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Memory Enhancing Effect of Low-dose Sevoflurane Does Not Occur in Basolateral Amygdala–lesioned Rats

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Background: **Certain anesthetics might enhance aversive memory at doses around 0.1 minimum alveolar concentration. This issue was investigated in a rat model of learning and memory. In addition, evidence for basolateral amygdala (BLA) involvement in mediating memory enhancement was sought.**

Methods: **First, the memory-enhancing potential of various anesthetics was determined. Rats underwent single-trial inhibitory avoidance training (0.3 mA shock/1 s) during exposure to air, 0.11% sevoflurane, 0.10% halothane, 0.77% desflurane, or 0.12% isoflurane. Memory was assessed at 24 h. Second, the BLA contribution to sevoflurane memory enhancement was determined. Rats received bilateral excitotoxic *N*-methyl-D-aspartate (12.5 mg in 0.2 μl per BLA) lesions of the BLA 1 week before training. Memory of lesioned and control rats was compared 24 h after training in air or sevoflurane.**

Results: **Sevoflurane exposure during training significantly enhanced 24-h retention performance for both nonoperated and sham-operated rats ($P < 0.005$ for both *vs.* their respective controls). Halothane, but not desflurane or isoflurane, also enhanced retention performance ($P < 0.05$). However, halothane-induced hyperalgesia during learning clouds interpreting enhanced retention performance solely as a memory consolidation effect. BLA lesions significantly reduced and equalized retention performance for both sevoflurane- and air-exposed animals. Lesions blocked memory enhancement without also causing a generalized inability to learn, because additional training revealed essentially normal task acquisition and 24-h memory.**

Conclusions: **Sevoflurane enhances aversive memory formation in the rat. The BLA likely contributes to this effect. The risk of aversive memory formation may be enhanced during exposure to low-dose sevoflurane.**

DOSES of volatile anesthetic agents around 0.3 minimum alveolar concentration (MAC) inhibit learning and cause amnesia.[1–7] Alkire and Gorski[8] further defined in the rat inhibitory avoidance (IA) model of learning and memory that the dosage threshold for a long-term 24-h amnesic effect is agent dependent and lower than classically thought, with a potent amnesic effect evident for some drugs at doses in the 0.1- to 0.2-MAC range.

In contrast to the general trend that inhalation agents have a potent amnesic effect at relatively low doses, Alkire and Gorski[8] also unexpectedly demonstrated that low-dose halothane exposure (*i.e.*, 0.1 MAC) during learning significantly enhanced 24-h retention performance. This was attributed to a drug-induced hyperalgesic effect, which likely caused a more memorable shock experience in rats given 0.1 MAC halothane. Nevertheless, demonstrating that a low dose of any volatile anesthetic agent has memory-enhancing properties could have important clinical and theoretical implications.

Anesthetic-induced memory enhancement is known to occur in the special case of diminished retroactive interference,[9] where memory is enhanced for information learned immediately before an anesthetic is given because such recently acquired information is not subject to degradation by the interfering effect of subsequent information. Other than the potential memory-enhancing effect of halothane,[8] we are unaware of any demonstration showing that an anesthetic-induced memory enhancement can be caused by exposure to a low dose of anesthesia. Here, in one set of experiments, the rat IA model of learning and memory is used to determine whether exposure to low doses of various anesthetics at the time of learning can enhance subsequent memory for an aversive learning experience.

A drug-induced enhancement of memory for an aversive "emotional" stimulus suggests involvement of the brain's amygdala memory modulation system. This system plays a key role in mediating the memory modulation effects of emotional arousal and is thought to be a brain site through which drugs influence consolidation of long-term memory.[10–14] Therefore, we determined, in a separate experiment, whether the basolateral amygdala (BLA) might also play a role in mediating the memory enhancing effect of an anesthetic. We hypothesized that rats with bilateral BLA lesions would not show a 24-h memory-enhancing effect when trained on the IA task in the presence of a presumed memory-enhancing dose of sevoflurane.

