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Repetitive Post-training Exposure to Enflurane Modifies Spatial Memory in Mice

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Background: **Previously the authors found that a single post-training exposure to enflurane or isoflurane, but not halothane, enhanced memory storage in an active avoidance task, which is a behavior with underlying mechanisms that are poorly understood and still debated. In contrast, spatial tasks are known to depend on hippocampal functions. This study investigated the effects of repetitive post-training exposure to enflurane on spatial memory in mice.**

Methods: **Using an eight-arm radial maze, 80 mice were trained to eat a pellet placed on the end of each of the eight arms. Training occurred on four consecutive days with one trial per day. The number of errors in the first eight choices was recorded to determine performances for each day of training. Immediately after each training session, mice in the enflurane group received 1 h exposure to 0.5%, 1%, or 2% enflurane in air through a calibrated vaporizer. The performance ratios (the ratio of errors on each day compared with the first day of the 4 days) in the control and the enflurane groups were compared.**

Results: **The performance ratios (which equals the mean of the error in the fourth day/the error in the first day) in the control, and 0.5%, 1%, and 2% enflurane groups were 0.66, 0.65, and 0.32 ($P < 0.01$, *vs.* control), and 0.46 ($P < 0.05$, *vs.* control), respectively.**

Conclusions: **Repetitive post-training exposure to 1% and 2% enflurane significantly enhanced spatial memory in the eight-arm radial maze task. Enflurane enhances consolidation of spatial memory, possibly by affecting hippocampal activity. (Key words: ddN mice; eight-arm radial maze; hippocampus; learning; memory consolidation.)**

INVESTIGATION of the anesthetic action on higher brain function is essential to understand the neural mechanisms of anesthesia. Learning and memory are the most essential issues of such higher brain functions. Many studies have shown the depression of learning and explicit memory during anesthesia.[1] However, few studies have been done on the post-training effect of inhalation anesthetics on memory consolidation.

Recent studies have shown that memory can be divided into at least two general categories.[2] Explicit or declarative memory is the conscious recall of knowledge about places and things and is well developed in the vertebrate brain. Implicit or nondeclarative memory is the nonconscious recall of motor skills and other tasks and includes simple associative forms, such as classical conditioning, and nonassociative forms, such as sensitization and habituation.[3] Explicit memory depends on temporal lobe and diencephalic structures, whereas implicit memory involves the same sensory, motor, or associational pathways used in the learning process.[2]

Both explicit and implicit memory are graded, and the duration of the memory is related to the number of training trials and is commonly divided into at least two temporally distinct components: short-term memory, which lasts minutes, and long-term memory, which lasts days, weeks, and, in some cases, even a lifetime. Studies of long-term memory for explicit and implicit learning indicate that each uses a cascade of molecular events that occurs during their consolidation period—the initial phase of memory storage—that is labile and highly sensitive to disruption. In both cases the conversion of a transient short-term form, which requires only covalent modification of preexisting proteins, to a more stable and self-maintained long-term form that is accompanied by the growth of new synaptic connections, requires a cellular program of gene expression and increased protein synthesis.[2]

Previously we demonstrated memory facilitation by single post-training exposure to enflurane and isoflurane in an active avoidance task in ddN mice.[4] The ddN mice we used are an inbred strain of mice that we have been breeding for more than 78 generations. They were trained in a jump-box type of active avoidance and se-

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lected at about their 35th generation. They show higher scores in avoidance training than do C57BL mice, for example.[5] Avoidance tasks, however, are a behavior with underlying mechanisms that are poorly understood and still debated.[6] In contrast, spatial memory appears to depend more on hippocampal function,[7,8] especially on N-methyl-D-aspartate receptor-dependent synaptic plasticity at CA1 synapses.[9] In the current study, we hypothesized that repetitive post-training exposure to enflurane enhances consolidation of spatial memory, and we tested this by measuring the changes in performance assessed by certain ratios (day 2–4 to day 1) of errors in ddN mice using an eight-arm radial maze task. We used enflurane because our previous research showed that it more effectively enhanced memory compared with halothane or isoflurane.[4]

Materials and Methods

Animals

All studies were approved by the Institutional Animal Care and Use Committee of Kagawa Medical University. We used 80 ddN mice (10 ± 2 weeks) that had been bred and raised in the animal colony of the Animal Research Center of Kagawa Medical University. All animals were kept under a 12-h–12-h dark–light cycle, with lights on at 6 A.M. Food and water were available *ad libitum*. All experiments were performed between 10.00 A.M. and 3.00 P.M. in consideration of the animals' circadian rhythm. The animals were divided into four groups (control, 0.5% enflurane, 1% enflurane, and 2% enflurane; n = 20 in each group) at random. Four mice were tested each week and were randomized to control (one or two) or the same concentration of enflurane (three or two). The order of the tests was randomized for each mouse each day.

