Toward a Unified Theory of Narcosis: Brain Imaging Evidence for a Thalamocortical Switch as the Neurophysiologic Basis of Anesthetic-Induced Unconsciousness

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Introduction

Despite extensive research investigating the cellular mechanisms of general anesthesia (Franks and Lieb 1994), the fundamental question of why anesthesia produces unconsciousness remains unanswered. Findings of animal studies examining anesthetic-induced changes in evoked potential recordings suggest that the primary basis of anesthesia may be the blocking or disruption of sensory information processing through the thalamus (Angel 1991, 1993). This view is consistent with the findings of the effects of anesthetics on evoked potential recordings in humans, as well as some findings from human brain imaging experiments. The magnitude of the drug-induced reduction in thalamic metabolism induced by the benzodiazepine lorazepam correlates with its degree of sleepiness (Volkow et al. 1995). Furthermore, a dose-dependent reduction in thalamic activity accompanies sedative levels of the benzodiazepine midazolam (Veselis et al. 1997). Similarly, regional thalamic functional activity suppression was found during halothane general anesthesia, provided a pixel-based data analysis method (statistical parametric mapping) was used (Alkire et al. 1999). Most recently, a correlational link between a person's level of consciousness and their level of thalamic functioning at various doses of propofol anesthesia has been demonstrated in humans (Fiset et al. 1999).

A number of theories on consciousness propose that a fundamental part of the neural substrate for consciousness is likely to involve thalamocortical-corticothalamic loops (Crick 1994; Joliot, Ribary, and Llinás 1994; Llinás, Ribary, Contreras, and Pedroarena 1998; Lumer, Edelman, and Tononi 1997; Newman 1997). If such loops are involved in generating consciousness, then a change in their functional activity should likely be evident during experimentally induced states of unconsciousness (Llinás and Ribary 1993). Thus, these theories would seem to predict that a specific consequence of anesthetic-induced unconsciousness might be a change in functional thalamocortical activity.

This study, therefore, addressed two issues concerning the role of the thalamus in mediating the anesthetic state in man.

1. Do the regional effects of halothane and isoflurane, when examined with statistical parametric mapping, show commonalities of brain metabolism that offer clues to their mechanism of producing unconsciousness?

2. Will the common effect of these agents, as suggested by findings of animal studies (Angel 1991), be suppression of thalamic activity?

Positron emission tomography (PET) and statistical parametric mapping (SPM) were used to study brain states associated with unconsciousness during general anesthesia in humans. Regional cerebral glucose metabolism using \(^{18}\)fluorodeoxyglucose (FDG) was recorded as an index of neuronal activity in 11 young, healthy, right-handed male volunteers at baseline and during inhalational anesthesia with either halothane or isoflurane anesthesia titrated to the point of unresponsiveness. The details of the anesthetic administration procedures and the individual anesthetic effects have been reported previously (Alkire, Haier, Shah, and Anderson 1997; Alkire et al. 1999). Presented here are the three-dimensional results of the SPM conjunction analysis between the two different volatile anesthetic agents, which reveals the three-dimensional intersection of those brain regions commonly affected by both inhalational agents.

Further explanation may help clarify the logic of the analysis technique. If, on the one hand, the
two agents have completely different neuroanatomic mechanisms for producing unconsciousness, then the conjunction analysis will not reveal any regionally significant differences between the conscious and unconscious conditions. This would suggest that no overlapping brain areas of effect exist between the two agents. Such a situation could occur, for example, if one anesthetic primarily “turns off” the cerebral cortex, whereas the other agent primarily “turns off” the thalamus. Additionally, such a situation could occur if anesthetic-induced unconsciousness results simply from the global decrease in CNS functioning caused by anesthesia (i.e., subtracting the whole brain from itself would leave nothing). On the other hand, if the two agents have similar neuroanatomic mechanisms for producing unconsciousness, then the conjunction analysis should reveal which key brain regions differ in their functional activity between states of consciousness, irrespective of each agent’s particular extemporaneous effects on regional cerebral metabolism.

