PAIN® 155 (2014) 356–366

www.elsevier.com/locate/pain

Analgesic treatment with pregabalin does not prevent persistent pain after peripheral nerve injury in the rat

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 26 August 2013
Received in revised form 11 October 2013
Accepted 21 October 2013

Keywords:
Postoperative pain
Neuropathic pain
Preventive analgesia
Pregabalin

ABSTRACT

Reducing the risk of chronic postoperative pain through preventive analgesia is an attractive therapeutic concept. Because peripheral nerve lesions are a major cause of chronic pain after surgery, we tested in rats whether analgesic treatment with pregabalin (PGB) has the capacity to mitigate the development of persistent neuropathic pain-like behavior. Starting on the day of spared nerve injury or 1 week later, we treated rats with a continuous intrathecal infusion of PGB (300 or 900 μg/24 hours) or vehicle for up to 28 days. Rats receiving early PGB treatment had almost normal withdrawal thresholds for punctate mechanical stimuli and were clearly less sensitive to pinprick or cold stimulation. The responses to punctate mechanical and cold stimulation were still reduced for a brief period after the infusion was terminated, but the difference from vehicle-treated rats was minor. Essentially, the analgesic effect of PGB was limited to the duration of the infusion, whether analgesia started at the time of surgery or with a delay of 1 week, independently of the length of the treatment. PGB did not suppress the activation of spinal microglia, indicating that analgesia alone does not eliminate certain pain mechanisms even if they depend, at least partially, on nociceptive input. Unexpectedly, intrathecal infusion of PGB did not inhibit the nerve injury-induced accumulation of its binding target, the voltage-gated calcium channel subunit α2δ1, at primary afferent terminals in the spinal cord. Interference with the synaptic trafficking of α2δ1 is not required to achieve analgesia with PGB.

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1. Introduction

Peripheral nerve injury is a major risk factor for chronic pain after surgery. Persistent pain occurs in 10%–50% of patients undergoing procedures such as thoracotomy, breast surgery, or inguinal hernia repair, which expose local nerves to possible damage from pressure or transection [33]. In as many as two-thirds of patients with chronic postoperative pain, the pain is of probable or definite neuropathic origin [27]. Neuropathic pain following surgery involves multiple mechanisms. Injured and adjacent unaffected nerve fibers develop spontaneous activity and become more sensitive to mechanical or thermal stimulation [9,68]. This rise in input leads to enhanced synaptic efficacy in central nociceptive pathways, a process termed central sensitization [36]. Nociceptive transmission may increase further as spinal inhibition is reduced and descending modulation from the brainstem shifts toward facilitation [17,26,56,65]. Additional sources of nociceptive input include protracted wound healing or sustained inflammation, which may occur after the implantation of synthetic material, for example, a prosthetic mesh for hernia repair [9,58].

The anatomy of an operation site often limits the options for modifying surgical techniques in order to minimize the risk of nerve injury. Pharmacological strategies that have been developed to reduce the incidence, duration, or intensity of postoperative pain can be divided into preemptive and preventive approaches. Preemptive analgesia aims to curb the acute postoperative pain by starting pain treatment ahead of the surgery. A variety of medications have been clinically tested for this purpose, with mixed results [4,45]. The concept of preventive analgesia is based on the hypothesis that the risk of chronic pain can be decreased by blocking pain mechanisms (such as central sensitization) that depend on nociceptive input. However, evaluating the efficacy of preventive analgesia in a clinical trial is difficult, because multiple

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http://dx.doi.org/10.1016/j.pain.2013.10.024

variables, including preoperative pain, surgical technique, and anesthetic regimen, need to be controlled to ensure comparability of the treatment groups [18]. In addition, it is unknown when the transition from acute to chronic postoperative pain occurs, or whether there is a distinct transition period at all [58].

We employed a rat model of nerve injury-induced chronic pain to test whether analgesia can achieve a "disease-modifying" effect beyond the immediate attenuation of pain-like behavior. We treated the rats with pregabalin (PGB), a first-line recommended analgesic for neuropathic pain. PGB binds to the α2δ1 subunit and, with less affinity, the α2δ2 subunit of voltage-gated calcium channels (VGCC) [24]. PGB interferes with the synaptic targeting of VGCCs [5,30] and, as a result, reduces glutamate and neuropeptide release [35,66]. PGB is considered a prime candidate for the prevention of postoperative pain because of its efficacy against neuropathic pain, even though not every patient responds to it equally well [18,25]. The drug does not impede motor or somatosensory functions other than pain, an important advantage over sodium channel blockers, which also possess the capacity to inhibit activity-dependent changes in nociceptive transmission [4,64]. And it is better tolerated than antagonists of the *N*-methyl-d-aspartate (NMDA)-type glutamate receptor, which have been used to decrease central sensitization [22,71].

2. Methods

2.1. Animals

We used male Sprague-Dawley rats (Charles River Laboratories) aged 2–3 months for all experiments. Animal procedures adhered to the guidelines of the Committee for Research and Ethical Issues of the International Association for the Study of Pain and were approved by the Subcommittee on Research Animal Care of Massachusetts General Hospital and the Institutional Animal Care and Use Committee of Columbia University Medical Center.

