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European Journal of Pharmacology 282 (1995) 11–17

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The effect of urethane anesthesia on evoked potentials in dentate gyrus

Yukiyoshi Shirasaka [a,b], Claude G. Wasterlain [a,b,*]

[a] *Epilepsy Research Laboratory, Veterans Affairs Medical Center, 16111 Plummer Street, Sepulveda, CA 91343-2099, USA*

[b] *Department of Neurology, RNRC, and Brain Research Institute, UCLA school of medicine, 710 Westwood Plaza, Los Angeles, CA 90024-1769, USA*

Received 4 April 1995; accepted 20 April 1995

Abstract

We examined the effect of urethane (1000 mg/kg, followed by 50 mg/kg per h, i.v.), an anesthetic commonly used by physiologists, on evoked potentials recorded in dentate gyrus in adult Wistar rats by stimulating the ipsilateral perforant path, via chronically implanted electrodes. Urethane decreased paired-pulse inhibition. Under urethane, with paired-pulse stimulation, the ratio of the second population spike amplitude to the first increased by 11.1–20.7% at 25–60 ms interstimulus interval ($n = 18$, $P < 0.05$). At 25 ms, the proportion was 3.6 ± 1.6 while awake, and 14.7 ± 3.5 under urethane. Urethane depressed granule cell excitability and strength of synaptic responses. Under urethane, the ratio of the population spike amplitude obtained at 250 μA stimulation to the maximal response in the same input/output response examination decreased by 20%, and the ratio of the excitatory postsynaptic response slopes fell by 10%. These results indicate that urethane affects neurotransmission in the hippocampus, and suggest that its effect may be exerted in part on excitatory neurotransmission.

Keywords: Urethane (ethyl carbamate); Dentate gyrus; Perforant path; Evoked potential; GABAergic inhibition

1. Introduction

Urethane (ethyl carbamate) is an anesthetic widely used in physiological or pharmacological studies of the nervous system in animals (Maggi and Meli, 1986). Although there is some debate about its effect on acetylcholine release mainly in the peripheral nervous system (Halliday et al., 1979; Kewitz and Pleul, 1977; Matthews and Quillian, 1964), the mechanisms of urethane anesthesia is not known. However Cain et al. (1989, 1992) reported an anticonvulsant effect of urethane in the kindling model of epilepsy and in pentylenetetrazol-induced convulsions, and suggested that this drug was not appropriate for studies of epileptiform phenomena. Several reports showed that urethane decreased EEG frequencies in several sites of the central nervous system (Kramis et al., 1975; McClung et al., 1976; Moulin et al., 1978), and decreased spontaneous firing rates in hippocampus (Mercer et al., 1978). It was also reported that urethane prolonged latency and decreased amplitude of cortical sensory evoked potentials (Angel and Gratton, 1982), and suppressed acoustically evoked field potentials recorded from deep nuclei (McClung et al., 1976).

In this study, we examined the effect of urethane anesthesia on the evoked potentials recorded in dentate gyrus by stimulating the perforant path via chronically implanted electrodes. Interstimulus interval-dependent paired-pulse examinations, voltage-dependent paired-pulse examinations, and frequency-dependent paired-pulse examinations were carried out to examine paired-pulse inhibition, which is mainly γ-aminobutyric acid (GABA)-mediated, and input/output examinations were done to examine granule cell excitability and strength of synaptic response. We used the intravenous route for the administration of urethane, because intraperitoneal administration causes various adverse effects (Maggi and Meli, 1986; Severs et al., 1981).

2. Materials and methods

2.1. Anesthesia

18-week-old male Wistar rats (400–500 g Simonsen Labs) were housed on a 12 h light/dark cycle (6

* Corresponding author. Neurology Service (127), Veterans Affairs Medical Center, 16111 Plummer Street, Sepulveda, CA 91343-2099, USA. Tel. 818-895-9473, fax 818-895-5801.

