Effects of Adrenoceptor Antagonists on the Cutaneous Blood Flow Increase Response to Sympathetic Nerve Stimulation in Rats with Persistent Inflammation

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Abstract: There is some evidence that the sympathetic nervous system plays a role in the development and/or maintenance of painful states, and that sympathetic nervous function is altered in these conditions. Our previous experiments showed that electrical stimulation of the lumbar sympathetic trunk (sympathetic stimulation: SS), which normally induces a decrease in blood flow (BF) of plantar skin, induced its BF increase in about 50% of adjuvant-inflamed rats. To investigate the mechanism of this BF-increase response, we examined whether noradrenaline (NA) plays any role in this changed response to SS, and which receptor subtype is involved. We measured paw cutaneous BF response with a laser Doppler flowmeter in rats chronically inflamed with complete Freund’s adjuvant. SS induced the BF-increase response in 50–67% of measured sites. Close-arterially injected NA induced the BF-increase response at dosages between 10–100 ng/kg only at the sites with the BF-increase response to SS. The BF-increase and -decrease responses to NA were significantly reduced after the close-arterial injection of either α1- or α2-adrenoceptor antagonists (p<0.05, respectively). In contrast, although the BF-decrease responses to SS were significantly reduced by administration of α1- and α2-adrenoceptor antagonist, BF-increase response was reduced only by α1-adrenoceptor antagonist, and that only at a higher dose. In addition, the β-adrenoceptor antagonist had no effects on both responses. These results suggest that the BF-increase response to SS involves, additionally to NA, a non-adrenergic mechanism. [Japanese Journal of Physiology, 52, 521–530, 2002]

Key words: sympathetic nerve stimulation, chronic inflammation, adrenoceptor, blood flow, rats.

Sympathectomy, or sympathetic ganglion blockade, has been shown to reduce pain in some chronic pain conditions such as complex regional pain syndrome (CRPS) [1–3]. Abnormalities of the skin temperature, coloring of the affected areas, and sweating have been observed in this condition [3]. These clinical findings suggest sympathetic nerve activity plays important roles in the development and/or maintenance of pain and accompanying changes of the affected tissues in these pathological conditions. Some efforts have been made to identify the mechanism of sympathetic involvement in pain, and α-adrenoceptor-mediated changes in nociceptive afferents, have been reported [4–7]. Some of these changes are common to inflamed conditions [7–10]: This would be plausible since recent studies suggest that CRPS has the distinct components of inflammation at its early stage [11]. On the other hand, sympathetic involvement in tissue changes has been less intensively investigated. Levine et al. [12] reported that sympathetic nerve activity affected...
the degree of joint injury in the hind limb of experimentally arthritic rats. The vasoconstriction response to electrical stimulation of the sympathetic or saphenous nerve was diminished in a model of chronic inflammation induced by complete Freund’s adjuvant (CFA) in rats [13, 14]. Lam and Ferrell also reported the vasoconstriction response to electrical stimulation of the sympathetic nerve was reduced in carrageenan inflammation rats [15]. Recently, it has been shown that chronic joint inflammation by CFA compromises α1- and α2-adrenoceptor function [16]. In our previous experiment investigating the involvement of sympathetic nervous activities in tissue changes in inflamed condition, we found that electrical stimulation of lumbar sympathetic nerve trunk (sympathetic stimulation: SS), which generally produces vasoconstriction of cutaneous blood vessels in normal animals, induced an increase in blood flow (BF) in the plantar skin of some adjuvant-inflamed (AI) rats [17]. The mechanism for this altered vascular response is not yet understood.

The aims of the present study, therefore, was to examine whether noradrenaline (NA), the major sympathetic nerve transmitter, plays any role in the altered vascular response, i.e., vasodilating response, to SS and which receptor subtypes are responsible for this effect. Before analyzing these points, we re-examined the distribution of the sites with increased BF in response to SS.

Preliminary accounts have appeared in abstract form [18–20].