Materials and Methods

Animals

After obtaining Institutional Animal Care and Use Committee (University of California, Irvine, California) approval, 88 male Sprague-Dawley rats (250–280 g on arrival) were obtained from Charles River Laboratories (Wilmington, MA). They were housed individually in a temperature-controlled (22°C) colony room, with food and water available *ad libitum*. Animals were maintained on a 12-h light–12-h dark cycle (7:00 AM to 7:00 PM, lights on). Rats were maintained in the animal colony for 1 week before IA training or surgery. To minimize han-

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dling stress, the rats were exposed to a daily 2-min handling session by the experimenter for the 5 days before behavioral training and testing. Rats undergoing surgery were allowed an additional 1-week recovery period before IA training.

Within each study, rats were randomly assigned to receive either no anesthesia (air–control) or a target dose of anesthetic at or just under 0.1 MAC during IA training. The anesthetic targets were 0.1% sevoflurane (*i.e.*, 0.05 MAC), 0.12% isoflurane (0.08 MAC), 0.09% halothane (0.1 MAC), and 0.78% desflurane (0.1 MAC).

Surgical Procedures

Rats for the BLA lesion experiment were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneal) and given atropine sulfate (0.2 mg, intraperitoneal). Rats were placed into a stereotaxic frame (Benchmark Digital Stereotaxic Instruments, Tujunga, CA), and bilateral lesions of the BLA were produced by *N*-methyl-D-aspartate (Sigma-Aldrich Corp, St. Louis, MO) 12.5 mg/ml in distilled H_2O. The *N*-methyl-D-aspartate solution was backfilled into a 30-gauge needle, which was attached by a polyethylene tube to a 10-microliter syringe (Hamilton Co., Reno, NV) driven by a minipump (Sage Instruments, Boston, MA). The needle was targeted toward the BLA at a single injection site (coordinates: anteroposterior, −2.8 mm from bregma; mediolateral, ±5.0 mm from midline; dorsoventral, −8.5 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 25 s. The injection needle remained in place for an additional 3 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 minimize damage to surrounding tissue.

Anesthetic Procedures

A standard IA apparatus was modified to be airtight. 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 the targeted anesthetics in air. Anesthesia was delivered through standard vaporizers at 0.5 l/min during training of each animal but adjusted as needed between animals to maintain a steady concentration of agent in the chambers or IA apparatus. 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 the IA apparatus, which had also been filled with the targeted anesthetic in air.

Chamber and apparatus agent concentrations were monitored continuously during the experiment using a Datex-Ohmeda Ultima Capnomac (Helsinki, Finland) and separately verified for each animal with gas chromatography (model 80123B; SRI Instruments, 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 experiments were conducted in a large fume hood. The IA apparatus consisted 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 "safe" compartment (31 cm long) was white colored 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 anesthetic concentrations associated with the transfer to stabilize. We separately determined that this rapid transfer process did not appreciably change the agent concentration in the IA apparatus. Control rats were treated identically except they were only exposed to air.

Behavioral Procedures

A single-trial IA training procedure was used to assess each agent's memory enhancement potential. Each animal was placed into the light–safe compartment of the training apparatus facing away from the door. After 3 min, the door was lowered into the floor to reveal the dark–shock compartment. The rat instinctively prefers a dark environment. After the rat stepped into the dark–shock compartment with all four paws, the door was closed behind the rat, and then an inescapable foot shock (0.3 mA, Master shocker; Lafayette Instruments, Lafayette, IN) was delivered for 1 s. Animals were then removed directly from the dark compartment of the apparatus and returned to their home cages. This single-trial technique gave each animal essentially the same learning experience and after pilot experiments was expected to provide unoperated–control retention latencies in the 100- to 200-s range.

