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Anesthesia, Amnesia, and the Amygdala

Reducing the Fear of Intraoperative Awareness

THERE are three fundamental goals of anesthesia: unconsciousness, amnesia, and immobility. In years past, most people would have assumed that anesthetics act in the brain to produce all three of these goals. In the past decade, data have emerged indicating that immobility is likely produced by anesthetic action in the spinal cord, prompting a reexamination of "macroscopic" sites of anesthetic action.[1,2] With regard to amnesia, the hippocampus is certainly involved in declarative memory, and hippocampal lesions can result in profound amnesia. However, the role of other brain areas, such as amygdala and entorhinal cortex, in memory formation is complex and apparently dependent on subtle aspects of the memory task.[3] What is the role, if any, of these structures in anesthetic-induced amnesia? The report by Alkire and Nathan[4] in this issue of ANESTHESIOLOGY provides interesting data supporting the amygdala as a site at which inhaled anesthetics exert an amnestic effect on fear conditioning, one form of memory.

The amygdala is strongly implicated in learning under emotionally charged settings such as fear. An inhibitory avoidance paradigm was used by Alkire and Nathan in which rats were placed in a lighted chamber facing a dark tunnel, which they normally prefer to enter. However, entrance into the dark area was negatively reinforced by electrical shock; rats quickly learned to avoid entering the dark tunnel and remained in the nonpreferred but "safe" lighted environment. When retested the next day, the rats continued to avoid entering the dark tunnel; their memory retention latency (*i.e.*, time to enter the dark tunnel) was very long, indicating that they remember being shocked. If a low concentration of sevoflurane was administered during the initial training period, the animals quickly entered the dark tunnel the following day, *i.e.*, sevoflurane prevented avoidance learning. However, after bilateral lesion of the basolateral amygdala, rats exhibited equally long memory retention latencies regardless of whether low-dose sevoflurane was given. These data suggest that, at least for this type of learning, the basolateral amygdala is not the critical site for memory storage and that sevoflurane (and propofol[5] and diazepam[6]) acts in that structure to block this learning. It should be noted that the absence of amnesia in the amygdala-lesioned animals reported by Alkire and Nathan is at odds with the findings of other groups.[7–9] In any event, the data imply that in the intact animal, sevoflurane activates pathways in the basolateral amygdala that exert an inhibitory effect on avoidance learning at sites outside the lesioned area of the basolateral amygdala.

The data of diazepam, propofol, and sevoflurane with respect to inhibitory avoidance are remarkably similar. Figure 2 in Tomaz *et al.*,[6] figure 4 of Alkire *et al.*,[5] and figure 3 of Alkire and Nathan,[4] aside from slight differences in control latency, are virtually superimposable. Because diazepam and propofol act almost exclusively at the γ-aminobutyric acid receptor type A ($GABA_A$) receptor and sevoflurane also enhances $GABA_A$ receptor function, it seems logical to conclude that sevoflurane produces its effect on the amygdala at the $GABA_A$ receptor. Ketamine, however, has virtually no action at the $GABA_A$ receptor, but it produces amnesia in a dose range equipotent to that of volatile anesthetics.[10] Therefore, it would be folly to assume that, for amnesia, all anesthetics must act at the amygdala and/or *via* a $GABA_A$ receptor effect. Furthermore, the nonimmobilizer 1,2-dichlorohexafluorocyclobutane abolishes fear conditioning, but low-dose isoflurane reverses, not potentiates, this action,[11] underscoring the complex nature of memory and anesthetic-induced amnesia. Clearly, more work is needed to identify the molecular and cellular mechanisms by which memory formation is prevented by inhaled and intravenous anesthetic agents.

The data of Alkire and Nathan indicate that the basolateral amygdala is quite sensitive to sevoflurane. The control animals in their study lost memory (or never learned) when the sevoflurane concentration was 0.3%—only 0.15 minimum alveolar concentration (MAC). It is unclear whether other structures associated with memory formation (*e.g.*, hippocampus) are more or less sensitive. Anesthetic effects on fear to context and tone have been extensively studied. Interestingly, fear to context has anesthetic sensitivity comparable to that of inhibitory avoidance, but ablation of fear to tone requires twice as much anesthesia.[12] Nonetheless, the results emphasize the importance of investigating the sites of anesthetic-induced amnesia. It is unknown, however, whether anesthetic action at one single anatomical site in humans prevents all intraoperative memories (implicit

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and explicit). If an anesthetic could be developed that had significant specificity at memory-formation sites, we would feel much better about giving a sub-MAC concentration of anesthesia. It is fortuitous that the anesthetic concentration needed to prevent memory is well below that needed to prevent movement. This fact, combined with the relative steepness of the population dose–response curves for amnesia and immobility, gives the anesthesiologist (and the patient) some reassurance that memories will be ablated even at anesthetic concentrations that otherwise would not prevent movement.

Memories differ in their emotional content. If you are a surgical patient, remembering what you had for dinner the night before surgery does not carry the emotional content that an intraoperative memory might have. Hence, the amygdala has a potential key role in ablation of those memories that we do not want patients to have. Patients who report intraoperative awareness sometimes do not describe these memories as distressful. Is this because the anesthetic sensitivity of the amygdala blocks the emotional aspects of the experience but not the experience itself? Nonetheless, memory during anesthesia and surgery can be distressing and is associated with posttraumatic stress disorder. Intraoperative awareness has received much recent attention and has prompted the recent sentinel event issued by the Joint Commission on Health Care Organizations.† Reports in the lay press have increased public awareness of this issue. Therefore, increased funding of research into anesthetic mechanisms and subsequent development of newer and safer anesthetics are likely to gain wider support, especially among the estimated 20,000–40,000 Americans who experience intraoperative awareness every year.

