Antinociceptive Effects of Phenobarbital in "Tail-Flick" Test and Deafferentation Pain

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Deafferentation pain has been related to abnormal electrical hyperactivity in the neurons of the sensory relays in the central nervous system. This electrical activity resembles the epileptoid pattern observed in experimental epileptoid foci. With the aim of preventing this hyperactivity, rats were given long-term treatment with phenobarbital after sciatic transection and dorsal cervical rhizotomy. Daily intramuscular injections of saline solution or 5 and 10 mg/kg of phenobarbital were administered for 20 days, starting 10 days before surgery. Larger doses of phenobarbital delayed the onset and reduced the severity of autotomy. In a test of acute pain, the effect of intraperitoneal (1–16 mg) and intrathecal (100–500 μg) phenobarbital was studied by measuring the "tail-flick" response latency. Intraperitoneal phenobarbital did not modify acute pain, but 500 μg of intrathecal phenobarbital increased the threshold of pain. These results indicate that (a) phenobarbital, a drug with anticonvulsant activity, reduces deafferentation behavior in rats, and (b) intrathecal phenobarbital has an antinociceptive action in acute experimental pain.

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There is a relation between the clinical characteristics of deafferentation pain experienced after injury and painful sensations felt by the patient before deafferentation (1,2). This fact has been explained by hypothesizing that chronic pain produces changes in the central nervous system (3); however, little is known about the pathophysiologic basis of this phenomenon. Sensory neurons are normally under the inhibitory action of the sensory and descending pathways. After deafferentation procedures in animals, such as dorsal rhizotomy or section of peripheral nerves, the surgery is followed by the development of spontaneous hyperactivity of spinal cord dorsal horn neurons (4–7) and other somatosensory nuclei. Similar electrical hyperactivity in patients suffering chronic benign pain in neurons located in the spinal cord was recorded perioperatively by Loeser et al. (8) and, more recently, by Hirayama et al. (9) and Rinaldi et al. (10) in the thalamus of patients with deafferentation pain. Such hyperactivity may be one of the mechanisms involved in the cause of deafferentation pain.

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A few clinical studies report methods for preventing the development of deafferentation pain. Recently, Bach et al. (11) showed that preoperative lumbar epidural blockade with bupivacaine and morphine reduces the incidence of phantom limb pain after amputation. In an experimental study in the model of sciatic section in rats, we showed that autotomy behavior is reduced when the nerve is blocked with bupivacaine before section (12) and a local surgical procedure, such as a centrocentral anastomosis, is performed on the central stump (13).

We designed an experiment aimed at studying the effect of phenobarbital on the prevention of the autotomy behavior that follows deafferentation procedures in rats. Autotomy is now considered to be a response to pain or dysesthesia, and its intensity related to the degree of those abnormal sensations. Blumenkopf and Lipman (14) showed that autotomy is not related to limb anesthesia. Autotomy has also been modified through the use of many surgical and pharmacologic treatments (12,13,15). Phenobarbital is a drug with anticonvulsant activity that can be administered by any route, including intrathecally (16). The rationale for this therapeutic approach is that phenobarbital might reduce the spontaneous activity of deafferented hyperactive neurons and, subsequently, the autotomy behavior. We also tested the effect of phenobarbital in a nociceptive test of acute

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pain to determine whether phenobarbital had any direct antinociceptive effect.

Methods

Animals and Anesthesia

Adult male Wistar rats, weighing 200–225 g, were used in the studies. For surgical procedures, the animals were intraperitoneally anesthetized with a mixture of ketamine (60 mg/kg) and diazepam (6 mg/kg). The study was conducted in accordance with the guidelines of the Ethics Committee of the International Association for the Study of Pain and was approved by the Research Laboratory of the Faculty of Medicine of Càdiz.

Deafferentation Models of Pain

Animals were randomly assigned to one of two experimental models of deafferentation pain. In the first group, the left sciatic nerve was sectioned cleanly at the midthigh level. Approximately 5 mm of the proximal stump of the nerve was removed to prevent its spontaneous regeneration into the distal nerve stump. In a second group of animals, a cervical posterior rhizotomy was performed by sectioning the C-4 to T-1 dorsal roots. The roots were sectioned on the left side with microsurgical techniques. Animals were given long-term treatment with intramuscular phenobarbital. Rats received daily injections of 5 or 10 mg/kg of phenobarbital for 20 days, starting 10 days before deafferentation. Control animals received saline solution.

