Anesthesiology 2002; 97:447–53

Effect of a Nonsedative Dose of Propofol on Memory for Aversively Loaded Information in Rats

Laure Pain, M.D., Marie-Josée Angst, B.R.,† Laurence LeGourrier, M.D.,‡ Philippe Oberling, M.D., Ph.D.§*

Background: **The effects of propofol on memory for aversive information are not well determined. The authors evaluated the effects of a minimal nonsedative dose of propofol or midazolam on memory in rats, using an apparatus composed of two compartments: a large bright anxiogenic one and a small dark neutral one.**

Methods: **Groups of rat received propofol (9 mg/kg, intraperitoneally) or midazolam (3 mg/kg). Anxiety was assessed in rats placed in the anxiogenic compartment as the time before the animals entered the neutral compartment. Memory for an aversive event was assessed in rats placed in the anxiogenic compartment as the time to enter the neutral one where they previously experienced foot shocks (fear conditioning). To assess the memory for a nonaversive event, rats were placed in the neutral compartment with no shocks (preexposure). The following day, rats were placed in it and they experienced foot shocks. As a result of the preexposure, rats exhibit less fear to enter it.**

Results: **Propofol and midazolam increased the time to enter the neutral compartment. Propofol or midazolam was given to rats before experiencing foot shocks in the neutral compartment. When later tested, the time to enter it was decreased. Propofol or midazolam was given to rats before the preexposure to the neutral compartment. When later tested, the latency to enter it was not modified by the preexposure.**

Conclusions: **Propofol and midazolam impaired memory for aversive and for nonaversive experiences at equianxiolytic doses that do not produce locomotor impairment in rats.**

NUMEROUS studies have shown that propofol impairs memory.[1–5] It has been repeatedly suggested that propofol-induced sedation was responsible for this amnesic effect. Sedation can interfere with acquisition of information because of reduced perception.[6] However, propofol may also have specific effects on memory, which are independent of its sedative properties. Studies in human volunteers have largely suggested that propofol-induced amnesia is not correlated with sedation.[3,5,7] The aim of the current study was to determine whether propofol has an amnesic effect at nonsedative doses.

Memory for aversive information deserves consideration with regard to clinical practice.[8–10] Most of the previous studies showing propofol-induced amnesia at low doses were performed using memory tests after learning of neutral information (*e.g.*, words, pictures).[1,3–5] It is well known that an event is better remembered if it has an emotional component. The affective component of information interferes with the learning process by improving it.[11,12] Therefore, we were interested to assess propofol's effect on memory not only on a nonaversive event but also on an aversive event.

For this purpose, we used a rodent model of one-session Pavlovian (classic) contextual fear learning in a passive avoidance apparatus. Briefly, in the Pavlovian fear-conditioning paradigm, an initially neutral stimulus (the so-called conditioned stimulus [CS]), either a discrete signal such a tone or a light or the experimental surrounding itself, is paired with an aversive stimulus (the so-called unconditioned stimulus [US]), such as a brief electrical foot shock. After few pairings of the two stimuli, a robust memory is formed between the two so that the initially neutral stimulus CS alone will produce conditioned fear reaction, such as freezing, modification of escape, or avoidance latencies. In our procedure, the animal experienced passively mild electric foot shocks (US) in a distinctive environment (CS). As a result, a subsequent avoidance for this environment is observed, which is thought to reflect the memory for the association between the aversive stimulus and the environmental conditioned stimulus.[13–15]

We used 9 mg/kg of propofol, a light dose in rats, which does not impaired exploratory locomotion in our strain of rats.[16] The effect of propofol was compared with that of 3 mg/kg of midazolam. This dose has been previously shown to produce memory impairment for aversive and nonaversive information, independent of anxiolytic and sedative effects.[17] Initially in this study, the effects of propofol and midazolam were compared on memory of an aversive event. Anxiolytic effects of propofol and midazolam were controlled in our experimental conditions. Then, the effect of propofol on memory for a nonaversive event was compared with that of midazolam. For this purpose, we tested the effect of propofol and midazolam on an initial exposure (with no shock) to the environment. It has been demonstrated that an initial exposure to the CS with no aversive stimulus will exert a deleterious effect on the subsequent

* Consultant Anesthetist and Senior Researcher, Hôpitaux Universitaires de Strasbourg and U405 INSERM, † Research Technician, § Associate Professor of Physiology, Institut de Physiologie, Université Louis Pasteur, Strasbourg and U405 INSERM, and ‡ Resident in Anesthesiology, Hôpitaux Universitaires de Strasbourg.

