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# Effects of propofol and thiopental on the central nervous system during nociceptive stimulation in cats

Takefumi Inada, Kohhei Murao, Koh Shingu, Koh Yamada, Shin-ichi Nakao, and Atsushi Nagata

Department of Anesthesiology, Kansai Medical University, 10-15 Fumizono-cho, Moriguchi, Osaka 570-8507, Japan

**Abstract**
*Purpose.* Nociceptive stimulation may increase central nervous system (CNS) activity during anesthesia. However, it is not known whether propofol and thiopental have a similar inhibitory effect on the CNS during nociceptive stimulation. Therefore, we compared the antinociceptive effects of propofol and thiopental in cats.
*Methods.* In 12 cats, anesthesia was induced with 4% halothane in oxygen and maintained with 0.5% halothane in oxygen. The cortical electroencephalogram (EEG) and the electrical activity from the midbrain reticular neurons (R-MUA) were measured before and after sciatic nerve stimulation. The cats were then allocated to receive cumulative doses of either propofol ($n = 6$) or thiopental ($n = 6$) i.v. at 5-min intervals. Two minutes after each dose, the cortical EEG and the R-MUA were compared before and after sciatic nerve stimulation.
*Results.* Propofol and thiopental depressed the basal R-MUA to a similar degree at each dose. Sciatic nerve stimulation increased the R-MUA, and there were no differences in the maximum R-MUA values between propofol and thiopental. The cortical EEGs after each dose of anesthetic without stimulation showed similar patterns, and the patterns of change with stimulation were also similar for these two anesthetics.
*Conclusion.* Propofol and thiopental have similar antinociceptive effects in cats.

**Key words** Intravenous anesthetics · Propofol · Thiopental · EEG · Multiunit activity

## Introduction

One of the important effects of anesthetics is the depression of central nervous system (CNS) activity to make patients unconscious. Some nociceptive stimulations cause an increase in CNS activity, which has already been depressed by anesthetics [1–3], and excessive CNS activation may cause awareness during anesthesia. The ability of anesthetics to suppress any increase in CNS activity, induced by nociceptive stimulation is, therefore, of concern to anesthesiologists.

A previous study [3] has indicated that, although the effects of propofol and thiopental on the depression of EEG activity after induction of anesthesia in the absence of stimulation were similar, thiopental was associated with a greater increase in EEG activity than propofol after laryngoscopy and endotracheal intubation. For this reason, the authors concluded that the depressant effects of thiopental on EEG during nociceptive stimulation were weaker than those of propofol (i.e., the antinociceptive effect of thiopental is weaker than that of propofol) [3]. However, we suggest that it is too early to draw such a conclusion, because the study was done using a bolus injection of the drugs during induction of anesthesia, and thus it is not clear that a steady and comparable state of anesthesia was obtained between these two anesthetics at the time of stimulation.

It has been shown that it is possible to obtain a steady and comparable state of anesthesia between the anesthetics at the time of stimulation in cats [4]. Therefore, we compared the effects of propofol and thiopental on CNS activity during nociceptive stimulation in cats. To compare the effects, we recorded electrical activity from the midbrain reticular neurons (R-MUA) [4–8]. The R-MUA, which reflects the degree of neuronal firing in the midbrain reticular formation, also reflects the nonspecific activity of the brain [5]. Therefore, we can quantitatively determine the degree of CNS activity with R-MUA measurement. We also recorded the cortical electroencephalogram (EEG); the degree of CNS activity can be determined by its pattern only.

*Address correspondence to*: T. Inada
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## Methods

After approval by the Institutional Committee on Animal Research, 12 cats (both sexes, weights 2.5–3.5 kg) were studied. Each cat was anesthetized with 4% halothane in oxygen in a 50-l anesthesia box. After the cat fell asleep, the forepaw vein was cannulated and an endotracheal tube (5.0–6.0 mm ID) without a cuff was inserted into the trachea with the aid of vecuronium i.v. Anesthesia was maintained with 1% halothane in oxygen, and the lungs were ventilated mechanically using a nonrebreathing ventilator (Animal Respirator AR-300, Acoma, Japan) to maintain an end-tidal carbon dioxide pressure between 30 and 35 mmHg (Capnomac Ultima, Datex, Helsinki, Finland). Rectal temperature was maintained at 37°–39°C with a warm water mattress and a heating lamp. The femoral artery was cannulated for monitoring of arterial pressure, and systolic arterial pressure was maintained at more than 80 mmHg with phenylephrine infusion, when necessary.

