■ LABORATORY INVESTIGATIONS

Does the Amygdala Mediate Anesthetic-induced Amnesia?

Basolateral Amygdala Lesions Block Sevoflurane-induced Amnesia

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Background: Amnesia for aversive events caused by benzodi- azepines or propofol depends on the basolateral amygdala (BLA). Whether the amnesia of volatile anesthesia is also medi- ated through the BLA is unknown. If so, a general principle of anesthetic-induced amnesia may be emerging. Here, using an inhibitory avoidance paradigm, the authors determine whether BLA lesions prevent sevoflurane-induced amnesia.

Methods: Male Sprague-Dawley rats were separated into two groups: sham-operated controls (n = 22) and rats given bilat- eral *N*-methyl-D-aspartate lesions of the BLA (n = 32). After a 1-week recovery, the rats were randomly assigned to be trained during either air or sevoflurane (0.3% inspired, 0.14 minimum alveolar concentration) exposure. Animals learned to remain in the starting safe compartment of a step-through inhibitory avoidance apparatus for 100 consecutive seconds by adminis- tering foot shock (0.3 mA) whenever they entered an adjacent shock compartment. Memory was assessed at 24 h. Longer latencies to enter the shock compartment at 24 h imply better memory.

Results: Sham–air (n = 10) animals had a robust memory, with a median retention latency of 507 s (interquartile range, 270–600 s). Sham–sevoflurane (n = 6) animals were amnesic, with a latency of 52 s (27–120 s) (*P* < 0.01, *vs.* sham–air). Both the air-exposed (n = 5) and the sevoflurane-exposed (n = 8) animals with BLA lesions showed robust memory, with laten- cies of 350 s (300–590 s) and 378 s (363–488 s), respectively. The latencies for both did not differ from the performance of the sham–air group and were significantly greater than the latency of the sham–sevoflurane group (both *P* < 0.01).

Conclusions: BLA lesions block sevoflurane-induced amnesia. A role for the BLA in mediating anesthetic-induced amnesia may be a general principle of anesthetic action.

THE *amygdala* is a small, almond-shaped part of the brain that is located deep within the medial temporal lobes just anterior to the hippocampus in each hemi- sphere. The amygdala is thought to play a role in emo-

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tional and autonomic functions[1] but it is also thought to play a role in memory.[2] It has been hypothesized that the amygdala, and more specifically the basolateral nucleus of the amygdala (BLA), is a brain structure that modu- lates the strength of long-term memories (*i.e.*, memory lasting longer than 1–2 h) according to how emotionally arousing an experience is to an organism.[3] The more emotionally arousing an experience is, the better it will be remembered. The memory-enhancing and, more im- portantly for this work, memory-impairing effects of drugs seem to occur through a neurobiologic mecha- nism that involves the BLA.[4] In fact, the long-term (*i.e.*, 24–48 h) memory-impairing effects of systemically ad- ministered benzodiazepines or the anesthetic agent propofol do not occur in rats with lesions of the BLA.[5–7]

Here we test the hypothesis that the BLA is also a critical neuroanatomical site involved with mediating amnesia of low-dose inhalational anesthesia. A positive result here would establish that the BLA plays a more generalized causative role in mediating anesthetic-in- duced amnesia than previously thought and that a role for the BLA in mediating anesthetic-induced amnesia may be a general principle of anesthetic action. To clar- ify the logic, if the BLA is required for inhalational anes- thetic-induced amnesia to occur, removing the BLA should also remove the ability of a systemically adminis- tered known amnesic dose of an inhalational anesthetic agent to impair memory. Therefore, an animal with a BLA lesion that is exposed to an amnesic dose of an inhaled agent during aversive training should remember the training experience as well as a control animal that is not exposed to anesthesia during training. In essence, a BLA lesion should make an animal immune to the long- term memory-impairing effects usually produced by a low dose of an inhaled anesthetic agent.