Received from Groupe de Recherche Experimentale sur les Répercussions Cognitives de l'anesthésie (GRERCA) and Laboratoire de Psychopathologie et Pharmacologie de la Cognition (U405 INSERM), Strasbourg, France. Submitted for publication February 2, 2001. Accepted for publication February 14, 2002. Supported by the Faculté de Médecine de Strasbourg 1998, Ministère de l' Education Nationale, de la Recherche et de la Technologie/Institut National Santé Et Recherche Médicale 1999, Paris, France (projet de soutien des IFR aux sciences du vivant), and Université Louis Pasteur, Strasbourg, France (Institut Fédératif de Recherche Neurosciences 37). Presented in part at Congrés national d'anesthésie reanimation, SFAR, Paris, France, September 23, 1999, and at the European Congress of Anesthesiology, Amsterdam, The Netherlands, May 6, 1999.

Address reprint requests to Dr. Pain: Department of Psychology, University of Vermont, Burlington, Vermont 05405. Address electronic mail to: Laurepain@aol.com.

CS–US association.[18,19] In our procedure, the animal was preexposed to the environment (CS) with no shock and was then placed again in it where it experienced foot shocks (CS–US). As a result of the initial preexposure to the environment, the animal exhibit less avoidance of it, which is thought to reflect the memory for information about the environment retained during preexposure (CS preexposure effect).[20–22] Finally, two additive experiments controlled for the lack of deleterious effect of this minimal dose of propofol on the forced locomotion and the perception of mild electrical shock used here as the aversive stimulus (experiment 4).

Materials and Methods

Animals

We used 198 male Long Evans rats (Janvier, France) that weighed 330–350 g. They were housed two per cage in a colony room maintained on a 14-h light, 10-h dark cycle (light on at 7:00 AM) with food and water provided *ad libitum*. Procedures and care of the animals were performed in accordance with the national and international guides (council directive #87848, October 19, 1989, Ministère de l'Agriculture et de la Forêt, Service Vétérinaire de la Santé et de la Protection Animales—NIH publication, N°86–23, revised 1985).

Drugs

Propofol (5 mg/ml Diprivan, Zeneca, London, UK) was dissolved in 5% "intralipid." Midazolam (5 mg/ml Hypnovel, Roche, Basel, Switzerland) was dissolved in 0.9% sodium chloride. All drugs were prepared immediately before use and injected intraperitoneally in a volume of 2 ml/kg.

Passive Avoidance Apparatus

Passive avoidance apparatus consisted of two adjacent compartments, a bright large one and a small dark one, separated by a guillotine door. The bright compartment had white Plexiglas walls (46 cm long, 42 cm large, and 44 cm high) and was illuminated by a 25 W bulb fixed on the wall opposite to the entrance to the dark one. This latter compartment had black Plexiglas walls and roof (30 cm long, 15 cm large, and 15 cm high). The roof could be opened to place directly and observe the animal in this compartment. The floor of the two compartments was made of stainless steel bars (0.6 cm diameter) regularly spaced apart by 1.8 cm. Scrambled foot shocks could be delivered through the bars of the dark compartment. The scrambler was set to deliver two moderate foot shocks at t_1 = 2:00 and t_2 = 3:30 min during a 5-min session (effective intensity, 0.1 mA; 5 s: duration; 20 ms ON–140 ms OFF).

In this apparatus, naïve undrugged rats exhibit a spontaneous fear for the bright large compartment and escape quickly (within 10 s) from it to enter the adjacent dark small one.

Rotarod Apparatus

The effect of propofol on forced locomotion was studied using a "Rotarod" apparatus as previously described.[17] Briefly, the Rotarod apparatus used here consisted of an elevated (40 cm high) rotating (2 rotations/min) bar (40 cm long; diameter, 6 cm), divided into three 11-cm sections by four perpendicular disks (diameter, 50 cm).

In this apparatus, naïve rats were shaped daily, until each of them reached a criterion of stability on the rotating cylinder for at least 60 s.

Behavioral Situations

The principles behind the behavioral situations performed using the passive avoidance apparatus are described here and separately for clarity.