Memory retention was tested 24 h after the training session. Each rat was placed back into the starting light–safe side of the apparatus without anesthesia exposure, and the time taken (600 s maximum) for each rat to again cross into the dark–shock side with all four paws 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.

For BLA-lesioned animals, an additional second training and memory testing session was performed on the next subsequent day to establish whether these BLA lesioned animals could learn and remember the IA task. Animals were given additional training in air using the continuous multitrial IA technique. With this different training

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technique, the door between the safe and shock compartments of the IA apparatus was left open, and once an animal entered the dark compartment of the apparatus, the animal was given a continuous foot shock (0.3 mA) until it escaped back into the light compartment. Animals were left in the apparatus until they demonstrated short-term learning by reaching a preset behavioral criterion of staying out of the dark–shock compartment of the apparatus for at least 100 consecutive seconds. With this technique, the total number of entries into the dark compartment was an indication of how difficult the task was for a particular animal to learn it. The number of entries was, in part, dependent on the intensity of the foot shock. With a sufficient foot shock intensity, animals learn this task with a single shock.

Histology

Rats that received BLA lesions were anesthetized with an overdose of sodium pentobarbital (250 mg/kg) and perfused intracardially with a 0.9% saline solution followed by 10% formalin solution. Brains were then removed from each animal and placed into a 10% formalin solution overnight and then transferred to a 20% sucrose–10% formalin solution for 3–5 days. Brains were then sectioned into 40-μm sections using a freezing microtome and then stained with thionin. Lesion extent was rated with blinding to each animal's condition. 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 any 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. Only animals with bilateral lesions discretely confined to the BLA were included in the behavioral analysis.

Statistical Analysis

Given the low levels of shock intensity used, the retention test data were normally distributed, allowing for the use of standard parametric statistics. An analysis of variance test was used to assess group effects, and pairwise comparisons were made using the Student *t* test. A probability level of $P < 0.05$ was considered significant, after Bonferroni/Dunn correction for multiple comparisons where appropriate. Data are presented as mean ± SD.

Results

Exclusions

Four animals died after surgery. Fourteen animals were excluded from further analysis after the histologic examination. Six animals were from the air control group, and 8 were from the sevoflurane group. Four animals had massive lateral damage in the temporal lobes, involving parts of the BLA but also extending out to cortex. The central and medial amygdala nuclei were extensively damaged in 2 of these 14 cases. Seven animals had only unilateral damage to the BLA, and 1 animal showed no damage to the BLA. Four behavioral exclusions were made secondary to handling errors, such as an animal's tail or foot getting transiently pinched in part of the apparatus. All exclusions were made blind to the retention test data.

Experiment 1

Animals targeted to receive 0.05 MAC sevoflurane (n = 17) actually received 0.11 ± 0.02% sevoflurane by gas chromatography measurement. Animals targeted to receive 0.08 MAC isoflurane (n = 5) actually received 0.12 ± 0.02% isoflurane. Animals targeted to receive 0.1 MAC desflurane (n = 6) and halothane (n = 5) received 0.77 ± 0.03% and 0.10 ± 0.01% concentrations, respectively. Figure 1 shows the effect of exposure to these various low doses of anesthetics during training on 24-h retention latency for the single-trial learning experience in nonoperated animals. Longer retention latency implies greater memory of the training experience. The underlying assumption of this model is that animals take longer to cross over into the dark side of the IA apparatus when they have better memory of the foot shock experience. Mean retention latency for nonoperated air-exposed animals (n = 14) was 170 ± 132 s. Retention latency was not significantly different from control performance for animals exposed to isoflurane or desflurane during learning. However, retention latency was significantly increased for animals exposed to sevoflurane ($P < 0.005$) and halothane ($P < 0.05$).