We began by stating the basic goals of anesthesia, but some have argued that amnesia, along with immobility, is all that is needed[13]; intraoperative awareness is immaterial if it cannot be remembered. This approach, at the very least, minimizes the role of implicit memories. In any case, as anesthesiologists, we would like for our patients to have a pleasant perioperative experience. Is it any wonder that we are intensely interested in how anesthetics affect brain sites associated with unpleasant events and memories? If we could affect those areas, would patients otherwise have any problems with their perioperative experience, including the possibility of intraoperative awareness? After all, if we can ask our patients if their experience was pleasant, and they always say yes, what more could we ask for?

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† Available at: http://www.jcaho.org/about+us/news+letters/sentinel+event+alert/sea_32.htm. Accessed December 15, 2004.

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Brain Cell Damage and S-100B Increase after Acute Lung Injury

ACUTE respiratory distress syndrome (ARDS) is a severe, inflammatory disease of the lung with a high mortality rate. It is characterized by the sudden onset of pulmonary edema and respiratory failure, usually in the setting of other acute medical conditions resulting from local (*e.g.*, pneumonia) or distant (*e.g.*, multiple trauma) injury. Previous outcome studies of ARDS have mainly focused on survival, pulmonary function, or both as the primary outcome measures. However, there is increasing evidence that patients with ARDS are at risk for brain injury through hypoxemia or other mechanisms. In this issue of ANESTHESIOLOGY, Fries *et al.*[1] demonstrate histopathologic findings of neuronal cell damage in the vulnerable CA1 subregion of the hippocampus and serum S-100B protein increases in a porcine acute lung injury model. Hippocampal damage is a major cause of cognitive impairment and a substantial portion of ARDS survivors exhibit impaired health status and long-term cognitive sequelae.[2,3]

The article delivers two important messages. First, acute lung injury in an animal model may cause brain cell damage. However, the observed time course of changes of serum S-100B protein concentrations and the significant differences between the two experimental groups do not allow us to draw conclusions about neuronal damage. S-100B is not specific for the brain, it is believed to originate from glial cells (that are more resistant to hypoxemia than neurons), and increases may also be caused by extracranial injuries,[4–6] such as in the setting of an acute lung injury model. Likewise, the differences in S-100B between the two experimental groups may simply reflect the use of two different experimental models. However, the histopathologic finding of argyrophilic dark neurons is considered a reliable and early sign of damaged neurons. The CA1 subregion of the hippocampus is an established model often used to investigate brain damage in the experimental setting. This region of the brain is especially vulnerable to a variety of pathologic conditions, such as ischemia, inflammation, and hypoxia. The study of Fries *et al.*[1] was designed in a way that both experimental groups, the acute lung injury group and the hypoxia-only group, had nearly the same time course of changes in pulse oxymetry saturation. Therefore, the degree of hypoxemia was comparable between the two groups. The observation of argyrophilic dark neurons in the CA1 subregion of the hippocampus in both groups as a result of hypoxemia was not unexpected but until now unproven. However, there is a difference between the two groups in terms of the degree of brain cell damage. In the lung injury group, the relative percentage of damaged neurons was three times higher compared with the hypoxia group.

This leads us to the second message, which is the intriguing hypothesis that acute lung injury may result in brain cell damage independent of the level of hypoxemia. The authors speculate that the inflammatory response induced by the lavage model of the acute lung injury group but not in the hypoxia-only group is accountable for the difference in neuronal injury.

Repetitive lung lavage leads to lung injury similar to ARDS, resulting in poor gas exchange, protein leakage, infiltration of polymorphonuclear neutrophils into the alveolar spaces, and other local and systemic inflammatory responses.[7–11] Conversely, in acute lung injury or ARDS, lung-protective ventilation strategies reduce both hypoxemia and sustained mediator release[12–14] with effect on multiorgan failure[15] and further mediator production.[16]

The brain is believed to be an immunologically privileged organ, normally sheltered from the systemic immunologic defense by the blood–brain barrier. However, there is increasing evidence for a marked inflammatory response in the brain after traumatic brain injury[17] and after remote organ injury.[18] Using a rodent cecal ligation and puncture model of sepsis, measurements of the proinflammatory cytokine tumor necrosis factor α were increased threefold in septic rat brain ($P < 0.02$), and electron microscopic examination revealed scattered injury in approximately 0.25% of glial cells.[19] Within minutes after acute myocardial infarction, proinflammatory cytokines increase in the brain, heart, and plasma. It was demonstrated recently that the appearance of proinflammatory cytokines in the brain after myocardial infarction was independent of blood-borne cytokines, suggesting that cardiac sympathetic afferent nerves activated by myocardial ischemia signal the brain to increase cytokine production.[18] In turn, local activation of cellular inflammatory responses may exacerbate hypoxic or ischemic brain injury.

It is tempting to see the findings of the study by Fries

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et al.[1] in the light of inflammation. Unfortunately, this remains speculative, because there were no measurements of cytokines in this study and, hence, there is no evidence that the lung injury and hypoxia-only groups were different in this aspect. We are left with hard evidence of histopathologically proven neuronal cell damage and the feeling that in the clinical setting, a presumably safe arterial partial pressure of oxygen may not be safe enough to protect the vulnerable neurons in the brain from damage during ARDS. The data presented by Fries *et al.*[1] challenge the clinician because they suggest that in patients with ARDS, we treat not only the lung but also the brain.

This is an important article that provides answers, raises new questions, and should stimulate further research about the cause and prevention of neuronal cell damage after ARDS.

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