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Short communication

Inhibitory effect of oxcarbazepine on high-frequency firing in peripheral nerve fibers

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Abstract

We assessed the effects of oxcarbazepine, an antiepileptic derivative of carbamazepine, on discharges in single cutaneous afferent fibers produced by repetitive high-frequency stimulation (mimicking the abnormal excitation of peripheral nerves in neuropathic pain and paresthesia). After intravenous administration of oxcarbazepine, the later responses in the train dropped out without the earlier ones being affected and, thus, the total number of spikes decreased. The latency of the responses to an individual pulse was unchanged. These results, which indicate that oxcarbazepine inhibits the generation of high-frequency firing without affecting impulse conduction, suggest that this drug may be useful against neuropathic pain and paresthesia. © 2001 Published by Elsevier Science B.V.

Keywords: Oxcarbazepine; Excitation; Repetitive; Peripheral nerve; (Animal)

1. Introduction

It is well known that carbamazepine is effective in the treatment of seizure disorders and trigeminal neuralgia. In addition, carbamazepine treatment has been reported to be successful in the management of neuropathic pain (Tanelian and Brose, 1991). However, carbamazepine has unwanted side effects (e.g., allergy, rash, headache, nausea, leukopenia) that are attributed to its epoxide metabolite. In addition, because carbamazepine induces the P450 hepatic enzyme, it may interact with concomitant medications. Oxcarbazepine, the 10-keto analog of carbamazepine, has an antiepileptic effect similar to that of carbamazepine and is superior to carbamazepine with regard to side effects and clinical handling because it is metabolized via a P450-independent pathway (Dam et al., 1989; Grant and Faulds, 1992; Schmuts et al., 1994; Schwabe, 1994). Oxcarbazepine might be expected also to have an analgesic effect because it is a derivative of carbamazepine; however, no reports of such an effect have been published.

In painful neuropathic states, abnormal high-frequency discharges occur in the injured nerve (Kajander and Bennet, 1992; Xie and Xiao, 1990). Moreover, in normal subjects high-frequency impulses have been observed during episodes of paresthesia, immediately after release from nerve compression (Ochoa and Torebjork, 1982). At therapeutic free-serum concentrations, carbamazepine has been reported to reduce the number of action potentials evoked by high-frequency electrical stimulation without having an effect on the production of single action potentials (MacDonald, 1995). Moreover, lidocaine, which decreases the number of spikes in injured nerves (Tanelian and Maclver, 1991), has been demonstrated to have an effect similar to that of carbamazepine in normal cats (Koyama et al., 1997). In the present study, repetitive high-frequency stimuli were applied to a peripheral nerve in order to mimic the high-frequency firing observed in neuropathic pain and paresthesia. The possible effectiveness of oxcarbazepine in treating these states was assessed by looking for changes in the pattern of the evoked discharges.

2. Materials and methods

2.1. Materials

Oxcarbazepine, supplied by Novartis Pharmaceuticals, was dissolved in #400 polyethylene glycol (obtained from

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Nakarai Tesque, Tokyo, Japan). Other chemicals were obtained from commercial sources.

2.2. Methods

Experiments were performed as in a previous report (Koyama et al., 1997). The present study was approved by the Animal Care and Use Committee of the Shiga University of Medical Science.

2.2.1. Animal preparation

Adult cats were used for the experiments. Anesthesia was initially induced with ketamine HCl (20 mg/kg, i.m.) and maintained with urethane (125 mg/kg)–chloralose (10 mg/kg) solution (3.5 ml/kg, i.v.) via a catheter inserted into a cephalic vein. A tracheal cannula was inserted, and the animal was then paralyzed by an intravenous injection of pancuronium bromide (2–4 mg/kg/h) and artificially ventilated. Body temperature was maintained at 37–38°C with the aid of a heating lamp. The left superficial peroneal nerve was exposed, and all other branches of the sciatic nerve were cut to avoid recording spontaneous activity in these branches. A bipolar stimulating electrode was placed on the exposed superficial peroneal nerve. A laminectomy was performed over the lumbar enlargement to expose the spinal cord, and a recording electrode was placed on a dorsal-root filament. Single fibers were split from the filament, and those with a latency of more than 4 ms in response to single-pulse stimulation of the superficial peroneal nerve were used for the study.

2.2.2. Assessment of effects of oxcarbazepine

Spike discharges in a single fiber were displayed using a dot-raster processing program (QP-130; developed in cooperation with Nihon Koden, Tokyo, Japan). First, we selected the stimulus parameters in each animal. To select the interpulse interval, the superficial peroneal nerve was stimulated using pairs of pulses with various intervals