2.2. Peripheral nerve injury

Surgery for spared nerve injury (SNI) was performed on animals anesthetized using 3% isoflurane inhalation for induction and 2% isoflurane during maintenance. We ligated the tibial and the common peroneal nerves with nylon (5–0) and transected them distally, leaving intact the third branch of the sciatic nerve, the sural nerve [19].

2.3. Drug treatment

PGB was provided by Pfizer. We dissolved the drug in phosphate-buffered saline (PBS), pH 7.4, and employed subcutaneously implanted osmotic pumps (Alzet, Cupertino, CA) for continuous intrathecal delivery of 300 or 900 μg PGB/24 hours at an infusion rate of 1 or 10 μL/h, respectively. PBS served as vehicle control. The osmotic pumps were implanted either at the time of nerve injury or 7 days later. They were connected to a polyurethane catheter (Alzet), which we inserted into the lumbar subarachnoid space with the catheter tip positioned on the dorsal surface of the spinal cord at segmental level L3. We verified the integrity of the catheter by dissection following completion of the experiments. Seven animals with neurological deficits or signs of infection after the catheter implantation were excluded from the experiments.

2.4. Behavioral testing

Investigators were blind to the treatment in all experiments. Behavioral assessments were performed in the morning to avoid interference of circadian differences in animal activity.

Somatosensory function was examined after habituating the rats to the testing environment. We obtained 2 baseline measurements in the week preceding the surgery. Following SNI, we tested neuropathic pain-like behavior at defined intervals during the infusion of PGB or vehicle and for up to 12 days after the treatment was terminated. The animals were placed on an elevated wire grid and stimulated on the plantar surface of the hind paw, in the territory of the "spared" sural nerve. We used calibrated von Frey monofilaments of logarithmically increasing force (range 0.0174 to 34.7 g) to determine the withdrawal threshold for punctate mechanical stimulation. The threshold was defined as the lowest force that provoked a brisk paw withdrawal at least twice in 10 applications. To test for mechanical hyperalgesia, we measured the withdrawal duration after pricking the plantar surface of the hind paw with a medium-sized safety pin. The response to cold stimulation was tested by applying a drop of acetone, which produces a cool sensation on the skin upon evaporation. The acetone drop was dispensed from a syringe without touching the skin. We recorded behavioral responses to the acetone application over 1 minute and measured the cumulative time the animal spent licking, shaking, or lifting the paw [19,55].

Motor performance was evaluated in a group of uninjured rats 7 days after the intrathecal drug treatment started. We assessed walking and spontaneous exploratory behavior in an open field. To test the righting reflex, we turned the rats on their backs and observed how they regained a normal upright position through coordinated twisting of the body. We considered the reflex intact if the rats righted themselves promptly and successfully [10]. To evaluate the hopping response, the examiner supported the trunk of the animal, fixed one hind leg in his hand and moved the body laterally. We recorded the ability of the rat to hop with the weight-bearing limb in the direction of the movement. Righting and hopping were scored as 1 if intact or 0 if compromised. The stepping reflex was evoked by drawing the dorsum of the hind paw across the edge of a table while supporting the animal's trunk. A normal reflex consists of a flexion and upward movement of the hind leg and repositioning of the paw with toes spread on the surface of the table. We rated the performance as 0 if the repositioning failed, 1 for severe impairment, 2 for slight impairment, and 3 if the repositioning was completed without deficit [62].

2.5. Immunohistochemistry

We deeply anesthetized the rats and perfused them transcardially with PBS, followed by a phosphate-buffered solution of 4% paraformaldehyde. The L4 segment of the spinal cord was dissected, postfixed for 2 hours, cryoprotected overnight in 20% sucrose, and embedded in Tissue-Tek (Sakura Finetek, Torrance, CA). Transverse sections through the spinal cord were cut at a thickness of 10 μm on a cryostat. We blocked unspecific protein binding sites by incubating the sections for 1 hour in PBS containing 0.5% bovine serum albumin (Sigma-Aldrich, St. Louis, MO), 1% blocking reagent (Roche Applied Science, Madison, WI) and 0.1% Triton X-100 (Sigma-Aldrich). The sections were incubated overnight at 4°C with primary antibodies directed against the VGCC subunit α2δ1 (1:500, produced in mouse; Sigma-Aldrich), Cd11b (1:500, mouse; AbD Serotec, Raleigh, NC) or ionized calcium-binding adaptor molecule 1 (1:500, rabbit; Wako Chemicals, Richmond, VA). The immunostaining was completed by incubating the sections for 1 or 2 hours at room temperature with species-specific secondary antibodies that were conjugated with Alexa Fluor dyes (1:500; Life Technologies, Grand Island, NY). Immunodetection of α2δ1 was enhanced by warming the slides in Tris buffer (pH 8.0) for 1 hour at 70°C before the blocking of unspecific protein binding sites [67]. We used the antifading reagent ProLong Gold (Life Technologies) to mount the stained sections.

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