Understanding how a lesion of the brain could allow for an enhancement of memory performance during exposure to an anesthetic is a bit counterintuitive. In fact, one point of view suggests that fear-related memo- ries are formed and stored within the BLA itself.[8] There- fore, a lesion of the BLA might be expected to prevent learning and memory of the aversive fear-conditioned response on which the inhibitory avoidance (IA) para- digm is based. Another point of view, however, pro- poses that the amygdala is not a site of memory storage[9] but plays a time-limited modulatory role in the formation of memories for aversive events. The proposed modula- tory framework of amygdala function provides the logi-

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cal basis for understanding drug-mediated effects on con-solidation of long-term memory.[10] It is not the intention of this work to try to resolve the controversy regarding the role of the amygdala in memory consolidation *versus* memory storage. Nonetheless, one clear prediction can be made in regard to this controversy: According to the fear-conditioning point of view, the animals with BLA lesions should have great difficulty in learning the IA task. This learning difficulty will be directly assessed by noting how many shocks each animal needs to acquire the IA task. Increased difficulty in task acquisition for animals with BLA lesions will support the fear-condition-ing point of view. However, finding only minimal effects on learning and memory in BLA lesioned animals will support the memory-modulation view of amygdala func-tion. Therefore, we examined the role of the BLA in mediating inhaled anesthetic–induced amnesia using the rat model of learning and memory provided by the step-through IA paradigm with a continuous multiple-trial training technique. We used sevoflurane to examine this question because it is a potent amnesic agent in this model.[11]

Materials and Methods

Animals

After approval was obtained from the institutional an-imal care and use committee (University of California, Irvine, California), 54 male Sprague-Dawley rats (250–280 g or approximately 9 weeks old on arrival) were obtained from Charles River Laboratories, Inc. (Wilming-ton, MA). They were housed individually in a tempera-ture-controlled (22°C) colony room, with food and water available *ad libitum*. Animals were maintained on a 12-h light–12-h dark cycle (0700–1900 lights on). The rats were randomly assigned to one of two surgery groups: sham-operated controls or bilateral *N*-methyl-D-aspartate lesions targeting the BLA.

Surgery

Rats were maintained in the animal colony for 1 week before surgery. Rats were anesthetized with sodium pen-tobarbital (50 mg/kg, intraperitoneal) and given atropine sulfate (0.2 mg, intraperitoneal). Rats were placed into a stereotaxic frame (Benchmark Digital Stereotaxic, MyNeu-rolab.com, St. Louis, MO) and bilateral lesions of the BLA were produced by *N*-methyl-D-aspartate (Sigma-Aldrich, Co., St. Louis, MO; 12.5 mg/ml distilled H_2O).[7,12] The *N*-methyl-D-aspartate solution was back-filled into a 30-gauge needle, which was attached by a polyethylene tube to a 10-μl syringe (Hamilton, Reno, NV) driven by a minipump (Sage Instruments, Boston, MA). The needle was placed into the targeted BLA subnuclei at a single injection site (coordinates: anteroposterior, −2.3 mm from bregma; me-diolateral, ±5.05 mm from midline; dorsoventral, −8.3 mm from skull surface; incisor bar, −3.3 mm from interaural line), and a volume of 0.2 μl *N*-methyl-D-aspartate was injected over 1 min. The injection needle remained in place for an additional 2 min to maximize diffusion of the solution.

Sham operations used the same general procedure except that an empty needle was lowered only to the level of the caudate. No infusion was delivered, to min-imize damage to surrounding tissue. All animals were allowed 6–7 days to recover before IA training.

Behavioral Procedures

On the training day, the rats were taken from their home cages, weighed, and then placed into small (*i.e.*, 3.2 l) anesthetizing chambers that were filled with either 0.3% sevoflurane in air or only air. Anesthesia was deliv-ered through a standard vaporizer at 0.5 l/min. Chamber and apparatus agent concentrations were monitored continuously during the experiment using a Datex-Ohm-eda Ultima Capnomac (Helsinki, Finland) and verified with gas chromatography (model 80123B; SRI Instru-ments, Redondo Beach, CA). The gas chromatograph was calibrated against known standard calibration gases and by measuring gas concentrations after injection of a known amount of drug into a known calibrated volume. The animals remained in the anesthetizing chamber for at least 45 min. They were then quickly (*i.e.*, < 4 s) removed from the chamber and placed into the "safe" compartment of an IA apparatus, which had also been filled with the targeted dose of sevoflurane in air.