Elsevier Science B.V.
SSDI 0014-2999(95)00244-8

a.m./6 p.m.) and given free access to food and water. Rats were placed in a metofane (methoxyflurane, 3–4 ml) jar until they lost consciousness, then injected with urethane intravenously through the tail vein (loading dose, 1000 mg/kg in saline), and placed in a stereotaxic frame. We set the infusion rate of urethane at 50 mg/kg per h, and this dose induced enough anesthesia in most rats examined. When rats showed any movement, we increased the rate of infusion transiently. Rectal temperature was maintained at 37.0 ± 0.5°C with a warm water coil placed under the animal.

2.2. Surgery

Two holes were drilled on the left side of the skull to accommodate the stimulating and recording electrodes. The burr hole for the stimulating electrodes was 8.1 mm posterior and 4.4 mm lateral to bregma, and that for the recording electrode was 3.5 mm posterior and 2.2 mm lateral to bregma. Four jewelry screws (two anterior, one right, and one posterior) were drilled into skull holes. Bipolar electrodes made of twisted Teflon-coated 0.005 inch diameter stainless steel wires (California Fine Wire Co.; tip separation < 1.0 mm for recording electrodes and < 0.5 mm for stimulating electrodes) were cemented with dental acrylate. Final electrode location was determined by maximizing the amplitude of the characteristic potentials recorded in the dentate gyrus in response to the ipsilateral perforant path stimulation. Chromium non-coated wires (Consolidated Wire and Associated Co.) were connected to screws on the skull and used as ground electrodes. The skin was cleaned with Povidine solution (Rugby Laboratories) and 95% alcohol, and 100 mg of Chloramphenicol (Warner Lambert Co.) was injected subcutaneously once per day during 3 days after surgery.

2.3. Electrophysiological examination

We used a Grass S88 stimulator and stimulus isolation units (Grass SIU5, Grass PSIU6) to stimulate the perforant path, a type 502 Dual-Beam Oscilloscope to measure stimulation voltage, and a R2 Digital Oscilloscope Software (Rapid Systems) to record and analyze evoked potentials.

4 weeks after surgery, we investigated interstimulus interval-dependent paired-pulse excitation and/or inhibition at intervals of 10, 15, 25, 40, 60, 100, 200, 300, 400, 1000, 3000 and 5000 ms (0.1 Hz, 0.1 ms duration, 30 V monophasic stimulation); voltage dependency at 10, 20, and 30 V (and 40 V in some cases, 40 ms apart, 0.1 Hz, 0.1 ms duration, monophasic stimulation); input/output responses at 250, 500, 750, 1000, 1250, 1500 and 5000 μA (0.1 Hz, 0.2 ms duration, biphasic stimulation); frequency-dependency (Sloviter, 1991a) at 0.1, 1, and 2 Hz (40 ms apart, 0.1 ms duration, 30 V monophasic stimulation), in the awake state and 30 min after the beginning of urethane anesthesia (1000 mg/kg i.v. as loading dose followed by continuous intravenous injection of 50 mg/kg per h). We used 30 V stimulation in interstimulus interval-dependent paired-pulse examinations and frequency-dependent paired-pulse examinations, because paired-pulse inhibition saturated at 20–30 V stimulation in preliminary studies. In input/output response, we used 250 μA as the lower stimulus intensity because it was near the threshold for population spike generation under urethane anesthesia, and 5000 μA as the strongest stimulus intensity because stronger intensity than this elicited no larger response, in preliminary studies. To ensure comparability of our results with previous studies (Cain et al., 1992; De Jonge and Racine, 1987; Errington et al., 1987; Joy and Albertson, 1988; Sloviter, 1991a,b), we measured stimulus intensity by voltage in paired-pulse examinations and by amperage in input/output responses.

To study urethane anesthesia, rats were placed in a metofane jar until they lost consciousness, and an Angiocath (Becton Dicksons Vascular Access) was placed in a tail vein. Then, rats were taken out from jar, and after recovering from metofane anesthesia, injected with the loading dose over 5 min, because rapid injection sometimes caused death. A 30 min duration of anesthesia was taken before all examinations in the anesthetized state. To minimize their effect on other examinations, frequency-dependent studies were performed at the end of the experiments. The awake state recordings were performed while the rats were resting quietly with their eyes open. 10 consecutive waveforms were recorded after waveforms had become stable. In the frequency-dependent studies we started recording after 10 stimulations at 2 Hz in the awake state in order to avoid prolonged 2 Hz stimulation which could potentially induce some kindling-like phenomena.

