Influences of Several Vasodilators on the Pain Threshold in healthy Men

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＝국문 초록＝

건강인에 있어서 각종 혈관확장제가 동통 역치에 미치는 영향

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정상인에서 Guanethidine Nicardipine Nitroglycerine Prostaglandin E_1을 피하주사하고 지속적인 복사열을 주사한 후에 Pain Meter NYT-5를 이용하여 동통역치를 측정하였다.

통증역치는 Guanethidine과 Nicardipine에 의해 상승되었으며 Nitroglycerine에 의해서는 거의 변화가 없고 Prostaglandin E_1에 의해서는 감소되었다.

이러한 변화는 지각신경섬유의 말단 감각수용체에 대한 감수성이 이들 혈관확장제에 대하여 서로 다른 작용을 나타내는 것 같다.

INTRODUCTION

Intravenous regional administration of guanethidine, nicardipine, and nitroglycerin (NTG) and topical application of prostaglandin E_1 (PGE_1) ointment were reported to be effective, in the treatment of reflex sympathetic dystrophy (RSD)[1~3]. Still it is uncertain why these vasodilators are effective in relieving the pain from RSD. RSD is a syndrome of pain, decrease in local temperature and sweating due to persistent sympathetic hyperactivity after nerve trauma, leading to nutritional impairment and atrophy of the affected skin and bone tissues[4~6]. From the point of the mechanism of RSD, it is easy to understand that drugs having sympatholytic property would be effective in the treatment of RSD. Of the above drugs, only guanethidine has major sympatholytic activity. Other drugs improve the regional blood flow resulting from vasodilation via mechanisms other than sympatholysis. A increase in the regional blood flow of the affected area would lead to increase in the clearance and secretion of pain mediating substances from capillaries.

It would be possible to postulate that the interaction between these vasodilator drugs and the nociceptive receptors of the sensory nerve endings might be attributed to the pain relieving property of these

drugs. PGE_1 acts as a pain potentiating substance at the peripheral level and increases the sensitivity to pain by binding to the nociceptive receptors of sensory nerve endings[7,8]. Actions of other vasodilator drugs on the nociceptive receptors are not well-known. We investigated the influence of some vasodilators on the pain threshold in healthy men using radiant heat stimulation.

METHODS

The pain threshold was measured by Nakayama pain meter (Pain Meter NYT-5, Kudo electric Co.) connected to six channel temperature detecting device (STD-61, Kudo electric Co.)[9] which is a modification of Hardey's apparatus using radiant heat. Temperature sensors are attached to the skin and the heating unit is applied gently on a sensor. When an examiner pushes the start button, the skin under the heating unit is warmed to a certain degree (34 centi degree) at which time the stimulating system is automatically activated and the radiant heat of constant intensity is emitted. When an examinee feels pricking pain on the stimulated skin, he turns off the system by pushing the turn off button, the skin temperature at that time and the duration of stimulation are recorded. The maximal stimulating time was set to 10 seconds to prevent a subject from burns.

We tested guanethidine (2 mg/ml), nicardipine (0.2 mg/ml), nitroglycerin (0.3 mg/ml), and prostaglandin E_1 (1 μg/ml). We made three intradermal injections with 0.5 ml of each drug on the anterior surface of the forearm in six healthy male volunteers. Another three injections were made on the contralateral side with the same volume of physiologic saline solution for cntrol study. Intradermal lidocaine (10 ml/ml) was also tested in three volunteers. To decide the pain threshold we measured the time from the start of the stimulation to the point with the subject felt pain (response time) and the skin temperature at that time (peak temperature) following continuous stimulation with radiant heat of 200 mcal/sec/cm^2. Data was collected four times at ten minute intervals starting 20 minutes after the intradermal injection of a drug in each sequence of experiment, according to the input program using a personal computer and were recorded to the x-y recorder. Each drug was injected to the right and the left arm alternately in a subject. Mean values of six experiments were analyzed and $p<0.05$ was regarded as statistically significant with Students t-test.