The IA apparatus was airtight, and experiments were conducted in a large fume hood. The apparatus con-sisted of a V-trough–shaped alley (91 cm long, 15 cm deep, 20 cm wide at the top and 6.4 cm wide at the floor) that was divided into two compartments separated by a manually controlled sliding door that opened by retracting into the floor. The starting compartment (31 cm long) was colored white and illuminated, whereas the shock compartment (60 cm long) was dark colored and not illuminated. Animals sat for 3 min in the safe compartment of the apparatus before the beginning of training to allow for the small fluctuations in anes-thetic concentrations associated with the transfer to sta-bilize. We separately determined that this rapid transfer process did not appreciably change the agent concen-tration in the IA apparatus. Control air–sham and air-lesioned rats were treated identically, except they were exposed only to air.

A continuous multiple-trial IA training procedure was used. When the rat stepped into the dark–shock com-partment with all four paws, a 0.3-mA foot shock (Master Shocker model 82400; Lafayette Instrument Co., Lafay-ette, IN) was delivered until the animal escaped back into the starting light-safe compartment. The door to the dark compartment remained open, and the animals could choose to either stay in the light–safe compart-

ment or again cross into the dark–shock compartment. Animals crossing back into the dark–shock compartment were again given a foot shock and allowed to escape back to the light–safe compartment.

Learning was considered to have occurred when animals avoided the dark–shock compartment for more than 100 consecutive seconds. This learning criterion is a variable parameter that was selected at 100 s based partly on much previous experience with the continuous multiple-trial IA technique[5] and partly on the behavior of the animals during anesthetic exposure. Lower set points (*i.e.*, < 50 s) would be expected to correlate with weaker encoding of the learning experience and would result in noisier data during the memory testing. Higher set points would increase the overall training time without yielding much additional encoding benefit. An animal that reaches the 100-s criterion might likely remain in the safe compartment of the apparatus for an extended period of time, if no time limit were imposed. Qualitatively, animals that needed more than a single training shock would often return to the dark–shock compartment within approximately 30 s. Few if any additional crosses into the dark–shock compartment were made in the 60- to 100-s range. After the animals attained the 100-s learning criterion, they were removed from the apparatus and returned to their home cages. The number of shocks required for each animal to learn the task was taken as an index of how difficult the task was for a particular group of animals to learn it. It is important to note, however, that even though the exposure to the anesthetic condition might be expected to make the task more difficult for some animals to learn, the use of the continuous multiple-trial technique assures that all animals eventually did acquire the task information (*i.e.*, they all learned to stay out of the dark chamber to avoid a shock).

Memory retention was tested 24 h after the training session. Each rat was placed back into the starting light–safe side of the apparatus, and the time taken (600 s maximum) for each rat to again cross into the dark–shock side was recorded. Longer latencies to cross into the dark side were interpreted as indicating better retention of the training experience. No shock or drug was delivered during the memory testing.

Histology

The rats were killed with an overdose of sodium pentobarbital (250 mg/kg) and subsequently given an intracardiac perfusion of 0.9% saline followed by 10% formalin. Brains were removed from each animal, placed into a 10% formalin solution overnight, and transferred to a 20% sucrose solution for 3–5 days. Brains were sectioned into 50-μm sections using a freezing microtome and stained with thionin. Lesion extent was rated by an investigator (S.V.N.) blinded to each animal's condition, and inclusions/exclusions were based on *a priori* histo-

logic lesion criteria.[7] All exclusions were made blind to the retention test data. Lesions were histologically categorized into one of three categories: (1) discrete-confined lesions of the BLA, (2) inadequate or missing lesions, or (3) extensive lesions of the BLA with significant collateral damage to surrounding structures. Confined lesions had to include bilateral damage to the BLA at a minimum of 1.5 mm anterior–posterior to the injection site, as well as minimal damage to surrounding structures (confined to borderline areas around the BLA). Extensive lesions included a massive lesion of the BLA at a minimum of 1.5 mm anterior–posterior to the injection site along with accompanying extensive damage to a number of other surrounding structures, including (1) the piriform and entorhinal cortical areas, (2) the striatum, (3) the endopiriform nucleus, or (4) the central nucleus of the amygdala (CE). Only animals with discrete-confined approximately equivalent bilateral lesions of the BLA were included in the behavioral analysis.

