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Propofol facilitates the development of long-term depression (LTD) and impairs the maintenance of long-term potentiation (LTP) in the CA1 region of the hippocampus of anesthetized rats

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Abstract

Memory is sensitive to the short-acting anesthetic (2,6-diisopropylphenol) propofol, but the underlying mechanism is little known. Here, we have examined the effects of propofol on synaptic plasticity in the CA1 region of the hippocampus of anesthetized rats. We found that low dose of propofol (20 mg/kg, i.p.) did not affect the basal transmission, but enhanced prominently the development of long-term depression (LTD) and impaired the maintenance of long-term potentiation (LTP). The impairment of LTP maintenance and enhancement of LTD development may contribute to propofol-induced deficits in memory following propofol anesthesia.

Keywords: Long-term potentiation; Long-term depression; Memory; Anesthetics; Propofol; Hippocampus; Wistar rat

Propofol is a short acting anesthetic, thus continuation of propofol infusion is needed to maintain proper anesthesia in clinical [7,8]. It was found that cognitive functions were suppressed for several hours after cessation of propofol administration [10,13].

Although propofol induced neuronal inhibition mainly through gamma-aminobutyric acid type A (GABA-A) receptors and modulated synaptic properties are well documented [5,16], and the effect of propofol on paired-pulse inhibition is very high even though at a dose as low as 2.5 mg/kg [1], it is not known whether it influence synaptic plasticity. However, there is evidence support that GABA-A receptors can modulate cAMP-mediated long-term potentiation (LTP) or change the direction of synaptic plasticity [6,20]. Since propofol inhibits *N*-methyl-D-aspartate (NMDA) receptors through neither voltage- nor use-dependent manner [19], the effect of propofol on synaptic plasticity might be different with that of GABA-A receptors mediated response.

It is widely accepted that activity-dependent synaptic plasticity is necessary for learning and memory [3,9]. It is reasonable to suppose that propofol induces deficits in memory and may also induce some changes in synaptic plasticity. To test this hypothesis, we have studied the effects of propofol on synaptic plasticity whether propofol can modulate NMDA-dependent LTP or long-term depression (LTD) induction and expression.

Male Wistar rats (weighing 200–300 g) were used. Experiments were carried out under pentobarbitone sodium (50–60 mg/kg, i.p.) anesthesia and core temperature was maintained at 37 ± 0.5°C. Recordings of field excitatory postsynaptic potential (EPSP) were made from the CA1 stratum radiatum of the hippocampus in response to ipsilateral stimulation of the Schaffer collateral/commissural pathway and in some animals a second stimulating electrode was placed ipsilaterally to stimulate a separate, independent pathway by using techniques similar to those described [18].

For LTD induction, low frequency stimulation (LFS) consisted of 900 pulses at 3 Hz. High frequency stimulation (HFS) protocol for inducing LTP consisted of ten trains of

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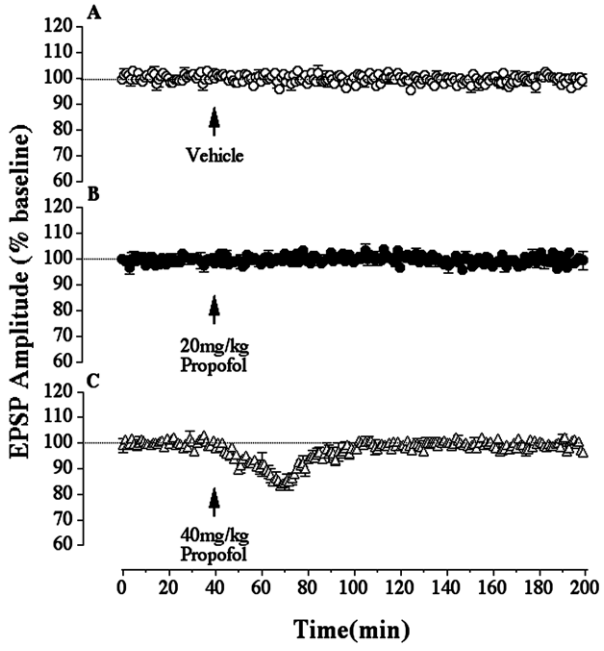

Fig. 1. The effect of propofol on the field EPSP of CA1 region of the dorsal hippocampus. (A) There was no baseline change with vehicle injection (fat emulsion, arrow, i.p) ($n = 5$). (B) There was no baseline change with 20 mg/kg propofol treatment (arrow) ($n = 5$). (C) In the animals with 40 mg/kg propofol injection (arrow, i.p.) the field amplitude EPSP was inhibited temporarily ($n = 5$).