To record the R-MUA, parallel stainless-steel wire electrodes (0.2 mm in diameter, insulated with epoxylite resin except at the tips, with a vertical separation of 0.5–1.0 mm at the tips) were inserted bilaterally so as to place the tip of the electrodes in the midbrain reticular formation [4–8]. The position of the tip of the electrode was determined according to the atlas of Snider and Niemer (A2; L3; H-2) [9]. The R-MUA was measured using a multiunit activity technique [5]. With this technique, neuronal discharges are picked up from an area of about 1-mm radius around the tip of the electrode [6]. Stainless steel screws (2.0 mm in diameter) were also inserted into the skull over the temporal cortex and in the frontal bone of the skull (for reference) to record the cortical EEG. The sciatic nerve was then exposed.

Cats were allocated to receive either propofol ($n = 6$) or thiopental ($n = 6$). One hour after the inspired concentration of halothane was decreased to 0.5%, the R-MUA and cortical EEG recordings were started and continued until the end of the study (Polygraph WT685G and Polygraph AB621G, Nihon Kohden, Tokyo, Japan). The sciatic nerve was clamped with an arterial clip for 15 s to obtain the baseline value. Ten minutes later, 2, 3, and 5 mg·kg$^{-1}$ propofol was administered i.v. cumulatively at 5-min intervals; 4, 6, and 10 mg·kg$^{-1}$ thiopental was administered i.v. cumulatively at 5-min intervals (each bolus dose was given over 15 s). A previous study showed that, during 0.5% halothane anesthesia, the depression of R-MUA (and thus, the activity of CNS) observed when 2, 3, and 5 mg·kg$^{-1}$ propofol was administered cumulatively at 5-min intervals was similar to that observed when 4, 6, and 10 mg·kg$^{-1}$ thiopental was administered cumulatively at 5-min intervals [4]. In addition, the R-MUA depression remained constant for the 5 min after the administration of each drug [4]. Therefore, the method of administration ensures the 5-min duration of comparable steady states of CNS anesthetic level between each dose of propofol and thiopental [4]. Two minutes after each dose, the sciatic nerve was clamped for 15 s. Our preliminary study showed that the clamping of the sciatic nerve with the arterial clip for 15 s caused a consistent and reproducible degree of increase in R-MUA, which returned to a preclamping value within 2 min after the clamping, during 0.5% halothane in oxygen.

The R-MUA signal was measured as the distance from the lower limit of the rectified trace to the 10-kΩ line. The R-MUA was expressed as the percent of activity obtained during the baseline prestimulation value. Comparisons were made within and between groups using two-way repeated-measures analysis of variance (ANOVA) with Bonferroni correction. $P < 0.05$ was considered significant.

## Results

Propofol and thiopental depressed the basal R-MUA to a similar degree at each dose (Fig. 1), indicating that these two drugs depressed the activity of the brain to a similar level (produced similar anesthetic depth) at doses used. Sciatic nerve stimulation increased the R-MUA, and there were no differences in the maximum R-MUA values between propofol and thiopental (Fig. 1). The cortical EEGs after each dose of anesthetic without stimulation showed similar patterns, and the patterns of change with stimulation were also similar for these two anesthetics (Fig. 2).

## Discussion

The R-MUA reflects the degree of neuronal firing in the midbrain reticular formation, which also reflects the nonspecific activity of the brain [5]. Therefore, we can quantitatively determine the degree of CNS activity with R-MUA measurement. The degree of CNS activity can also be determined by the pattern of cortical EEG. In the present study, the R-MUA was increased by sciatic nerve stimulation, and there was no difference in the degree of increase between the two anesthetics. The cortical EEG was altered by sciatic nerve stimulation, and the changes in the EEG pattern were similar in the propofol and thiopental groups. Thus, the depressive effect of propofol and thiopental on nociceptive processing, which occurs from the sciatic nerve through the spinal cord to the ascending reticular formation of the brain stem, and to the cortex [10,11], were similar.

We used cats because a steady and comparable state of anesthesia between propofol and thiopental can