Statistical Analysis

A nonparametric analysis approach was used because the behavioral data were not normally distributed. The Kruskal–Wallis test was used to assess group effects, and *post hoc* comparisons were made using the Mann–Whitney U test. A probability level of $P < 0.05$ was considered significant.

Results

Exclusions

Twenty-five animals were not included in the final analysis. Four animals died during recovery from the initial surgery. Two animals would not perform the IA task. Nineteen animals were excluded from further analysis based on histology, 5 from the air–lesioned group and 14 from the sevoflurane–lesioned group. Four of these animals had massive lateral damage in the temporal lobes, as if they had undergone temporal lobectomies. Also, the CE and medial amygdala nuclei were extensively damaged in nine animals. Three animals showed no verifiable damage to the BLA, and three animals had only unilateral damage to the BLA.

Histology of Included Animals

Figure 1 shows a schematic composite diagram of the minimum and maximum lesion extents for the animals in this study that were included in the final behavioral analyses. These lesions clearly all centered on the BLA subnucleus within the BLA complex (defined as the basolateral and lateral subnuclei). The smaller lesions affected an area approximately equal in size to that of 60–80% of the entire BLA subnuclei, and the larger included lesions extended this area of damage to encompass most of the lateral subnuclei as well.
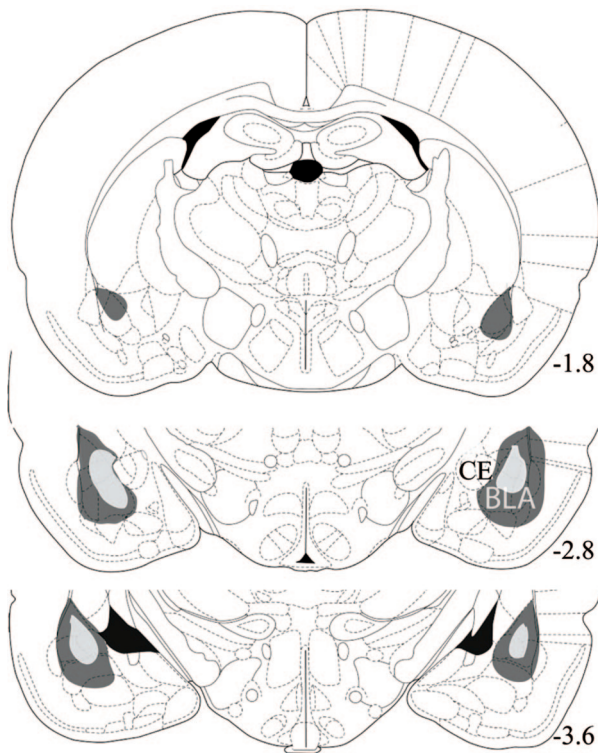
Fig. 1. Schematic representation of the minimal (*light gray*) and maximal (*dark gray*) extent of the lesions involving the basolateral amygdala. Numbers indicate distance posterior to bregma, in millimeters. BLA = basolateral amygdala nucleus; CE = central amygdala nucleus.
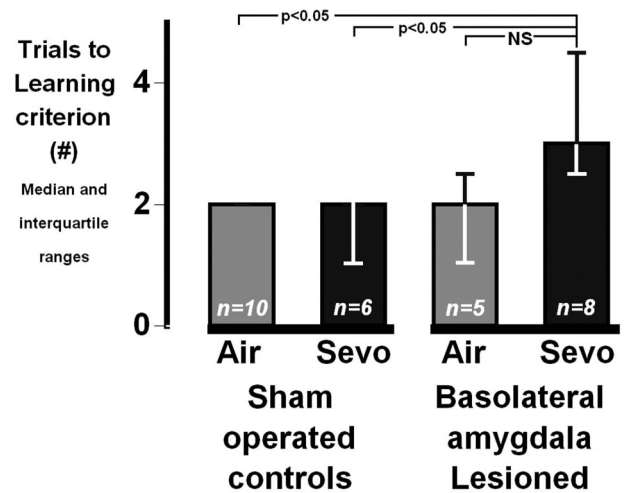