Spontaneous Anxiety: Experiment 1. Spontaneous anxiety was assessed by a "light–dark" situation in rats. Undrugged rats exhibit a spontaneous fear for bright large open spaces. Therefore, naïve undrugged rats, when initially placed in the large bright compartment, escape rapidly from it to enter the small dark secure-feeling one. The fact that a drugged animal stays in the large bright compartment while its spontaneous locomotion is not impaired indicates an anxiolytic effect of the drug.[17]

Memory of an Aversive Event: Experiment 2. To assess the memory for an aversively loaded event, we used a "classic fear-conditioning preparation" for the acquisition phase of learning.[14,15] Each rat was placed (*via* opening the roof) and confined in the small dark compartment where it experienced two mild electrical foot shocks. The following day, the animal was tested for memory of the aversive experience by assessing the passive avoidance of the small dark compartment. When initially shocked in the small dark compartment, the rat has to remember this event to refrain from its natural tendency to enter this compartment when subsequently exposed to the bright large compartment. The fact that an animal enters the small dark compartment while he has been previously drugged during the conditioning session indicates no memory of the initial training.

Memory of a Nonaversive Event: Experiment 3. To assess the memory of a nonaversive experience, we used the "CS-preexposure effect" based on previous works showing that an initial exposure to a CS alone will debilitate the subsequent association between this CS and an US.[18,20] We showed in our preparation that an initial preexposure to the small dark compartment in the absence of shock, followed later by an association between this compartment and shocks, resulted in rats avoiding entering this compartment but to a lesser extent than when not initially preexposed.[17] The fact that a debilitating effect of the preexposure on fear conditioning is suppressed when the rat is drugged during

preexposure indicates no memory of this nonaversive experience.

Procedures

Behavioral testing started after three daily handling sessions. All experiments were conducted between 10:00 AM and 4:00 PM.

Experiment 1. Comparative effect of propofol (0; 9 mg/kg) and midazolam (0; 3 mg/kg) on spontaneous anxiety was observed. Each rat was injected with the drug or its solvent 15 min before being placed in the bright large compartment, with the door open. We measured the latency to enter the small dark compartment (s). In this and subsequent experiments, the rat must have its four paws in the small dark compartment to be considered being in this compartment.

Thirty-six rats were randomly assigned to one of four groups (n = 9) according to the dose of midazolam or propofol they received (0 mg/kg midazolam = sodium chloride, 3 mg/kg midazolam, 0 mg/kg propofol = intralipid, 9 mg/kg propofol).

Experiment 2. Comparative effect of propofol (0; 9 mg/kg) and midazolam (0; 3 mg/kg) on memory of an aversive event was noted. On day 1, each rat was injected with the drug or its solvent 15 min before being confined into the small dark compartment, with the door closed, where they received two moderate foot shocks during a 5-min session. On day 2, each rat was placed in the bright large compartment, with the door open, without receiving any drug. We measured the latency to enter the dark small compartment (s). Thirty-six rats were randomly assigned to one of four groups (n = 9) according to the dose of midazolam or propofol they received (0 mg/kg midazolam = sodium chloride, 3 mg/kg midazolam, 0 mg/kg propofol = intralipid, 9 mg/kg propofol).

Experiment 3. Effect of propofol (0; 9 mg/kg) and midazolam (0; 3 mg/kg) on memory of a nonaversive event was evaluated. On day 1, rats were injected with the drug or its solvent. Fifteen minutes later, they were placed into the small dark compartment for 30 min with no shock (preexposure). A control group was injected with the solvent and remained in the home cage (no preexposure). On day 2, each rat of the three groups was confined in the small dark compartment where it experienced two moderate foot shocks during a 5-min session, without receiving any drug. On day 3, each rat was placed in the bright large compartment, with the door open, without receiving any drug. We measured the latency to enter the dark small compartment (s). In Experiment 3a (midazolam), 33 rats were randomly assigned to three groups (n = 11). Rats in two of the groups were injected either with midazolam, 0 mg/kg (sodium chloride), or midazolam, 3 mg/kg, and then placed in the small dark compartment. Rats of the control group were injected with sodium chloride and remained in their home cage. In Experiment 3b (propofol), 33 rats were randomly assigned to three groups (n = 11). Rats in two of the groups were injected either with propofol, 0 mg/kg (intralipid), or propofol, 9 mg/kg, and then placed in the small dark compartment (preexposure). Rats of the control group were injected with intralipid and remained in their home cage.

Experiment 4. In Experiment 4a, behavioral response to electrical shocks after propofol (0; 9 mg/kg) administration was observed. Each rat was injected with the drug or its solvent. Fifteen minutes later, each rat was placed in the small dark compartment where it experienced electrical foot shock. After an initial period of 20 s, the scrambler was set to deliver one foot shock (5 s: duration; 20 ms ON–140 ms OFF) every 10 s. To detect the threshold of shock perception, the effective intensity of the shock was gradually increased from 0.04 to 0.14 mA, by 0.02-mA increments. Two experimenters unaware of the treatment recorded the smallest intensity for which they observed a behavioral response (cry) to the shock.