Materials and Methods

Subject Preparation

All subjects were studied with IRB approval and informed consent. Each of the 11 subjects underwent two separate PET scan procedures, with at least one week between scanning sessions. One scan assessed baseline awake metabolism and the other scan assessed metabolism during the period of unconsciousness induced with either halothane ($n = 5$) or isoflurane ($n = 6$) general inhalational anesthesia. Subjects denied any previous neurological, psychological, or medical problems, and they had a mean ($\pm$sd) age of $22 \pm 4$ years. All subjects were instructed to avoid caffeine, or any medications, for at least 48 hours prior to each scan. Additionally, subjects fasted at least 8 hours prior to each scan and they received oral antacid (Sodium Citrate, 30 cc P.O.) before receiving anesthesia. Subject preparation was as similar between sessions and conditions as possible. Each volunteer had two intravenous catheters inserted, one to administer the FDG-PET tracer and one to sample blood for FDG quantification. Monitoring equipment used included a three-lead electrocardiograph, an automated noninvasive blood pressure monitor, a pulse oximeter, end-tidal carbon dioxide monitor, a temperature monitor, and a precordial stethoscope. The experiments took place in a small, darkened, sound-shielded room. One of the subjects participated in both the halothane and isoflurane portions of the study. The baseline-aware scan was obtained while subjects lay quietly on a gurney with their eyes closed. Baseline scans were counterbalanced between subjects and conditions.

Anesthetic Administration

Subjects inhaled the anesthetics (or air, for the baseline condition) through a tight-fitting face-mask attached to a semicircle breathing system. The expired end-tidal concentration of each agent was incrementally adjusted upwards in steps of 0.1% every 10–15 min. As the volunteers approached unconsciousness, the eyelash reflex was tested every 3 min., and they were asked to open their eyes until they no longer followed commands. When the volunteers no longer responded to verbal commands, they were stimulated further by mild prodding and shaking. Loss of consciousness was defined as unresponsiveness to both verbal and tactile stimuli (Alkire 1998). Testing for unresponsiveness assured that each subject was actually anesthetized and not just sleeping during the anesthesia scan sessions. Airway instrumentation was not used, and the volunteers maintained spontaneous ventilation throughout each anesthetic. Subjects were thus titrated to a light stage of anesthesia in the 1/2 to 1 minimum alveolar concentration range.
(MAC = the minimum alveolar concentration of inhaled anesthetic agent at one atmosphere pressure needed to prevent 50% of patients from moving in response to a surgical skin incision; Eger, Saidman, and Brandstater 1965). The mean ± SD expired isoflurane and halothane concentrations were 0.5 ± 0.1% and 0.7 ± 0.2%, respectively.

Once unresponsive, 5 mc of FDG were injected intravenously as a bolus and the expired agent concentration remained fixed for the duration of the 32-min. deoxyglucose radiotracer uptake period. Uptake of FDG and metabolic trapping of FDG in the brain as FDG-6-phosphate is 80–90% complete at 32 min. (Phelps et al. 1979). It is primarily the trapped FDG-6-phosphate that reflects regional functional brain activity over time and is the source of the PET scan signal. Thus, following the labeling of brain with the tracer, subjects were allowed to emerge from the anesthetic before being taken to the PET scanner. The resultant PET scan images obtained for the anesthesia condition represent the functional activity of the brain evident during the period of unresponsiveness at the near-steady state level of anesthesia used for each subject and are not representative of the time actually spent in the scanner. The time between the injection of the FDG and the start of the scanning process was standardized across conditions to ensure that it was similar for all subject. Scanning began within 20 min. of the end of each uptake period for each condition. It took approximately 6 min. on average for subjects to open their eyes and become responsive following the discontinuation of the anesthetic agent. In order to standardize cognitive processing during the radiotracer uptake period, the subjects listened to an audiotape of repeated words spoken in normal conversational tone by a pleasant female voice with a frequency of one word every five seconds (Alkire, Haier, Fallon, and Cahill 1998).

**PET Imaging**

The regional cerebral metabolic rate of glucose utilization (rCMRglu) was measured with a GE2048 head-dedicated scanner. Arterialized venous blood sampling was used, and rCMRglu was calculated (mg/100 gm/min.) using established PET methodology (Huang et al. 1980, Phelps et al. 1979). The scanner has a resolution of 4.5 mm (full-width-half-maximum, FWHM) in plane and 6.0 mm axially. Two sets of 15 image planes, resulting in 30 PET images across the whole brain, were obtained per subject. Subjects were positioned using laser guidance and a thermostetting plastic facemask was used to hold each subject’s head stationary during the period of image acquisition for both the awake-baseline and anesthesia conditions. In vivo attenuation correction was obtained by previous transmission scanning using a (68Ge/68Ga)-rod source. PET data were corrected for attenuation and background activity, and reconstructed with a Hanning filter.

