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Short communication

Individual differences in the sensitivity of cold allodynia to phentolamine in neuropathic rats

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Abstract

In neuropathic rats sensitive to phentolamine (α-adrenoreceptor antagonist, 2 mg/kg, i.p.), prazosin (α_1-adrenoreceptor antagonist, 0.5 mg/kg, i.p.) significantly attenuated cold allodynia whereas yohimbine (α_2-adrenoreceptor antagonist, 0.5 mg/kg, i.p.) had no significant effect. In neuropathic rats insensitive to phentolamine, yohimbine significantly exacerbated cold allodynia whereas prazosin had no significant effect. These results suggest that the individual differences in the sensitivity of cold allodynia to phentolamine may be due to the difference in the α-adrenoreceptor subtype predominantly involved in cold allodynia.

Keywords: Neuropathic pain; Cold allodynia; Phentolamine; Prazosin; Yohimbine; α-adrenoreceptor

1. Introduction

Peripheral nerve injury often leads to neuropathic pain, which is divided into either sympathetically maintained pain or sympathetically independent pain (Campbell et al., 1993; Roberts, 1986). Although the amount of sympathetic sprouting in the injured nerve and corresponding dorsal root ganglion has been the likely factor in determining the sympathetic dependence of neuropathic pain (Chung et al., 1996; Ramer and Bisby, 1998), it has been reported that this sympathetic sprouting is not responsible for the production, severity and sympathetic dependence of neuropathic pain behaviors (Kim et al., 1998, 1999; Rubin et al., 1997). Therefore, it is still unclear why peripheral nerve injury leads to sympathetically maintained pain in some cases, but sympathetically independent pain in others.

In our previous study (Kim et al., 2005), prazosin (0.5 mg/kg, i.p.) significantly relieved cold allodynia in the rat tail model of neuropathic pain while yohimbine (0.5 mg/kg, i.p) exacerbated it. Intriguingly, during the experiments, we found that some rats responded strongly to prazosin and little to yohimbine whereas others displayed the opposite responses. From these observations, we hypothesized that the first group could be assigned as sympathetically maintained pain group while the second group were sympathetically independent pain group. The present study was performed to explore our hypothesis by examining the effects of prazosin or yohimbine on the behavioral signs of cold allodynia in the sympathetically maintained pain and sympathetically independent pain groups. Prazosin is a very potent and selective α_1-adrenoreceptor antagonist, whereas yohimbine is a competitive antagonist that is selective for α_2-adrenoreceptors (Hoffman, 2001).

2. Materials and methods

Young adult male Sprague–Dawley rats weighing 180–220 g were used. Neuropathic surgery and behavioral tests

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were performed as previously described (Kim et al., 1998, 1999). 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. The cold allodynia signs were tested by immersing the tail in cold water (4 °C) and the latency to an abrupt tail movement was measured with a cut-off time of 15 s.

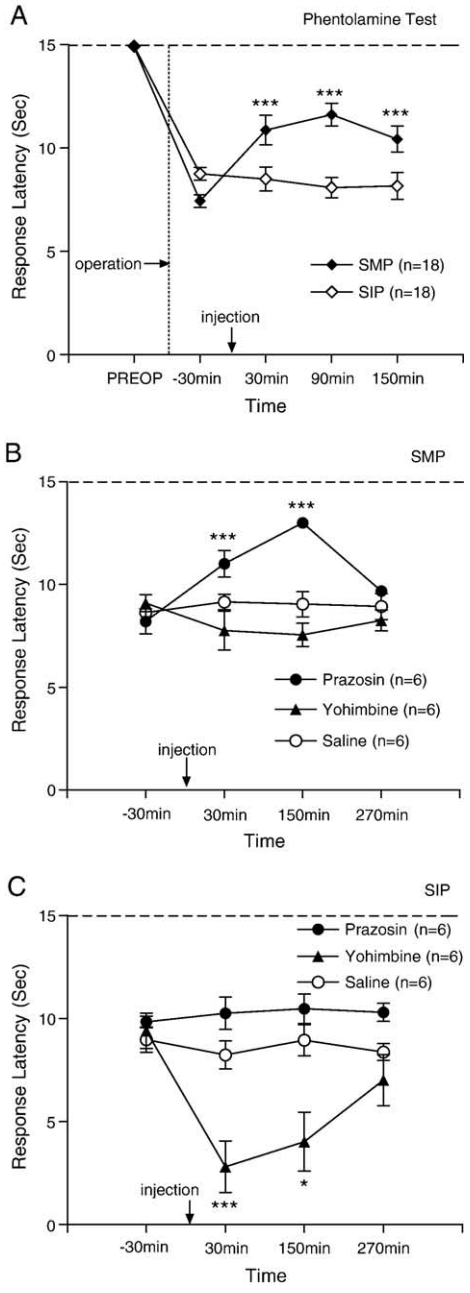

Fig. 1. The effects of intraperitoneal injection of prazosin or yohimbine (0.5 mg/kg) on cold allodynia in the sympathetically maintained pain (SMP) and sympathetically independent pain (SIP) groups. (A) SMP group showed a significant reduction in cold allodynia after an intraperitoneal injection of phentolamine (2 mg/kg), while SIP group showed no significant changes. (B) In the SMP group, prazosin significantly attenuated cold allodynia, whereas yohimbine produced no significant effect. (C) In the SIP group, yohimbine significantly exacerbated cold allodynia, whereas prazosin had no significant effect. Asterisks indicate the values that are significantly different from the value before injection (*$P<0.05$; *** $P<0.001$, Dunnett's post-hoc test after one-way ANOVA). PREOP=preoperative values.