Training Apparatus and Experimental Procedure

The radial maze and training procedure were similar to those described by Schwegler *et al.*[10] The radial maze consists of a central platform and eight arms made of transparent acrylic resin (fig. 1). The central platform measures 22 cm in diameter. The closed arms are 25 cm long, 6 cm high, and 6 cm wide. A food pellet weighing approximately 10 mg was deposited at the end of each arm behind a bar. This prevented the animals from selecting a baited arm by looking for the presence or absence of a reward. We provided no special means to dispel the effect of smell because, in radial maze tasks, vision is more important than smell.[11] The maze was placed in a box, the walls of which were colored white, and an extramaze cue (a sports drink can, 65 mm in diameter and 120 mm in height, covered with yellow paper) was provided close to the maze and between the arms to facilitate learning.[12]

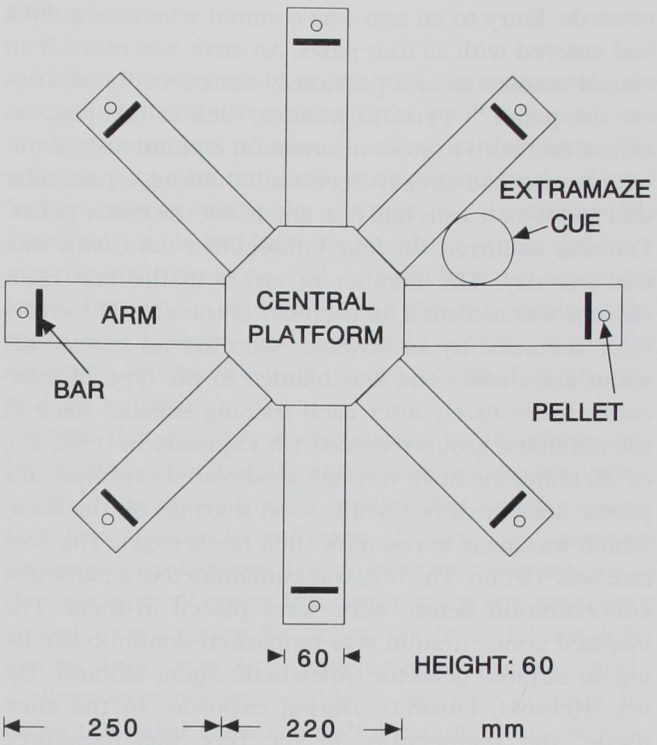

Fig. 1. An eight-arm radial maze (a top view). Numbers indicate sizes in millimeters. Mice were placed in the center of the maze and allowed free choice of all eight arms. Each pellet is expressed as a small circle. An extramaze cue is expressed as a large circle. See the text for additional details.

Mice received a 10-min habituation trial with free access to all arms 24 h before day 1 training. During this habituation trial, the mouse freely visits each arm without food pellets as many times as it likes. These were neither counted nor recorded. The extramaze cue was present at this time. Subsequently, using a formula developed from our previous experience, mice were given food in a manner to stimulate hunger by maintaining body weight at 80–90% of normal. Before each training session, an open-field activity was measured in a plastic home cage (20 cm wide, 41 cm deep, and 13 cm high) for 5 min on a counter triggered by crossing an infrared beam (Animex, Muromachi, Tokyo, Japan). At the start of each trial, the mouse was placed in the center of the maze and allowed free choice of all eight arms. A trial was terminated when the animal had eaten all eight

rewards. Entry to an arm was counted when the animal had entered with all four paws. An error was noted if an animal entered an arm previously visited, or if it did not eat the pellet.[10] Thus, to perform well in this task, an animal had both to store information continuously about which arms had already been visited during a particular trial and which arms had not, and to eat the entire pellet. Training occurred on four consecutive days with one trial per day. The number of errors in the first eight choices was recorded for each day of training. The errors were recorded by an observer who has no knowledge about anesthetics and was blinded to the type of treatment. Immediately after each training session, mice in the enflurane group received 1 h exposure to 0.5%, 1%, or 2% enflurane in air through a calibrated vaporizer in a plastic anesthesia box with wood shavings on the floor, which was made to resemble their home cages. The flow rate was 5 l/min. The box was equilibrated to a particular concentration before mice were placed in them. The inspired concentration was monitored continuously using an infrared detector (Anesthetic Agent Monitor; Datex, Helsinki, Finland). During exposure to the anesthetic, the temperature in the box was monitored continuously and maintained carefully between 34 and 35°C by an electric heater outside the box to maintain animal rectal temperature > 36°C.[13] The control animals were tested almost concurrently with the enflurane-treated mice (within a 10-min difference). After the training, the control mice were once placed in the anesthesia box for 1 h under the normal air flow (5 l/min), followed by transfer to their home cage. Thus the control animals were treated identically to the enflurane-treated animals, except that no enflurane was added to the air to which they were exposed. We divided the number of errors each day by that of the first day to establish "each-day performance ratios."