RESULTS

Skin temperature and the pain threshold were measured at both left and right forearm before the experiment in all six volunteers. It was confirmed that there was no right to left side difference in both parameters. The response time had large individual variations among subjects; the first resonse time varied from 4.0 seconds to 8.0 seconds and the time was significantly prolonged with repeated stimulation in control expriments. The difference between the response time of the first examination and that of the second examination was the greatest (Fig. 1). The peak temperature had some individual variations also, though the differences were not significant; the first measurement ranged from 44.2℃ to 49.1℃. The peak temperature had a tendency to increase a little with repeated stimulation again, without statistical significance (Fig. 2). These indicated the deactivation phenomenon in the response time, though this phenomenon was not definitely seen in the peak temperature. Intradermal lidocaine caused the maximal response time (10 seconds) and a marked increase in the peak temperature compared to that of the control side in all three subjects. Fig. 3 and 4 show changes in the response time and the peak temprature caused by the four vasodilator drugs. Guanethidine showed an increase in the response time in four of the six subjects and an in-

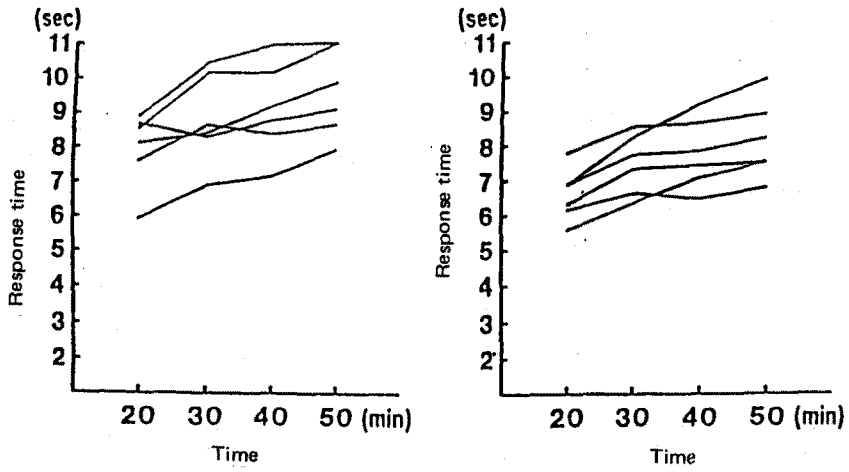

Fig. 1. Changes in the response time after intradermal injection of nicardipine (right) and saline (left).

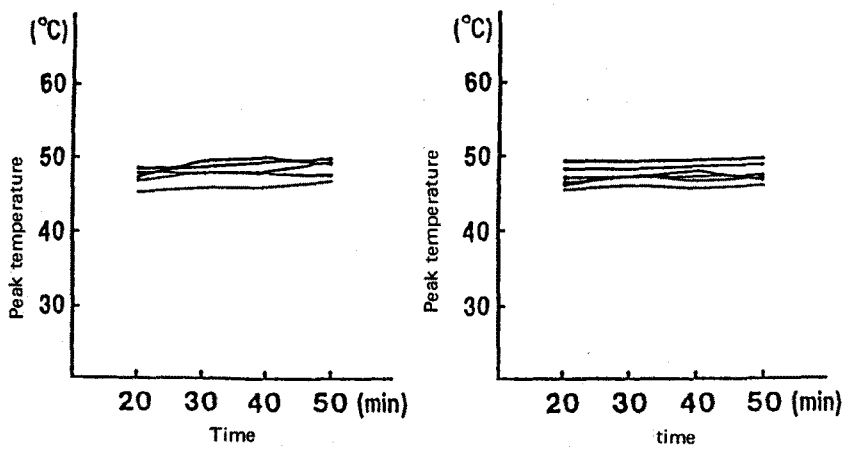

Fig. 2. Changes in the peak temperature after intradermal injection of nicardipine (right) and saline (left).

crease in the peak temperature in two subjects. Nicardipine also caused an increase in the response time and the peak temperature in four subjects respectively. Nitroglycerin caused an increase in the response time in one subject and little change in the peak temperature. With prostaglandin E_1, the response time was decreased in all subjects and the peak temperature was decreased in two subjects.

In summary, the pain threshold, measured by the response time following continuous radiant heat stimulation, was increased by guanethidine and nicardipine, changed little by nitroglycerin, and was decreased by prostaglandin E_1.

