学 位 論 文 の 要 旨

氏名　　奈良井　康宏

学　位　論　文　名　Gabapentin Augments Anti-Hyperalgesic Effects of Diclofenac Sodium Through a Spinal Action in the Postoperative Pain Model of Rats

発　表　雑　誌　名　Anesthesia & Analgesia
（巻: 初頁～終頁等, 年）　(115, 189-193, 2012)

著　　者　　名　Yasuhiro Narai, Noritaka Imamachi, Yoji Saito

論 文 内 容 の 要 旨

INTRODUCTION

Systemic administration of gabapentin or nonsteroidal anti-inflammatory drugs (NSAIDs) is effective for neuropathic and postoperative pain. In a rat postoperative pain model, hind paw incision produced mechanical hyperalgesia. Intrathecal administration of gabapentin or NSAIDs inhibits mechanical hyperalgesia in this model. Gabapentin is a structural analog of γ-aminobutyric acid (GABA) and binds to the $\alpha_{2\delta}$ subunit of voltage-dependent calcium channels in the dorsal horn. Furthermore, gabapentin indirectly affects the adrenaline α_2 receptor, 5-HT receptor, and muscarinic receptor. The spinal noradrenaline level increased after systemic administration of gabapentin in humans. In contrast, the main antinociceptive effects of NSAIDs at the spinal cord are due to an inhibition of cyclooxygenase (COX). Inhibition of COX-1 and COX-2 attenuates prostaglandin (PG) E_1 production through the arachidonic acid cascade. Preoperative intrathecal administration of a COX-1 inhibitor attenuates mechanical hypersensitivity in a rat postoperative pain model. A COX-2 inhibitor reduces endocannabinoid breakdown at the spinal cord. COX-2 may play an important role in inflammatory pain at the spinal level. A combination of gabapentin and a COX-2 inhibitor has clinical utility for postoperative pain and enhances functional recovery after surgery, but systemic administration of a combination of gabapentin and a COX-2 inhibitor does not reduce the frequency of side effects, including nausea, sedation, and dry mouth. No information is available regarding the effects of intrathecal administration of a combination of gabapentin and NSAIDs. We therefore

investigated the antihyperalgesic effects of an intrathecal administration of a combination of gabapentin and diclofenac sodium, a non-selective COX inhibitor, in a rat model of postoperative pain.

MATERIALS AND METHODS

Male Sprague-Dawley rats (200–250 g) were used in all experiments. To reduce the influence of the experimental environment, all rats were caged for test stimulation 2 hours per day for at least 4-5 days before intrathecal catheterization and testing in our experiment room. Rats were prepared for intrathecal catheters under halothane anesthesia. The catheter (double-stretched PE-10 joined to normal PE-10, then to PE-20) was passed caudally at lumbar level 3-4. The catheter was tested by assessing motor strength following an injection of 20 μl of 2% lidocaine. Only these animals without neurological dysfunction after catheter insertion and the testing as above, were studied. Two days after catheterization, gabapentin (4, 40, or 400 μg per 20 μl of saline), diclofenac sodium, a non-selective cyclooxygenase inhibitor (2, 20, or 200 μg per 20 μl of 6% glucose), 20 μl saline and 20 μl 6% glucose as the vehicle controls, and 2 sets of combination (40 μg gabapentin + 20 μg diclofenac; and 4 μg gabapentin + 2 μg diclofenac) in 20 μl 6% glucose were injected intrathecally. We performed a hind-paw incision 30 minutes after injection. A 1-cm longitudinal incision was made through the skin and fascia, starting 0.5 cm from the edge of the heel and extending toward the toes. The wound was closed with 5-0 nylon sutures and covered with an antibiotic medicine. Each group consisted of six rats. Behavioral studies were performed about 2 hours after being placed in the cage. Von Frey filament testing was conducted at a site, approximately 10 mm distal to the incision wound, to determine the punctuate mechanical withdrawal threshold. The 50% likelihood withdrawal threshold was calculated using the Dixon up-and-down method. The mechanical threshold was measured to evaluate secondary hyperalgesia using Von Frey filaments before intrathecal catheterization and at 2 hours, 1, 3, 5, and 7 days after paw incision.

RESULTS AND DISCUSSION

Sixty rats were used in this study and no rats were excluded from the study. In the postoperative pain model, the withdrawal threshold on the ipsilateral side decreased 2 hours after the paw incision and then returned gradually to the pre-incision baseline threshold. The withdrawal threshold on the contralateral side remained unchanged from the pre-incision threshold. Saline and 6% glucose did not induce antihyperalgesic effects in the postoperative rat model. Gabapentin 400 μg attenuated mechanical hyperalgesia from 2 hours to 7 days compared to the control group ($P < 0.05$). Diclofenac 200 μg inhibited hyperalgesia from 2 hours to 5 days compared to the control group ($P < 0.05$). The group of “40 μg gabapentin + 20 μg diclofenac” had a significantly reduced secondary

hyperalgesic response in 2 hours and 1 day, compared to 40 μg gabapentin and 20 μg diclofenac ($P < 0.05$, respectively). The group of "4 μg gabapentin + 2 μg diclofenac" had a significantly reduced secondary hyperalgesic response in 2 hours and 1 day, compared to 2 μg diclofenac ($P < 0.05$, respectively). The withdrawal threshold on the contralateral paw did not change compared with the pre-incision threshold.

The current study had two main findings. First, high-dose gabapentin and diclofenac showed antihyperalgesic effects at the spinal level in a rat model of postoperative pain. Second, we showed that the intrathecal administration of gabapentin in combination with diclofenac reduced mechanical hyperalgesia at doses that had no antihyperalgesic effects when given alone. These results suggest that intrathecal administration of gabapentin combined with diclofenac produces antihyperalgesic effects for postoperative pain. The mechanism of antihyperalgesic effects at the spinal level for the combination of gabapentin and diclofenac is unknown. Repeated afferent stimuli produce hyperalgesia and allodynia at the spinal level. Gabapentin inhibits the release of substance P and glutamic acid from primary afferent fibers. This may attenuate the activation of secondary neuron fibers. NSAIDs inhibit the production of PGs through the arachidonic acid cascade in secondary neuron fibers. Gabapentin is known to attenuate primary neuronal excitation and NSAIDs are known to reduce PG production in secondary neurons. This combination may inhibit some pathways to produce hyperalgesia and allodynia, permitting gabapentin augmentation of the antihyperalgesic effects of diclofenac.

CONCLUSION

Intrathecal administration of gabapentin and diclofenac in combination reduced secondary hyperalgesia at doses having no antihyperalgesic effects when given individually. Our results suggest that gabapentin and diclofenac play an important role in postoperative pain reducton at the spinal level, and that gabapentin augments the antihyperalgesic effects of diclofenac through an action in the spinal cord.