**METHODS**

**Induction of adjuvant inflammation.** Fifty-eight male Lewis rats (LEW/Crj, Charles River Co., Yokohama, Japan) were used. They were 9 weeks old when CFA was injected. Adjuvant inflammation was induced in 53 rats by subcutaneously inoculating 0.1 ml of CFA, a suspension of heat-killed *Mycobacterium butyricum* (Difco Laboratories, Detroit, MI, USA) in paraffin oil (6 mg/ml), into the distal third of the tail. Five rats served as controls. All rats were kept on a 12-h light/dark cycle at 23°C with free access to food and water.

**Surgery and lumbar sympathetic trunk stimulation.** Rats that survived more than 2 weeks (maximum 11 weeks) after inoculation of the CFA were used for the experiment, since the symptoms of inflammation such as limping and redness of the feet appear about 2 weeks after the inoculation [21]. We did not find any difference in the response of the blood vessels between 2 and 11 weeks. Animals were initially anesthetized with α-chloralose and urethane (90 and 450 mg/kg i.p., respectively). The right jugular vein was cannulated for later administration of anesthetics. The animals spontaneously breathed the room air through a tracheal cannula. The right carotid artery was cannulated to measure mean arterial pressure (MAP). A branch of the femoral artery was cannulated for drug administration. Rectal temperature was maintained at 37.5 ± 0.5°C using a heating pad and a lamp throughout the surgery and the recording period.

The lumbar sympathetic trunk (LST) was sectioned between L3 and L4 ganglia and communicating branches of spinal nerves in L4 ganglion were cut using a retroperitoneal approach under a binocular microscope, because sympathetic ganglia of L4 and below innervate the vascular bed of the surface of the hind paw [22]. An oil pool was made in the retroperitoneal cavity with skin flaps and the LST was kept in paraffin oil. The peripheral cut end of LST was placed on a bipolar platinum-stimulating electrode. The LST was stimulated by rectangular pulses of 0.2 ms duration and 10 V strength, at 1–5 Hz for 5 s. The frequency of the SS was adjusted so that the greatest vasodilating response was obtained; 5 Hz was the most frequently used frequency. The effects of SS were tested at intervals longer than 10 min. When supplemental anesthetic drug was added, a minimum of 10 min elapsed before the next SS. At the end of the experiments the rats were killed with an anesthetic overdose.

**Laser Doppler flowmetry.** The relative change in local BF was measured in the plantar skin of the right hind paw by a laser Doppler flowmeter (ALF21, Advance Co., Ltd., Tokyo, Japan). BF was simultaneously measured at two sites except a few antagonist-experiments. Electrical signals from the laser Doppler flowmeter and blood pressure monitor were simultaneously recorded and fed into a computer through an AD converter (DIGIDATA 1200, Axon Instruments, Inc., Foster City, CA, USA) using a data analysis program (AXOTAPE, Version 2.0, Axon Instruments, Inc.). The sampling intervals of the AD converter were 40 ms in the SS experiment and 100 ms with the administration of drugs. The sampled data were averaged every 1 s and expressed as arbitrary units for the BF and mmHg for the MAP. An apparent vascular conductance (VC) was calculated as the ratio of the BF to the MAP. However, we showed only the BF changes in the present results because the VC was similar to the BF. The BF, MAP, and VC values over 60 s before stimulation or drug administration were averaged and used as the baseline values. A change in the BF and MAP exceeding the baseline by
more than twice the standard deviation of the baseline value was used as the criterion for a response. To quantitatively analyze vascular changes, the difference between the baseline value and the maximum (or minimum) value after SS or injection of NA was calculated (as shown by $\Delta$BF). We confirmed in every experiment that BF decreased to zero when rats were sacrificed.

**Drug administration.** NA (Sigma, St. Louis, MO, USA) and $\alpha$-adrenergic antagonists were infused through a cannula inserted into a branch of the femoral artery by a microsyringe pump (EP-60, EICOM, Inc., Kyoto, Japan) with an infusion speed of 90 $\mu$L/min. A $\beta$-adrenoceptor antagonist, propranolol, was injected intravenously. NA was injected at dosages between 3 and 300 ng/kg up to a maximal BF-increase response was obtained. The effects of prazosin (Sigma), an $\alpha_1$-adrenoceptor antagonist, CH-38083, which is an $\alpha_2$-adrenoceptor antagonist having 400 times higher selectivity than yohimbine [23], and propranolol (Sigma), a $\beta$-adrenoceptor antagonist, were examined. Prazosin was dissolved in distilled water and another drugs were dissolved in saline and the infused volume was 30 $\mu$L. Saline was infused before and after administration of drugs without interruption since the BF was affected by the infusing fluid itself when the microsyringe pump was used.