DISCUSSION

In the study, the deactivation phenomenon was seen in the response time, but was not seen in the peak temperature following radiant heat stimulation for determining the pain threshold. Deactivation is a

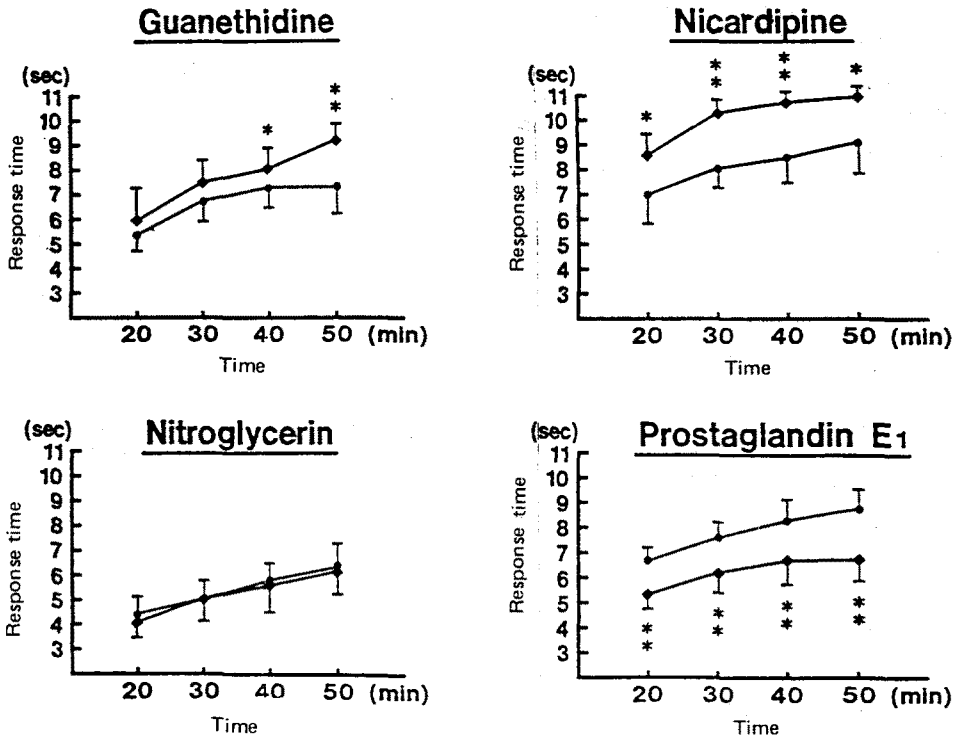

Fig. 3. Chnages in the response time after intradermal injection of four vasodilators.
●——● : control group, ◆——◆ : experimental group, * : $p<0.05$, * * : $p<0.01$

phenomenon reported by LaMotte and Campbell[10] in which pain decreases with repeated heat stmulations on the same surface area. Yamamoto et al. reported the deactivation phenomenon both in the response time and in the peak temperature in a healthy person and in patients with lower back pain, with greater degree in the latter. The reason we could not see the deactivation in the peak temperature is uncertain.

0.5 ml of 1% lidocaine caused the maximal response time. This means that the 0.5 ml of solution is a sufficient amount for the local infiltration for this experiment. The pain threshold was increased by guanethidine and nicardipine, changed little by nitroglycerin, and was decreased by prostaglandin E_1. Although all these drugs may be effective for relieving the pain from reflex sympathetic dystrophy[1~3], each of the drug may have different actions on the nociceptive receptors in the sensory nerve ending as shown in this study.

Besides a strong sympathetic blocking activity, guanethidine has a weak local anesthetic effect[12,13] by which the sensory nerve fibers may be blocked resulting in an increase in the pain threshold. Schmidt and Way[14] and Benedek et al.[15] reported that calcium channel blockers such as nicardipine potentiate the analgesic effect of opioids. Calcium channel blockers would interfere with impulse production at the nociceptive receptors by blocking the influx of calcium ions through cell membrane[14]. Juan et al.[16] described that calcium channel blockers reduced the pain-producing effect of bradykinin. He suggested that calcium channel blockers decreases the effects of bradykinin by inhibiting release of