20 stimuli, interstimulus interval 5 ms (200 Hz), intertrain interval 2 s.

A guide cannula was implanted in the lateral cerebral ventricle (0.5 mm anterior to bregma and 1.2 mm right of midline) just prior to electrode implantation. Intracerebroventricular (i.c.v.) injections of volumes of 6 μl were made over a 6 min period through the internal cannula. 2-Amino-5-phosphonovaleric acid (D-APV, 120 nM) was obtained from Sigma (St. Louis, MO) and dissolved in saline for i.c.v. injection. Propofol was obtained from Zeneca (Zeneca Limited, Sweden) and dissolved in fat emulsion and was injected intraperitoneally in a dose of 40 and 20 mg/kg at a volume of 0.2 ml.

Statistical comparison was made by using paired *t*-test (two tail) or Newman–Keuls test of analysis of variance (SPSS 10.0). Significance level was set at $P \leq 0.05$. Values are expressed as the mean % of the baseline field EPSP amplitude ± SEM over a 40-min baseline period.

The first set of experiments is to determine the inhibitory effect of propofol on the field EPSP of CA1 region of the dorsal hippocampus. After 40 min baseline field EPSP recordings, 40 mg/kg propofol (i.p.) inhibited the field EPSP temporarily, the depression reached to maximum in 30 min ($n = 5$, 84.6 ± 1.6% of baseline EPSP, $P < 0.01$, compared with vehicle) and recovered to baseline in 60 min ($P > 0.05$, compared with vehicle) (Fig. 1). But in the animals with 20 mg/kg propofol treatment (i.p.), the field EPSP was unchanged compared with vehicle ($P > 0.05$). The temporary depression of basal transmission induced by 40 mg/kg propofol (i.p.) may reveal a dose-dependent short interplay between GABAergic and glutamatergic transmission in anesthetic action but not in the animals with 20 mg/kg propofol (i.p.) treatment.

Analysis the effect of propofol on LTD revealed that with low dose of propofol (20 mg/kg, i.p.) treatment before LFS 30 min, a stable LTD was induced by LFS ($n = 5$, 76.3 ± 3.3% of baseline EPSP after LFS 120 min, $P < 0.01$ compared with vehicle) (Fig. 2C). Without propofol treatment, the same LFS only induced small LTD ($n = 7$, 91.9 ± 3.0% of baseline EPSP after LFS 60 min, $P < 0.05$ compared with baseline) (Fig. 2A). Therefore, LTD expression was enhanced by propofol.

The following experiments showed that propofol impaired the maintenance of LTP. LTP was induced with propofol treatment (20 mg/kg, i.p.) 30 min before HFS ($n = 5$, 119.9 ± 2.8% of baseline after HFS 60 min, $P < 0.05$ compared with baseline) (Fig. 3B), which was no different compared with that of vehicle ($n = 5$, 124.3 ± 2.7% of baseline after HFS 60 min) ($P > 0.05$) (Fig. 3A), but the declining of this potentials implied that previous treatment with propofol might affect the maintenance of LTP. Consistent with this experiment, 20 mg/kg propofol (i.p.) was applied after LTP induction 60 min, the LTP declined to baseline in following 60 min in the test pathway ($n = 5$, 106.6 ± 1.9% of baseline after HFS 120 min) (Fig. 3C) without affecting the response in the control pathway ($P > 0.05$ compared with baseline). These results