**Analysis.** Results were expressed as the mean±SEM. The statistical significance was determined as follows: One way analysis of variance (ANOVA) with repeated measures followed by Bonferroni’s test was used for comparison of the BF and MAP changes after drug administrations, and paired $t$-test for comparisons of the BF change after the injection of NA or SS in the presence as well as the absence of antagonists. Results were considered significant if $p<0.05$.

All experimental procedures were approved by the Animal Care Committee, Nagoya University.

**RESULTS**

**The vasodilatation by SS in the AI rats**

SS induced a decreased BF in the majority of normal rats, while it induced either an increase or a decrease of BF in the AI rats. Typical BF response to SS in the AI rats is shown in Fig. 1A. Two probes of the laser Doppler flowmeter were placed on the plantar skin in the case shown Fig. 1, and the BF responses to SS at these two sites were recorded simultaneously. A small (mean 4.6 mmHg, at 1 Hz), transient increase in MAP by SS was observed in 67.6% of the rats (a significant increase, $p<0.001$). The magnitude of SS-induced MAP-increase response was not different from that of control rats in preliminary experiment.

To determine whether there is any area with a preferential BF increase response, we trisected the plantar skin from the heel to the base of the toes and measured the BF at only one randomly selected site in each area. The BF responses in this series of experiments were successively examined in each trisected area. The frequency of the SS was fixed at 1 Hz in this experiment. SS decreased the BF in all sites except one in the control group (Table 1). In contrast, all ($n=12$) except one AI rat had BF-increase responses in more than one area measured. We found sites with a BF-increase response even in this exceptional rat.
when we moved the probe to other sites within the respective areas. Thus, we found both BF-increase and decrease responses in all AI rats, different from a previous report [17]. The ratio of randomly sampled sites exhibiting the BF increase response was 66.7% at the heel, 50.0% in the middle of the sole, and 58.3% at the base of the toes in the AI rats. There was no significant difference in these ratios among the three areas ($\chi^2$ test, $p>0.05$).

The following experiments were carried out in the AI rats only. When we simultaneously recorded BF at two sites, we firstly selected one site where the BF clearly increased in response to SS, and then we searched for a site where the BF decreased.

### The BF response to NA
NA was close-arterially administered at doses between 3 and 300 ng/kg. The BF was increased when a lower dosage of NA was injected. Representative recordings of the BF responses to SS and NA injection (100 ng/kg) are shown in Fig. 1. Responses to SS and NA injection were similar at the same site, i.e., when SS induced BF increase, a small dosage of NA (Fig. 1B) did as well, and vice versa. Typical BF and MAP responses to different dosages of NA are shown in Fig. 2. NA with 3 ng/kg did not alter the BF. The BF-increase response was observed at between 30 and 100 ng/kg in the case shown in Fig. 2, and the response pattern to 30 ng/kg of NA was comparable with that to SS. At the same site, the BF increase became smaller with higher doses of NA ($>100$ ng/kg), suppressed by the developing BF decrease component. MAP was not changed at NA dosages that induced a BF increase only. In contrast, the magnitudes of the BF decrease at sites where BF decreased in response to SS increased unidirectionally with the concentration of NA, and the BF increase responses were never induced. The NA of doses between 10 and 100 ng/kg with some individual variations increased the BF (for criteria see the METHODS section) at sites with the BF-increase response to SS, and the BF de-

### Table 1. Effect of the sympathetic stimulation on the blood flow (BF).

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<th>No.</th>
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| Adjuvant |  | |  |
| Adjuvant |  | |  |
| 1  | +     | +     | +     |
| 2  | +     | +     | +     |
| 3  | +     | +     | -     |
| 4  | +     | +     | -     |
| 5  | +     | -     | +     |
| 6  | +     | -     | +     |
| 7  | +     | -     | +     |
| 8  | +     | -     | +     |
| 9  | +     | -     | -     |
| 10 | +     | -     | -     |
| 11 | -     | -     | -     |
| 12 | -     | -     | -     |
| Total | 8/12  | 6/12  | 7/12  |

+, BF increase response; -, BF decrease response. Each number shows one rat.

