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Short communication

Effects of α1- and α2-adrenoreceptor antagonists on cold allodynia in a rat tail model of neuropathic pain

Sun Kwang Kim[a], Byung-Il Min[a,b,*], Ji Hoon Kim[a], Byung Gil Hwang[a], Gi Yong Yoo[a], Dong Suk Park[c], Heung Sik Na[d]

[a]Department of East-West Medicine, Graduate School, Kyung-Hee University, Seoul, South Korea
[b]Department of Physiology, College of Medicine, Kyung-Hee University, Seoul, South Korea
[c]Department of Acupuncture and Moxibustion, College of Oriental Medicine, Kyung-Hee University, Seoul, South Korea
[d]Department of Physiology, College of Medicine, Korea University, Seoul, South Korea

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Abstract

Systemic administrations (0.1, 0.5, and 2 mg/kg) of α1-adrenoreceptor (AR) antagonist prazosin dose-dependently attenuated cold allodynia in a rat tail model of neuropathic pain, whereas α2-AR antagonist yohimbine exacerbated it. These results suggest that the functions of α1- and α2-AR in this model are excitatory and inhibitory, respectively, consistent with their general properties. It is also proposed that cold allodynia can be reversed by α1-AR antagonist and exacerbated by α2-AR antagonist.

Theme: Sensory system
Topic: Pain modulation: pharmacology

Keywords: Neuropathic pain; Cold allodynia; Prazosin; Yohimbine; α1-adrenoreceptor; α2-adrenoreceptor

Peripheral nerve injury often leads to neuropathic pain, which is characterized by spontaneous burning pain, allodynia, and hyperalgesia [3]. The underlying mechanisms are complex and appear to involve peripheral and central components of the nervous system, including activity in the sympathetic nervous system [4]. Sympathetic nerve block by phentolamine (α-adrenoreceptor (AR) antagonist) administration has long been used for diagnosis and treatment of neuropathic pain patients [2,24]. In experimental animal models, peripheral nerve injury also results in the sprouting of sympathetic fiber into dorsal root ganglion [21] and neuropathic symptoms can be alleviated by surgical sympathectomy or sympathetic nerve block such as phentolamine administration [9,12,14,28], although a few studies reported the opposite [25,26]. Accordingly, numerous studies have recently attempted to elucidate the effects of specific α-AR subtype antagonists on neuropathic pain. However, the administration of α1- or α2-AR antagonists has produced inconsistent results [9,18,22,33]. Information is thus unclear regarding the roles of α1- and α2-AR and the effects of their antagonists in neuropathic pain.

The present study, employing a rat tail model of neuropathic pain [13,23], was performed to examine how α1- and α2-AR antagonists act upon cold allodynia and then explore the roles of α1- and α2-AR. To this aim, the effects of systemic administration of prazosin (α1-AR antagonist) or yohimbine (α2-AR antagonist) on the behavioral signs of cold allodynia were evaluated. Preliminary results of the present study have been reported in an abstract form [11].

Young adult male Sprague–Dawley (SD) rats (180–220 g) were used. Neuropathic surgery and behavioral test were

* Corresponding author. Department of Physiology, College of Medicine, Kyung-Hee University, #1 Hoegi-Dong, Dongdaemoon-Gu, Seoul 130-701, South Korea. Fax: +82 2 964 2195.
E-mail address: mbi@khu.ac.kr (B.-I. Min).

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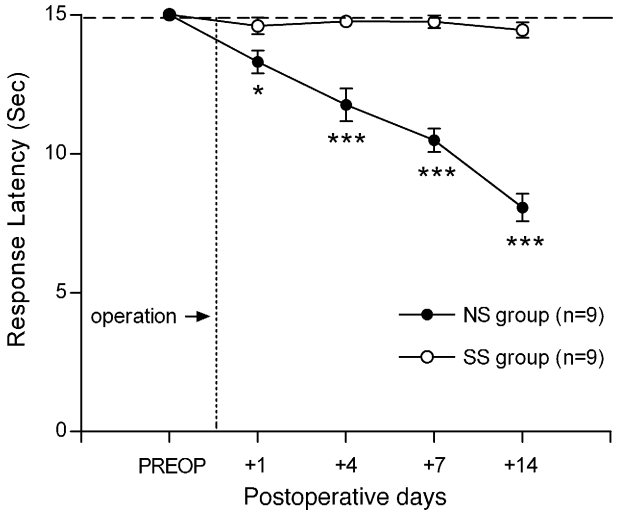

Fig. 1. Temporal course of cold allodynia after the neuropathic surgery. Mean (±SEM) tail response latencies to cold (4 °C) water stimulation are plotted against postoperative day. Asterisks indicate the scores that are significantly different from the preoperative value. (*$P < 0.05$; ***$P < 0.001$, Dunnett's post-hoc test after one-way ANOVA). PREOP = preoperative values; NS group = neuropathic surgery group; SS group = sham surgery group.

performed as previously described [13,23]. Briefly, under sodium pentobarbital anesthesia (40 mg/kg, i.p.), the right superior caudal trunk was exposed, freed from the surrounding tissues, and transected at the level between the S1 and S2 spinal nerves. Control rats underwent sham surgery, i.e. the same surgical procedures as the model rats except for transection of the nerve. The behavioral test for cold allodynia was conducted 1 day prior to the nerve injury and 1, 4, 7, and 14 days postoperatively. The cold allodynia signs were sought by immersing the tail in cold water (4 °C) and the latency to an abrupt tail movement response was measured with a cut-off time of 15 s.

