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Pentobarbital, in subanesthetic doses, depresses spinal transmission of nociceptive information but does not affect stimulation-produced descending inhibition in the cat

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Summary The present study evaluates the effect of systemic pentobarbital on the spinal transmission of nociceptive information and on stimulation-produced descending inhibition in the deeply anesthetized, paralyzed cat.

Single neuronal responses to noxious skin heating were recorded extracellulary in the lumbar dorsal horn and found to be depressed by pentobarbital at subanesthetic doses (4.0, 8.0, 17.0 and 24.5 mg/kg) in a dose-dependent manner. At 0.5 and 1.5 mg/kg, depression by pentobarbital was positively correlated with the depth of the recording site in the spinal cord (laminae IV–VI), i.e., neurons in deeper laminae (V–VI) were attenuated, while neurons in lamina IV were unaffected.

At all doses tested, pentobarbital failed to affect stimulation-produced descending inhibition from either the midbrain periaqueductal gray or the medullary nucleus raphe magnus.

The present data furnish evidence for the antinociceptive potency of pentobarbital, they do not support the view that a 'partial pharmacological spinal cord transection' would attenuate stimulation-produced descending inhibition of nociceptive dorsal horn neurons.

Key words: Barbiturates; Pain; Periaqueductal gray; Nucleus raphe magnus; Dorsal horn cell; Antinociception

Introduction

Barbiturates are widely used and their general anesthetic properties are well described [e.g., 11,33,39]. In addition to anesthesia, barbiturates may also interfere with nociception and antinociceptive mechanisms. It has been proposed that

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barbiturates may cause hyperalgesia [27,35], or hypoalgesia or may have no effect on nociception [cf., 14].

Light pentobarbital anesthesia may reduce tonic descending inhibition of either the spinally mediated nocifensive tail flick reflex [35] or of nociceptive dorsal horn neurons [31] and may reduce descending inhibition produced by morphine administered intracerebrally but not intrathecally [1,5,17,29]. It was hypothesized that pentobarbital may induce a state of 'partial pharmacological spinal cord transection' [26]. In these studies nociception was compared in the awake versus the lightly anesthetized state, thus in different stages of wakefulness.

The present study was undertaken to evaluate the effect of pentobarbital on the spinal transmission of nociceptive information and on stimulation-produced descending inhibition of spinal nociceptive neurons. Pentobarbital was chosen for this study as (1) a representative of barbiturates having an intermediate duration of action and (2) an anesthetic commonly used in electrophysiological studies.

Descending inhibition was induced by electrical stimulation in the midbrain periaqueductal gray (PAG) or in the medullary nucleus raphe magnus (NRM); both brain-stem structures are believed to play a central role in endogenous- and morphine-induced analgesia [3,7–9,13,22,35]. Studies were performed in deeply anesthetized animals in an attempt to minimize changes in the depth of anesthesia by pentobarbital and to mimick the clinical situation of surgical anesthesia or many electrophysiological animal preparations designed to study central mechanisms of nociception and antinociception.

Materials and methods

Experiments were performed on 9 adult cats weighing between 2.5 and 3.4 kg. Surgical level of anesthesia was initiated with sodium pentobarbital (40 mg/kg, given intraperitoneally) and maintained throughout the experiment by ventilation with a gaseous mixture of 70% N_2O, 30% O_2 and fluothane (0.2–0.8 vol%). Blood pressure in a carotid artery, central venous pressure, urinary output and rectal temperature were continuously monitored and kept within physiological limits.

The superficial peroneal (SP) and posterior tibial (PT) nerves were dissected free for bipolar electrical stimulation and left in continuity. The lumbar spinal cord was exposed from L4 to S1 by laminectomy. Extracellular recordings from dorsal horn neurons were made through glass micropipettes filled with 3 M NaCl. Neurons responding to hind limb nerve stimulation at A-fiber strength and with an additional late discharge to C-fiber stimuli were tested for responsiveness to noxious radiant heat applied to the glabrous foot pad (typically 50 °C or 52 °C for 10 sec) given at intervals of not less than 3 min. Recordings were begun 15–28 h (22.7 ± 4.9 h, mean ± S.E.M., n = 9) after the initiation of anesthesia with pentobarbital.