**Statistical Analysis**

Data were processed using the statistical parametric mapping (SPM-96) software from the Wellcome Department of Cognitive Neurology, London, United Kingdom, implemented in Matlab (Mathworks, Sherborn, MA). This process determined regionally significant condition effects for every pixel in standardized space (Friston, Frith, Liddle, and Frackowiak 1991; Friston et al. 1989). This process involved several steps.

1. The data were reconstructed in three-dimensional space.
2. The intercommissural (anterior commissure–posterior commissure) line was identified by an automated routine, and the three-dimensional images were rotated on axis to fit a reference template. A least-squares approach was used to esti-
mate the six parameters of this rigid body transform (Woods, Cherry, and Mazziotta, 1992).

3. After realignment, all images were transformed into a standardized space (according to the atlas of Talairach and Tournoux 1988).

4. To increase signal-to-noise ratio, and to reduce the effect of variable functional anatomy, the images were smoothed using an isotropic Gaussian kernel (10-mm FWHM).

5. Finally, global differences in glucose metabolic rates were normalized across conditions and volunteers using proportional scaling. This correction ensures that variations in activity caused by differences in global metabolic rates among the volunteers and between the conditions did not obscure the relative regional changes caused by the anesthetics.

Comparisons of regional relative glucose metabolism were performed between conditions on a pixel-by-pixel basis using $t$ statistics. A design matrix was specified such that the locations where a significant conjoint effect of both anesthetics on regional metabolism could be localized. The resulting maps ($\text{SPM}_t$) were transformed to the unit normal distribution ($\text{SPM}_z$) and thresholded at $P < 0.05$, corrected for multiple comparisons. The results are displayed as a three-dimensional volume of pixels in coronal, transverse and sagittal views of the brain.

### Results

General inhalational anesthesia compared to baseline, induced both a global reduction of, and specific regional changes of, brain glucose metabolism. The mean ($\pm$ sd) global whole-brain metabolic reduction seen during isoflurane anesthesia was $42 \pm 13\%$, and that seen during halothane was $40 \pm 10\%$ (see table 55.1). For all subjects the anesthetic state was associated with a global decrease in brain metabolism throughout the brain. There were no regions (within the spatial limitations of the scanner) that appeared to increase their absolute metabolic rate under anesthesia to a value greater than that found at baseline. Also, there were no significant differences in relative baseline metabolism between groups, suggesting comparable subjects were sampled between groups.

<table>
<thead>
<tr>
<th>Isoflurane</th>
<th>Halothane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>Anesthetized</td>
</tr>
<tr>
<td>4.9</td>
<td>3.5</td>
</tr>
<tr>
<td>5.8</td>
<td>4.4</td>
</tr>
<tr>
<td>6.3</td>
<td>3.5</td>
</tr>
<tr>
<td>7.2</td>
<td>3.9</td>
</tr>
<tr>
<td>7.2</td>
<td>3.3</td>
</tr>
<tr>
<td>8.8</td>
<td>3.9</td>
</tr>
<tr>
<td>average (SD) =</td>
<td>6.7 (1.4)</td>
</tr>
</tbody>
</table>
global metabolism accompanied the anesthetic-induced loss of consciousness seen here, areas with significantly decreased relative metabolism indicate those brain regions which were most affected by the anesthetic agents. The intersection of the relative functional regional neuroanatomic effects common to both agents are shown in figure 55.1 and listed in table 55.2.

The results show a significant conjoint effect between the two different anesthetics clearly centers primarily on the thalamus, and our subjects were anesthetized to a loss of consciousness endpoint, our data support the idea that a reduction of thalamo-cortical output may underlie the loss of consciousness associated with the anesthetic state in humans. The mechanism of anesthetic-induced thalamic processing disruption appears from animal work to be dependent on how anesthetics interact with a few specific brain sites including: the thalamus, the cerebral cortex (especially layer V) and the thalamic reticular nucleus (Angel 1991). An anesthetic-induced decrease in cortico-thalamic and cortico-recticulo-thalamic signaling is thought to increase inhibition on excitatory thalamic neurons, thereby decreasing their output to the cortex (Angel 1991).
Toward a Unified Theory of Anesthetic-Induced Unconsciousness