Fourteen days after the nerve injury, the effects of phentolamine (2 mg/kg, i.p.) on cold allodynia were assessed 30 min before and 30, 90, and 150 min after injection. Thereafter, the rats were divided into two groups; those where signs of cold allodynia were significantly relieved by phentolamine were called the sympathetically maintained pain group, and those displaying no significant change were called the sympathetically independent pain group. Three days after the phentolamine test, the effects of a systemic injection of prazosin or yohimbine (0.5 mg/kg, i.p.) on cold allodynia in the sympathetically maintained pain and sympathetically independent pain groups were assessed 30 min before and 30, 150, and 270 min after injection. All drugs except for prazosin were dissolved in physiological saline on the day of testing. Prazosin was dissolved in 50% dimethyl sulfoxide (DMSO). Intraperitoneal injection of physiological saline and 50% DMSO (1 ml/kg) served as control.

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

3. Results

Preceding the nerve injury, rats did not show an abrupt tail movement in response to cold water stimuli. However, following the injury, rats showed an increased sensitivity to cold stimuli. We interpreted this as a sign of cold allodynia. The cold allodynia sign appeared one day after surgery, with maximal allodynia being observed in the second week. The effects of systemic administration of prazosin or yohimbine on cold allodynia in the sympathetically maintained pain and sympathetically independent pain groups are shown in Fig. 1. The sympathetically maintained pain group showed a significant reduction in cold allodynia after an injection of phentolamine (Fig. 1A). In the sympathetically maintained pain group, prazosin significantly attenuated cold allodynia, whereas yohimbine produced no significant effect (Fig. 1B). The sympathetically independent pain group showed no significant changes in cold allodynia after an injection of phentolamine (Fig. 1A). In the sympathetically independent pain group, yohimbine significantly exacerbated cold allodynia, whereas prazosin had no significant effect (Fig. 1C). Physiological saline (1 ml/kg, i.p.) had no significant effect in the sympathetically maintained pain and sympathetically independent pain groups (Fig. 1B, 1C), and neither did 50% DMSO (data not shown).

4. Discussion

The present study shows that rats of the sympathetically maintained pain group are sensitive to prazosin and insensitive to yohimbine whereas rats of the sympathetically independent pain group are sensitive to yohimbine and insensitive to

prazosin. These results indicate that α_1-adrenoreceptor is predominantly involved in cold allodynia in the sympathetically maintained pain group while α_2-adrenoreceptor is predominantly involved in the sympathetically independent pain group. Therefore, it is suggested that individual differences in the sympathetic dependence of cold allodynia in neuropathic rats may be due to the difference in the α-adrenoreceptor subtype predominantly involved in cold allodynia.

Among the many possible explanations for our results, the difference of genetic factors between the sympathetically maintained pain and sympathetically independent pain groups seems to be the main cause. Lee et al. (1997) found that different batches of Sprague–Dawley rats following peripheral nerve injury showed different sensitivities to the α-adrenoreceptor blocker, and finally demonstrated the strain differences in the sensitivity of mechanical allodynia signs to phentolamine. In fact, the importance of genetic factors in neuropathic pain behaviors has already been established. Two sub-strains of Sprague–Dawley rats displayed different degrees of neuropathic pain behaviors (Xu et al., 2001; Yoon et al., 1999) and the genotype also significantly affected the responses of 11 inbred mouse strains on 12 nociceptive measures, including neuropathic pain (Mogil et al., 1999). Alternatively, the differences of change in specific α-adrenoreceptor subtype density and/or function after nerve injury might contribute to the present results. It has been reported that the mean density of α_1-adrenoreceptors was significantly greater in the hyperalgesic skin of patients with reflex sympathetic dystrophy than in the skin of normal individuals (Drummond et al., 1996). In contrast, a few studies reported that injured afferent fibers and their dorsal root ganglion developed novel α_2-adrenoreceptors (Millan, 2002). Moreover, α_1-adrenoreceptor hyperresponsiveness or α_2-adrenoreceptor presynaptic dysfunction with diminished norepinephrine reuptake can lead to neuropathic pain (Teasell and Arnold, 2004). To explore these possibilities, the differences of gene expressions and α-adrenoreceptor subtype density in the dorsal root ganglion between the sympathetically maintained pain and sympathetically independent pain groups are to be investigated in future studies.

In conclusion, it is proposed that the individual differences in the sensitivity of cold allodynia signs to phentolamine may be due to the difference in the α-adrenoreceptor subtype (i.e. α_1- or α_2-adrenoreceptor) predominantly involved in cold allodynia.

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