Fig. 2. Trials to learning criterion. The median values (and interquartile ranges) for the number of trials each group of animals needed to learn the inhibitory avoidance task are shown. In essence, for most animals, approximately two trials were needed to learn the task. However, amygdala lesions and sevoflurane (0.3% inspired) exposure during training clearly impaired task learning such that animals in this group required approximately one additional trial to learn the task. The number of animals included in the final analysis is shown. NS = not significant.
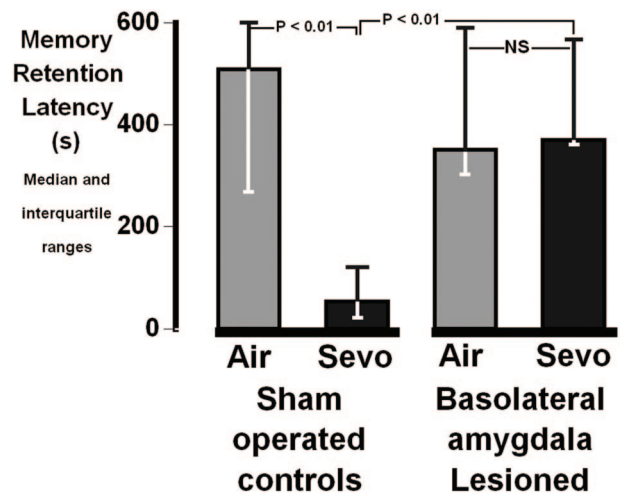

Fig. 3. Memory retention latency at 24 h. The median values (and interquartile ranges) for the number of seconds taken before the previously trained animals that were placed back into the safe–light side of the inhibitory training apparatus again crossed into the dark–shock compartment. Animals were not exposed to sevoflurane on memory testing. Longer latencies imply better memory. An amnesic effect of sevoflurane is clearly seen in the sham-operated control animals that had been exposed to 0.3% sevoflurane during training 24 h previously. The sevoflurane–sham group had a significantly lower memory retention performance score, as compared with any other group. Note the important result that the expected amnesic effect of sevoflurane does not occur in animals with basolateral amygdala lesions (the far right column), as evidenced by a retention latency (memory) equivalent to that of the air–sham control animals and the air–lesioned control animals. Therefore, lesions of the basolateral amygdala prevent low-dose sevoflurane from causing long-term (*i.e.*, 24-h) amnesia for an aversive training experience. NS = not significant.

Learning

Figure 2 shows the number of trials each group of animals needed to learn the task to the 100-s acquisition criterion. There was an overall significant effect of the drug treatment and lesion condition on task acquisition ability ($P < 0.05$). In essence, all animals needed approximately two trials to learn the task. However, the sevoflurane-lesioned group of animals needed approximately one additional trial to learn the task. Therefore, learning was significantly more impaired for the sevoflurane-lesioned animals than the air–sham ($P = 0.005$) and sevoflurane–sham animals ($P < 0.05$). Learning in the sevoflurane–lesioned animals, however, was not significantly different from learning in the air–lesioned animals ($P = 0.07$). Importantly, relative to the controversy regarding the BLA as a site of memory storage, learning in the air–sham animals did not differ from learning in the air-lesioned animals ($P = 0.92$).

Memory

Figure 3 shows memory performance as determined by differences in median retention latency. There was an overall significant effect of the drug treatment and lesion condition on retention performance ($P < 0.01$). Air-sham control animals had a robust memory with a median retention latency of 507 s (interquartile range, 270–

600 s). Sevoflurane–sham animals had a significant amnesic effect with a median retention latency of 52 s (27–120 s) ($P < 0.01$, *vs.* air–sham controls). Therefore, a 0.3% inspired (0.14 minimum alveolar concentration [MAC]) dose of sevoflurane induced a statistically significant amnesia in the sham-operated control animals.

The air–lesioned animals had a median retention latency of 350 s (300–590 s), which was equivalent to that seen for the air–sham controls at 507 s (270–600 s) ($P = 0.71$, air–lesioned *vs.* air–sham). Therefore, as expected on the basis of previous studies,[5,7] BLA lesions did not by themselves have a significant effect on long-term memory retention performance for an aversive event. This strongly suggests the BLA cannot be the site of memory storage for this fear-conditioned response.