Fourteen days after the nerve injury, the effects of a systemic injection of prazosin or yohimbine (0.1, 0.5, and 2 mg/kg, i.p., Tocris) on cold allodynia were assessed 30 min before and 30, 150, 270 min, and 24 h after the injection. Prazosin was dissolved in 50% DMSO and yohimbine was dissolved in physiological saline on the day of testing. Intraperitoneal injection of 50% DMSO and physiological saline (1 ml/kg) served as control.

Data are presented as mean ± SEM. Differences between pre- and post-injection times were assessed by using one-way analysis of variance (ANOVA) followed by Dunnett's post-hoc test for multiple comparisons. In all cases, $P < 0.05$ was considered significant.

The results of the tail immersion test are shown in Fig. 1. Preceding the nerve injury, rats did not show an abrupt tail movement in response to the cold water stimuli. However, following the injury, rats showed an increased sensitivity to cold stimuli. We interpreted this as a sign of the cold allodynia. The cold allodynia sign appeared 1 day after surgery, with maximal allodynia being observed in the second week. The sham surgery group showed no change.

The effects of systemic administration of prazosin or yohimbine (0.1, 0.5, and 2 mg/kg, i.p.) on cold allodynia are shown in Fig. 2. Prazosin dose-dependently attenuated cold allodynia (Fig. 2A). A 0.5 mg/kg dose significantly attenuated cold allodynia for up to 150 min and a 2 mg/kg dose did so for 270 min ($P < 0.001$), but a 0.1 mg/kg dose produced no effect ($P > 0.05$). In contrast, yohimbine dose-dependently exacerbated cold allodynia (Fig. 2B). A

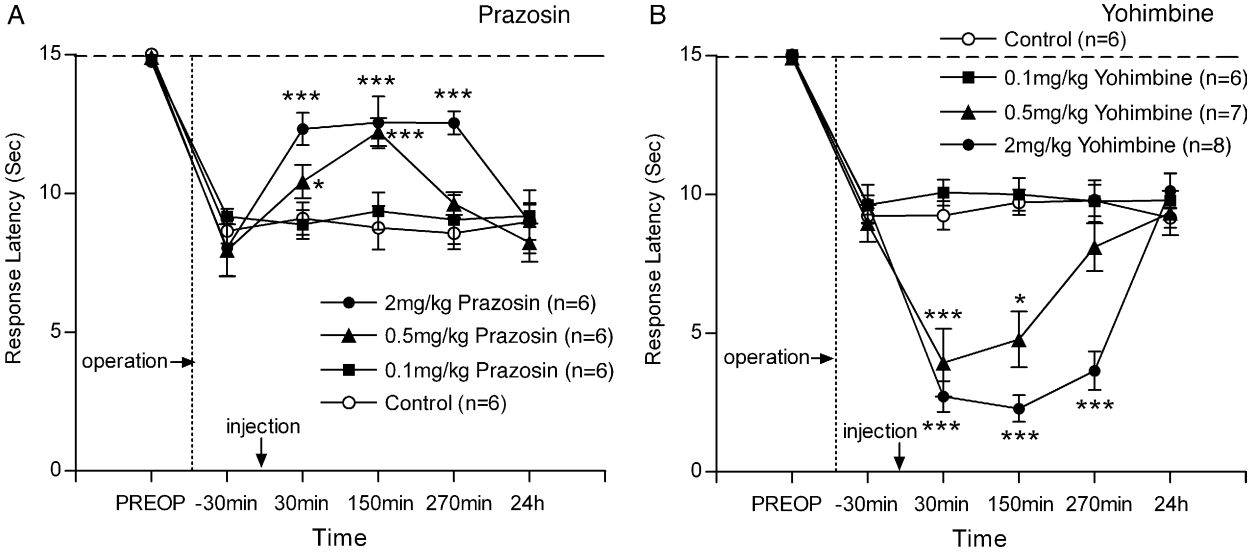

Fig. 2. The effects of intraperitoneal injection of prazosin or yohimbine (0.1, 0.5, and 2 mg/kg) on the behavioral signs of cold allodynia in a rat tail model of neuropathic pain. Mean (±SEM) tail response latencies to cold (4 °C) water stimulation are plotted as a function of time and dose. (A) Prazosin dose-dependently attenuated the signs of cold allodynia. (B) Yohimbine dose-dependently exacerbated the cold allodynia signs. Asterisks indicate the values that are significantly different from the value preceding the injection (*$P < 0.05$; ***$P < 0.001$, Dunnett's post-hoc test after one-way ANOVA). PREOP = preoperative values.