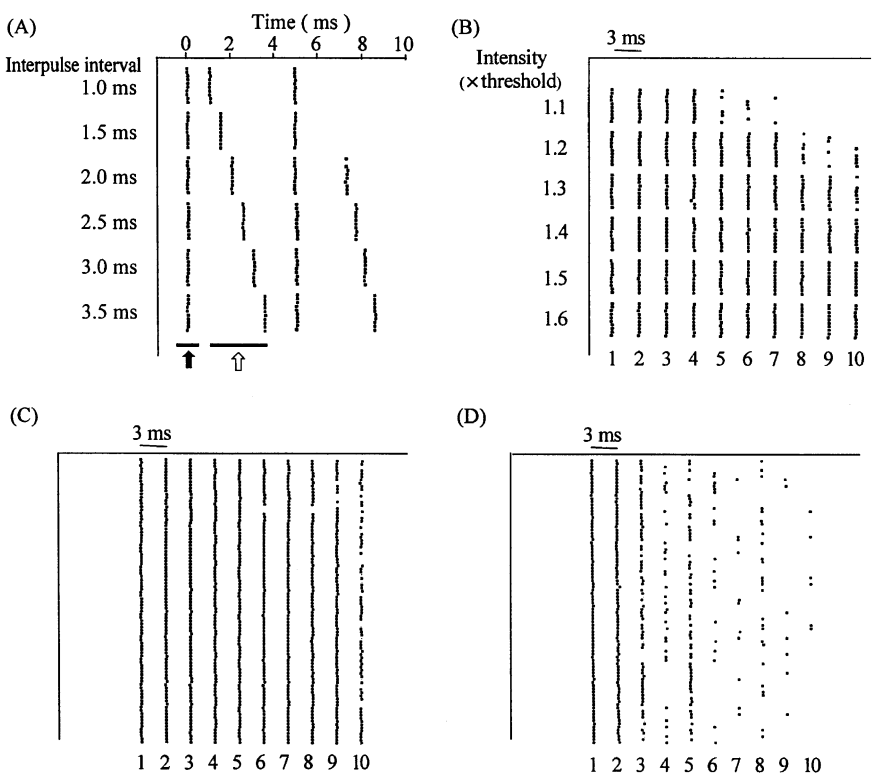

Fig. 1. Representative dot-raster displays derived from recordings from a dorsal rootlet single fiber. Pairs of pulses with various interpulse intervals (intensity, 1.3 times threshold) (A) and trains of 10 pulses of various intensities (interpulse interval, 3.0 ms) (B) were applied to the superficial peroneal nerve. Ten trials were performed for each interpulse interval or intensity. The first trial at a given interpulse interval or intensity is indicated by the top row of dots. In A, each dot in the vertical column marked with a solid arrow (i.e., at "Time 0") is a stimulus artifact representing the first stimulus in a pair. Each dot in the column marked with an open arrow (i.e., between "Time 1 ms" and "Time 3.5 ms") is a stimulus artifact representing the second stimulus in a pair. It can be seen that the gap between these columns is the same as the interpulse interval indicated to the left of the panel. Each dot in columns not marked with an arrow represents a single-spike response. It can be seen that the response latency was constant, whatever the interpulse interval, and that a second response did not appear if the interpulse interval was less than 2.0 ms. In B, each dot indicates a response. The numbers along the horizontal axis indicate the ordinal number of the responses to each pulse (from the first pulse to the 10th one) in a train. (C) and (D): Recordings obtained just before (C) and 15 min after (D) the administration of oxcarbazepine (20 mg/kg). The fiber was stimulated by a train of 10 pulses/s (delivered 90 times). The interpulse interval was 3 ms. A single dot indicates a single-spike response. The numbers along the bottom indicate the responses to each applied pulse (from the first pulse to the 10th one) in a train. The top dot in each column shows the response to the first trial, and the bottom one the response to the 90th trial.

(intensity, 1.3 times threshold). Then, to select the stimulus intensity, trains of 10 pulses of various intensities were delivered (the interpulse interval was chosen to be longer than the refractory period). From these results, the stimulus parameters evoking more than 90 responses per 100 stimuli were selected. Next, the effect of oxcarbazepine was assessed. Oxcarbazepine was administered intravenously via a catheter inserted into the cephalic vein. Ninety trains of 10 pulses each (i.e., 900 pulses in total), with the stimulus parameters selected as above and with a 1-s intertrain interval, were delivered to the superficial peroneal nerve. The number of evoked spikes was counted for each stimulation point in the sequence (i.e., in each column of dots marked 1–10 in Fig. 1C and D). The number of evoked spikes was then expressed as a percentage of the number of applied pulses.

2.2.3. Statistical analysis

Statistical analysis was performed using a paired t-test, values obtained after oxcarbazepine administration being set against the value obtained before its administration. For this, a Stad View 4.0 software program was used (Abacus Concepts, Berkley, CA, USA). Data are expressed as means ± S.E.M.

3. Results

The preliminary tests used to select the stimulus parameters for use in a given cat are illustrated in Fig. 1A and B. These two panels show representative recordings in which pairs of pulses with various interpulse intervals (intensity, 1.3 times threshold) or trains of 10 pulses at various intensities (the interpulse interval, 3.0 ms in the recording shown, was chosen to be longer than the refractory period) were delivered to the superficial peroneal nerve. When the interpulse interval was 3.0 ms and the pulse intensity was 1.3 times threshold, the number of responses was more than 90% of the number of stimuli. Thus, we selected these stimulus parameters for use in the experiment proper in this particular animal.