In the sciatic section group, 12 and 15 rats were treated with phenobarbital (5 and 10 $mg \cdot kg^{-1} \cdot day^{-1}$, respectively), and 7 control rats received saline solution. In the cervical dorsal rhizotomy group, 13 and 16 rats were treated with phenobarbital (5 and 10 $mg \cdot kg^{-1} \cdot day^{-1}$, respectively), and 8 control rats received saline solution. After surgery, the wounds were closed in layers. No other drugs were administered, and the animals were observed for 4 wk. Each rat was lodged individually in a cage under standard colony conditions. Animals were checked daily to score the autotomy behavior. The following autotomy scale was used: 1 point for the chewing off of one or more nails and an additional point for the removal of each half-toe or metatarsus/carpus and tarsus/carpus (maximum 13 points in upper limb and 7 points in lower limb, due to cutaneous innervation of sciatic nerve).

Acute Antinociceptive Test: "Tail-Flick" Response

A different group of rats underwent long-term implantation of a lumbar intrathecal catheter with an original technique (17). For this purpose, a small microsurgical lumbar laminectomy was performed and the dura mater opened with the tip of a needle. Through this slit, a polyvinyl catheter (0.64 outside diameter; 0.28 inside diameter) was carefully introduced and advanced caudally 1.5 cm. The catheter was firmly secured to paraspinal muscles, tunneled subcutaneously, and pulled out atop the calvarium. The catheter tip was sealed by heat. These animals were studied 4 days later in an short-term algesiometer test. For this test, the tail of the animal was placed under a focused radiant infrared source (Hugo Basile, Milan, Italy) (100-W bulb) to measure the "tail-flick" latency. A humane cutoff time of 10 s was preset to avoid burning. In control animals, 50 μL of saline solution was injected intrathecally through the catheter; in experimental animals, the same volume containing 100, 200, or 500 μg of phenobarbital was delivered. The test was done before injection and 10, 20, and 30 min later. Three measurements were performed at each time on three different points on the tail, and the mean value was considered the latency. The same algesiometer test was also performed in nonimplanted rats receiving saline solution or phenobarbital intraperitoneally. In these experiments, the injected volume was 1 mL, containing 1, 2, 4, 8, or 16 mg of phenobarbital.

The following groups were formed in which tail-flick latency was studied: intraperitoneal saline solution (6 rats) and 1–16 mg of phenobarbital (5–10 rats each group); intrathecal saline (6 rats) and 100, 200, and 500 μg of phenobarbital (5–8 rats each group).

At the end of each experiment, the animals were killed and the spinal column was removed in each case. Specimens from the surgical levels were processed for routine pathological study.

Statistical Analysis

Statistical analysis was done using the χ^2 test and a nonparametric test for comparison of means of paired (Wilcoxon test) and nonpaired (Mann-Whitney test) data. Statistical differences of $P \leq 0.05$ were considered to be significant. Results are expressed as mean values ± SEM. Latency times in the tail-flick test are expressed in the figures as a percentage of the baseline values obtained before phenobarbital injections.

Results

Autotomy Behavior

Table 1 shows the day of onset of autotomy and the percentage of animals developing autotomy after sciatic section. Although there is a delay in the mean day of onset of autotomy in both groups of animals

Table 1. Day of Onset of Autotomy and Percentage of Animals Developing Autotomy (≥1) and Severe Autonomy (≥5)

Group	Day of onset	Autotomy ≥1				Severe autotomy ≥5			
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4
Sciatic section									
Saline solution (n = 7)	3.3 ± 1.1	86	100	100	100	0	15	15	15
PB-5 (n = 12)	6.7 ± 1.4	75	100	100	100	0	0	25	25
PB-10 (n = 15)	7.2 ± 3.5[a]	60	60	60	73	0	0	13	26
Dorsal rhizotomy									
Saline solution (n = 8)	2.8 ± 0.9	87	87	87	87	0	0	12	37
PB-5 (n = 13)	4.7 ± 1.1	85	85	85	85	15	15	23	23
PB-10 (n = 16)	11.8 ± 2.5[b]	44	50	75	75	0	0	0	0

PB-5, phenobarbital (5 mg·kg^{-1}·day^{-1}); PB-10, phenobarbital (10 mg·kg^{-1}·day^{-1}); wk, week.
Onset of autotomy expressed in days ± SEM.
[a] $P < 0.05$, Mann-Whitney test versus saline solution.
[b] $P < 0.01$, Mann-Whitney test versus saline solution.