Experiment 2

Figure 2 shows a schematic composite diagram of the minimum and maximum lesion extents for the animals included in the final analyses of the BLA lesion experiment. These lesions clearly all involved the BLA subnuclei within the BLA complex. The smaller lesions affected an area approximately equal in size to that of one half the entire BLA subnuclei, and the larger lesions extended this area of damage to encompass most of the basolateral subnuclei as well as the lateral subnuclei. The center of the regional overlap between the minimal and maximal lesion extents is qualitatively identified as being on the ventral–medial border region between the lateral and BLA subnuclei.

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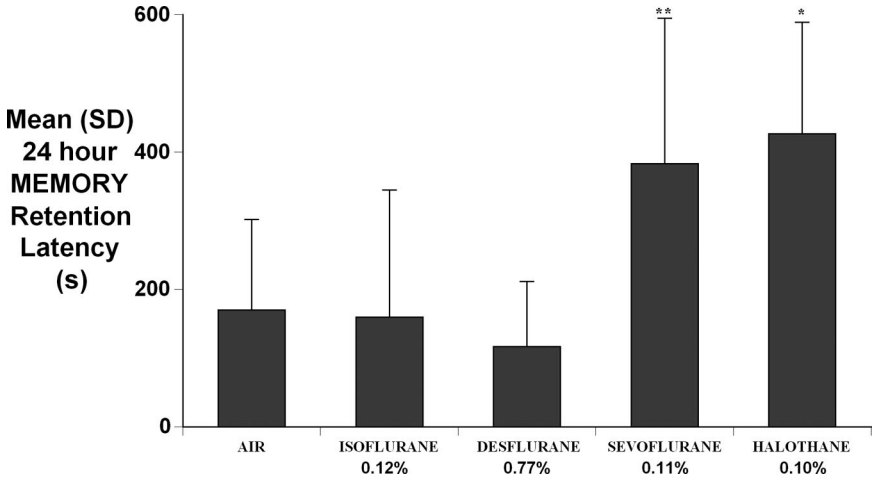

Fig. 1. The 24-h memory retention latency performance for unoperated animals that were exposed to air, isoflurane, desflurane, sevoflurane, or halothane during a single trial of inhibitory avoidance learning. Animals were not exposed to anesthetic on memory testing. Longer latencies imply better memory. Exposure to sevoflurane or halothane at training resulted in a significant increase of 24-h memory retention latency. Data are presented as mean ± SD. * $P < 0.05$. ** $P < 0.005$.

Figure 3 shows the effects of sevoflurane on retention performance in sham-operated control animals and animals with BLA lesions. As a replication of the results with the nonoperated animals, sevoflurane exposure at the time of learning in sham-operated animals significantly increased 24-h memory retention latency ($P < 0.001$) compared with air-exposed sham-operated control animals (374 ± 209 *vs.* 35 ± 25 s, respectively). In animals with BLA lesions, the lesions did significantly affect retention performance of both lesioned groups when they were compared with their respective sham controls. The retention latency in the lesioned sevoflurane exposed group was significantly lower than that of the nonlesioned sevoflurane exposed group ($P < 0.001$), and the latency in the lesioned air exposed group was significantly lower than that of the nonlesioned air exposed group ($P < 0.05$). Most importantly, however, retention latency in the lesioned sevoflurane exposed group (13 ± 7 s) was not significantly different ($P > 0.94$) from retention latency in the lesioned air–control group (6 ± 6 s). This demonstrates that the memory-enhancing effect of low-dose sevoflurane does not occur in animals with bilateral lesions of the BLA.