**Fig. 2.** Responses of the BF and MAP to different dosages of NA-a representative recording. **A**: BF increase response to SS. **B**: BF responses to NA injection. **C**: MAP responses to NA injection. The scale for BF is at the left and for MAP at the right. Bars indicate the period of SS (5s) or injection of NA (20s). NA was close-arterially administered at dosages between 3 and 300 ng/kg. BF was measured at the same site in an AI rat. Note that a BF increase was observed at dosages between 30 and 100 ng/kg, a BF decrease followed the BF increase at 100 ng/kg, and only the BF-decrease response was induced at 300 ng/kg (B). In this case, the BF response to NA of 30 ng/kg showed the same pattern as to SS. MAP was not changed by NA injection at any of the doses except 300 ng/kg (the MAP change by 100 ng/kg was not considered to be a drug effect because it was induced when the animal breathed deeply).
crease followed at higher concentrations. These changes appear to be unaffected by repetitive injection of NA, as we did not observe any tachyphylaxis in preliminary experiments when we injected the same dosage of NA twice or three times with intervals of 10 min (data not shown).

**Effects of \( \alpha \)-adrenoceptor antagonists on BF responses to NA and SS**

In the previous section we found that NA induced the BF increase in AI rats. However, this would not assure that NA mediated the SS-induced BF-increase response. Therefore, we examined the effects of two \( \alpha \)-adrenoceptor antagonists on NA- and SS-induced BF responses and of a \( \beta \)-adrenoceptor antagonist on SS-induced BF-increase response in the AI rats. Prazosin (0.03 mg/kg, close-arterially injected) significantly decreased the baseline BF at the sites where BF decreased in response to SS, and thereafter the BF remained at this decreased level (Fig. 3, \( p<0.01 \)). Prazosin did not significantly influence the baseline BF at the sites where the BF increased in response to SS. The MAP decreased significantly and then stabilized at a somewhat lowered level 5 min after injection of prazosin (\( p<0.01 \)). This MAP change suggests that the observed BF decrease was mainly due to the decreased perfusion pressure, rather than that \( \alpha \)-adrenoceptor exerted a vasodilating action. The BF response to NA was examined when the BF and MAP reached this stable level. NA dosage was chosen for each rat that induced the maximal BF increase in the experiment described above. The BF increase in response to NA was significantly reduced by prazosin in 6 AI rats (Fig. 4A, B, \( p<0.05 \)). The BF-decrease response to NA observed simultaneously but at a different site was also significantly reduced by prazosin in 6 AI rats (Fig. 4C, D, \( p<0.05 \)).

When CH-38083 (0.3 mg/kg) was close-arterially injected, in contrast, the baseline BF value both at the sites where BF increased and decreased in response to SS tended to increase with considerable variation; however, these changes were not significant, and BF returned to the level previous to the antagonist injection in 5 min (Fig. 3A). The MAP was not changed by CH-38083 (Fig. 3B). This result suggests that \( \alpha \)-adrenoceptors were vasoconstrictory rather than vasodilatory both at the BF increase and decrease sites. The BF response to NA was examined when the BF reached a steady level. Both the BF increase and decrease responses to NA were significantly reduced at 8 min after the close-arterial injection of CH-38083 as well in 6 AI rats (Fig. 5, \( p<0.05 \)). The effects of adrenoceptor antagonists were different on the SS-induced BF-responses from the NA-induced BF-responses. Figure 6 shows a summary of the effects of prazosin (0.03 and 0.1 mg/kg, close-arterial injection) on the BF responses to SS. The BF-increase response to SS was significantly reduced by prazosin at higher dose (0.1 mg/kg, \( p<0.05 \), \( n=5 \)) although prazosin at lower dose (0.03 mg/kg) did not affect the BF-increase response induced by SS (\( p=0.12 \), \( n=8 \)). In contrast, the BF-decrease response to SS was significantly reduced by prazosin at both dosages (Fig. 6, \( p<0.05 \)). MAP-increase response to SS was also
reduced by prazosin \((p<0.05, n=7)\).