Thirty rats were randomly assigned to one of three groups (n = 10): propofol, 0 mg/kg (intralipid); propofol, 9 mg/kg; and control group (same volume of 0.9% sodium chloride).

In Experiment 4b, forced locomotion after propofol (0; 9 mg/kg) administration was evaluated. Rats were shaped during two daily sessions until each reached a criterion of stability on the rotating cylinder for at least 60 s. On the third day, rats were given propofol or intralipid 15 min before testing. The number of animals falling during the 60-s test session was recorded.

Thirty rats were randomly assigned to one of three groups (n = 10): propofol, 0 mg/kg (intralipid); propofol, 9 mg/kg; and control group (same volume of 0.9% sodium chloride).

Statistical Analysis

For Experiments 1–3, the dependent variable was the latency to enter the small dark compartment (cutoff, 900 s). Statistical analysis[23] was performed on the Log10 of this variable (Log latency) to better approximate the normal distribution necessary for the use of parametric statistics. Statistical analyses were realized using analysis of variance (ANOVA) followed, if necessary, by a pairwise test with Bonferroni correction adjusted to the number of comparisons (two in Experiments 1 and 2 and three in Experiments 3a and 3b). For Experiment 4a, the dependent variable was the smallest intensity of shock inducing the behavioral response. Statistical analysis was realized using a one-way ANOVA.

Results

Experiment 1

Comparative effect of propofol (0; 9 mg/kg) and midazolam (0; 3 mg/kg) on spontaneous anxiety was ob-

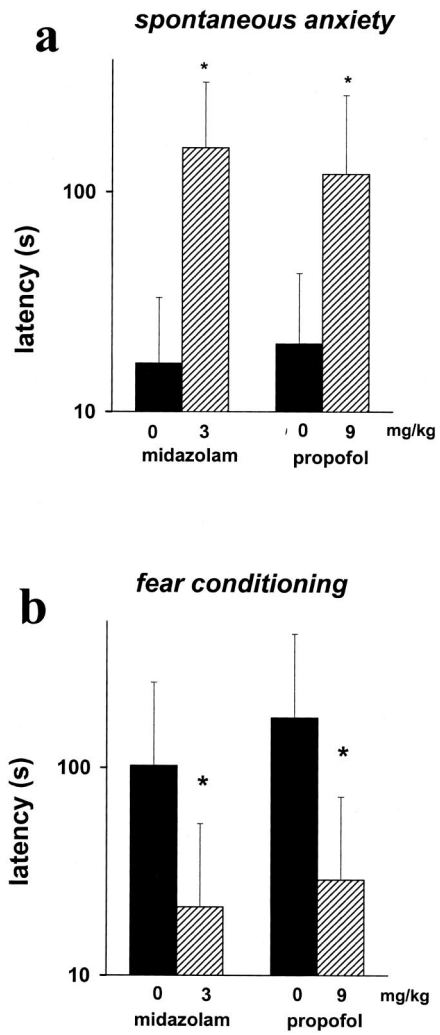

Fig. 1. Effects of 0 and 3 mg/kg midazolam (left) and 0 and 9 mg/kg propofol (right) on spontaneous anxiety (*A*) and on memory of aversive effect (*B*) are shown. Spontaneous anxiety (Experiment 1) was assessed by the latency to enter a neutral dark compartment when rats were placed in an anxiogenic bright one. Memory of an aversive event (Experiment 2) was assessed by the latency to enter the small dark compartment where rats previously experienced electric foot shocks. Results are expressed on a log scale as mean latency and SD. *$P < 0.05$ when compared with the 0-mg/kg dose (with Bonferoni's correction for two comparisons).

served. Figure 1A depicts the effect of propofol and midazolam on the latency to escape from the large bright compartment to enter the small dark compartment. In the control groups (propofol, 0 mg/kg, and midazolam, 0 mg/kg), rats entered the small dark compartment quickly, which indicates the anxiogenic effect of the large bright compartment. Propofol, 9 mg/kg, and midazolam, 3 mg/kg, similarly increased the latency to enter the small dark compartment and appeared to be equivalent doses for inducing anxiolysis. Two-way ANOVA using treatment (propofol *vs.* midazolam) and dose (solvent *vs.* drug) as the between factors showed a significant main effect for the dose ($P < 0.0001$) but no effect for the treatment and no interaction between dose and treatment. The pair-wise test (with Bonferroni correction for two comparisons) showed that the latency was increased significantly for the propofol, 9 mg/kg, and midazolam, 3 mg/kg, groups compared with their respective control groups (propofol, 0 mg/kg, and midazolam, 0 mg/kg).