PAG or NRM stimulation to produce descending inhibition in the cord consisted of 100 Hz trains of 0.1 msec monophasic pulses, 100 msec train duration, given 3 times/sec at an intensity of 400–600 μA. Brain stimulation was applied through bipolar concentric electrodes stereotaxically positioned vertically into the PAG

ipsilateral to the recording site and at an angle of 45° to the horizontal into the midline NRM. Pentobarbital (Nembutal, 60 mg/ml) was administered intravenously in single doses of 0.5, 1.0, 2.5, 5.0, 7.5 or 10.0 mg/kg in intervals of 30 min. Cumulative doses are used for comparison. At the conclusion of each experiment, animals were sacrificed by an overdose of pentobarbital; stimulation sites were electrolytically marked and later histologically verified to be in the PAG or NRM, respectively (Fig. 1C).

Data are presented as means ± S.E.M. Statistical comparisons were made using Student's t test for grouped or paired data, $P \leq 0.05$ was considered significant (two-tailed). Correlations were calculated using the Pearson product-moment correlation formula.

Results

Recordings were made from 9 dorsal horn neurons in 9 cats (1 neuron per cat). Recording sites were located 1532–2496 μm below the cord surface, corresponding to laminae IV–VI of Rexed [32]. All neurons responded to electrical stimulation of the SP and/or PT nerves at A-fiber strength and also with a late discharge to electrical stimuli suprathreshold for activation of C-fibers. All neurons also responded to innocuous mechanical stimuli and to noxious radiant skin heating applied within the receptive fields of the glabrous skin of the ipsilateral hind paw. Thus, neurons were classified as multireceptive (convergent or wide dynamic range) neurons [16,20,23,41]. An example of a neuron's response to skin heating is shown in Fig. 1A. Heat-evoked responses were calculated as total numbers of impulses in 25 sec, beginning with the onset of the heat stimulus, corrected for spontaneous activity, and served as a parameter to evaluate the effect of systemic pentobarbital and/or stimulation-produced descending inhibition from the PAG or NRM (see Fig. 1A, B for examples).

Before administration of pentobarbital, mean heat-evoked responses (1704 ± 326 imp/25 sec, range 504–3191 imp/25 sec) were reduced by electrical stimulation in the PAG at 600 μA to 44.9 ± 5.4% of control and by stimulation in the NRM at 400 μA to 32.5 ± 10.9% of control (see Fig. 1B for an example). The efficacy of stimulation-produced descending inhibition was not correlated with the magnitude of the control heat responses ($r_S = 0.4146$, $P > 0.05$, $n = 9$ for PAG-stim and $r_S = 0.1849$, $P > 0.05$, $n = 7$ for NRM-stim).

Pentobarbital at cumulative doses of 0.5 or 1.5 mg/kg i.v. insignificantly reduced heat responses to 92.4 ± 5.9 and to 80.4 ± 10.4% of control ($t = 1.29$, $n = 6$ and $t = 1.17$, $n = 5$, respectively), and at doses of 4.0–24.5 mg/kg i.v. significantly to 60.6 ± 9.4 and to 22.2 ± 10.2% of control ($t = 4.21$, $P \leq 0.02$, $n = 5$ and $t = 7.66$, $P \leq 0.02$, $n = 3$, respectively). The complete dose–response relationship is illustrated in Fig. 2A. For lesser doses of pentobarbital, a strong positive correlation was found between the depression of the heat-evoked responses by pentobarbital and the depth of the recording site in the dorsal horn ($r_S = +0.8380$, $P \leq 0.05$, $n = 6$ for 0.5 mg/kg and $r_S = +0.9515$, $P \leq 0.02$, $n = 5$, for 1.5 mg/kg see Fig. 3A), but not for