Statistical Analysis

Open-field activity data were analyzed using repeated-measures analysis of variance after certifying a homogeneity of variance and a normal distribution. The comparative frequencies of the two types of errors (*i.e.*, entering an arm previously visited, or not eating the pellet) were analyzed by goodness test of fit for chi-squared analysis. The performance ratios were compared among the control and enflurane groups on the second, third, and fourth days. After certifying a homogeneity of variance and a normal distribution, each day's performance ratio data were analyzed by analysis of variance followed by Scheffé's F test. Differences were considered significant if $P < 0.05$.

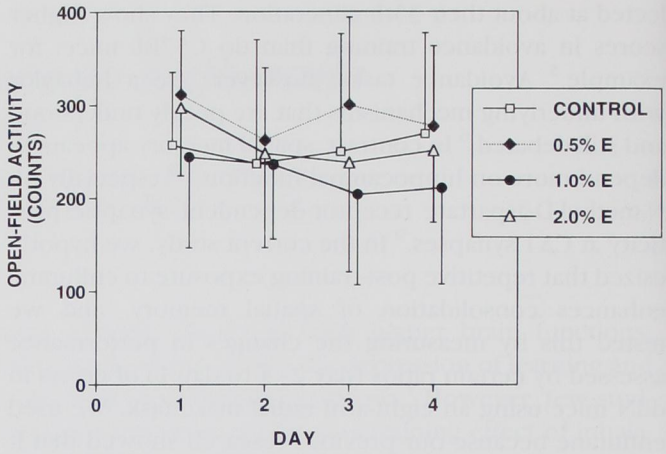

Fig. 2. Daily counts (5 min) of open-field activity (820 cm^2) are shown as mean ± SD. There were no significant differences among either of the four (control and three enflurane-treated) groups on each day or in the daily counts in each group.

Results

Mice Demographics

Mean (± SD) body weights of the day before training day 1 were 31.9 ± 2.1 g, 30.9 ± 2.9 g, 31.9 ± 3.2 g, and 31.0 ± 2.6 g in the control, 0.5%, 1%, and 2% enflurane groups, respectively, and there were no significant differences among the groups.

Radial Maze Task

The mean 5-min open-field activity before each radial maze task showed no differences among the control, 0.5%, 1%, or 2% enflurane groups (fig. 2). The error for entering an arm previously visited was always dominant and occupied 86.5% of all errors (4 days, four groups). On day 4, it was 92%, 100%, 90%, and 76% in the control, 0.5%, 1%, and 2% enflurane groups, respectively. There were no significant differences among the groups.

The mean numbers of errors in the initial eight choices on day 1 were 3.7, 3.6, 4.2, and 3.9 in the control, 0.5%, 1%, and 2% enflurane groups, respectively, and there were no significant differences among the groups.

Figure 3 shows the each-day performance ratios (mean ± SD) in the control and 0.5%, 1%, and 2% enflurane groups.

The performance ratios (day 4/day 1) were 0.66 ± 0.19, 0.65 ± 0.18, 0.32 ± 0.12 ($P < 0.01$, *vs.* control), and 0.46 ± 0.16 ($P < 0.05$, *vs.* control and 1% enflurane

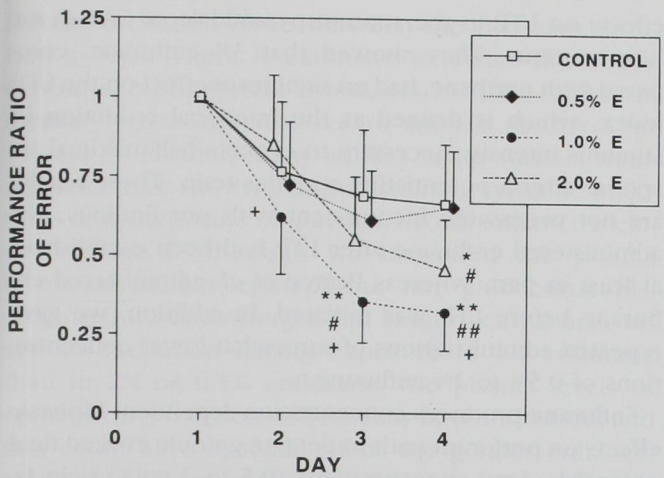

Fig. 3. The performance ratios of each-day results (errors) to the first-day results are shown as mean ± SD. E refers to enflurane. * and ** indicate differences from the control group, at $P < 0.05$ and 0.01, respectively. # and ## indicate differences from the 0.5% enflurane group, at $P < 0.05$ and 0.01, respectively. + indicates different from the 2% enflurane group, at $P < 0.05$. See the text for additional details.