In contrast to the sevoflurane–sham animals, the sevoflurane–lesioned animals showed a robust memory with a median latency of 378 s (363–488 s), which was not significantly different from air–sham ($P = 0.33$) or air–lesioned controls ($P = 0.88$). Retention in the sevoflurane–lesioned animals was significantly greater than retention in the sevoflurane–sham animals ($P < 0.01$). Therefore, an amnesic dose of sevoflurane in animals with confined BLA lesions did not produce an otherwise expected amnesic response for long-term retention of an aversive training experience. These results are illustrated in figure 3.

Discussion

The current study examined the hypothesis that the BLA is a critical brain region involved with mediating the amnesia (*i.e.*, the memory-impairing effect) caused by an inhalational anesthetic agent for an aversive training experience. We found that the expected amnesic effect of low-dose (*i.e.*, 0.3% inspired or 0.14 MAC) sevoflurane did not occur in animals with BLA lesions. This demonstrates that the BLA is a required critical component of the neuroanatomy mediating the amnesia of low-dose sevoflurane. When the current results are coupled together with previous similar, but completely independent, demonstrations that both the benzodiazepines and the intravenous anesthetic agent propofol each also requires an intact BLA to have its amnesic effect,[5,7] a general principle of anesthetic action seems to emerge. The findings support the hypothesis that anesthetic actions involving the BLA are a central critical component of the mechanism of anesthetic-induced amnesia.

This work localizes the BLA as a key site involved with producing the amnesic component of anesthesia related to long-term memory of an aversive experience. The work directly adds support to the idea that anesthetics exert their various behavioral effects by interacting with a select number of specific sites throughout the brain and spinal cord. It seems that any specific behavioral change caused by anesthetic exposure might ultimately prove to be attributed to anesthetic interactions with the neuroanatomy normally responsible for mediating that particular behavior. Previous evidence indicates that anesthetic-induced immobility is mediated through anesthetic actions in the spinal cord[13–16] and that anesthetic-induced unconsciousness may be mediated through anesthetic actions at the level of the thalamus or thalamocortical loops.[17–22] Furthermore, a strong link has been established between the sedative component of anesthesia and anesthetic-induced inhibition of endogenous sleep pathways.[23] It seems that overwhelming evidence now exists to support the "multiple sites, multiple mechanisms" concept of anesthetic action.[24,25]

The animals in this experiment were not under a full "anesthetic" dose of the sevoflurane. Using the IA technique requires that animals be affected enough by the anesthetic to show an amnesic effect but not so sedated that they are unable to learn the task. It is not known whether higher doses of sevoflurane would have overwhelmed the mechanisms involved in this BLA blockade of amnesia effect. This is important information to know before one can completely conclude that activity in the BLA is required for the amnesia of general anesthesia to occur. There may be a way to test the amnesia associated with deeper levels of anesthesia in completely anesthetized animals using some form of conditioning,[26–28] but exactly how best to do this,[29] especially in relation to the BLA, is not entirely clear.

Sevoflurane clearly impaired acquisition of the avoidance task (assessed in trials-to-criterion performance) in the lesioned rats (fig. 2). Part of the increase in 24-h memory retention latency seen in the sevoflurane–lesioned group might therefore be attributable to an increased level of encoding that would have occurred in the sevoflurane–lesioned rats because they were given relatively more shocks than the other groups. However, this explanation is unlikely to be much of a factor in the overall results because it is not true that the animals receiving more shocks within this group were also the ones that had better retention performance. Rather, the animals with the higher retention latencies (*i.e.*, better memory) actually learned the task in the typical one to two trials, and the animals with the lower retention latencies were the ones that increased the overall median. This suggests that the number of trials in the sevoflurane–lesioned animals is actually a rough behavioral indicator of the effectiveness or extensiveness of the lesions in a particular animal, such that the animals with high retention and low trials tended to be the ones with the more discrete BLA lesions. However, the limited sample size used in the current study prevents a more detailed quantitative analysis of this point. Nevertheless, the work by Tomaz *et al.*[5,30] directly supports this contention because they found that lesions of the lateral amygdala were less effective at blocking diaze-

pam-induced amnesia than were discrete BLA lesions (CE lesions were completely ineffective).