Thalamocortical cells have two primary modes of firing—tonic and burst. Onset of physiologic sleep switches these cells from a predominately tonic-firing pattern to a predominately burst-firing pattern (Steriade, McCormick, and Sejnowski 1993). The change in firing pattern occurs coincident with changes in the EEG pattern from one of behavioral arousal (i.e., low voltage, fast activity) to one of slow-wave sleep (i.e., spindle and delta wave oscillations, high voltage, slow activity) (Steriade 1992). Animal physiology studies show that the switch in thalamocortical cell firing and the change in the EEG oscillation pattern happens because the thalamocortical cells become hyperpolarized. This hyperpolarization establishes a block to the transmission of sensory information through the thalamus, which results in the cortex being functionally disconnected from outside sensory

Table 55.2
Areas of significant relative glucose metabolic decreases during anesthesia

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann’s Area</th>
<th>Coordinates</th>
<th>Cluster size (voxels)</th>
<th>Corrected P value of Cluster size</th>
<th>Voxels z-Score</th>
<th>Corrected P value of Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuneus (L)</td>
<td>18</td>
<td>-4 -78 20</td>
<td>338</td>
<td>0.003</td>
<td>5.50</td>
<td>0.001</td>
</tr>
<tr>
<td>Cuneus</td>
<td>18</td>
<td>-6 -92 12</td>
<td></td>
<td></td>
<td>3.62</td>
<td>ns</td>
</tr>
<tr>
<td>Medial Frontal gyrus (L)</td>
<td>47</td>
<td>-36 32 -10</td>
<td>552</td>
<td>0.003</td>
<td>5.13</td>
<td>0.005</td>
</tr>
<tr>
<td>Inferior Frontal gyrus (L)</td>
<td>47</td>
<td>-46 38 -2</td>
<td></td>
<td></td>
<td>4.42</td>
<td>ns</td>
</tr>
<tr>
<td>Inferior Frontal gyrus (L)</td>
<td>47</td>
<td>-26 28 -14</td>
<td></td>
<td></td>
<td>4.42</td>
<td>ns</td>
</tr>
<tr>
<td>Thalamus—anterior nucleus (R)</td>
<td>10</td>
<td>-12 18</td>
<td>1800</td>
<td>&lt;0.001</td>
<td>4.98</td>
<td>0.009</td>
</tr>
<tr>
<td>Thalamus—VLN (R)</td>
<td>14</td>
<td>-16 10</td>
<td></td>
<td></td>
<td>4.81</td>
<td>0.02</td>
</tr>
<tr>
<td>Midbrain (L)</td>
<td>-2</td>
<td>-32 -12</td>
<td></td>
<td></td>
<td>4.73</td>
<td>0.03</td>
</tr>
<tr>
<td>Inferior Temporal gyrus (L)</td>
<td>-58</td>
<td>-34 -16</td>
<td>2319</td>
<td>&lt;0.001</td>
<td>4.71</td>
<td>0.03</td>
</tr>
<tr>
<td>Temporal lobe (L)</td>
<td>-40</td>
<td>-60 -44</td>
<td></td>
<td></td>
<td>4.52</td>
<td>ns</td>
</tr>
<tr>
<td>Fusiform gyrus (L)</td>
<td>36</td>
<td>-42 -34</td>
<td></td>
<td></td>
<td>4.40</td>
<td>ns</td>
</tr>
<tr>
<td>Cerebellum (R)</td>
<td>32</td>
<td>-66 -42</td>
<td>454</td>
<td>0.007</td>
<td>3.81</td>
<td>ns</td>
</tr>
<tr>
<td>Cerebellum (R)</td>
<td>40</td>
<td>-58 -48</td>
<td></td>
<td></td>
<td>3.78</td>
<td>ns</td>
</tr>
<tr>
<td>Cerebellum posterior lobe (R)</td>
<td>26</td>
<td>-64 -36</td>
<td></td>
<td></td>
<td>3.50</td>
<td>ns</td>
</tr>
</tbody>
</table>

Only areas with a z-score >3.09 (P < 0.05, corrected) and an extent threshold >223 voxels (P < 0.01, corrected) are listed. The coordinates are given (in millimeters) for the maximally significant pixel in each cluster (BOLD), and the next highest maxima within each cluster (plain text) according to a standard stereotactic space (Talairach and Tournoux, 1988). x = lateral displacement from the midline (+ for the right hemisphere), y = anteroposterior displacement relative to the anterior comm (+ for positions anterior to the latter), z = vertical position relative to the AC-PC line (+ if above this line); R = right, L = left, VLN = Ventral lateral nucleus.
experience with the onset of sleep-induced unconsciousness (Steriade 1994). During sleep this hyperpolarization block develops because of a decrease in tonic excitation from brainstem arousal centers (Steriade 1994). During anesthesia a hyperpolarization block likely develops not only from anesthetic effects on brainstem arousal centers, but also from direct effects of certain anesthetics themselves.