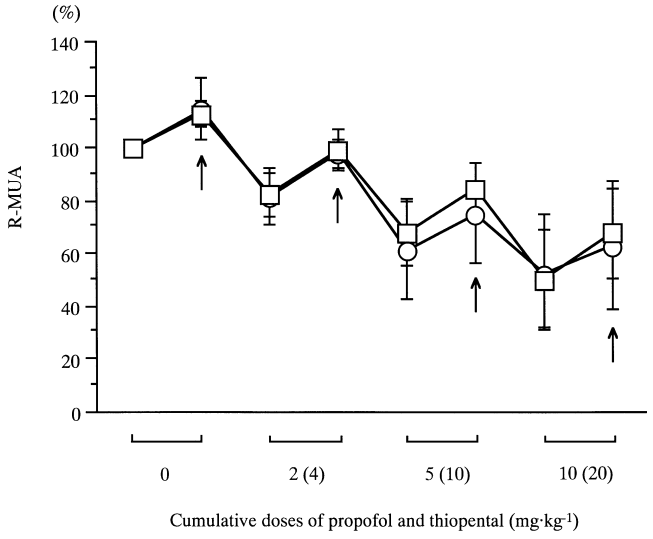


**Fig. 1.** Effect of sciatic nerve stimulation on multiunit activity in the midbrain reticular neurons (R-MUA) during propofol (*circles*) and thiopental (*squares*) anesthesia. Control basal anesthesia was with 0.5% halothane in oxygen. After cumulative doses of 2, 5, and 10 mg·kg$^{-1}$ propofol or cumulative doses of 4, 10, and 20 mg·kg$^{-1}$ thiopental, the sciatic nerve was stimulated. The values of R-MUA were expressed as percent of activity obtained during the baseline prestimulation period with 0.5% halothane in oxygen. The depression of R-MUA after cumulative doses of either anesthetic was similar, and the degree of increase in R-MUA after sciatic nerve stimulation was also similar with both anesthetics. Cumulative doses of propofol and thiopental are shown at the bottom, with thiopental in parentheses. Arrows indicate sciatic nerve stimulation. Data are presented as mean ± SD

easily be obtained [4]. Furthermore, in cats, we can obtain the R-MUA, the straightforward measure to assess the overall neuronal activity in the brain. We assume that the R-MUA is better for comparing the degree of CNS excitation than the EEG. The higher the value of the R-MUA, the greater the firing rate of the midbrain reticular formation and, thus, the greater the CNS activity as a whole [5]. On the other hand, assessing the CNS activity with EEG is an indirect measure, because such assessment can only be done by evaluating the pattern of the EEG. By evaluating the pattern only, it may be difficult to assess the level of the CNS activity. For example, as the level of the CNS activity increases, the EEG generally becomes higher in frequency and smaller in amplitude, but this is not always true [1–3]. The power spectral analysis and the bispectral analysis may allow us to perform a quantitative analysis of the EEG, but the derived "number" merely reflects the pattern of the EEG [12,13].

In humans, comparison of the effects of propofol and thiopental on the CNS during nociceptive stimulation is difficult, if not impossible. For example, during induction of anesthesia, steady-state comparable anesthetic conditions cannot be expected [3,14]. During maintenance of anesthesia, it may be possible to have comparable steady-state conditions using computer-assisted continuous infusions [15,16]. However, stimulation may become a problem. At least two conditions are required for the stimulation employed. First, it should be reproducible and consistent. Second, it should be sufficiently intense to alter the EEG, because the EEG is the only reasonable measure to assess the CNS activity in humans. Tetanic electrical stimulation is reproducible and consistent in intensity and is intense enough to increase blood pressure [17,18], but it is not sufficiently intense to alter the EEG during propofol anesthesia [19]. Laryngoscopy and endotracheal intubation is intense enough to cause EEG changes and is a relatively consistent and reproducible stimulation [3,14]. However, to have an anesthetic depth suitable for laryngoscopy and intubation, the cortical EEG is sometimes required to be at the level of burst suppression [14]. The burst-suppression pattern precludes the analysis with EEG band power calculations [1,2]. Studying the effect on the CNS of laryngoscopy and intubation during lighter levels of anesthesia may be hazardous to patients.

The basal anesthesia in the present study was induced by halothane in oxygen. Halothane is a simple CNS depressant, and the depressant effects of propofol and thiopental are additive to that of halothane [4,20]. However, the inspired concentration of halothane was low, and the influence of halothane should be small. Therefore, the results from the study model reasonably reflect the effects of propofol and thiopental on the CNS during nociceptive stimulation.

We found that there was no difference between the effects of propofol and thiopental on the CNS. This raises the question as to why thiopental was associated with a greater increase in EEG activity than propofol after laryngoscopy and endotracheal intubation in the previous study [3]. After induction of anesthesia with a bolus injection of anesthetic, the effect-site concentrations of the anesthetic rapidly increase to peak levels and then decrease by re-distribution from the CNS [15,16]. Since the EEG reflects the effect-site concentrations of hypnotics [21,22], the EEG pattern changes dramatically in response to changes in the effect-site concentrations after induction of anesthesia [3,14]. When comparable doses of propofol and thiopental are used, the time taken to reach the peak effect-site concentration after bolus injection is shorter with thiopental than with propofol, and the rate of decrease in the effect site concentration is slower with propofol than with thiopental [15,16]. Therefore, the greater activation of the EEG with thiopental than propofol after laryngoscopy and intubation may be explained by the faster clearance of thiopental from the CNS.

