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The Search for Structures and Mechanisms Controlling Anesthesia-induced Unconsciousness

ONE of the main effects of general anesthesia is the suppression of consciousness, *i.e.*, prevention of awareness. This must not be confused with absence of recall. A patient who does not have recall for events during general anesthesia may still have been conscious during the procedure. Recently, a case report in ANESTHESIOLOGY described a patient who had awareness without recall during electroconvulsive therapy.[1] In several studies, Veselis *et al.*[2–4] identified amnestic effects at subanesthetic concentrations of anesthetics and the according anatomical structures. In the current issue of ANESTHESIOLOGY, two research groups try to identify the effect sites of anesthesia-induced loss of consciousness. At first glance, results of the two studies seem to be in conflict with one another.

Velly *et al.*[5] studied patients undergoing intracerebral electrode placement for deep brain stimulation. Scalp electrodes and a deep brain electrode were used for recording of electrical activity of cortical and subcortical structures. During general anesthesia, the first effect was slowing of cortical electroencephalogram with prominent amplitudes in the δ range, whereas the signal obtained from the deep brain electrode showed faster spindle activity with less prominent slowing of the power spectrum. As cortical slowing of electroencephalographic activity was more prominent and occurred earlier, the authors concluded that the main effect site of anesthesia-induced unconsciousness is the cerebral cortex.

In contrast, Alkire *et al.*[6] identified subcortical structures as one of the main effect sites of anesthesia-induced unconsciousness in animals. In their study, microinjection of nicotine into the central medial thalamus, a subcortical structure, reversed loss of righting reflex induced by sevoflurane. Given the specificity of both drug effect and localization, the authors conclude that general anesthesia blocks endogenous cholinergic arousal mechanisms in the central medial nucleus of the thalamus, *i.e.*, the main targets of general anesthesia are thalamic structures.

Therefore, these reports provide evidence in support of both cortical as well as for subcortical structures as target sites of general anesthesia (fig. 1).

This Editorial View accompanies the following two articles: Velly LJ, Rey MF, Bruder NJ, Gouvitsos FA, Witjas T, Regis JM, Peragut JC, Gouin FM: Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. ANESTHESIOLOGY 2007; 107:202–12; Alkire MT, McReynolds JR, Hahn EL, Trivedi AN: Thalamic microinjection of nicotine reverses sevoflurane-induced loss of righting reflex in the rat. ANESTHESIOLOGY 2007; 107:264–72.

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Cerebral Cortex as Effect Site for Anesthesia-induced Unconsciousness?

Velly *et al.*[5] found that at loss of consciousness after sevoflurane or propofol administration, cortical δ activity increased and (faster) β activity decreased. As a consequence, spectral edge frequency (SEF_{90}), median frequency, and the nonlinear parameter dimensional activation decreased. Similar changes occurred at the subcortical level, but these changes occurred later and more gradually. The coincidence of loss of consciousness with changes at the cortical level suggests that anesthesia-induced unconsciousness is induced by changes at the cortical level. Even if these aspects seem convincing, there may be several limitations in the current approach. For cortical electroencephalographic analysis, only a frontal channel (F3–C3) was used, which may only in part reflect spatiotemporal distribution of cortical electroencephalographic activity. In addition, differences in the power spectrum may—at least in part—be due to higher frequency spindle activity in deep brain signals. Cortical spindle activity may not primarily appear in frontal leads but may be picked up by central or occipital leads. It remains to be determined whether analysis of a multichannel electroencephalogram would have led to identical differences in the power spectrum.

Another concern relates to the type of signal analysis which may give erroneous results during spindle activity. As used in the current approach, frequency analysis may result in increases in both SEF_{90} and median frequency during slow δ activity. This seems to be crucial because γ-aminobutyric acid type A ($GABA_A$) agonists induce spindle activity (14 Hz) reflecting inhibitory effects rather than less inhibition as suggested by analysis of SEF or median frequency. It must also be remembered that anesthetics induce slowing of cortical activity independent from subcortical structures.[7]

Timing of signal changes is the strongest point supporting the primary role of the cortex.[5] Still, it remains unclear whether anesthesia-induced changes at the subcortical level are related to the signal changes seen at the cortical level, *i.e.*, slowing of electrical activity may not be an uniquely valid representation of anesthetic effect,

