Anesthetic-induced Amnesia

Suppression of Memory Protein Formation Underlies Anesthetic-induced Amnesia

HOW anesthesia causes amnesia remains unclear. Understanding this is clinically important because amnesia is a fundamental component of a proper general anesthetic. It has long been assumed that drugs cause amnesia by working on the hippocampus. This hippocampal-centered view is largely based on the 1957 study by Scoville and Milner, who reported that patient H.M. lost the ability to form new memories after bilateral lesions of his hippocampus. It follows that if the hippocampus is needed to form new memories and if people cannot form new memories during anesthesia, anesthetics probably cause amnesia by acting on the hippocampus. However, this view of drug-induced amnesia may be too simplistic. The hippocampus does not work in isolation. Indeed, other brain regions, such as the basolateral amygdala (BLA), may be important for mediating amnesia.3–6

The work of Ren et al.7 in this issue of Anesthesiology provides the missing bridge needed to unite the hippocampal-centric view of anesthetic-induced amnesia with an amygdala-centric view, by showing how anesthetic actions in the BLA may influence the hippocampus and modulate memory. Understanding this study requires integrating two key facts about memory. First, memory is a time-dependent process. Memories are not formed and stored instantly; rather, they take time to consolidate.9 In time-dependent terms, memory is often categorized into one of three types, based on the interval between learning and memory. These time frames are called (1) immediate (i.e., seconds), (2) short term (from seconds to around 60–90 min), and (3) long term (generally >90 min). New memories exist in short-term memory in a labile state. During this time window, the actions of the BLA can modulate the process of memory consolidation occurring in other brain regions, such as the hippocampus.10 This modulatory aspect of memory allows for a sort-of biologic memory filter, whereby the most important experiences tend to be the best remembered. Enhanced amygdala activity, usually through strong emotional arousal, enhances the consolidation process and creates long-lasting memories.9 Conversely, suppressing amygdala activity likely hinders consolidation, creating weak, easily forgotten memories. Most drugs seem to exert their amnesic effects on long-term memory through a BLA-dependent mechanism.6,10,12–15

Second, in contrast with short-term memory, long-term memory is thought to involve a change in brain structure at the synaptic level. This learning-related change is called synaptic plasticity. It represents the fact that when two neurons routinely (or strongly) communicate with each other, it becomes easier for them to do so in the future because their synapses are physically changed. To change neuronal structure likely requires de novo synthesis of new cellular proteins. For many cellular genes, and in particular the so-called immediate-early genes, increased protein expression requires synthesis of new messenger RNA (mRNA) in response to a learning event.16 The induction of mRNA implies that a rather complex chain of molecular events has occurred to transform a learning experience from an excitable neuronal membrane receptor signal into a molecular signal that reaches the cell’s nucleus and interacts with its deoxyribonucleic acid (DNA) to “turn on” the genes of memory formation.16 This chain of events has been well reviewed elsewhere,17 and a summary of the steps involved is shown in figure 1A. Anesthetics could interact with multiple points along this chain, ranging from stopping the initial ligand–receptor interactions to stopping the cellular processes related to immediate-early gene expression.

The learning-related gene product measured by Ren et al. in the hippocampus of rats trained to avoid a foot shock was the mRNA level for activity-regulated cytoskeletal (Arc)-associated protein. This is only one of a handful of potential memory-related immediate early effector genes,16 but it is an important one that shows many of the characteristics one would anticipate from a learning-related gene. Of these attributes, Arc is implicated in directly altering synaptic function (reviewed in Miyashita et al.16), and past studies have shown learning-induced Arc protein expression in the hippocampus is critical for consolidation of inhibitory avoidance and water maze learning.12,18 Importantly, Ren et al. found that when animals were trained on the long-term memory task, even during exposure to an amnesic dose of propofol, the level of Arc mRNA increased in their hippocampus, to the same extent as that expected with normal learning (their fig. 3).16 This strongly suggests that the amnesic effect of propofol does not occur by
Fig. 1. A number of molecular mechanisms involved in long-term memory formation. Currently, long-term memory is thought to involve the de novo synthesis or transcription of new messenger RNA originating from learning-related immediate early genes. The molecular pathways involved in this process of transcription are shown in A (adapted by permission from Macmillan Publishers Ltd: Nature Neuroscience, 17 copyright 2001). Subsequently, the messenger RNA is used to make new cellular proteins through the process of translation that eventually change the structure of the neuronal synapses that were associated with a particular learning experience. The rather complex molecular mechanisms involved in the regulation of translation are shown in B (adapted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience, 20 copyright 2004). The work of Ren et al., 7 in this issue of Anesthesiology, suggests that the amnesic effect of propofol occurs through γ-aminobutyric acid related mechanisms in the amygdala, which interact with and perhaps regulate the process of memory-related protein translation in the hippocampus.
blocking learning at any stage in the process before the transcription of the mRNA for Arc (i.e., this essentially rules out all procedures illustrated in fig. 1a). This animal finding integrates well with one recent human study where propofol did not seem to block memory encoding. Therefore, it might be. Amnesic doses of both agents were produced amnesia for long-term aversive memories? Our hypothesis is raised that anesthesia acts to protein a common method by which anesthetics act to.

So, if propofol causes amnesia by blocking Arc protein production in the hippocampus and if we know from previous study that lesions of the BLA remove the amnesic effect of propofol, perhaps it is the effect of propofol on the BLA that causes the suppression of the Arc protein in the hippocampus. Ren et al., followed this logic and reasoned that if propofol acts on the BLA as a γ-aminobutyric acid agonist, then putting a γ-aminobutyric acid antagonist directly into the BLA should counteract propofol's amygdala effects and restore both its behavioral memory deficit and its suppression of Arc protein levels in the hippocampus. This is exactly what they found and report in their figure 4. Therefore, it seems that propofol's amnesic effect (at low doses) on long-term (aversive) memory can reasonably be attributed to its γ-aminobutyric acid-like interactions within the BLA.

Is anesthetic-induced suppression of hippocampal Arc protein a common method by which anesthetics act to produce amnesia for long-term averse memories? Our recent results with sevoflurane and desflurane suggest that it might be. Amnesic doses of both agents were found to suppress hippocampal Arc protein. Our pattern of results follows that found by Ren et al., in that an amnesic dose of sevoflurane did not suppress hippocampal Arc mRNA but did suppress hippocampal Arc protein. Therefore, the hypothesis is raised that anesthetic-induced amnesia occurs in part through the suppression of protein products derived from the immediate-early genes that respond to a learning event. It is worth noting that previous studies have shown that postlearning intra-BLA injections of compounds that either enhance or impair long-term memory also function by respectively either increasing or decreasing Arc protein expression in the hippocampus. Therefore, the findings of Ren et al. can be seen as important further support for the general idea that the amygdala modulates memory consolidation by regulating the expression of plasticity-related gene products in the hippocampus. These findings offer an encouraging theoretical framework and an experimental basis for contemplating the idea that memory-erasing drugs might someday form a part of our clinical armamentarium.

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