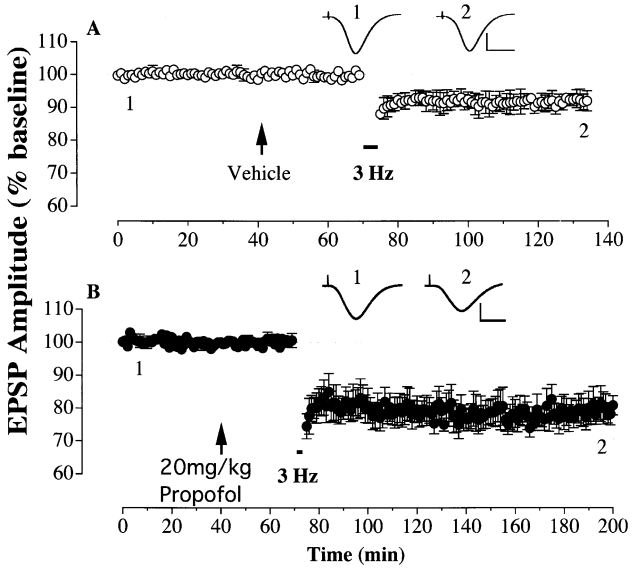

Fig. 2. Propofol facilitated low frequency stimulation-induced LTD expression. (A) With vehicle injection (arrow, i.p.), low frequency stimulation (3 Hz, bar) induced a small LTD of the field EPSP amplitude in the CA1 region of hippocampus ($n = 7$). (B) With 20 mg/kg propofol injection (arrow, i.p.) 30 min before LFS, the same low frequency stimulation (3 Hz, bar) was able to induce a reliable and bigger LTD of the field EPSP amplitude ($n = 5$).

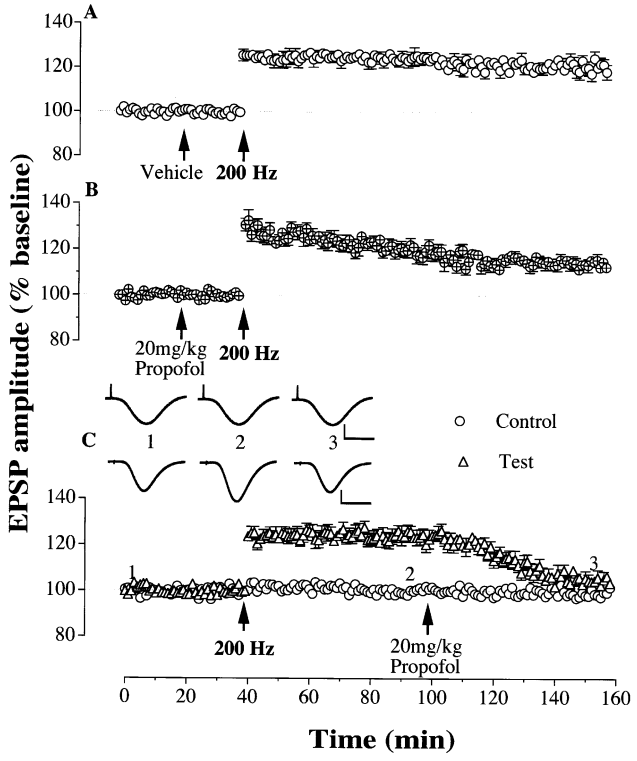

Fig. 3. Propofol impaired high frequency stimulation-induced LTP maintenance. (A) LTP of the field EPSP amplitude was able to induce by high frequency stimulation (200 Hz, arrow) in the animals with vehicle injection (arrow, i.p.) ($n = 5$). (B) LTP of the field EPSP amplitude was able to induced by high frequency stimulation (200 Hz, arrow) with 20 mg/kg propofol treatment 30 min before HFS (arrow, i.p.) ($n = 5$), with a tendency of decaying. (C) When 20 mg/kg propofol (arrow, i.p.) was given at the time after high frequency stimulation 60 min (200 Hz, arrow), LTP of the field EPSP declined to baseline in 60 min ($n = 5$).

showed that LTP induction was little touched but maintenance of LTP was impaired by propofol.