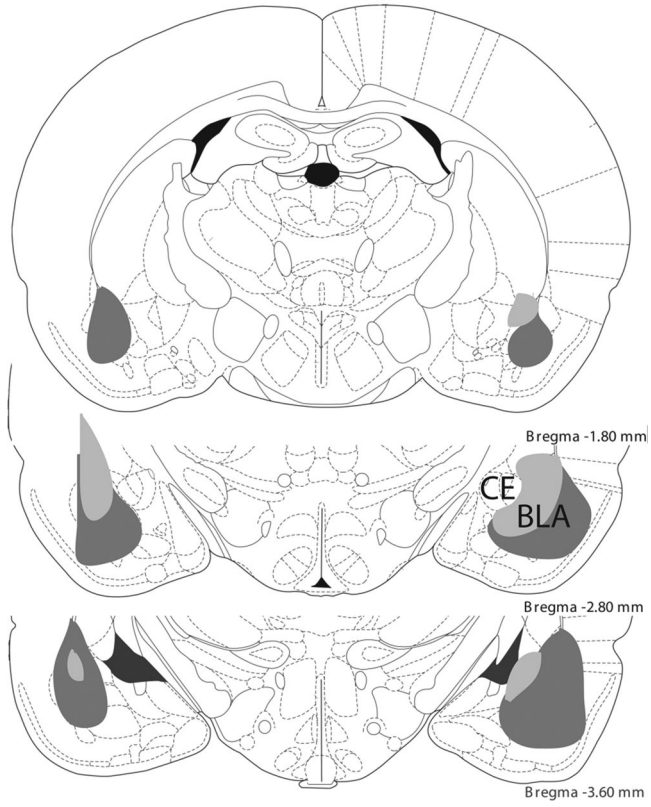

Fig. 2. Schematic representation of the minimal (*light gray*) and maximal (*dark gray*) extent of the lesions involving the basolateral amygdala (BLA). *Numbers* indicate distance posterior to bregma, in millimeters. CE = central amygdala nucleus.

Figure 3 also shows the resultant effect from the subsequent additional continuous multitrial IA training in air on the subsequent second memory test. The lesioned animals readily learned this task and needed only 1.2 ± 0.4 additional crosses into the dark side to reach the predefined training criterion. This additional training and testing session reveals that a BLA lesion large enough to block the memory-enhancing effect of sevoflurane is, at the same time, not so large as to completely prevent learning and memory of the IA task.

Discussion

These data reveal that exposure to a low inspired subanesthetic dose of sevoflurane (0.11% or 0.05 MAC) in rats during learning of an aversively motivated task significantly enhances memory retention for that task at 24 h. The data further show that halothane exposure, but not isoflurane or desflurane exposure during equivalent learning conditions, also increases memory retention of the training experience. In a subsequent experiment, the memory-enhancing effect of sevoflurane was shown to be blocked in animals previously given bilateral lesions of the BLA. When taken together with the previous demonstration that the BLA is also involved with mediating sevoflurane-induced amnesia,[13] the BLA emerges as a key brain site involved with mediating the dose-dependent memory modulation effects of sevoflurane.

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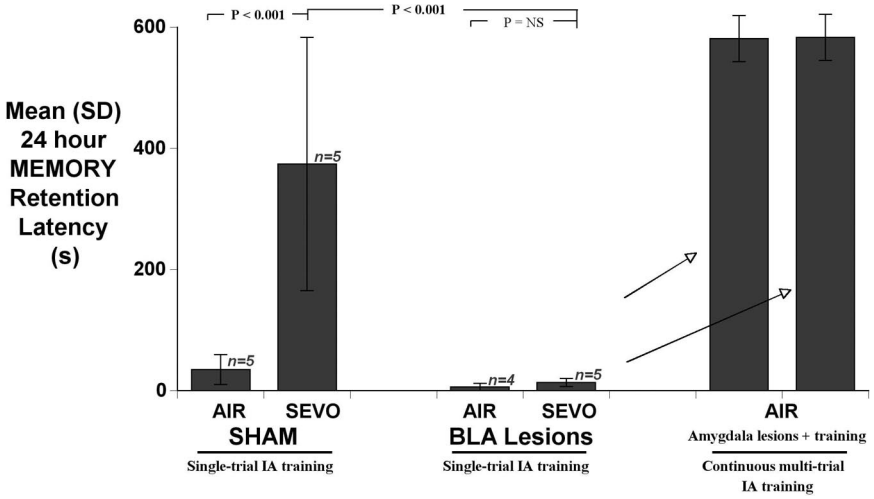

