energy-demanding process. A decrease in rCBF would more likely be related to a diminished input to the region that results from active inhibition occurring at a preceding level of processing. There could also be a passive shunting of blood to nearby activated areas. Deactivation in regions of the occipital lobe is a common feature of changes in cortical activity associated with the processing of other sensory modalities, including skin and muscle pain (Svensson et al. 1997). The occipital deactivations observed in the present study disappeared at high propofol concentrations. The physiological significance of those observations remains unclear.

Conclusions

In conclusion, the present study confirms our previous findings that propofol differentially decreases rCBF in specific brain regions and that those concentration-dependent decreases are associated with changes in the level of consciousness. The present study also shows that propofol differentially affects the brain regions involved in the processing of somatosensory information. At low concentrations, it suppresses vibration-induced blood-flow response in the primary somatosensory cortex. At intermediate concentrations, it suppresses all cortical activation induced by vibration and alters the perception of stimuli. The loss of consciousness occurs only at higher propofol concentrations and coincides with a suppression of vibration-induced blood-flow response in the thalamus. Those differential effects may be critical mechanisms mediating the effect of anesthetic drugs on the patient’s conscious perception of the external environment and on consciousness. They may reflect sequential effects of these agents on the complex reciprocal thalamocortical system sustaining the concerned higher brain functions.

We thank the following persons for help in data analysis, technical support during PET data acquisition, and volunteer management before, during, and after the completion of the experiments: M. Vafaee, S. Milot, F. Neelin, G. Sauchuk, R. Fukushima, M. Shingler, L. Ulliat, and the main operating room and recovery room staff of the Royal Victoria Hospital.

This study was supported by the Medical Research Council (Canada), the Canadian Anaesthetists’ Society (Abbott Laboratory Research Award), le Fonds de la Recherche en Santé du Québec (G. Plourde), the Centre Hospitalier Universitaire de Liége, Belgium, and the Government of Quebec (V. Bonhomme), l’Association des Anesthesistes du Québec, and the Associated Anesthetists of the Royal Victoria Hospital.

REFERENCES