Based on direct in vitro demonstration of halothane’s ability to hyperpolarize thalamic parafascicular nucleus neurons, Sugiyami and colleagues (Sugiyama, Muteki, and Shimoji 1992) proposed that a hyperpolarization block of thalamocortical neurons may be mechanistically related to the loss of consciousness seen during halothane anesthesia. Our previous in vivo human results with halothane did reveal that a relative decrease of thalamic activity accompanies halothane anesthesia, but a number of other areas, such as the basal forebrain and cerebellum, were also noted to be affected by halothane (Alkire et al. 1999). Thus, a clear relationship between thalamic suppression and “unconsciousness” was not obvious in the single-agent halothane study. However, the present intersection analysis clearly focuses attention to a relatively limited number of brain regions that are commonly affected by both halothane and isoflurane. Here, the fact that isoflurane appears to have mechanisms in common with halothane for affecting thalamic activity strengthens the idea that a hyperpolarization block of thalamocortical neurons has general import for understanding the loss of consciousness induced by anesthesia. Studies are underway to determine whether hyperpolarization of thalamocortical neurons is a general underlying principle of all anesthetics.

Our findings suggest that hyperpolarization of thalamocortical neurons and the transition of thalamocortical activity from tonic to burst firing is likely to be a general principle of anesthesia which can occur through different mechanisms with different anesthetic agents (see figure 55.2).

Anesthetics can affect the activity within thalamocortical-corticothalamic loops and cause thalamocortical hyperpolarization, coincident with the loss of consciousness, by at least four possible mechanisms including: direct cellular hyperpolarization, inhibition of excitement, enhancement of inhibition, or any combination of these. These points are elaborated below.

1. The inhalational agents are known to have direct hyperpolarizing effects on thalamic and cortical neuronal membrane potentials (Berg-Johnsen and Langmoen 1987; Nicoll and Madison 1982; Sugiyama, Muteki, and Shimoji 1992). How much this direct effect contributes to the solidity of the hypothesized hyperpolarization block of anesthetic-induced unconsciousness remains to be determined. However, this factor does predict that those agents with more potent hyperpolarization ability should induce unconsciousness easier than those agents that have limited hyperpolarization ability.

2. Consciousness is an energy-requiring active brain state. Keeping the brain awake requires arousing inputs to the corticothalamic-thalamocortico-reticulothalamic loops from central core structures (brainstem, diencephalon, and basal forebrain) and cortex (Steriade 1993a; Steriade, McCormick, and Sejnowski 1993). The central core structures impinge on the thalamus and thalamic reticular nucleus with tonic excitation from cholinergic, glutamatergic, and aminergic cellular inputs (Steriade 1993b). Our imaging data show that inhalational anesthesia has, as one of its effects, an ability to specifically suppress the functional activity in midbrain/pontine areas involved with regulating arousal. Thus, for the inhalational agents, anesthetic-induced suppression of normal tonic excitatory activity from lower brain structures will directly contribute to hyperpolarization of thalamocortical neurons and a functional decrease in thalamic metabolism. Therefore, just as with natural sleep, removal of excitatory arousal circuitry inputs to the thalamocortical-corticothalamic loops will contribute to thalamocortical hyper-
polarization. Anesthetics will accomplish this removal of excitatory inputs primarily through inhibition of glutamatergic and cholinergic synaptic neurotransmission (Dildy-Mayfield, Eger, and Harris 1996; Durieux 1996; Violet et al. 1997).

3. Enhancement of inhibitory circuitry functioning within the thalamocortical loops, primarily through enhancement of GABAergic synaptic neurotransmission is one of the primary mechanisms of sleep regulation (Juhasz, Emri, Kekesi, and Pungor 1989; Steriade, Dossi, and Nunez 1991). Enhancement of GABAergic synaptic neurotransmission has often been proposed as a possible mechanism of anesthesia (Cheng and Brunner 1987, Juhasz et al. 1989). The present empirical results provide a functional neuroanatomic bridge for understanding the link between endogenous sleep mechanisms, GABAergic signaling, and anesthetic-induced unconsciousness.