Fig. 3. The 24-h memory retention performance for sham-operated control rats and rats with bilateral basolateral amygdala (BLA) lesions. For sham-operated animals, exposure to 0.1% sevoflurane during learning significantly enhanced 24-h memory retention performance, as compared with those animals that were exposed only to air. This finding replicates that of the unoperated animals (fig. 1) and suggests the surgical procedures themselves were not the cause of the decreased overall retention performance in the lesioned animals. Memory performance in the BLA-lesioned animals was significantly lower than that of the sham-operated controls, but importantly did not differ according to whether an animal was exposed to air or sevoflurane during learning. Therefore, BLA lesions blocked the memory-enhancing effect of sevoflurane. At 24 h after this determination, the BLA-lesioned animals were given additional training on the inhibitory avoidance (IA) task. The *right two columns* show their 24-h retention latencies after the additional training.

A modulatory role for the BLA in memory processing is well established (for review, see McGaugh).[11] The modulatory viewpoint of amygdala function grew out of Müller and Pilzecker's "perseveration–consolidation" hypothesis of learning and memory.[15] This hypothesis suggests that neural activity caused by a learning experience perseverates for a while and that this perseveration is crucial for the eventual consolidation of memory.[15–17] In fact, many postlearning manipulations of memory consolidation have been found, and such manipulations can either enhance or impair memory.[14,18–24]

A tremendous amount of work has identified that memory consolidation effects for emotional or aversive material depend, to a large part, on the BLA.[25] Many substances are known to enhance memory in the IA paradigm when given systemically or directly into the BLA after learning.[26] Memory enhancement is seen with γ-aminobutyric acid–mediated antagonists, corticosterone, epinephrine, naloxone, glucose, and direct electrical stimulation of the BLA.[18-20,22,24,27-29] In addition, memory enhancement has been found in humans with postlearning systemic glucose or epinephrine administration.[30,31] The current results with sevoflurane fit well within the modulatory framework of memory consolidation and identify sevoflurane as another substance that has both a memory-enhancing (*i.e.*, the current results) and, at a slightly higher dose, a memory-impairing effect.[8]

In this study, halothane also enhanced memory retention performance. However, a clear effect of halothane on memory consolidation is difficult to establish because the memory-enhancing dose of 0.10% is also a dose associated with hyperalgesia.[32] Low-dose halothane causes a significant hyperalgesic effect to the electrical stimulus used in the IA paradigm.[8] Hyperalgesia would increase the aversiveness of the shock experience and would therefore increase memory retention in this model. It remains to be determined whether low-dose halothane would enhance memory using a nonaversively motivated paradigm.

Sevoflurane, at the dose used here to enhance memory, shows an analgesic response to the electrical pain stimulation.[8] Therefore, the memory enhancement of sevoflurane occurred in rats that likely felt a less aversive shock than the control rats. This implies that the memory-enhancing ability of sevoflurane may be underestimated with the current IA paradigm. However, it cannot really be known what a rat experiences during the foot shock stimulation, even though the stimulation is clearly painful to human touch. Therefore, because anesthetics have multiple dose-dependent effects on the brain and spine,[33,34] as well as having complex dose-dependent effects on neural networks,[35] it remains possible that sevoflurane may have enhanced the aversiveness of the shock and made it more memorable. Although this speculation seems unlikely, it does point out that memory consolidation effects can only be conclusively established with postlearning manipulations. Given the findings of this study, a postlearning sevoflurane exposure experiment now seems warranted.