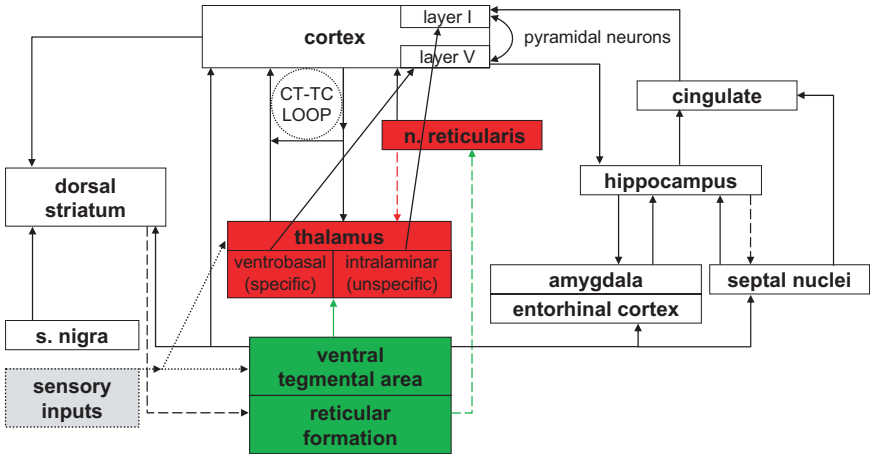

Fig. 1. Diagram of interactions among brain regions during sensory input, modified from John and Prichep.[11] The scheme illustrates the pathway of sensory inputs through the brainstem reticular formation (ascending reticular activating system) and thalamus to the cortex. It is suggested that corticocortical and corticothalamocortical loops (CT–TC loops) are essential for perceptive processes of the brain, providing the basis of "consciousness." Intralaminar (unspecific) and ventrobasal (specific) nuclei serve as gates to cortical layers I and V. (Cortical) pyramidal neurons (*top*) compare (unspecific) input into layer I and (specific) input into layer V. With concurrent stimulation, corticothalamic discharges are markedly enhanced, and γ frequency is back-propagated to cortical regions where the coincidence had occurred. As suggested by Velly *et al.*,[5] direct suppression of cortical cells by anesthetics (*red*) induces unconsciousness. This is supported by the coincidence of loss of consciousness with changes at the cortical level. As Alkire *et al.*[6] show, this mechanism can be reversed by nicotinic stimulation of the ascending reticular activating system (*green*), which reopens thalamic gates, allowing throughput of stimuli to the cortex (arousal).

and Velly *et al.*[5] do not exclude the role of the thalamus but suggest that the "main site" of action is the cerebral cortex.

Thalamus as Effect Site for Anesthesia-induced Unconsciousness?

The thalamus serves as a primary relay station for incoming sensory information and motor output from the brain. Previously, the existence of a thalamic consciousness switch has been suggested.[8] Alkire *et al.*[6] used an animal model to examine the influence of the cholinergic system at the thalamic level. They found that cholinergic stimulation of the central medial nucleus of the thalamus reversed sevoflurane-induced loss of righting reflex in both receptor- and site-specific manners (fig. 1, green). Cholinergic blockade of this area, however, did not reduce sevoflurane requirements. They concluded that thalamic acetylcholine receptors have a role in regulating the "on" switch, *i.e.*, arousal, and sevoflurane blocks endogenous cholinergic arousal mechanisms.

As discussed by Alkire *et al.*,[6] the role of cholinergic blockade is mainly supported by changes in the electroencephalogram and suppression of spontaneous motor movement, whereas knockout mice without β_2 nicotine receptor show no alterations of anesthetic requirements, and cholinergic antagonists *per se* do not produce unconsciousness.

Despite the meticulous localization experiments performed in this study, the central medial nucleus of the thalamus may not be the most crucial site of action with respect to the cholinergic theory of general anesthesia. Anesthesia may block arousal by inhibiting cells of the central medial nucleus of the thalamus, but this approach neglects the brainstem and the septal–hippocampal system, which in this context may also play an important role.