4. Any individual anesthetic agent might need to use only one of these proposed mechanisms, such as barbiturate enhancement of GABAergic activity. Alternatively some agents (like the inhalational) might use various proportions of nearly all of these different mechanisms (Franks and Lieb 1994). In essence, any substance or event that pushes thalamocortical cells towards hyperpolarization, through whatever mechanism, will drive the brain towards unconsciousness. Unconsciousness will result when the thalamocortical switch is “pushed” far enough and the thalamocortical cells change from tonic to burst firing.

Halothane and isoflurane are in the same general class of general anesthetic agents. Thus, after the fact, it seems not at all surprising that their global and regional effects on functional cerebral metabolism would be found to be somewhat similar. Nonetheless, prior to this study, a number of physiologic/functional differences were known to exist between these two agents, which made predicting a loci for a common effect between them a speculative proposition, at best. On an equal MAC basis, the agents differ in their ability to suppress cerebral metabolism, isoflurane is the most potent inhalational agent at suppressing cerebral metabolism, halothane is one of the least potent (Todd and Drummond 1984). Halothane is the most potent at increasing cerebral blood flow; isoflurane is one of the least potent. Halothane induces EEG “sleep” spindle activity that is morphologically nearly identical to the spindles found with natural sleep (Keifer, Baghdoyan, and Lydic 1996). Isoflurane also induces EEG spindle activity, but the spindles of isoflurane have a morphology more reminiscent of those found with the barbiturates and burst suppression patterns. Numerous functional differences between agents also exist on the cellular level (Chan and Durieux 1997, Nietgen et al. 1998, Schotten et al. 1998). Thus, though one could argue that the main theoretical hypothesis of this paper would have been better tested if different classes of general

Figure 55.2
A neuroanatomic/neurophysiologic model of anesthetic-induced unconsciousness. The key cellular players are the thalamocortical, corticothalamic, and reticulothalamic cells. (a) The system during consciousness, when sensory information can be processed through the thalamus. (b) The system during anesthetic-induced unconsciousness. Sensory information processing is blocked at the level of the thalamus secondary to thalamocortical hyperpolarization, which switches the thalamocortical cells from tonic to burst firing mode. The thalamus/thalamic reticular area (A) and the midbrain region (B) specifically suppressed by inhalational anesthesia in humans (from figure 55.1) are outlined. Anesthetics affect numerous interaction points within the thalamocortical-corticothalamic-reticulothalamic loops and cause thalamocortical hyperpolarization through many mechanisms including, direct hyperpolarization, GABA agonism, glutamate antagonism, and cholinergic antagonism. ACH = acetylcholine, 5-HT = 5-hydroxy-tryptamine, GABA = gamma amino butyric acid, Glut = glutamate, NE = norepinephrine.
anesthetic agents were studied (intravenous versus inhalational, for example), the agents that were studied were, nonetheless, functionally divergent in a number of important respects.

Strong support for the theoretical framework proposed here has recently emerged from the report by Fiset and colleagues (Fiset et al. 1999). They studied the effects of the intravenous anesthetic agent propofol on regional cerebral blood flow during different depths of sedation/anesthesia in humans. Using a correlational approach between propofol blood levels and PET blood flow images, they found a strong relationship exists between a person’s level of “consciousness” and the amount of activity in the thalamus, basal forebrain, and occipital lobe. The regional results from that study and the regional results presented here are remarkably similar. The regions identified in both studies qualitatively appear to differ only in the magnitude of how much each region is identified. Their occipital and frontal findings are larger than ours, and our thalamic finding is larger than theirs. By visual inspection, an intersection analysis between the three agents (i.e., halothane, isoflurane, and now propofol) would reveal the thalamus as the primary focus of the intersection. This overlap in findings is made even more striking when one considers that this completely different group of investigators used a different type of imaging technique (blood flow versus glucose metabolism), with a different type of analysis technique (correlational versus subtractive) to find similar regional effects on consciousness with a different class of anesthetic (intravenous versus inhalational). Thus, the regional results found by Fiset and colleagues integrate extremely well with the theoretical framework proposed here.

**Neural Correlates of Consciousness: Where or How?**

Do these data help us answer the questions: Does the neural substrate of conscious awareness depend upon activation of a particular set of neurons, or does it depend upon the resonant or regenerative patterns of activity across select groups of neurons? What do the present findings say about thalamocortical functioning as the basis of waking consciousness? These broader issues may come into focus with more discussion on how the present findings can be interpreted.