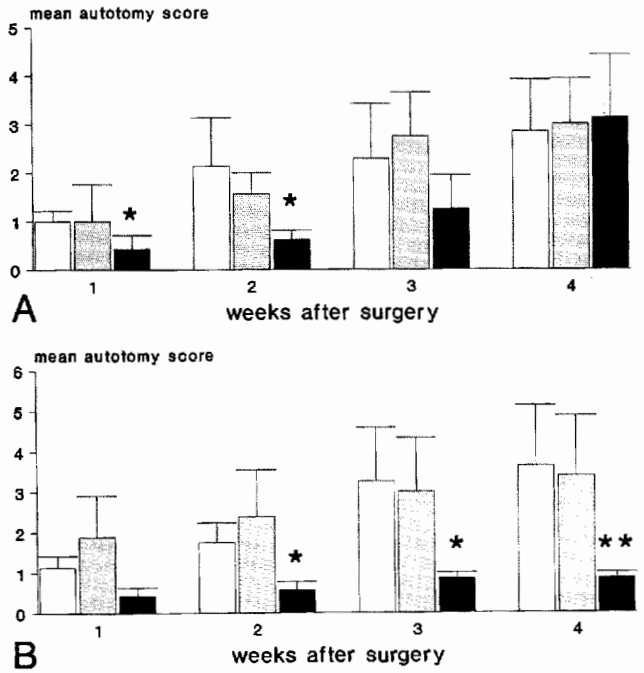

Figure 1. Postoperative course of autotomy after (**A**) sciatic section and (**B**) cervical dorsal rhizotomy. **Bars** indicate the mean value ± SEM. *$P < 0.05$; **$P < 0.01$; Mann-Whitney test versus control group. □, Saline; ▨, 5 mg·kg^{-1}·day^{-1} phenobarbital; ■, 10 mg·kg^{-1}·day^{-1} phenobarbital.

treated with phenobarbital, differences are statistically significant only between animals treated with phenobarbital (10 mg·kg^{-1}·day^{-1}) and control animals ($P < 0.05$; Mann-Whitney test). At the end of the observation period, almost all animals had begun autotomy of the denervated limb; the differences among groups were not significant. The average autotomy score increased smoothly in groups treated with saline solution and low doses of phenobarbital (Figure 1A). The differences between these two groups are not significant. However, animals treated with 10 mg·kg^{-1}·day^{-1} of phenobarbital showed low autotomy scores during the first and second weeks, and there are statistically significant differences compared with control animals treated with saline solution ($P < 0.05$; Mann-Whitney test). In this group, autotomy increases within days after halting treatment with phenobarbital.

The day of onset of autotomy and the percentage of animals developing autotomy after dorsal rhizotomy are also shown in Table 1. Both groups treated with phenobarbital showed a delay in the average day of onset of autotomy compared with control animals, but only the difference between the control group and the group treated with 10 mg·kg^{-1}·day^{-1} of phenobarbital is statistically significant ($P < 0.01$; Mann-Whitney test). As happens after sciatic section, at the end of the observation period almost all animals had begun autotomy of the denervated limb, and the differences among the groups were not significant. However, in the animals treated with larger doses of phenobarbital, there were no animals with severe autotomy (autotomy ≥5 points). The average autotomy score increased in the same way in groups treated with saline solution and low doses of phenobarbital (Figure 1B), and the differences between these two groups are not significant. However, animals treated with 10 mg·kg^{-1}·day^{-1} of phenobarbital displayed very low autotomy scores during the observation period. In this group, the mean autotomy score did not reach 1 point at any time. The differences between this group and the saline solution-treated group are statistically significant from the second week onward.

Pain Threshold in the Tail-Flick Test

The aim of this test was to determine whether phenobarbital has an analgesic effect on acute pain. Results of the tail-flick test for each experimental group are shown in Table 2. There were no significant

Table 2. Tail-Flick Latency After Intraperitoneal and Intrathecal Phenobarbital Injection