After examinations, rats were deeply anesthetized with metofane and were perfused transcardially, and serial paraffin sections from brain were stained with cresyl violet for determination of electrode placement.

2.4. Data analysis

Population spike amplitude and excitatory postsynaptic potential (e.p.s.p.) slope were measured from the waveforms made from the average of 10 consecutive evoked potentials. Population spike amplitude was calculated as: [(field potential at the beginning of population spike) + (field potential at the end of population spike)]/2 − (field potential at the peak of population spike), and e.p.s.p. slope was measured between two fixed points after the onset of the e.p.s.p. and before

the onset of population spike using the method of Tuff et al. (1983). In paired-pulse examination, the proportion of the population spike amplitude of the second pulse (S2) to that of the first (S1) was used as a measure of the paired-pulse inhibition and/or facilitation of each experiment. In input/output response examinations, the proportion of the population spike amplitude and e.p.s.p. slope at each stimulus intensity to the maximal response under the same conditions (awake or anesthetized) in the same experiment was used as an indicator of the number of granule cells firing and of the strength of synaptic response (De Jonge and Racine, 1987). The data obtained during urethane anesthesia were compared with the data in the awake state by Analysis of Variance (ANOVA), and $P < 0.05$ was considered significant.

3. Results

3.1. Behavioral and systemic effects of urethane anesthesia

Rats became immobile immediately after the beginning of urethane anesthesia. Rats showed regular respiration rate and no body movement even if some sensory stimulations were applied, although the blink reflex remained present. Evoked potential examinations in the awake state showed no behavioral effect. However, in preliminary studies, 20–30 s 2 Hz stimulation sometimes induced limbic seizure-like symptoms (behavioral arrest and/or chewing), and so, we limited 2 Hz stimulation to 10 s in this experiment.