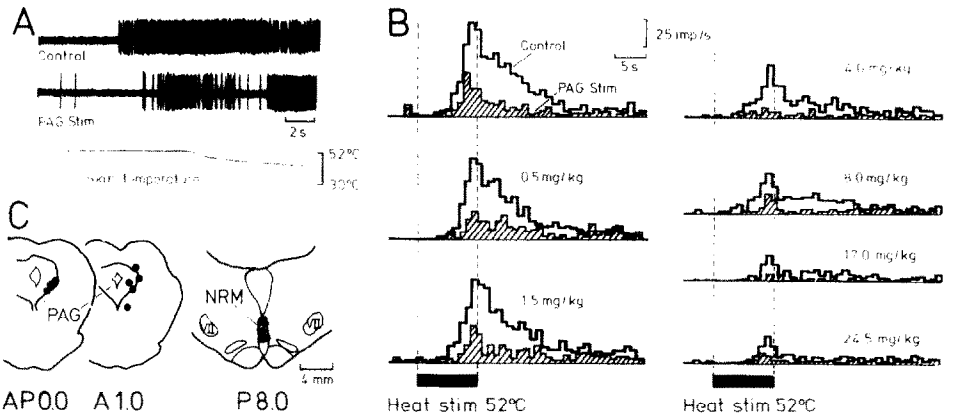

Fig. 1. Examples of the effect of pentobarbital on heat-evoked responses of dorsal horn cells and on stimulation-produced descending inhibition. In A, the time course of the skin temperature on the glabrous skin of a hind paw is given during a heat stimulus of 52° C for 10 sec. The oscillographic record of a dorsal horn neuron responding to this heat stimulus is illustrated above. Top: response in the absence of brain stimulation, middle: during PAG stimulation at 600 μA. In B, responses of another neuron to a heat stimulus of 52° C for 10 sec (horizontal bar at the bottom) are plotted as peristimulus time histograms; heavy lines represent responses in the absence of brain stimulation, hatched histograms responses during PAG stimulation at 600 μA. Examples of heat responses are given before (top left) and 12–15 min after the intravenous administration of pentobarbital at the indicated doses. In C, the stimulation sites in the PAG or NRM for 8 experiments are superimposed on representative coronal sections through the brain-stem. Histology was not recovered from one experiment. The anterior-posterior levels are derived from the stereotaxic atlas of Snider and Niemer.

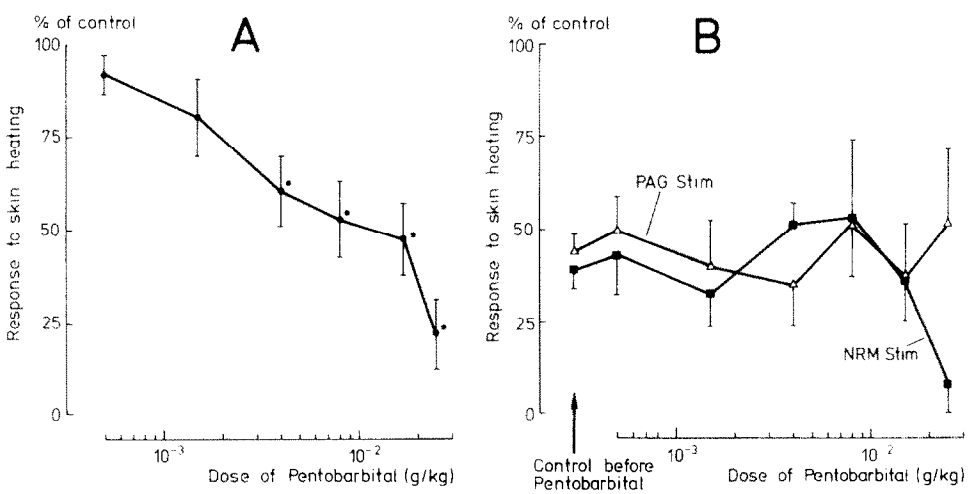

Fig. 2. Mean heat-evoked responses of 9 dorsal horn neurons are expressed as total number of impulses and plotted on the ordinate versus the dose of intravenous pentobarbital (logarithmic scale). A: the dose–response relationship for heat-evoked responses in the absence of brain stimulation is illustrated. For each neuron 6 heat responses 5–20 min after the pentobarbital injection were averaged. B: heat responses during electrical stimulation in the PAG (600 μA, triangles) or NRM (400 μA, squares) are expressed in percent of control and plotted on the ordinate versus the dose of pentobarbital. Before pentobarbital administration, PAG stimulation reduced heat-evoked responses to 44.9 ± 5.4% of control and NRM stimulation to 32.5 ± 10.9% of control. Pentobarbital at 0.5–24.5 mg/kg i.v. did not significantly attenuate this stimulation-produced descending inhibition.