Experiment 2

Comparative effect of propofol (0; 9 mg/kg) and midazolam (0; 3 mg/kg) on memory for an aversive event was evaluated. Figure 1B depicts the effect of propofol and midazolam on the latency to enter the small dark compartment. In the control groups (propofol, 0 mg/kg, and midazolam, 0 mg/kg), rats avoided the small dark

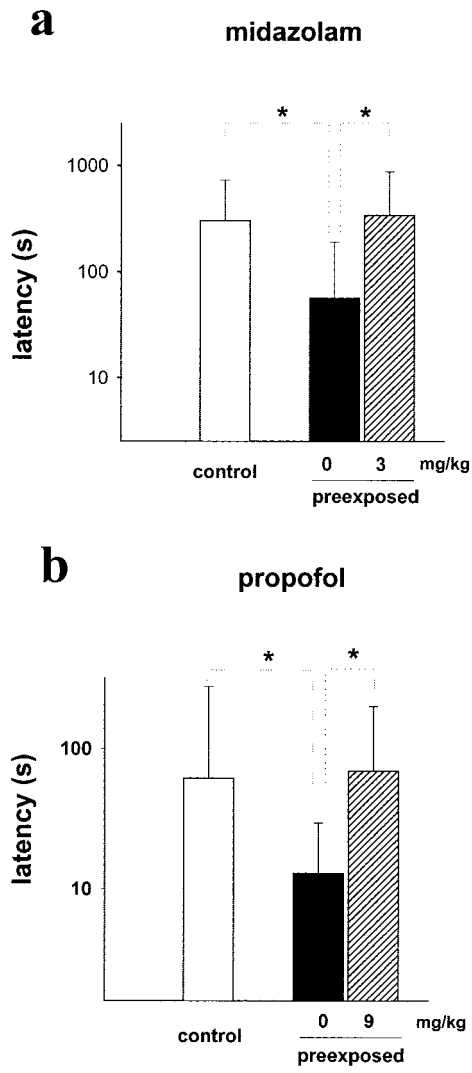

Fig. 2. Effect of 0 and 3 mg/kg midazolam (*A*) and 0 and 9 mg/kg propofol (*B*) on memory of a nonaversive event (Experiment 3), as assessed by the suppressing effect of an initial preexposure to the small dark compartment on the successive fear conditioning. Control rats were not preexposed (see Methods section for further explanation). Results are expressed on a log scale as the mean latency (and SD) to enter the small dark compartment where rats experienced electric foot shocks. *$P < 0.05$ (with Bonferoni's correction for three comparisons).

compartment, which indicates an effective fear conditioning. None of the rats reached the time cutoff of 900 s. Propofol, 9 mg/kg, and midazolam, 3 mg/kg, decreased the latency to enter the small dark compartment. Two-way ANOVA using treatment (propofol *vs.* midazolam) and dose (solvent *vs.* drug) as the between factors showed a significant main effect for the dose ($P < 0.0001$) but no effect for the treatment and no interaction between dose and treatment. The pair-wise test (with Bonferroni correction for two comparisons) showed that the latency was decreased significantly for the propofol, 9 mg/kg, and midazolam, 3 mg/kg, groups compared with their respective control groups (propofol, 0 mg/kg, and midazolam, 0 mg/kg).

Experiment 3a

Effect of propofol (0; 9 mg/kg) on memory of a nonaversive event was examined. Figure 2a depicts the effect of propofol, 0 and 9 mg/kg, administered before preexposure on the latency to enter the small dark compartment. A control group of rats received 0 mg/kg of propofol and was not preexposed. ANOVA showed a significant difference between the three groups ($P < 0.01$). The pair-wise test (with Bonferroni correction for three comparisons) showed that the latency to enter the small dark compartment was significantly reduced in the group of rats preexposed after propofol, 0 mg/kg, compared with the control group (significant preexposure effect). The latency to enter the small dark compartment was similar in the group of rats preexposed after propofol, 9 mg/kg, and in the control group, showing that propofol, 9 mg/kg, totally suppressed the effect of preexposure on the subsequent fear conditioning.