On the other hand, the cholinergic system may not be the exclusive effect site of general anesthesia. It has been suggested that volatile anesthetics act on $GABA_A$, serotonin, acetylcholine, and possibly glutamate receptors.

Microinjection of the $GABA_A$ antagonist gabazine into the tuberomammillary nucleus has been shown to attenuate the sedative response to propofol and pentobarbital, whereas microinjection of the $GABA_A$ agonist muscimol led to a dose-dependent sedation.[9] The role of $GABA_A$ is supported by known interactions between $GABA_A$ in the central medial nucleus of the thalamus and nicotinic mechanisms (as identified in the current study of Alkire *et al.*[6]).

Integrating cortical and subcortical effects on different receptors, the following mechanism of arousal is consistent with the results of Alkire *et al.*: If the ascending reticular activation system receives input, the brainstem reticular formation inhibits the nucleus reticularis, which itself opposes GABAergic inhibition by acetylcholine. Thalamic oscillators (in the frequency range of 8–12 Hz) are activated, thalamic gates are opened, and inputs from the exogenous system are transmitted *via* projection pathways to axosomatic synapses of pyramidal neurons in lower layers of cortex.

Thalamocortical Interactions and Anesthesia-induced Unconsciousness

In contrast to a prominent or exclusive role of either cortex or thalamus, the importance of intact thalamocortical–corticothalamic loops has been highlighted.[8,10] In the current study, Alkire *et al.*[6] suggest that their results support the role of a corticothalamic reentrant mechanism of neural activity.

In brain metabolism studies using positron emission tomography scans, a general depression from volatile anesthetics was found with pronounced effects on cuneate nucleus, thalamus, midbrain reticular formation, dorsolateral prefrontal cortex, medial frontal gyrus, inferior temporal gyrus, cerebellum, and occipital cortex.[8] This can be induced by a hyperpolarization block of thalamocortical relay nuclei in thalamic networks. Therefore, general anesthesia induces a change from thalamic throughput to closed thalamocortical gates.

In a recent review, John and Prichep[11] highlight the importance of synchronized activity of cortical and subcortical structures: Pacemaker neurons in the thalamic region that oscillate in the α frequency range (8–12 Hz) regulate and synchronize the excitability of thalamocortical pathways.

In thalamic nuclei, three main types of neurons interact: thalamocortical relay nuclei, whose axons project to the cortex; reticular nucleus neurons, which interact synaptically with thalamocortical relay cells (GABAergic inhibitory feedback control); and local intrinsic neurons. Thalamocortical relay nuclei consist of relay cells (producing spikes in response to input) and oscillatory cells (producing rhythmic bursts of high frequency spikes, repeated in rhythmic oscillatory pattern). The brainstem reticular formation receives collateral input from all afferent sensory pathways. The importance of this structure is supported by the following experiments: Bilateral transsection of this area induces long-lasting coma, whereas electrical stimulation leads to activation and desynchronization of the electroencephalogram. This system is denoted as the ascending reticular activation system. Cholinergic activation diminishes the influence of GABAergic reticular nucleus neurons, which removes hyperpolarization and thus facilitates throughput to the cortex. This results in cortical arousal, reflected by desynchronization of α waves. As a consequence of event-related desynchronization, corticocortical interactions generate β rhythms (12–25 Hz). With concurrent stimulation (reflecting coincident exogenous and endogenous input), corticothalamic discharges are markedly enhanced, and γ frequency is back-propagated to cortical regions where the coincidence had occurred. This feedback has been suggested to bind distributed fragments, and coherent corticothalamocortical loops reverberate at γ frequencies (25–50 Hz).

As a consequence of these findings, the coherence of β and γ activity seems crucial for consciousness. As suggested by John and Prichep,[11] fronto-occipital activity is functionally uncoupled with loss of consciousness. General anesthesia interrupts and consciousness restores corticothalamocortical reverberation resulting from detection by the pyramidal neurons of coincidence between the exogenous readout of episodic memories, endowing sensations with meaning.

Inhibition of either cortex or non–sensory-specific diffuse thalamic projection nuclei block corticothalamocortical reverberations hypothesized to be critical for awareness. Closing of the gates of the thalamic diffuse projection system will therefore induce loss of consciousness.