groups), respectively (fig. 3). No other pairwise differences were significant in the day 4/day 1 performance ratios.

Visual Observation of Behavior during Exposure to Enflurane

Mice exposed to 0.5% enflurane showed slightly increased activity involving jumping, running, trying to climb up a chamber wall during the initial 4 or 5 min, followed by a slightly decreased-below-normal state. They sometimes remained calm but never slept. They occasionally moved and ambulated unsteadily throughout the exposure. The mice exposed to 1% enflurane were intensely excited. They struggled, ran, and even overturned (dorsal side down) during the initial several minutes. After the initial period, they became calm and generally slept, but sometimes they moved their bodies, paws, and tails, and sometimes they ambulated. The mice exposed to 2% enflurane, after some 10 s of excitation, were rapidly anesthetized and remained in this state throughout the exposure. The duration of excitation in the 2% enflurane group was shorter than that in the 1% group. A transient opisthotonus (10- to 40-s duration) during anesthesia was observed in 8 of 20 animals in the 2% enflurane group, but in none in the 1% group. Recovery from anesthesia was complete, and no abnormal behavioral deviations compared with the control mice were observed at the start of the next day's performance.

Discussion

In our previous study, to increase experimental confidence we used littermates in the pair of control and anesthetic groups of mice, because at that time ddN was not yet an inbred strain but only a closed colony.[4] In the current study, we did not use littermates because ddN mice had become an inbred strain and their genetic quality was proved uniform by gene screening tests. In fact, as shown in the Results section, the mean day 1 scores and open-field activity were not different among the four groups (control, 0.5%, 1%, and 2% enflurane).

Given that memory consolidation in animals occurs immediately after learning and is completed within a few hours,[13] the current result implies that repetitive post-training exposure to enflurane (1% and 2%) enhances memory consolidation. The comparative frequencies of the two types of errors (*i.e.*, entering an arm previously visited, or not eating the pellet) on day 4 did not differ among the four groups, which suggest that our major findings were not attributable to one type of error. Because the radial maze is a useful paradigm to test functions of the hippocampus, specifically that of spatial memory,[7,10,14] our results suggest that repetitive post-training exposure to enflurane enhances spatial memory, possibly by affecting hippocampal activity. This speculation is supported, at least in part, by the study of local cerebral metabolism using [^{14}C] 2-deoxyglucose. At 1 minimum alveolar concentration enflurane (the minimum alveolar concentration of enflurane in ddN mice is 1.37% for loss of righting reflex[15]), cerebral metabolism in both gray and white matter was depressed an average of 14% from the awake controls. However, metabolism in the dentate gyrus and cornu ammonis of the hippocampus, the habenulae, the interpeduncular nucleus, and the pineal was increased by approximately 31%.[16]

Post-training treatment with drugs or hormones has been used in an attempt to identify the drug effect on memory consolidation. For example, alcohol administered immediately after learning produces retrograde facilitation.[17] Many studies using various training tasks have shown that post-training systemic injections of epinephrine and glucocorticoids also enhance memory.[18] A large body of similar work has suggested that norepinephrine, opiates, and various other peptides may play a role in the development of the engram.[19] Epinephrine and glucocorticoids enhance memory storage by influencing the amygdala, which is involved both in affectively influenced memory and spatial memory.[18,20] For

example, memory is enhanced by post-training intra-amygdala infusions of drugs that activate β-adrenergic and glucocorticoid receptors. In rats, lesions of the amygdala and the stria terminalis, a major amygdala pathway, block the effects of post-training administration of epinephrine and glucocorticoids on memory. However, as far as we know, there is no direct evidence for amygdala activation by enflurane.