Experiment 3b

Effect of midazolam (0; 3 mg/kg) on memory of a nonaversive event was observed. Figure 2b depicts the effect of midazolam, 0 and 3 mg/kg, administered before preexposure on the latency to enter the small dark compartment. A control group of rats received 0 mg/kg of midazolam and was not preexposed. ANOVA showed a significant difference between the three groups ($P < 0.01$). The pair-wise test (with a Bonferroni correction for three comparisons) showed that the latency to enter the small dark compartment was significantly reduced in the group of rats preexposed after midazolam, 0 mg/kg, compared with the control group ($P < 0.05$; preexposure effect). The latency to enter the small dark compartment was similar in the group of rats preexposed after midazolam, 3 mg/kg, and in the control group, which showed that midazolam totally suppressed the effect of preexposure on the subsequent fear conditioning.

Experiment 4a

Response to electrical shock after propofol (0; 9 mg/kg) was evaluated. The mean effective intensity (and SEM) inducing the behavioral response (cry) was 0.0815 (0.0040), 0.0800 (0.0038), and 0.0784 (0.0027) mA for sodium chloride; propofol, 0 mg/kg; and propofol, 9 mg/kg, respectively. A one-way ANOVA found no difference between the three groups.

Experiment 4b

Forced locomotion after propofol (0; 9 mg/kg) was examined. Rats given propofol exhibited no alteration of performance on the Rotarod test. All the animals stayed on the bar during the 60-s test; the number of falls was 0, 0, and 0 for sodium chloride; propofol, 0 mg/kg; and propofol, 9 mg/kg, respectively.

Discussion

Propofol, 9 mg/kg, injected before fear conditioning decreased the subsequent latency to enter the compartment where rats had previously been shocked, indicating a reduction of fear elicited by this compartment compared with the fear exhibited by rats that had not received propofol (Experiment 2). We observed that equipotent anxiolytic doses of propofol and midazolam display similar effects on fear conditioning during the same experiment (Experiment 1). The administration of propofol, 9 mg/kg, before preexposure to the compartment prevented preexposure from impairing subsequent fear conditioning to this compartment (Experiment 3). These results show clearly that propofol has impaired the memory of the nonaversive event (preexposure to the compartment with no shocks) and the memory of the aversive event (shocks in the compartment), which suggest an amnesic effect (propofol-induced anterograde amnesia).

To clearly assess the effects of propofol on memory, different factors that may be involved in the observed amnesic effect must be controlled. The dose of propofol used here has anxiolytic effect as previously described.[16] During fear conditioning, the aversive stimulus (here, foot shocks) induces an immediate emotional state that is responsible for the subsequent fear of the environment associated with it. Any anxiolytic effect could interact with fear conditioning by blunting the emotional state induced by the foot shocks.[24] We observed that the same dose of propofol impaired the memory of an aversive event and the memory of a nonaversive event (preexposure to the environment). If an anxiolytic effect may reduce the anxiety-producing aspects of an aversive stimulus, it probably plays a negligible role when compared with the main effect of propofol on memory processes. Propofol is an anesthetic drug. Its effect on awareness may interact with the perception of a nonaversive or aversive event because of reduced perception of the stimuli to be acquired.[12,25] We previously showed that midazolam-induced amnesia for an aversive event

could be observed at a low dose totally devoid of sensorimotor impairment.[17] The amnesic effect of propofol was also observed at a low dose (about 10% of the anesthetic dose for the strain of rats we used), for which we did not previously observe an impairment of spontaneous locomotor activity as assessed by the spontaneous movements between the sectors of an exploratory test cage.[16] Results of Experiment 4b emphasize and extend this previous finding, showing that this low dose of propofol has no deleterious effect on forced locomotor activity when rats were tested for their ability to stay on a rotating bar. At this minimal dose, it is unlikely that propofol has reduced the perception of the different components of the event by decreasing awareness. One could argue that propofol has reduced the perception of the aversive stimulus (shock) *via* an analgesic effect. We did not observe any modification of the behavioral response (cry) to the shock after propofol administration (Experiment 4a), showing the lack of analgesic effect of the minimal dose of propofol used here.

After Veselis *et al.*'s findings on emotionally unloaded information, our experimental data further illuminate a specific effect of propofol *per se* on memory processes. This effect was observed whatever the emotional component of the event (aversive or not) and appeared not to rely on sedation or anxiolysis. Insofar, the expression of a memory trace relies on numerous processes: acquisition of multiple components of an event, memory trace formation, and retrieval of it.[11,12] From our results, it is not possible to determine what mnemonic process(es) is(are) impaired by propofol. It remains to further characterize the memory process(es) that is(are) involved in propofol-induced amnesia.