Group	Preinjection	Latency after phenobarbital injection		
		10 Min	20 Min	30 Min
Intraperitoneal				
Saline solution (n = 6)	2.2 ± 0.2	2.0 ± 0.3	1.9 ± 0.2	2.1 ± 0.2
1 mg (n = 10)	2.1 ± 0.1	2.1 ± 0.1	1.8 ± 0.1	1.9 ± 0.1
2 mg (n = 5)	2.0 ± 0.3	2.3 ± 0.3	1.9 ± 0.1	1.8 ± 0.1
4 mg (n = 5)	2.4 ± 0.4	2.7 ± 0.3	1.9 ± 0.2	2.0 ± 0.0
8 mg (n = 5)	2.2 ± 0.1	2.9 ± 0.4	2.3 ± 0.2	2.3 ± 0.3
16 mg (n = 6)	2.2 ± 0.2	2.2 ± 0.2	2.0 ± 0.1	1.7 ± 0.1
Intrathecal				
Saline (n = 6)	3.1 ± 0.2	3.1 ± 0.3	3.3 ± 0.3	3.0 ± 0.2
100 μg (n = 6)	2.8 ± 0.3	3.7 ± 0.5	3.3 ± 0.6	3.2 ± 0.4
200 μg (n = 5)	3.5 ± 0.3	5.0 ± 0.6	4.7 ± 0.7	4.1 ± 0.6
500 μg (n = 8)	3.4 ± 0.2	5.9 ± 0.5[a]	4.4 ± 0.4[a]	4.2 ± 0.4[a]

Results are expressed as means ± SEM.
[a] $P < 0.05$, Wilcoxon test versus preinjection value.

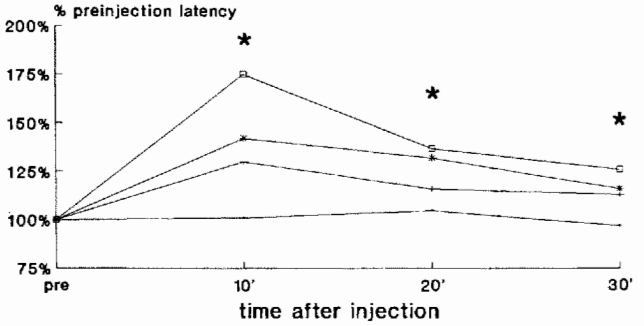

Figure 2. Latency in the tail-flick test after intrathecal administration of 100, 200, and 500 μg of phenobarbital. Latency is expressed as percentage change in relation to pretreatment values. There is a dose-related increase in the latency, with a significant difference after injection of 500 μg of phenobarbital. *$P < 0.05$; Wilcoxon test versus pretreatment values. —●—, saline; —+—, 100 μg phenobarbital; —*—, 200 μg phenobarbital; —□—, 500 μg phenobarbital.

changes in tail-flick latency after intraperitoneal administration of 1–16 mg of phenobarbital. The 16-mg dose produced somnolence a few minutes after the injection, but no other secondary effects were seen. Doses of 100 and 200 μg of intrathecal phenobarbital produced no significant changes in tail-flick latency, but after 500 μg, a significant increase was observed 10, 20, and 30 min after injection ($P < 0.05$, Wilcoxon test). Figure 2 shows the results of the tail-flick test after intrathecal administration of phenobarbital as a percentage of preinjection tests. There were no significant clinical findings after intrathecal injection. One rat developed a paresis of the lower limbs after an intrathecal injection of 100 μg of phenobarbital and was dropped from the study.

Pathological Findings

Specimens from all groups showed the same pathological changes in relation to the surgical procedures. There were no differences among neuromas or in the spinal cord at the level of the rhizotomy. Intrathecal catheters were surrounded by reactive tissue. No major lesions were observed in roots or spinal cord as a result of catheter placement.

Discussion

An understanding of the pathophysiology of deafferentation pain is an important objective if the successful treatment of this type of chronic pain is to be achieved clinically. Basic researchers have shown that deafferentation is followed by spontaneous firing in sensory pathway cells, namely, in dorsal root ganglion cells, dorsal horn, and nucleus cuneatus neurons, and also at the thalamic and cortical levels (4–7). The location of bursting neurons in the dorsal horn was anatomically placed by Albe-Fessard and Rampin (4) in layers IV and V; others found hyperactive cells in all of the layers of the dorsal horn (5). However, it is difficult to assign functional correlations, owing to the lack of peripheral receptive fields in deafferented animals. Clinical investigations (8–10) in patients with deafferentation pain showed similar hyperactivity in neurons in the dorsal horn of the spinal cord and in neurons in specific and intralaminar thalamic nuclei. These neurons show a spontaneous hyperactivity that resembles the electrical activity recorded in experimental alumina-induced epileptic foci (4,8,18). Moreover, the injection of alumina into the spinal cord subarachnoid space of the cat induces a painful dysesthesia with neuronal hyperactivity (18).