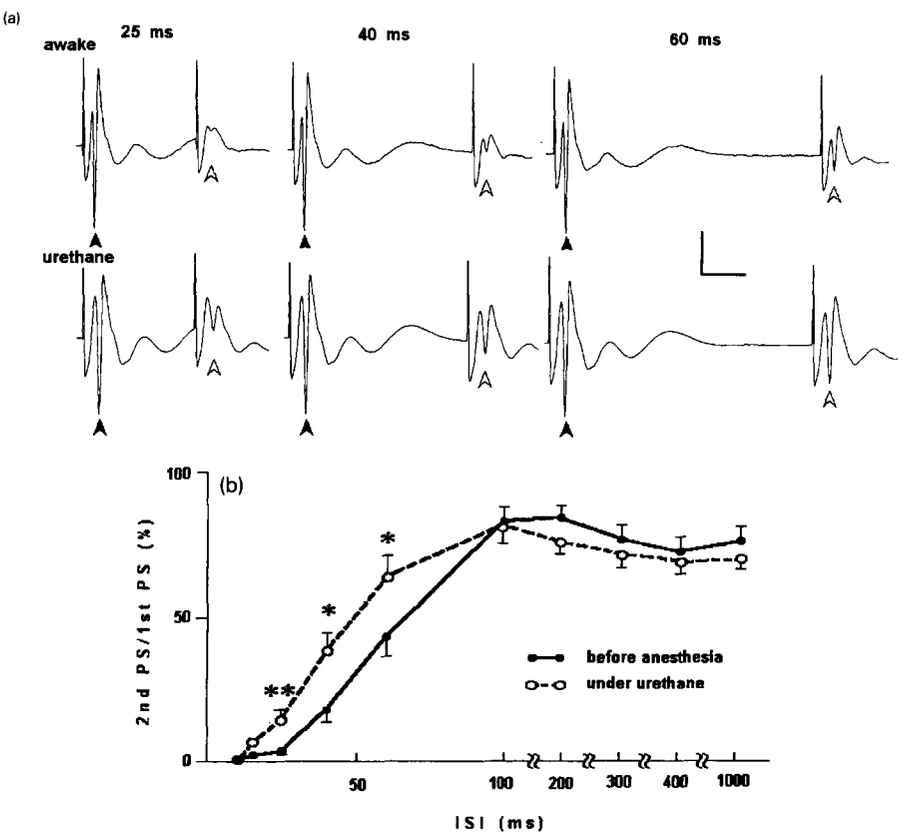

Fig. 1. (a) One example of short interstimulus interval-dependent paired-pulse inhibition. The waveforms show the average of 10 consecutive waves. The narrow positive deflection before e.p.s.p. in each trace is a stimulation artefact. Closed arrowheads indicate the first stimulation (S1) population spike discharges, and open arrowheads indicate the second stimulation (S2) population spike discharges used to measure amplitude. Paired-pulse stimulations (0.1 ms duration, 30 V monophasic) were given at 0.1 Hz. Abbreviations: awake, in the awake state; urethane, under urethane anesthesia; 25 ms, 40 ms, and 60 ms, indicate the interstimulus intervals; vertical scale bar 1 mV, horizontal scale bar 10 ms. (b) Interstimulus interval-dependent paired-pulse inhibition in the awake state and under urethane anesthesia is shown ($n = 18$, each). The interstimulus interval (ISI) in ms was plotted along the abscissa, and the ratio of the S2 population spike amplitude to the S1 (2nd PS/ 1st PS) was plotted along the ordinate. Results represent the means ± S.E.M. of ((S2 population spike amplitude)/(S1 population spike amplitude) × 100). $^{*}P < 0.05$, $^{**}P < 0.01$.

3.2. Interstimulus interval-dependent paired-pulse examination

Fig. 1a,b shows the results of interstimulus interval-dependent paired-pulse examination in the awake state, and under urethane anesthesia. In the awake state, rats showed marked paired-pulse inhibition at short interstimulus intervals. Under urethane anesthesia, the proportions of the S2 population spike amplitude to the S1 were significantly higher at short interstimulus intervals (25–60 ms) compared with the awake state. With long interstimulus intervals (100–1000 ms), there was no significant difference between those in two states, although the inhibition under urethane anesthesia showed a trend toward enhancement. There was no significant difference between the S1 population spike amplitude in the awake state and under urethane anesthesia (2.39 ± 0.33 mV, and 2.22 ± 0.32 mV, respectively). 7 of 18 rats showed a higher S1 population spike amplitude under urethane anesthesia than in the awake state, however, the reduction of paired-pulse inhibition at short interstimulus intervals under urethane anesthesia was consistent even in these rats.

Examinations of voltage-dependent changes of paired-pulse inhibition showed that this effect of urethane on short interstimulus interval-dependent paired-pulse inhibition increased as stimulus intensity increased.