Studies were performed in humans to compare the amnesic effects of propofol and midazolam.[26–30] Some found that propofol has equivalent amnesic effects to those of midazolam, whereas others found more profound and reliable amnesic effects of midazolam. Veselis *et al.* found that at equal light sedation, midazolam and propofol provided equivalent memory impairment for emotionally unloaded information.[6] From our results, low anxiolytic doses of propofol and midazolam display equivalent memory impairment of an aversively loaded event in a rodent model of contextual fear learning.

Propofol and midazolam can be used for conscious sedation (where verbal contact is maintained) or sedation.[31–33] One of the main goals of sedation is preventing memory of scary events in patients.[34,35] Fear conditioning is a fundamental associative learning observed in humans and animals that has relevance to clinical practice. This particular form of automatic learning may lead to an emotional memory trace in the absence of conscious thought[36] and appears more involved in the mechanism of anxiety disorders after a stressful experience.[37] In the present study, we used a Pavlovian fear-conditioning procedure in which the subject passively experienced information in a specific context. This form of learning has appeared to us particularly relevant for clinical practice as patients usually experience passively scary information in a specific environment, during sedation. Our results suggest that propofol and midazolam could prevent the subsequent conditioned anxiety resulting from an aversive event occurring during conscious sedation (where verbal contact is maintained in humans).

In conclusion, propofol impaired memory of an aversive event and of a nonaversive event. This amnesic effect may be demonstrated in rodents at a low dose of 9 mg/kg, which is devoid of locomotor impairment; the anesthetic dose of propofol being approximately 100 mg/kg for the strain of rats we used. From our results, propofol has specific effect on memory processes that did not rely on its sedative or anxiolytic properties. Such an observed amnesic effect was comparable with that observed with midazolam at a low anxiolytic and nonsedative dose in rats.

The authors thank Raymond Wilhelm, Animal Care Staff, for the care he lavished on the rats, and Christophe Mittelhauser, Technician, (both from the Institut of Physiology, Faculté de Médecine, Strasbourg, France) for his technical assistance in Experiment 4.

References

1. Veselis RA, Reinsel RA, Wronski M, Marino P, Tong WP, Bedford RF: EEG and memory effects of low dose infusions of propofol. Br J Anaesth 1992; 69:246–54
2. Pang R, Quatermain D, Rosman E, Turndof H: Effect of propofol on memory in mice. Pharmacol Biochem Behav 1993; 44:145–51
3. Leslie K, Sessler DI, Schroeder M, Walters K: Propofol blood concentration and the Bispectral Index predict suppression of learning during propofol/epidural anesthesia in volunteers. Anesth Analg 1995; 81:1269–74
4. Nordström O, Sandin R: Recall during intermittent propofol anaesthesia. Br J Anaesth 1996; 76:699–701
5. Veselis RA, Reinsel RA, Feshchenko VA, Wronski M: The comparative amnestic effects of midazolam, propofol, thiopental and fentanil at equisedative concentrations. ANESTHESIOLOGY 1997; 87:749–64
6. Smith I, Monk TG, White PF, Ding Y: Propofol infusion during regional anesthesia: Sedative, amnestic and anxiolytic properties Anesth Analg 1994; 79:313–9
7. Veselis RA, Reinsel RA, Feshchenko VA: Drug-induced amnesia is a separate phenomenon from sedation: Electrophysiologic evidence. ANESTHESIOLOGY 2001; 95:896–907
8. Chortkoff BS, Gonsowski CT, Bennett HL, Levinson B, Crankshaw DP, Dutton RC, Ionescu P, Block RI, Eger EI: Subanesthetic concentrations of desflurane and propofol suppress recall of emotionally charged information. Anesth Analg 1995; 81:728–39
9. Ghoneim MM, Block RI: Learning and memory during general anesthesia. An update. ANESTHESIOLOGY 1997; 87:387–410
10. Andrade J: Learning during anesthesia: A review. Br J Psychol 1995; 86:479–506
11. Blaney PH: Affect and memory: A review. Psychol Bull 1986; 99:229–46
12. Eich E: Searching for mood dependent memory. Psych Sci 1995; 6:67–75
13. Wasserman EA, Miller RR: What's elementary about associative learning? Annu Rev Psychol 1997; 47:573–607
14. Pang R, Turndrf H, Quatermain D: Pavlovian fear conditioning in mice anesthetized with halothane. Physiol Behav 1996; 59:873–5
15. Fendt M, Fanselow MS: The neuroanatomical and neurochemical basis of conditioned fear. Neurosci Biobehav Rev 1999; 23:243–60
16. Pain L, Oberling P, Launoy A, Di Scala G: Effect of nonsedative doses of propofol on an innate anxiogenic situation in rats. ANESTHESIOLOGY 1999; 90:191–6
17. Pain L, Launoy A, Oberling P: Effect of midazolam on memory for an aversive event: Sedative, affective or mnemonic processes? Memory and Awareness in Anaesthesia IV. Edited by Jordan C, Vaughan DJA, Newton DEF. London, Imperial College Press, 2000, pp 181–92
18. Lubow RE, Moore AU: Latent inhibition: The effect of nonreinforced preexposure to the conditioned stimulus. J Comp Physiol Psychol 1959; 52: 415–9