Representative recordings obtained before and 15 min after the administration of oxcarbazepine (20 mg/kg, i.v.) are shown in Fig. 1C and D, respectively. Responses to the later pulses in the train dropped out after oxcarbazepine administration without there being an effect on the response to the first pulse in each train. In fact, drop out of the first response was not observed at any counting point. After drug administration, the latency of the response to an individual pulse, if a response appeared, was unchanged.

Statistical analysis was performed on data obtained from 7 (10 mg/kg oxcarbazepine) and 5 (20 mg/kg oxcarbazepine) animals, and the results are shown in Fig. 2. At 20 mg/kg, oxcarbazepine reduced the number of spikes, the extent of the reduction increasing with time until, at 30 min after drug administration, it reached a plateau that was maintained until 45 min. Then, a slight recovery was observed. Between 10 and 60 min after oxcarbazepine administration, the reduction in the number of evoked spikes was statistically significant. In contrast, a significant effect was not observed following oxcarbazepine administration at a dose of 10 mg/kg.

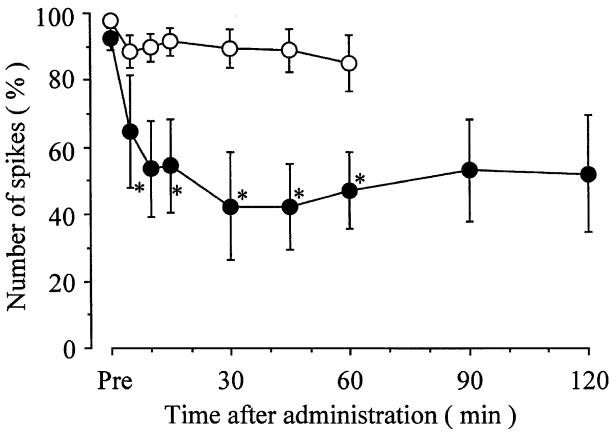

Fig. 2. Effect of oxcarbazepine on the number of spikes evoked by repetitive high-frequency stimulation. Number of spikes is expressed as a percentage of the number of applied pulses. Open circle = oxcarbazepine 10 mg/kg, i.v., Closed circle = oxcarbazepine 20 mg/kg, i.v. Each circle indicates mean ± S.E.M. from five to seven animals. Pre: Just before drug administration. *, $P < 0.05$ vs. Pre.

4. Discussion

Oxcarbazepine is rapidly metabolized to an active metabolite, its monohydrate derivative. In our preliminary study in the cat, the plasma concentration of the monohydrate derivative after an intravenous injection of 10 mg/kg oxcarbazepine (the lower dose used in the present study) was about the same or slightly greater than that reached after peroral administration of oxcarbazepine at antiepileptic doses in mice. Thus, we regarded the doses of oxcarbazepine used in the present study as appropriate, at least not markedly different, ones.

In the present study, oxcarbazepine reduced the number of spikes elicited by a train of high-frequency stimuli. However, the response to the first pulse in each train remained unchanged, and the latency remained constant in those responses to individual pulses that did appear. The persistence of the first response indicates that the stimulus intensity was sufficient to induce excitation and that oxcarbazepine did not increase the threshold for the first response. Indeed, we often checked the threshold during the experiment, but no increase was ever observed (data not shown). The constancy of the response latency indicates that oxcarbazepine did not affect the conduction velocity. Therefore, we postulated that oxcarbazepine suppresses the generation of high-frequency firing by prolonging the refractory period without affecting the conduction of nerve impulses.

The precise mechanism by which oxcarbazepine might prolong the refractory period was not revealed in our study. It has been suggested that carbamazepine prolongs the inactive period of the Na channel by binding to it only in the inactive state, and that this reduces the number of action potentials evoked by repetitive electrical stimulation without affecting the production of single-action potentials (MacLean and MacDonald, 1986). The inactivation of Na channels after depolarization is one of the causes of the refractory period. Therefore, it seems likely to us that oxcarbazepine prolongs the refractory period by a mechanism similar to the one that underlies the action of carbamazepine.

Chronic pain is associated with a number of complex changes, such as prolonged tissue damage, chronic inflammation, or injury to a peripheral nerve or to the central nervous system. The NMDA receptor is important in producing central hyperexcitability in chronic pain (Dray et al., 1994; Bernardi et al., 1996), and both carbamazepine (Bernardi et al., 1996; MacDonald, 1995; Watanabe et al., 1993) and lidocaine (Fracer et al., 1992) block this receptor. Carbamazepine also has antiinflammatory effects (Bianchi et al., 1995). To fully elucidate the effects of oxcarbazepine on pain, further investigations will be needed to determine whether, for example, it has actions on NMDA receptors and inflammation. Nevertheless, the effect of oxcarbazepine revealed here, even though the study was carried out with normal animals, suggests that it might inhibit the abnormal high-frequency discharge in peripheral nerves seen in neuropathic pain and paresthesia.

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