The overall logic of the experimental approach used here is rather straightforward. Subjects are studied in two conditions: conscious and unconscious. A subtraction image between these two conditions should reveal something about the functional neuroanatomy of “consciousness.” A number of possible results could be expected from such a subtraction analysis. At best, those brain areas that generate consciousness will be identified. In other words, the subset of brain regions whose functional activity results in a subjective experience of consciousness will be identified. In other words, the subset of brain regions whose functional activity results in a subjective experience of consciousness will be visualized (i.e., a neural correlate of consciousness). Alternatively, those brain areas whose functional activity is required for consciousness to occur will be identified. In other words, rather than identifying those neurons which directly contain consciousness itself, the subtraction analysis may reflect primarily those neurons required to be active in order to allow consciousness to occur (i.e., the power switch). Another possibility, is that no regions would be identified. This could happen if consciousness is a widely diffuse phenomenon that depends on the global functioning of the brain (i.e., the Dennett explanation; Dennett 1991). Or, this could happen if the neurons that mediate consciousness are clustered in groups smaller than the spatial resolution of the PET technique. The regions identified may have nothing to do with consciousness, per se, or the regulation of consciousness, but may simply reflect those areas most affected by the agents causing the unconsciousness. For example, Cohen and Hood showed that radio-labeled halothane had a particular affinity for the granular layer of the cerebellum (Cohen and Hood 1969). Therefore, it is
conceivable that the regional cerebellar metabolic decrease found in this report may be related to some unique ability of the inhalational anesthetics to specifically suppress metabolism in the cerebellum. Recently, Eckenhoff and colleagues showed that radio-labeled halothane has affinity for regions with high synaptic density (Eckenhoff and Eckenhoff 1998). Similar regional affinities may exist in other brain areas, perhaps the basal forebrain and thalamus are specifically sensitive to the effects of inhalational anesthesia because of a relatively higher synaptic density. Finally, a combination of any of these results could occur.

What did happen? We propose our results are best interpreted as a mixture of the above possibilities. Using neuroanatomy and neurophysiology as guides, we hypothesize that the thalamic and midbrain reticular formation findings are probably related to the suppression of a specific set of consciousness requiring neurons (i.e., the thalamocortical hyperpolarization hypothesis). Prior to these empirical results, these regions were often proposed as important by a number of authors expounding a number of theories about the functional neuroanatomy of consciousness (for review, see Smythies 1997). Furthermore, since the pioneering work of Moruzzi and Magoun (1949), the connection between the need for functional activity in these brain regions and the regulation of levels of consciousness is well established. In some sense then, these specific regional findings demonstrate and confirm in vivo what is to be expected from years of research related to regulation of levels of consciousness. As such, these results focus attention back to the old reticular formation hypothesis of anesthetic action. However, these results and our theoretical framework build on that older hypothesis by placing the most important region of anesthetic action not in the reticular formation itself, but rather in the thalamically gated regions regulated by the arousal centers located within the reticular formation. Given all of that, it would appear that these empirically demonstrated regional findings fit remarkably well with the extended reticular-thalamic activating system (ERTAS) theory of consciousness proposed by Newman and Baars (Newman and Baars 1993). Furthermore, these results fit well with the idea that the activity within some small subcortical structures may be required for the state of waking consciousness, whereas cortical projection areas may provide the perceptual content of consciousness (Baars 1995).

The findings of the left dorso-lateral prefrontal cortex and the left temporal gyrus are probably related to the fact that the subjects were listening to an audiotape during both awake and anesthetized conditions. During the awake scans the subjects would likely have been internally rehearsing the words on the audiotape. Yet, during the anesthetized scans such rehearsal was probably not possible. Hence, this region shows up in a subtraction analysis. However, a more intriguing possibility for why this region shows up is to suggest that the dorso-lateral prefrontal cortex finding might represent a neural correlate of consciousness, itself. For many people the internal perception of being conscious is having the ability to think to oneself and follow a “stream of consciousness” that is primarily a running verbal commentary. Putting the thalamic findings with the dorso-lateral prefrontal cortex findings and realizing that the subject’s attention was likely focused on the auditory input, raises the possibility that a functional “consciousness circuit” may have been directly visualized for the first time in the human brain. Such a functional circuit would fit well with the ERTAS model of consciousness. Of course, many more controlled brain imaging experiments, such as replicating the procedures done here without the auditory input, need to be performed to follow up on this speculative idea.