19. Lubow RE, Weiner I, Schnur P: Conditioned attention theory, The Psychology of Learning and Motivation, Vol. 15. Edited by Bower GH. New York, Academic Press, 1981, pp 1–49

20. Bouton ME: Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. Psych Bull 1993; 114:80–99

21. Graham NJ, Barnett RC, Gunther LM, Miller RR: Latent inhibition as a performance deficit resulting from CS-context associations. Anim Learn Behav 1994; 22:395–408

22. Oberling P, Gosselin O, Miller RR: Latent inhibition in animals as a model of acute schizophrenia: A reanalysis, Animal Models of Human Emotion and Cognition. Edited by Haug M, Whalen RE. Washington DC, American Psychological Association, 1999; pp 87–102

23. Dixon WJ: BMDP Statistical Software Manual. Los Angeles, University of California Press, 1998

24. Borde N, Krazem A, Jaffard, Beracochea DJ: Memory deficits following diazepam administration in mice: Evidence for a time-dependent retrieval impairment. Psychobiology 1997; 25:202–9

25. Mackintosh NJ: A theory of attention: Variations in the associability of stimuli with reinforcement. Psychol Rev 1975; 82:279–98

26. White PF, Negus JB: Sedative infusions during local and regional anesthesia: A comparison of midazolam and propofol. J Clin Anesth 1991; 3:32–9

27. Ghouri AF, Taylor E, White PF: Patient-controlled drug administration during local anesthesia: A comparison of midazolam, propofol, and alfentanil. J Clin Anesth 1992; 4:476–9

28. Polster MR, Gray PA, O'Sullivan G, McCarthy RA, Park GR: Comparison of the sedative and amnesic effects of midazolam and propofol. Br J Anaesth 1993; 70:612–6

29. Sarasin DS, Ghoneim MM, Block RI: Effects of sedation with midazolam or propofol on cognition and psychomotor functions. J Oral Maxillofac Surg 1996; 54:1187–93

30. De Roode A, van Gerven JMA, Schoemaker RC, Engbers FHM, Olieman W, Kroon JR, Cohen AF, Bovill JG: A comparison of the effects of propofol and midazolam on memory during two levels of sedation by using target-controlled infusion. Anesth Analg 2000; 91:1056–61

31. Randell TT, Kyttä JV: Conscious sedation in patients undergoing surgical and investigational procedures. CNS Drugs 1998; 10:329–42

32. McCollam JS, O'Neil MG, Norcross ED, Byrne TK, Reeves ST: Continuous infusions of lorazepam, midazolam, and propofol for sedation of the critically ill surgery trauma patient: A prospective, randomized comparison. Crit Care Med 1999; 27:2454–8

33. Havel CJ, Strait RT, Hennes H: A clinical trial of propofol vs midazolam for procedural sedation in a pediatry emergency department. Acad Emerg Med 1999; 6:989–97

34. Tinnin L: Conscious forgetting and subconscious remembering of pain. J Clin Ethics 1994; 5:151–2

35. Osterman JE, van der Kolb BA: Awareness during anesthesia and posttraumatic stress disorder. Gen Hosp Psychiatry 1998; 20:274–81

36. Ohman A, Mineka S: Fears, phobias, and preparedness: Toward an evolved module of fear and fear learning. Psychol Rev 2001; 3:483–522

37. Bouton ME, Mineka S, Barlow DH: A modern learning theory perspective on the etiology of panic disorder. Psychol Rev 2001; 108:4–32