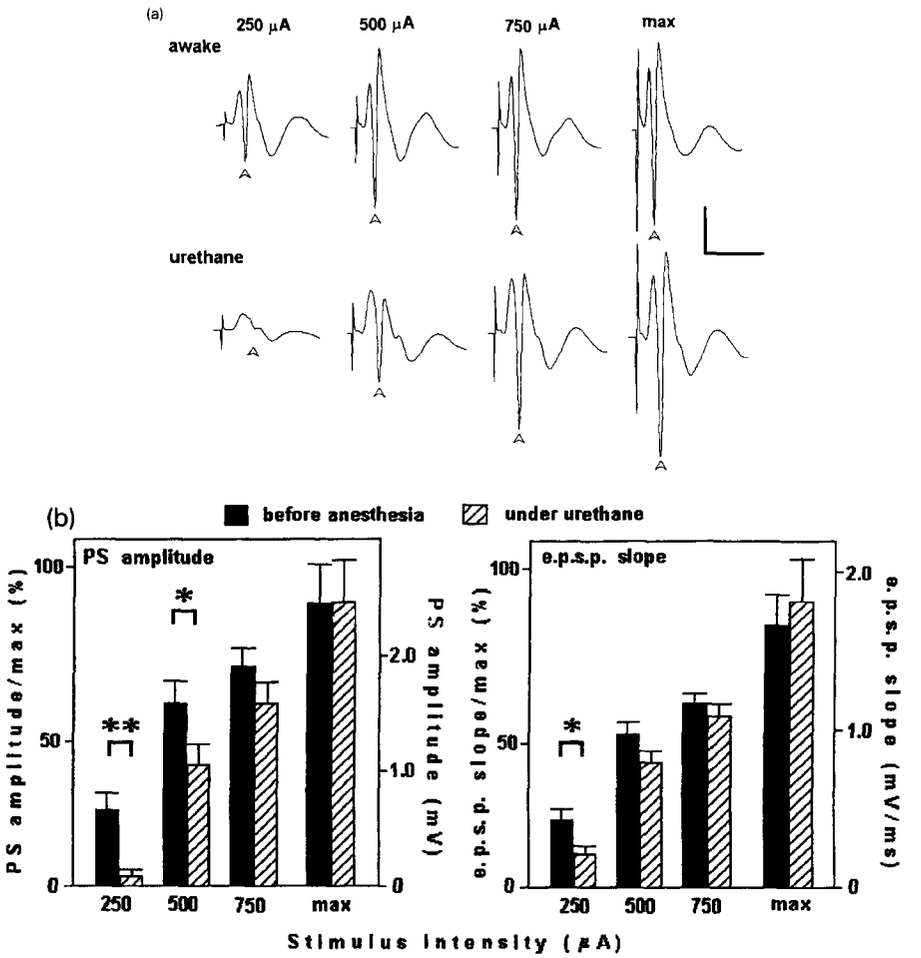

Fig. 2. (a) One example of input/output response. The narrow biphasic deflection before e.p.s.p. in each trace is a stimulation artefact. Open arrowheads indicate the population spike discharges in which we measured amplitude. Abbreviations; 250 μA, 500 μA and 750 μA, stimulated at 250 μA, 500 μA and 750 μA biphasic stimulation, respectively; other abbreviations and conditions are as in Fig. 1 (b). Input/output responses in the awake state and under urethane anesthesia ($n = 18$, each). Single stimulations (0.2 ms duration, biphasic) were given at 0.1 Hz. Shaded bars represent the means ± S.E.M. of ((population spike (PS) amplitude or excitatory postsynaptic potential (e.p.s.p.) slope at each stimulus intensity)/(maximal PS amplitude or e.p.s.p. slope) × 100) while awake, and hatched bars represent those under urethane anesthesia. The maximal population spike amplitude was shown on the left (mV), and the maximal e.p.s.p. slope on the right (mV/ms) (in the bars marked max). The ratio of responses at 250, 500 and 750 μA to maximal responses under the same conditions (awake or anesthetized) in the same experiment, is shown in the first three pairs of bars (on the left) of each graph. Maximal response (max) was obtained under the same state (awake or anesthetized) in the same experiment; $^{*}P < 0.05$, $^{**}P < 0.01$.

3.3. Input / output response

Fig. 2a shows examples of input/output responses. Fig. 2b shows the maximal population spike amplitude on the left, and the maximal e.p.s.p. slope on the right (in the bars marked max). Maximal responses were chosen from 7 averaged recordings under the same conditions (awake or anesthetized) in the same experiment. The ratio of responses at 250, 500 and 750 μA to maximal responses under the same conditions (awake or anesthetized) in the same experiment, is shown in the first three pairs of bars (on the left) of each graph (Fig. 2b).

The proportions of population spike amplitude at each stimulus intensity to maximal population spike amplitude under urethane anesthesia was significantly lower at 250 and 500 μA than those in the awake state, however, there were no significant differences at higher intensities and in maximal population spike amplitude.

The ratio of slopes showed a significant reduction at 250 μA under urethane anesthesia, compared with those in the awake state. There were no differences at higher intensities or in maximal e.p.s.p. slope.

3.4. Changes in frequency-dependent paired-pulse inhibition

The S1 population spike amplitude showed no significant differences at any frequencies between the awake state and urethane anesthesia. At 0.1 Hz, the ratio of the S2 population spike amplitude to the S1 was significantly higher in the anesthetized state than in the awake state (increased by 26.4%, $P < 0.01$). At 2 Hz, this ratio showed a similar trend (13.8%, $P = 0.052$, NS).