Effects of \(\alpha_2\)-adrenergic antagonist, CH38083, were also different from those on NA-induced BF changes. The BF-increase response induced by SS was not suppressed by close-arterial injection of CH38083 at both 0.3 and 1 mg/kg (Fig. 7, \(p=0.45, n=5\) and \(p=0.49, n=8\), respectively). We failed to obtain any suppression of the BF-increase response to SS with CH-38083 at 10 mg/kg (in 2 AI rats, data not shown). In contrast the BF-decrease response induced by SS was significantly suppressed by close-arterial injection of CH-38083, though only at a higher dose (1 mg/kg, \(p<0.05, n=7\)). SS-induced MAP-increase was not affected by CH-38083 at 1 mg/kg \((p=0.79, n=7)\).

Intravenously injected propranolol did not significantly modify the SS-induced BF-increase response \((5.13\pm3.62\) and \(5.76\pm4.31\) arbitrary unit before and after propranolol, respectively, \(p=0.42, n=5\)). Although MAP tended to increase after injection of propranolol, this effect was not statistically significant. SS-induced MAP-increase was not affected by propranolol at 1 mg/kg, either \((p=0.62, n=5)\).
DISCUSSION

The BF increase response to SS was observed in all AI rats. We found in the present experiment that the BF increase response to SS was induced in all AI rats while it was rarely observed in control rats. In our previous study, the AI rats were classified into two groups [17], i.e., rats with a BF-increase response to SS and those with a BF-decrease response. We found both the BF-increase and -decrease responses simultaneously in the same AI rat as we moved the probe of the laser Doppler flowmeter. Sites of BF increase in response to SS were scattered all over the sole of the hind paw. The ratio of sites with the BF-increase response was 50–67% in each of the trisected areas of the plantar skin with random placement of the BF probe. This percentage was similar to the previous observation in that the BF increased in about half of the AI rats. The adjuvant-induced inflammation used in the present experiment is a generalized chronic condition characterized primarily by arthritis in the forepaw and hind paw, especially one or both hind paws. At times a mild diffuse pinkish swelling of the ankle and dorsal aspect of the tarsus was observed, and several localized lesions of the skin and mucous membrane were observed scattered over the whole body [24, 25]. Therefore, the scattering of the sites with the BF-increase response in the AI rats would seem to be related to the localized pathological changes.

The role of α-adrenoceptors in the BF response to SS. We found the lower dose of NA induced the BF-increase at the sites with the BF-increase response to SS, whereas the BF at the sites with the BF-decrease response to SS was decreased by NA irrespective of doses injected. We previously observed only BF-decrease response to NA, but only 400 ng/kg was used at that time [17]. We found in the present experiment that NA induced BF-increase at 10–100 ng/kg and BF-decrease followed at higher doses. This suggests NA is involved in the BF-increase response to SS in a limited condition.

The BF-increase responses to NA at a small dosage were reduced by either prazosin or CH-38083 (Figs. 4, 5). These results suggest that both α1- and α2-adrenoceptors mediated the BF-increase response to NA. The NA-induced BF-decrease response was also suppressed by both antagonists, suggesting mediation of both α1- and α2-adrenoceptors.

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be a passive change secondary to vasoconstriction in other areas. Changes in the NA-induced BF increase by both α1- and α2-adrenoceptor antagonists mirroring the changes in the BF-decrease responses supports this passive mechanism hypothesis. This mechanism requires fewer adrenoceptors at the sites of BF increase than at those of BF decrease. McDougall recently reported that adrenergic sensitivity (both α1- and α2-) was decreased in the knee joint in monoarthritic rats induced by injection of CFA [16]. If these changes are scattered as patches of pathological tissue changes in polyarthritids induced by CFA, the distribution of adrenoceptors would perhaps not be even. If the site with the BF-increase response was less sensitive to NA, the passive mechanism would be most likely. Our observation that higher doses of NA induced only a BF decrease at the sites with the BF-increase response to SS would supports this hypothesis.