The cellular mechanism of memory facilitation by enflurane in the current study is unknown, but we have found some findings relating to our result. Long-term potentiation (LTP) is a long-lasting increase in synaptic efficacy, which follows a brief stimulus train. It has been shown to be established through activation of the N-methyl-D-aspartate subclass of excitatory amino acid receptors and is thought to be involved in memory processing.[21] A positive correlation between LTP and spatial memory behavior in rats has also been demonstrated.[22–25] Tsuchiya *et al.*[26] reported that halothane, enflurane, and isoflurane enhanced rat brain protein kinase C, and its activation is required for LTP.[27,28] Mice with lower hippocampal protein kinase C activity have problems performing spatial reference memory tasks to the same degree of accuracy as those with higher hippocampal protein kinase C activity.[29] These results indicate that some of the volatile anesthetics can enhance one of the processes of memory and support our current result.

Which part of the hippocampus is essential for spatial memory? The data from the knockout mice of the N-methyl-D-aspartate$_1$ receptor gene in only CA1-pyramidal cells of the hippocampus provide strong evidence in favor of the notion that N-methyl-D-aspartate receptor-dependent synaptic plasticity at CA1 synapse is required for both the acquisition of spatial memory and the formation of normal CA1 place fields.[9] Radial maze learning shows a high positive correlation with the size of the intra- and infrapyramidal hippocampal mossy fiber terminal field, which has a strong relation to activity of the CA1 pyramidal region and dentate gyrus neurons.[10] The CA3 pyramidal cells operate as a single autoassociation network to store new episodic information as it arrives *via* several specialized preprocessing stages from many different association areas of the cerebral cortex, and the dentate granule cell–mossy fiber system is important, particularly during learning to help produce a new pattern of firing in the CA3 cells for each episode.[30]

Pearce *et al.*[31] examined the effects of volatile anesthetics on excitatory transmission by observing their effects on LTP in the stratum pyramidale of CA1 in rat hippocampus. They showed that 3% enflurane, compared with urethane, had no significant effect on the LTP index, which is defined as the fractional reduction in stimulus intensity necessary to evoke a half-maximal response after a potentiating stimulus train. These results are not necessarily inconsistent with our findings. We administered enflurane after LTP had been established, at least in part, whereas Pearce *et al.* administered enflurane before LTP was initiated. In addition, we gave repeated administrations of somewhat lower concentrations of 0.5% to 2% enflurane.

Enflurane produces concentration-dependent biphasic effects on perforant path to dentate granule evoked field potentials. Low concentrations (0.5 to 2 vol%) help facilitate transmission in the dentate granule, whereas higher concentrations (2.5 to 4 vol%) produce depression.[32] Concentrations from 0.25 to 1 vol% produce increased population spike amplitudes accompanied by prolonged spike latencies and increased excitatory postsynaptic potentials onset latencies on perforant path inputs to dentate granule neurons. Higher concentrations of enflurane (1–6 vol%) produce further reduction in excitatory postsynaptic potential responses, resulting in depression of population spike amplitudes.[33] These *in vitro* studies were not necessarily done in connection with memory function, but it is possible that these alterations in hippocampal function produced by enflurane relate to the current result.

Our results also demonstrate that the memory facilitation effect by enflurane is not monotonically related to drug dose. According to our observation, mice were in a shallow sleep during exposure to 1% enflurane, and (although we did not record an electroencephalogram) Clark and Rosner[34] reported that an electroencephalogram shows high-frequency activity during exposure to 1% enflurane.[34] This strongly suggests that mice exposed to 1% enflurane were, at least in part, in a rapid eye movement sleep state, because rapid eye movement sleep appears in a shallow sleep with an activated (high frequency) electroencephalogram.[35] On the other hand, animals showed deep sleep during exposure to 2% enflurane, which suggests that they stayed in rapid eye movement sleep for a much shorter time than with 1% enflurane. Now there is a substantial body of data to suggest that accelerated neural plasticity occurs during elevated post-training rapid eye movement sleep.[36] This can explain the current result that 1% enflurane was more effective than 2% enflurane on memory storage.

Another possible reason is different central nervous

system excitation levels between the two concentration groups. There is extensive evidence that many central nervous system stimulants enhance long-term memory when administered to animals shortly after training.[37] Further, many studies using various training tasks have shown that post-training systemic injections of epinephrine or glucocorticoids enhance memory storage.[18] Although we measured the plasma levels of neither epinephrine nor glucocorticoids, judging from the stronger and longer central nervous system excitation during exposure to 1% enflurane than in 2% or 0.5% enflurane, the plasma levels of epinephrine, cortisol, or both may have increased, and this could have brought about the greater enhancement of memory consolidation in the 1% enflurane group compared with the other groups.

In conclusion, repetitive post-training exposure to 1% and 2% enflurane enhanced spatial memory in the eight-arm radial maze task in ddN mice. Because spatial memory is a process that depends on normal function of the hippocampus and amygdala, our findings indicate that enflurane may affect cellular memory processes in these structures.

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