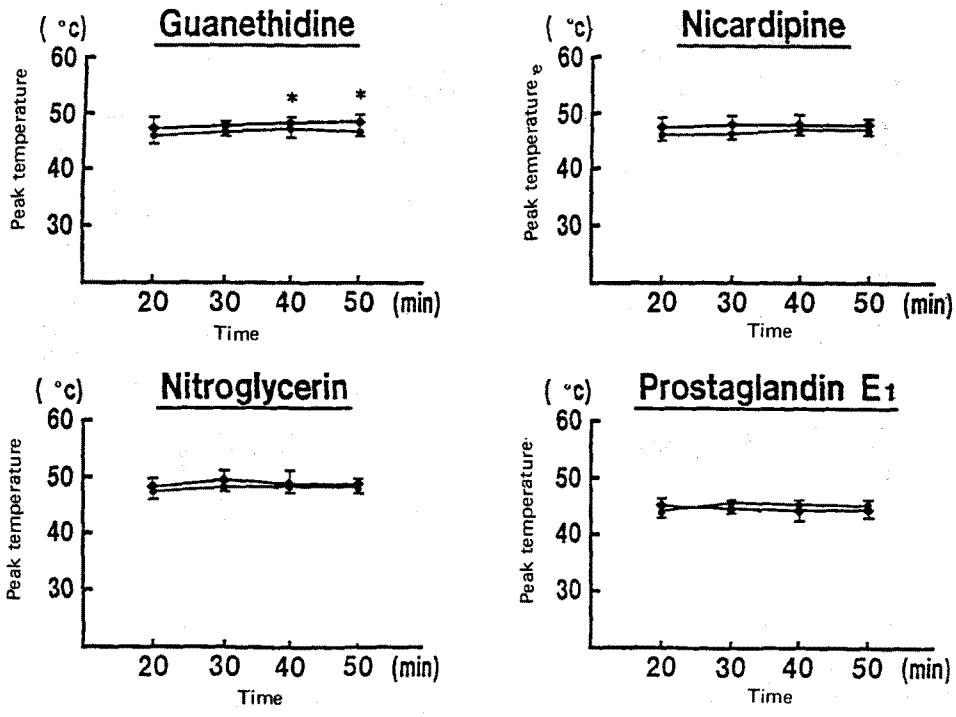

Fig. 4. Changes in the peak temperature after intradermal injection of four vasodilators.
●——● : control group, ◆——◆ : experimental group, * : $p<0.05$

prostaglandin-like pain-mediating substances. Nitroglycerin caused little change in the pain threshold; this suggests that the drug has little effect on the sensory nerve ending. Prostaglandin E_1 is known as one of the pain potentiating substances at the peripheral level[7,8,17]. Ferreira[7] reported that the pain threshold to bradykinin or histamine was decreased by subcutaneous infiltratin of prostaglandin E_1; the report is consistent with our results. This might be due to the binding of prostaglandin E_1 to terminal receptors of the sensory nerve fiber and facilitates the binding of pain mediating substances such as bradykinin to their receptors[17,18].

As stated above, guanethidine and nicardipine increased the pain threshold by decreasing the sensitivity of terminal receptors of the sensory nerve fibers. This decrease in the sensitivity of terminal receptors may be partially attributable, to the effectiveness of peripherally administered vasodilators in reducing the pain from reflex sympathetic dystrophy. Of course, strong sympatholytic effect of guanethidine[4~6] and vasodilating action of nicardipine[19] assumed a major role in relieving the pain of sympathetic origin in reflex sympathetic dystrophy. It has been shown that nitroglycerin has no effect on the sensory nerve terminal and that prostaglandin E_1 increase the sensitivity of terminal receptors of the sensory nerve fibers and decreases the pain threshold. These suggest that the effectiveness of peripherally administered vasodilators in relieving the pain from reflex sympathetic dystrophy may be mediated by a mechanism other than the sensory nerve fibers; nitroglycerin would increase the clearance of pain mediating substances by vasodilation, prostaglandin E_1 dilates blood vessels[20,21] and suppresses the release

of norepinephrine from the sympathetic nerve terminal[21]. Hadhazy et al.[22] described the inhibition of norepinephrine release by prostaglandin E_1 from sympathetic nerve ending in the isolated blood vessel preparations.

Conclusively, these vasodilator drugs diminish the pain from reflex sympathetic dystrophy through different actions on the terminal receptors in the sensory nerve fiber.

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