The BF-increase responses to SS observed in this experiment might also be a passive response resulting from redistribution of the BF after vasoconstriction in other areas. If this is the case, the redistribution of BF must be a local one, because only a slight and inconsistent increase of MAP was seen after SS in 67.6% of the rats. However, different efficacy of antagonists on SS-induced BF increase from NA-induced BF-increase would suggest redistribution of BF is not the sole cause for vasodilatation: The SS-induced BF-increase response was blocked by a higher dose of prazosin (0.1 mg/kg, I.A.) whereas prazosin suppressed the BF-decrease response to SS at 0.03 and 0.1 mg/kg. In contrast, the SS-induced BF-increase response was not blocked by α2-adrenoceptor antagonist even at as high as 10 mg/kg. Again the BF-decrease response to SS was suppressed by CH-38083, though at only 1 mg/kg. These differences in effectiveness of antagonists suggest an involvement of other mechanisms additionally to NA-mediation in the SS-induced vascular responses.

A few possible mechanisms can be suggested for this vasodilating response. The first is the β-adrenoceptor. Activation of this receptor induces increase in the contractility of cardiac muscle and relaxation of vascular smooth muscle. Our present result showed ineffectiveness of propranolol on the BF increase response to SS, thus excludes this possibility.

The second is release of vasodilator substances such as nitric oxide (NO) from endothelial cells by α2-adrenoceptor stimulation, but this action was not found in smaller vessels such as we measured in this experiment and the BF-increase response to SS was not suppressed after CH-38083 injection. Our previous report demonstrated the BF-increase response was not mediated by the NO system, either [17].

Another possibility for the active mechanism is that some vasodilating substance(s) might be released from sympathetic nerve terminals. The known vasodilating substances released from sympathetic nerves are adenosine 5’-triphosphate (ATP) acting through P2Y purinoceptors [27], acetylcholine (Ach) in certain areas and prostaglandins (PGs) through activation of presynaptic α2-adrenoceptor on the sympathetic post-ganglionic nerve terminals in pathological states [28]. Our preliminary study showed that a muscarinic antagonist, i.e., atropine, and aspirin, a blocker of cyclo-oxygenase, had no effect on the BF-increase response (data not shown), and that CH-38083 alone had no effect, either. Therefore, Ach and PGs would not seem to be involved. ATP has vasodilating action through P2Y purinoceptor, thus the possible involvement of ATP in the BF-increase response to SS should be studied.

The fourth possible mechanism for active vasodilatation is vasodilation mediated by neuropeptide(s). CP-96345 (1 mg/kg), a substance P (SP) antagonist, tended to reduce the BF-increase response [19]; thus, SP might have been involved in this phenomenon. Furthermore, since our preliminary experiment has shown up-regulation of SP expression in sympathetic ganglia (unpublished observation), SP co-released with NA from sympathetic terminals might mediate the BF-increase response to SS.

In conclusion, involvements of both adrenergic-passive and non-adrenergic-active mechanisms are suggested in this BF-increase response to SS.

Pathophysiological meaning of the present study. Along the same line as the present observation, McDougall et al. reported the vasoconstriction response to electrical stimulation of sympathetic or saphenous nerves was diminished in rats with CFA-induced knee joint inflammation [13, 14]. The vasoconstriction response to SS was reduced in rats with carrageenan inflammation as well [15]. These findings might be the result of altered regulation by postjunctional α-adrenoceptors in blood vessels and release of vasodilators from inflamed tissues.

Changed vascular response to sympathetic nerve stimulation was not limited to inflamed condition: Lundberg et al. reported that the electrical stimulation of the sympathetic nerve caused cutaneous vasodilatation in patients with obstructive vascular disease [29]. We also measured BF in rats with chronic constriction injury using the same methods as in the present experiment, and found a BF-increase response to SS similar to that in AI rats (data not shown). In that experimen-
tal series none of the sham-operated control rats showed a vasodilatation response.

The smooth muscles in resistance arteries regulate the vasoconstrictor tone, but in the present observations as well as others this vascular regulation was altered in pathological conditions. These changes in the response to sympathetic activation in pathological conditions might play some role in tissue changes in these conditions. In addition, these changes in vascular responses should be taken into consideration in the therapeutic treatment of patients and their everyday care.

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