On the background of these mechanisms, John and Prichep[11] suggest the following "anesthetic cascade":

1. Direct hyperpolarization of thalamic and cortical cell membranes[12]
2. Suppression of midbrain/pontine areas involved with regulation of arousal, removing excitatory input to thalamocortical loops (inhibiting glutamatergic and cholinergic neurotransmission)[13]
3. Enhancement of $GABA_A$ synaptic neurotransmission (inhibitory circuitry within thalamocortical loops) [14]

Different anesthetics may only use one of the mechanisms, some agents may use various combinations. This supports Alkire's view that any push toward hyperpolarization of thalamocortical loops will cause loss of consciousness. Therefore, the state of general anesthesia is produced by enhanced inhibition in a widespread manner, where the thalamus has a "filter" function, blocking the throughput of peripheral stimuli to the cortex.

No single effect on an isolated brain structure can possibly explain how anesthetics produce unconsciousness. Effects of general anesthesia involve a variety of neurotransmission processes, and the effects are widespread throughout the brain. Parts of this complex system have been elucidated by the work of Alkire *et al.*[6] This hypothesis may also be supported by the results of Velly *et al.*,[5] who suggest a primarily cortical effect. Their hypothesis is strongly based on activation of electroencephalographic δ activity, which may, however, not only reflect direct influence of anesthetics on cortical cells. It may also be induced by diminished activation of the cortex by the ascending reticular activation system and extreme depression of thalamic gates.

It seems unlikely that anesthetic effect on a unique neuroanatomical structure is both a necessary and a sufficient condition to produce loss of consciousness. Combinations of positron emission tomography and functional magnetic resonance imaging studies (providing spatial information) on the one hand and electroencephalographic and evoked potential studies (providing temporal information) on the other hand may finally identify brain targets of general anesthesia and their connectivity or disruption during anesthesia-induced loss of consciousness.

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The Impact of Lack of Standardized Definitions on the Specialty

HOW about a quick quiz? Intraoperative hypotension is associated with which perioperative event?

A. Stroke
B. Myocardial infarction
C. Cognitive dysfunction
D. Renal insufficiency
E. All of the above

Seems like a pretty straightforward question—one that you'd like to have been asked on your written board examination. The answer clearly is E, all of the above. Or is it? Ironically, it's more complicated than it seems. In this month's Journal, Jilles Bijker, M.D., a resident in anesthesiology from Utrecht, The Netherlands, and his colleagues ask two great questions that we all should ask, "Does everyone define intraoperative hypotension the same way?" and "What is the impact of different definitions for this event?"[1] If only we were all as smart as our residents.

Their study is simple in format but elegant in design. Bijker *et al.* first performed an extensive search of the four specialty journals with the highest impact factors in 2004, seeking articles from 2000 to 2006 that defined hypotension in their methodologies and used this definition in the intraoperative portion of their studies. They then retrospectively searched the intraoperative blood pressures of 15,059 adult patients at their medical center who underwent noncardiac surgery with general anesthesia and applied the various definitions of hypotension from the literature to their data. Their finding that the unique and widely variable definitions markedly impacted the prevalence of hypotension in their patient population is not surprising. What is surprising is the huge variation that they found, with prevalence rates ranging from 5% to 99%. For example, if the definition "a decrease in systolic blood pressure greater than 10% from baseline for any duration," used in several articles from our finest specialty journals, is applied, 99% of all patients in this population had at least one episode of hypotension. In contrast, if the definition "systolic blood pressure less than 70 mmHg for at least 5 min" is used, only 5% of these patients were hypotensive.

Why does this matter, especially enough to earn an editorial comment? There are three main reasons. First, the lack of standard definitions makes it impossible to compare outcomes among different institutions. Second, the definitions that we use drive the frequency and possibly even severity of the outcomes that we read in the literature, so it is crucial that we know and understand how perioperative events are defined and applied in both clinical trials and in our personal anesthesia practices (*e.g.*, assessment of performance improvement activities). Third, widely disparate definitions can be used both in and out of our specialty to influence the public's perception of the care that we provide. For example, medicolegal experts often exploit this issue with or without intent to lead juries to potentially inappropriate conclusions.

The authors correctly identify that future research should describe in much greater detail aspects of the

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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