Our findings unveiled that propofol facilitated LTD expression and impaired LTP maintenance. The following experiments showed that D-APV (120 nM, i.c.v.) blocked the induction of LTP and LTD both in the vehicle ($n = 5$, $103.4 \pm 1.1\%$ of baseline EPSP after HFS 60 min; $98.9 \pm 1.7\%$ of baseline EPSP after LFS 60 min) ($P > 0.05$, compared with baseline) (Fig. 4A) and 20 mg/kg propofol (i.p.) treatment ($n = 5$, $101.7 \pm 1.9\%$ of baseline EPSP after HFS 60 min; $96.7 \pm 3.9\%$ of baseline EPSP after LFS 60 min) ($P > 0.05$, compared with baseline) (Fig. 4B). Thus, LTD and LTP that modulated by propofol were NMDA receptors dependent.

We provided evidence here that propofol, which induces amnesia in clinical and animal experiments [12,17], affected the expression and the maintenance of NMDA receptors dependent LTD and LTP.

Consistent with a role for GABA-A receptors in mediating the facilitation of LTD induction [15], Propofol enhanced the LTD expression. However, no significantly effect of propofol on LTP induction was found. It was reported that GABA-A receptors mediated inhibition only impaired weak stimulation induced NMDA receptors-dependent LTP induction but not the strong stimulation protocol [14]. Our protocol for LTP induction was routinely used in vivo research [18] and was similar as the strong stimulation.

The reversal of established LTP induced by propofol was slow. The time course implied that the recurrent inhibition mediated by GABA-A receptors might involve and decreased the potentials by blocking their self-reinforcement. Some other mechanisms may involve since propofol also interacts on ion channels [11], NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazloe proprionic acid (AMPA) receptors [19], etc.

It is well documented that LTP induction is necessary for memory acquirement and storage, but not for memory recall. However, interventions of established LTP shall alter the memory of a prior learning experience and induces retrograde amnesia. Clinic and animal research showed that propofol induced anterograde amnesia but induced retrograde amnesia with higher dose [10,12].

Active dependent long-term potentiation in excitatory synaptic transmission of the hippocampus is believed to underlie certain types of memory [3,9]. Novelty facilitated LTD may also involve in hippocampal information storage [4]. How the changes of LTD expression and LTP maintenance together would affect memory, Bienenstock, Cooper, Munro theory may explained it, which implies that LTP and

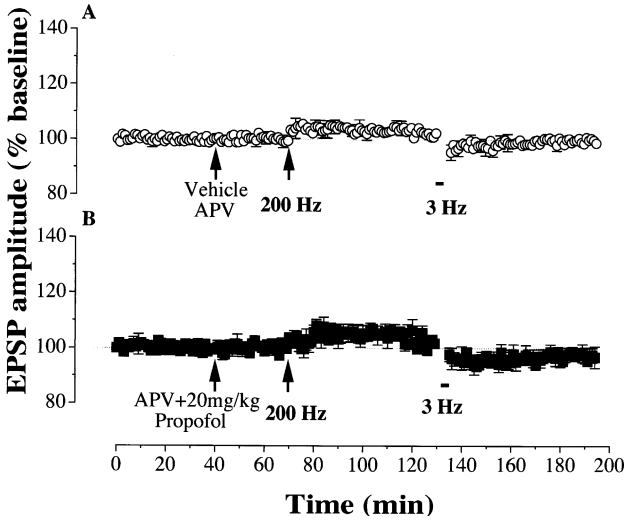

Fig. 4. That LTD and LTP modulated by propofol was NMDA receptors dependent. (A) With the NMDA receptors blockage by D-APV (arrow, 120 nM, i.c.v.), high frequency stimulation failed to induce LTP of the field EPSP amplitude (200 Hz, arrow) and following low frequency stimulation failed to induce depression of the field EPSP amplitude (3 Hz, bar) ($n = 5$). (B) Pretreated with APV (120 nM, i.c.v.) and 20 mg/kg propofol (arrow), high frequency stimulation failed to induce LTP of the field EPSP amplitude (200 Hz, arrow), subsequent low frequency stimulation failed to induce depression of the field EPSP amplitude (3 Hz, bar) ($n = 5$).

LTD are to operate together to underlie learning and memory process [2], but they must follow a certain rule. Once the harmony of LTP with LTD was broken like present findings, it caused behavioral effects in memory deficits.

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