The cerebellar and occipital lobe changes seen here may be related to the decreased sensory state the subjects were in while unconscious. Or, as previously suggested, they might simply represent some regional selectivity of the anesthetic
agents themselves. If the cerebellum was involved with mediating waking consciousness then it would likely have shown up in the propofol study of Fiset and colleagues (1999). Likewise, the large occipital lobe effect seen by Fiset and colleagues (1999), which was not seen here (with the study of the inhalational agents), is likely related to a specific effect of propofol. As one can see by this example, separating the regional functional brain changes associated with consciousness itself from the extemporaneous effects agents can have on regional brain metabolism can be significantly helped by utilizing an intersection analysis approach.

Were subjects conscious while “unconscious”? The word anesthesia literally means to be without sensation (an + aisth* sis). On emergence from the anesthetic experience all subjects reported a sensation of complete oblivion during the anesthetic. No subject could remember anything about the time they were unconscious, even after repeated questioning. Many offered the statement that their mind was a complete blank for the period of anesthesia, and many had a sensation that time had stopped while they were unconscious. Thus, in the proposed model, with the thalamic “consciousness” switch thrown, sensory information would have been prevented from reaching each subject’s cortex and the subjects were likely rendered in a cognitive state of sensory deprivation. Nevertheless, even though no new sensory information was coming into each subject’s cortex, perhaps some subjects were in some sort of “dreamlike” state and still able to ruminate about thoughts already within their brains.

The idea that these subjects may have retained some level of consciousness during anesthesia should be considered to be highly unlikely. Most anesthetics, including alpha-chloralose and urethane cause a significant decrease in global brain metabolism (Dudley, Nelson, and Samson 1982; Ito, Miyaoaka, and Ishii 1984), even though functional brain reactivity may remain somewhat intact (Dudley, Nelson, and Samson 1982). Remember that the appearance of the thalamic switch, in the present report, is really superimposed on the back of a large global reduction in brain functioning for both of these inhalational agents (see table 55.1). Such a large global decrease in brain functioning means that cortical brain functioning is dramatically reduced during the anesthetic exposure. If one presupposes that cortical projection areas may contain the content of consciousness (Baars 1995), then a direct anesthetic effect on the cortex should directly suppress consciousness.

Did consciousness go away in our subjects because of neuronal suppression or discharge disruption? In other words, it may not be which neurons are firing that determines the presence or absence of consciousness; rather it may be how select groups of neurons fire that generates consciousness. This distinction underlies a number of theories on consciousness related to oscillatory neuronal firing patterns. Given that the imaging technique used has a relatively long temporal resolution and can only really measure suppression (or activation) of activity, it is not really possible to address this question with these data. Nonetheless, to speculate on this issue and as a prelude to future experiments, only a few anesthetics might fit into the disruption rather than the suppression category. These agents include ketamine, nitrous oxide, and xenon. Interestingly, these agents may have their primary anesthetic affects mediated primarily through the NMDA receptor (Franks et al. 1998).

Although it is common usage to state that a patient under anesthesia has been “put to sleep,” our data suggest that this statement may not be far from the truth. Our findings reveal that the physiology of the unconsciousness induced by anesthesia likely shares a common mechanism with that of the unconsciousness caused by non-REM sleep (Lydic and Biebuyck 1994). This is not to say that anesthesia is a form of sleep. Anesthesia fundamentally differs from sleep in a number of important respects, such as the inability to be aroused from anesthesia and an-
esthetic-induced inhibition of thermoregulation and vasomotor tone. Another primary difference between the two states of awareness is that anesthetics inhibit those systems that allow cortical arousal and REM functioning to occur (e.g., primarily basal forebrain and reticular formation cholinergic activation) (Keifer, Baghdoyan, and Lydic 1996), and thus anesthesia can be likened to a form of slow-wave sleep from which one can not be aroused. Therefore, it might be more precise to state that anesthetics do not “put one to sleep”; rather, they “prevent one from being awake.” In any event, the novel idea here is that the underlying neurophysiology that produces the “unconsciousness” of both slow-wave sleep and anesthesia is likely to be the same.

Conclusion

Functional brain imaging data of two different commonly used inhalational anesthetic agents obtained from volunteers rendered unconscious with anesthesia revealed the thalamus and midbrain reticular formation to be at the intersection of the anesthetic effect on human consciousness. These data offer strong support for theories attempting to relate the neuronal basis of consciousness to the functional activity in thalamocortical-corticothalamic loops. Moreover, these data lead to the proposal of a new unifying neurophysiologic model of anesthetic-induced unconsciousness. The essence of the model explains the multiple different pathways through which various anesthetic agents may act to produce unconsciousness by all ultimately causing the development of a hyperpolarization block in thalamocortical neurons.

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