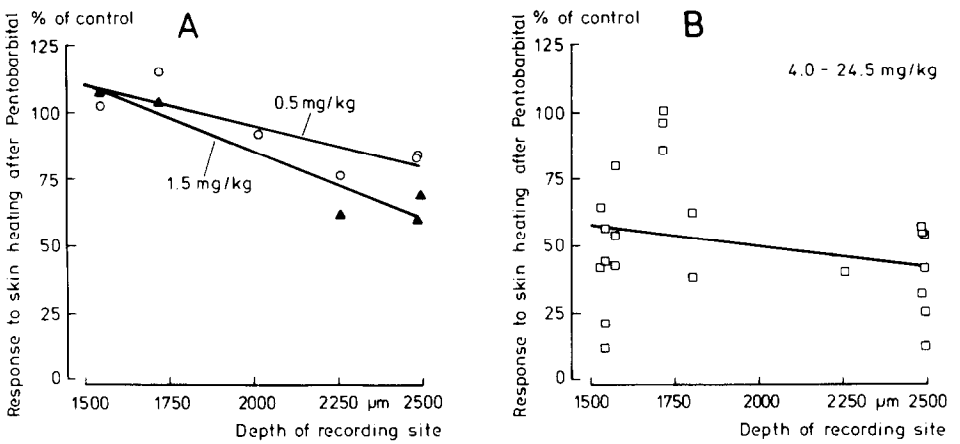

Fig. 3. Effect of systemic pentobarbital on heat-evoked responses of 9 dorsal horn neurons in relation to the depth of the recording site. Each data point represents the response of one neuron recorded 11–14 min after an intravenous bolus injection of pentobarbital. A: depression of heat-evoked responses by pentobarbital at 0.5 mg/kg (○) or 1.5 mg/kg (▲) is shown to correlate significantly with the depth of the recording site. B: pentobarbital at greater doses (4.0–24.5 mg/kg) depressed all neurons tested.

greater pentobarbital doses (4.0–24.5 mg, r_S values ranged from -0.1035 for 17 mg/kg pentobarbital to $r_S = -0.4960$ for 4 mg/kg pentobarbital, $P > 0.05$, see Fig. 3B). Spontaneous neuronal activity was usually low (mean 6.7 ± 2.1 imp/sec, range 0.0–18.1 imp/sec) and occurred sometimes in irregular bursts and was not significantly affected by pentobarbital at any dose tested ($P > 0.05$).

Pentobarbital at all doses tested failed to significantly alter the efficacy of stimulation-produced descending inhibition from the PAG or NRM (t values ranged from $t = -3.88$, $n = 2$, $P > 0.1$ for NRM-induced inhibition after 24.5 mg/kg pentobarbital to $t = 1.26$, $n = 4$, $P > 0.2$ for NRM-induced inhibition following 8.0 mg/kg pentobarbital). Fig. 2B illustrates the complete dose–response relationship.

TABLE I

EFFECT OF INTRAVENOUS PENTOBARBITAL ON MEAN ARTERIAL BLOOD PRESSURE, WHICH WAS ANALYZED IN 3 min INTERVALS AND AVERAGED FOR 40 sec

For each experiment 3 consecutive measurements before and 14–20 min after the injection of pentobarbital were used for comparison. Pentobarbital was given in doses of 0.5, 1.0, 2.5, 5.0, 7.5 and 10.0 mg/kg in 30 min intervals. Cumulative doses are given.

Blood pressure (mm Hg)	Cumulative doses of pentobarbital (mg/kg body weight)						
	Control	0.5	1.5	4.0	8.0	17.0	24.5
Mean	105.9	112.7	107.5	105.5	88.8	86.4	80.0
S.E.M.	6.9	7.2	9.0	9.5	8.5	8.0	
n	7	5	5	4	5	5	1

Mean arterial blood pressure was analyzed in 3 min intervals and averaged for 40 sec in some experiments. The effect of cumulative doses of pentobarbital on blood pressure is shown in Table I.

Discussion

Pentobarbital was shown to suppress transmission of nociceptive information in the spinal cord at doses below those required to produce surgical level of anesthesia. Stimulation-produced descending inhibition, however, was not affected by pentobarbital at the same doses. Wall [39] reported that pentobarbital may affect dorsal horn cells in laminae IV, V and VI differently; Kitahata et al. [19] found a lamina-specific suppression of dorsal horn cells by nitrous oxide or hyperventilation. Here, a strong positive correlation was found between the depth of the recording site and the depression of the heat-evoked discharges by pentobarbital at the lower doses tested (0.5 and 1.5 mg/kg i.v.), i.e., neurons in the deeper layers of the dorsal horn were depressed by pentobarbital while neurons located in more dorsal layers were unaffected. No correlation with the depth of the recording sites was found for greater pentobarbital doses (4.0–24.5 mg/kg) which indiscriminatively depressed all neurons tested.