Along similar lines, a comment on our apparently relatively low hit rate is warranted. A substantial number of our misses were due to the exclusion of animals with extensive collateral damage to the CE (9 of 19). These animals may have been counted as hits in other studies of amygdala memory function.[31] However, our experience with anesthetics in both this study and our previous study with propofol focused our attention on minimizing damage to the central amygdala.[7] This raises speculation that the important effect of interest here might be attributed, in some way, not simply to the BLA itself but to the interaction that occurs between the BLA and the CE during exposure to an anesthetic.

It is known that the BLA has a strong feed forward inhibition effect on the CE that is mediated in part by a dense γ-aminobutyric acid–mediated cell population that is interposed between the BLA and the CE.[32] Therefore, removing the BLA with a lesion removes a strong tonic inhibitory influence from the CE that would normally be present. Given that the blockade of anesthetic-induced amnesia effect does not seem to occur when there is collateral CE damage, it seems logical to suggest that the CE may also play a critical role in producing the current results, and further detailed study of this circuitry is warranted.

The work here has focused on the BLA as a site involved with mediating the amnesic component of anesthesia because of the extensive literature demonstrating the role of the BLA in memory modulation for long-term recall of emotional information and its involvement in working memory.[2,33,34] This work should not be taken to imply, however, that other sites like the CE might not also be involved in mediating anesthetic-induced amnesia, especially when higher doses of anesthetic agents are used to produce the amnesic state[27] or when less aversive stimuli are used. Numerous studies clearly show anesthetics have effects on hippocampal neurons and on the functioning of the hippocampus at clinically relevant concentrations.[35-40] In addition, the effects of anesthetics on other brain circuits and systems, such as the ability of anesthetics to interfere with working memory systems, may prove to be important to understand for a complete elucidation of the amnesic component of anesthesia.[41,42]

Why might the BLA be so important for anesthetic-induced amnesia? The BLA has significant connections with numerous brain areas involved in memory processing. It connects strongly with the hippocampus, striatum, thalamus, and basal forebrain.[43] The exact pathways and mechanisms involved with amygdala-mediated memory modulation are only just now beginning to be worked out.[34] Nevertheless, the current results suggest that a low amnesic dose of an anesthetic agent actively changes how the BLA functions and causes the output of the BLA to change in some manner such that, during anesthesia, it suppresses memory consolidation through its normal modulatory mechanisms. A lesion of the BLA then removes the ability of the anesthetic to interact with the BLA and prevents an active memory suppression process from occurring.

Lesions of the BLA did not inhibit learning or prevent memory of the IA task in the air-exposed animals. This is not consistent with the view that fear-conditioned memories are dependent on and stored in the BLA.[9] Nonetheless, it could be argued that the lesions found here, although sufficient to prevent anesthetic-induced amnesia, were simply not extensive enough to completely eliminate learning or storage of memory for the aversive event.

A final issue concerns the cellular mechanisms underlying the amnesic effect of sevoflurane. Because we have used lesions in this experiment, our data do not speak directly to this issue. However, a number of potential target receptor systems exist within the amygdala that have also been implicated in various aspects of anesthetic action and could therefore prove to be important in mediating anesthetic-induced amnesia. Given the role of γ-aminobutyric acid function in mediating the sedative component of anesthesia[23] and the well-established amnesic properties of the benzodiazepines,[44] this system seems to be an important system for future study. Also of interest is the fact that nicotinic acetylcholine receptors are known to be quite sensitive to both inhalational anesthetic agents and propofol,[45-47] and these receptors are well represented in the amygdala,[48] raising the possibility that these receptors could be involved in mediating anesthetic-induced amnesia. Furthermore, given the recent demonstrations that two-pore-domain background potassium channels are activated by both volatile agents and gaseous anesthetic agents[49,50] and that these channels are also well represented in the amygdala,[51] the study of these channels seems to be in order. Future experiments involving intraamygdala infusions of various agonist and antagonists to these and other potential target systems should help to fully elucidate the mechanisms of anesthetic-induced amnesia.

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