4. Discussion

Our results clearly show an effect of urethane on evoked potentials in dentate gyrus. Under urethane anesthesia, short interstimulus interval-dependent paired-pulse inhibition was significantly decreased (Fig. 1b), and frequency-dependent paired-pulse inhibition decreased non-significantly at 2 Hz compared with the awake state. Because maximum response could always be evoked with S2, the observed effect is unlikely to be due to differences in occlusion of postsynaptic responses. Short interstimulus interval-dependent paired-pulse inhibition in dentate gyrus is thought to be $GABA_A$-mediated (Adamec et al., 1981; Albertson and Joy, 1987; Matthews et al., 1981; Wilson and Racine, 1985), and frequency-dependent paired-pulse inhibition at 2 Hz may also be GABA mediated (Sloviter, 1991a). Although these two types of inhibition are not mediated by the same neuronal system because they showed different responses to sustained perforant path stimulation (Shirasaka and Wasterlain, 1994), these results indicate that urethane has no agonist effect on the $GABA_A$ system.

There are two possible explanations for this phenomenon. One is that urethane directly antagonizes GABAergic systems and decreases GABAergic inhibition. There are several reports which show differences between the central nervous system effects of urethane and GABA mimetic drugs (Carrer and Ferreyra, 1980; Engstrom et al., 1990; Moore and Appenteng, 1980; Rogers et al., 1980; Stewart and Scott, 1976). Urethane decreased GABAergic inhibition in olfactory bulb as shown by a paired-pulse technique (Stewart and Scott, 1976), and urethane decreased inhibition in hypothalamic ventromedial nucleus while pentobarbital increased inhibition (Carrer and Ferreyra, 1980). However, it is unlikely that urethane has a direct antagonistic effect on the GABAergic system, because GABA receptor antagonists, like bicuculline, usually have convulsant effects on the central nervous system, while urethane has anticonvulsant effects (Cain et al., 1989,1992), and because urethane, like a GABA receptor agonist (Albertson and Joy, 1989), suppressed population spike amplitude in the input/output response (Fig. 2).

Another possibility is that urethane suppresses excitatory neuronal activity. Urethane decreased population spike amplitude and e.p.s.p. slope in input/output response (Kamondi et al., 1988) at lower intensities (Fig. 2). These phenomena could happen whether urethane affects dentate granule cell excitability pre-or postsynaptically. These effects are similar to those of 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX), a non-*N*-methyl-D-aspartate (NMDA) receptor antagonist, on CA1 and dentate neurons (Watanabe et al., 1993), and of the NMDA receptor/channel antagonists, 3-((±)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP), (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclo-hepten-5,10-imine maleate (MK801) (Abraham and Mason, 1988), and D(−)aminophosphonovalerate (APV) (Errington et al., 1987), on dentate granule cells. Although there was no significant effect of urethane anesthesia on S1 population spike amplitude, there might be some difference in granule cell excitability which does not alter the S1 population spike amplitude, but appears as effects on excitation of inhibitory neurons which recurrently inhibit granule cells.

Previous reports suggested a relationship between urethane and excitatory amino acid neurotransmitters. Moroni et al. (1981) reported that urethane decreased glutamate release in cerebral cortex but not GABA release. Evans and Smith (1982) reported that urethane antagonized excitation induced by NMDA, quisqualate and kainic acid, and not by substance P in isolated spinal cord. Piña-Crespo and Daló (1992) re-

ported that urethane suppressed spinal seizures evoked by sudden cooling of isolated toad spinal cord, which are probably mediated by release of excitatory amino acids, and Daló and Larson (1990) reported that urethane antagonized NMDA, quisqualate, and kainic acid-induced behavioral changes but not those induced by substance P. All these results including ours raise the possibility that urethane may antagonize excitatory amino acid-mediated neuronal systems. Several possible mechanisms can be proposed: urethane might raise the threshold for axonal stimulation to dentate granule cells; urethane might reduce excitatory amino acid release; and/or urethane might affect excitatory amino acid receptors (Evans and Smith, 1982). The answer to these questions must await further experiments.

Acknowledgements

We wish to express our thanks to Mr. Roger A. Baldwin for his skillful assistance. This work was supported in part by the VA research service, by research grant NS13515 from NINDS, and by an EFA fellowship (YS).

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