In some earlier studies pentobarbital, in comparable doses, was shown to cause shorter tail flick latencies, i.e., hyperalgesia (3–6 mg/kg/h i.v. infusion in rats [35]), or lowered thresholds in vocalization test (30 mg/kg i.p. in mice [27]) or enhanced responses of spinal WDR neurons to C-fiber but not A-fiber stimuli (10 mg/kg i.v. in monkeys [16a]) or the proportion of spinal neurons responding also to noxious stimuli (20 mg/kg in cats [31]). Besides obvious differences in species, drug regime, route of administration and the nociceptive parameters assessed, nociception was compared in those studies in the awake, decerebrate or spinalized state versus the lightly anesthetized state. Here, pentobarbital was given supplementary to deeply anesthetized animals and did therefore not produce noticeable changes in depth of anesthesia. Since a reversed relation between wakefulness and nociception is well documented for the awake versus the stressed state ('stress-induced analgesia' [see, e.g., 21,40]), it may be hypothesized that a reduction in wakefulness from the awake state to the lightly (pentobarbital-) anesthetized state might further facilitate nociception and nocifensive reflexes. This hypothesis is supported by results obtained from single unit recordings in freely moving cats [38]. A significant positive correlation between 10 differentiated states of wakefulness (from arousal to REM sleep) and the discharge frequencies of neurons in the nucleus raphe dorsalis was established. Some of these neurons may play an important role in descending inhibition and antinociception, since electrical stimulation in the raphe nuclei, including the nucleus raphe dorsalis, strongly suppresses nocifensive behavior and nociceptive dorsal horn neurons [see 3 for a review]. Thus, a possible antinociceptive effect of low dose pentobarbital in some previous studies may have been masked by a reduction of wakefulness during the excitement stage of anesthesia.

This is the first study related to the effect of pentobarbital on stimulation-produced descending inhibition of nociceptive spinal dorsal horn neurons. Efficacy of descending inhibition was evaluated by comparing the total number of action potentials in response to identical heat stimuli in the absence of (control) and during electrical stimulation in the brain. Since control responses were suppressed by pentobarbital in a dose-dependent fashion, comparisons were based on different baseline responses (as illustrated in Fig. 1B), which possibly could have influenced the present results. Although our data do not rule out this possibility, it seems unlikely, since the efficacy of stimulation-produced descending inhibition was not significantly correlated with the magnitude of the control heat responses when compared in different neurons.

At all doses tested, pentobarbital failed to affect descending inhibition induced either from the PAG or the NRM. It is not likely that this lack of effect is due to an insufficient dose, since a wide range of doses were tested (0.5–24.5 mg/kg i.v.). Further, pentobarbital, at comparable doses, has been shown to block the reticulospinal inhibitory pathway activated by electrical stimulation in the nucleus reticularis gigantocellularis (2.5–20 mg/kg in cats [10]), the descending inhibition produced by morphine microinjection into the PAG or NRM (3–6 mg/kg/h in rats [1,29]), or tonic descending inhibition (3–6 mg/kg/h in rats [35]).

It is now widely accepted that multiple and possibly independent inhibitory systems may be activated from the brain-stem, descend diffusely through the medulla [12,36] to various laminae of the dorsal and ventral horn [24] via different parts of the spinal lateral funiculi [18,34]. A variety of putative spinal neurotransmitters have been proposed to mediate this descending inhibition [see, e.g., 2,4,8]. Thus, it is likely that multiple descending systems were activated in the present study when stimulating electrically in the PAG or NRM. Part(s) of these systems could have been attenuated by pentobarbital (e.g., those which are tonically active in the awake state or which were activated by intracranial morphine and depressed by systemic pentobarbital [1,29,35]), while others were unaffected (e.g., those which were activated by electrical stimulation in the brain-stem [35]).

The mechanisms of pentobarbital-induced depression of spinal nociceptive neurons are not known. The reduction in systemic arterial blood pressure by pentobarbital could have influenced the results, however, a significant effect seems unlikely, since reduction was mild and anesthesia was never deeper than stage III according to the classification of Gillespie [15]. Pentobarbital may directly block nerve conduction [37]; small diameter nerve fibers (Aδ-, C-fibers) are more readily depressed by pentobarbital than large diameter fibers (Aα-, Aβ-fibers [37]) and may be partially blocked at pentobarbital concentrations of 0.5 mM. This pentobarbital concentration may be gained in the extracellular fluid initially, after a single intravenous injection of 25 mg/kg pentobarbital (with a given molecular weight of 248 and an estimated extracellular fluid volume of 25% of total body weight). Effective concentrations of pentobarbital, however, will be significantly lower due to redistribution and binding to plasma albumin. Thus, an attenuation of nerve conduction may not be a prominent mechanism of the depression by pentobarbital of spinal nociceptive neurons, especially at lower pentobarbital doses.

A spinal site of action may play an important role, since intrathecal pentobarbital (100 μg) inhibits the spinally mediated nocifensive tail flick reflex [6]. Inhibition may be produced by a reduction of the release of transmitters from the presynaptic nerve terminals of primary afferent fibers [33] or by enhancing GABAergic inhibition [25,28,30], e.g., by decreasing the rate at which GABA dissociates from its receptor.

The present data furnish evidence for the antinociceptive potency of pentobarbital at subanesthetic doses. The hypothesis of a 'partial pharmacological spinal cord transection' by pentobarbital may not play an important role for the stimulation-produced descending inhibition of spinal nociceptive transmission.

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