The cellular mechanisms of postlearning and BLA-mediated memory enhancement are not fully known, but evidence converges on intra-BLA norepinephrine and/or acetylcholine concentrations as playing a pivotal role in memory modulation effects.[11] Beta blockers, given into the amygdala in animals or systemically in humans, have been shown to block the memory enhancing effect of emotional arousal.[21,36–38] The foot shock stimulation used in the IA task is known to cause norepinephrine release in the BLA,[39,40] and the magnitude of this norepinephrine release correlates with the eventual memory performance in the IA task.[41] Sevoflurane and isoflurane have been shown to release norepinephrine from the rat preoptic area at clinically relevant concentrations, so at least some interaction with noradrenergic systems exits.[42] However, the effects of these agents on

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BLA norepinephrine release at the low subanesthetic dose concentrations used here remains to be determined. A role for BLA norepinephrine release in mediating the memory enhancement of sevoflurane could be inferred from a future experiment if intraamygdala β blockade were found to prevent the memory-enhancing effect of sevoflurane.

Inhalation anesthetics are known to have *in vitro* effects on a plethora of protein receptor systems.[43] However, anesthetic actions within the cholinergic system may have particular importance for understanding anesthetic memory effects. The nicotinic receptor is one of the most sensitive to inhaled anesthetics.[44,45] One report showed sevoflurane and isoflurane effects at concentrations that were 100–1,000 times lower than typical clinical concentrations.[46] *In vitro* acetylcholine induced currents of the $\alpha_4\beta_2$ nicotinic receptor are reduced by inhaled agents with ED_{50} values for halothane, isoflurane, and sevoflurane of 0.21, 0.24, and 0.61 MAC, respectively.[47] These values compare favorably with the recently determined amnesic ED_{50} values for halothane, isoflurane, and sevoflurane of 0.25, 0.13, and 0.11 MAC, respectively.[8] Given that other recent animal memory work reveals important contributions of nicotinic action in the BLA to memory of the IA task[48] and that low doses of sevoflurane can affect the nicotinic receptor, the anesthetic-induced modulation of BLA nicotinic activity emerges as an important system for further study.

The lesion findings implicate the BLA as a potentially necessary brain site involved with mediating the memory-enhancing effect of sevoflurane, but it does not identify the BLA as the only site sufficient for mediating this effect. The BLA is only one node in a complex neural network of connections involved in both regulation of emotion and modulation of memory.[11,49] Elucidating the amygdala circuits involved in mediating memory effects and the influences of BLA activity in mediating memory modulation in other brain regions remains an intensely active area of research.[25,50–55] Ultimately, a combination of effects at the receptor level and the system level likely underlie the memory enhancement effect of sevoflurane.

It could be argued that a lesion large enough to block a memory-enhancing effect of a drug might also be large enough to simply prevent learning and memory in the first place. We behaviorally explored for this possibility in the same BLA-lesioned animals after their initial memory assessment. The BLA-lesioned animals were given additional training in the IA apparatus during exposure only to air, and their memory of this second training experience was again tested 24 h after this second training session. We found that BLA lesions sufficient to block sevoflurane-induced memory enhancement do not necessarily prevent learning and memory of the IA task. This result supports the view that the amygdala may function to modulate rather than store memory.[56,57]

Until now, the idea that an anesthetic agent might enhance memory has not been seriously considered, and no attempt has been made to establish the parameters that would allow sevoflurane memory enhancement to be demonstrated in humans. Clinically, enhanced memory for an aversive experience in humans might translate into greater pain and suffering for patients who experience intraoperative awareness. From the current animal work, it seems that memory enhancement would require exposure to both the correct dose (*i.e.*, 0.11%) of sevoflurane and exposure to aversive stimulation. Therefore, these findings do not suggest that low-dose sevoflurane exposure would be expected to enhance human explicit memory of nonemotional information.

The memory-enhancing dose of sevoflurane would generally be encountered at least two times during a sevoflurane anesthetic, namely at induction and again during emergence. In addition, it could occur when a patient's hemodynamic status is too tenuous to tolerate higher anesthetic doses. The current work suggests the clinical possibility that additional amnesic agents may be needed around these times to insure the prevention of awareness during a sevoflurane-based anesthetic.

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