Anticonvulsant drugs have been used in the treatment of some types of pain, including trigeminal neuralgia and other types of neuralgic pain (19). Recently, some researchers pointed out that benzodiazepines, another type of drug with anticonvulsant activity, delivered by different routes, including intrathecal injection, have an analgesic effect on acute pain (16,20,21). Electrophysiologic studies suggest that benzodiazepines have a prevailing anticonvulsant activity that depresses the spontaneous hyperactivity of deafferented dorsal horn neurons, rather than a direct antinociceptive action that reduces or blocks C- or Aδ-evoked responses (22).

Given this background, it seems reasonable to attempt to prevent or reduce deafferentation pain by the use of anticonvulsant drugs. In our study we used long-term treatment with phenobarbital in an attempt to prevent autotomy behavior in the sciatic section and dorsal rhizotomy models of pain. The

pathophysiologic bases of these models are different. In the sciatic section model, at least two sources of nociceptive discharges have been implicated: spontaneous discharges from neuroma and dorsal root ganglia in the peripheral nervous system and hyperactive deafferented neurons in the sensory relays of the central nervous system (6,7). Dorsal cervical rhizotomy is followed by spontaneous hyperactivity in the central nervous system and has no peripheral component (4,5). Long-term phenobarbital treatment (10 $mg \cdot kg^{-1} \cdot day^{-1}$) reduces the autotomy score and also delays the day of onset of autotomy in both experimental models when compared with control groups. If autotomy is related to those proposed mechanisms, then the effect on autotomy behavior might be explained by the antiepileptic action of phenobarbital reducing the hyperexcitability of the cell membrane. Three mechanisms of action have been postulated for phenobarbital: at high concentrations, phenobarbital activates the γ-aminobutyric acid-related choride channels and reduces the sodium and calcium influx, but at therapeutic concentrations, phenobarbital enhances the postsynaptic response to γ-aminobutyric acid and blocks the excitatory response to glutamic acid (23,24). In our experience, changes in autotomous behavior are obtained with high doses of phenobarbital; however, reduction of autotomy could not be attributed to a sedative or hypnotic effect of phenobarbital. Treated rats were alert and showed a normal social behavior as did control rats receiving saline solution.

Results are better in deafferentation by dorsal root section than by sciatic section. The rhizotomy deafferentation syndrome should be more susceptible to phenobarbital, given the fact that it is entirely due to central hyperexcitability, whereas deafferentation after sciatic section adds peripheral mechanisms that are eventually less susceptible to the action of phenobarbital.

There have been few attempts to modify autotomy by means of an anticonvulsant drug. In 1977, Duckrow and Taub (25) demonstrated that intraperitoneal diphenylhydantoin reduced the incidence of self-mutilation when it was given at doses of >10 $mg \cdot kg^{-1} \cdot day^{-1}$. Albe-Fessard and Lombard (26) tested carbamazepine, clonazepam, and valproic acid in light doses, with inconclusive results. Our results also show a clear action of the long-term treatment with phenobarbital on autotomy. These findings suggest the possibility of reducing autotomy behavior in rats with the use of anticonvulsant drugs. However, when treatment is discontinued 10 days after sciatic section, autotomy increases, although there are no changes in animals that have had a rhizotomy.

Our results also indicate that the effect of phenobarbital on autotomy behavior is probably related more to its anticonvulsant properties than to any direct analgesic action of the drug. In our experience, only high doses of intrathecal phenobarbital increase the pain threshold in tests of acute pain. Anticonvulsant doses of phenobarbital are less than sedative or hypnotic doses, although the margin of safety is narrow (16,23). Potentially analgesic intraperitoneal doses were not reached in our short-term experiments, because 16 mg caused drowsiness and somnolence in the rat. However, 500 μg of intrathecal phenobarbital had a clear but weak analgesic action without secondary effects.

In conclusion, autotomous behavior after peripheral deafferentation in rats is delayed and reduced after long-term treatment with 10 $mg \cdot kg^{-1} \cdot day^{-1}$ of phenobarbital. From a clinical point of view, the administration of phenobarbital before deafferentation is only possible when this event is scheduled, such as amputations or ablative surgical procedures for the treatment of pain. The results of this study suggest that this analgesic action is related to the anticonvulsant activity of phenobarbital. Moreover, intrathecal phenobarbital has an analgesic action.

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