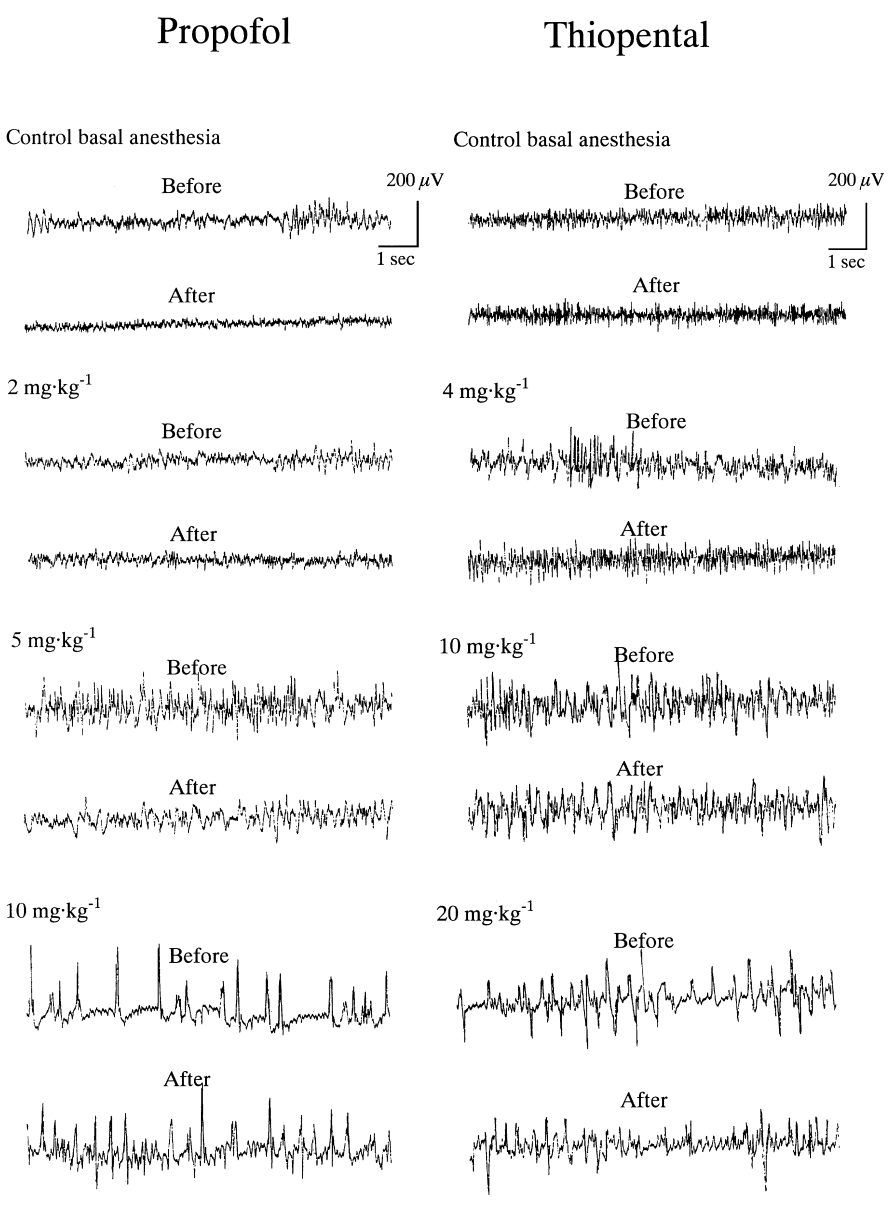


**Fig. 2.** Effect of sciatic nerve stimulation on cortical electroencephalograph (EEG) during propofol and thiopental anesthesia. Control basal anesthesia was with 0.5% halothane in oxygen. After cumulative doses of 2, 5, and 10 $mg \cdot kg^{-1}$ propofol or cumulative doses of 4, 10, and 20 $mg \cdot kg^{-1}$ thiopental, the sciatic nerve was stimulated. Before injection of propofol and thiopental, the cortical EEG consisted of small-amplitude and fast waves. The EEG after each dose of propofol or thiopental changed similarly to slow and large-amplitude waves, and finally, burst suppression. The burst-suppression pattern was induced with the highest dose of each anesthetic. Stimulation changed the cortical EEG to faster and smaller-amplitude waves or from the burst-suppression pattern to complexes of fast and slow, large-amplitude waves with both anesthetics. The patterns of change with stimulation were similar between the anesthetics. *Before*: before stimulation. *After*: after stimulation

In summary, the antinociceptive effects of propofol were no different from those of thiopental in cats. Whether this is true also in humans remains to be elucidated.

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