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Endogenous calcitonin gene-related peptide suppresses vasoconstriction mediated by adrenergic nerves in rat mesenteric resistance blood vessels

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Abstract

The role of perivascular calcitonin gene-related peptide (CGRP)-containing nerves in the modulation of adrenergic nerve-mediated vasoconstrictions was studied in the rat perfused mesenteric vascular bed. A frequency-dependent vasoconstriction induced by periarterial nerve stimulation (1–6 Hz) of the bed was significantly potentiated by perfusion of 1 μM CGRP-(8–37) (CGRP receptor antagonist) or to a similar extent after treatment with 500 nM capsaicin. In the preparations treated with capsaicin, CGRP-(8–37) caused a small potentiation of periarterial nerve stimulation-induced vasoconstriction. Exogenous CGRP (0.1–1 nM) concentration-dependently attenuated the augmented vasoconstriction in response to periarterial nerve stimulation after treatment with capsaicin. However, exogenous CGRP (1 nM) did not attenuate the periarterial nerve stimulation-induced vasoconstriction in the bed untreated with capsaicin. These results suggest that endogenous CGRP, which is released from CGRP-containing nerves, suppresses the adrenergic nerve function involved in mechanisms regulating the tone of resistant blood vessels.

Keywords: CGRP (Calcitonin gene-related peptide)-containing nerve; Vasoconstriction, adrenergic; Capsaicin; CGRP-(8–37); Mesenteric vascular bed, rat

1. Introduction

After many decades of experimentation, evidence has accumulated that the tone of the peripheral blood vessels is mainly regulated by vascular adrenergic nerves through release of the neurotransmitter, noradrenaline. Indeed, in isolated blood vessels, periarterial nerve stimulation or transmural nerve stimulation could produce a neurogenic vasoconstriction mediated by noradrenaline released from vascular adrenergic nerves (Kawasaki and Takasaki, 1984; Kawasaki et al., 1987).

However, we have demonstrated that periarterial nerve stimulation of contracted mesenteric resistant blood vessels produces a neurogenic vasodilation, which is mediated by non-adrenergic, non-cholinergic (NANC) nerves (Kawasaki et al., 1988). Exogenous calcitonin gene-related peptide (CGRP) causes vasodilation of the precontracted mesenteric artery, which mimics the effects of periarterial nerve stimulation (Kawasaki et al., 1988), and periarterial nerve stimulation in mesenteric vascular beds produces tetrodotoxin-sensitive release of CGRP associated with the vasodilator response (Fujimori et al., 1989). Periarterial nerve stimulation-induced vasodilation is inhibited by CGRP-(8–37), an antagonist for CGRP receptors (Chiba et al., 1989), CGRP receptor desensitization, and antiserum against CGRP, or treatment with capsaicin, a toxin for peptidergic and sensory neurons (Han et al., 1990a,b; Kawasaki et al., 1990). Thus, we have proposed that the rat mesenteric artery is innervated by NANC nerves in which CGRP acts as a vasodilator transmitter. Therefore, periarterial nerve stimulation of the mesenteric vascular bed excites not only vascular adrenergic nerves but also vascular CGRP-containing nerves.

Capsaicin has been shown to deplete CGRP from CGRP-containing neurons (Kawasaki et al., 1988; Holzer, 1991) to abolish the periarterial nerve stimulation-induced vasodilation (Kawasaki et al., 1990). This finding would suggest that the preparation treated with capsaicin is a

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useful preparation with dysfunction of the endogenous CGRP-vasodilator mechanism. As neural vasodilator mechanisms mediated by endogenous CGRP influence the major physiological vasomotor mechanisms, the diminution of CGRP nerve function should cause changes in another vasomotor nerve function, which interacts with CGRP nerves. Indeed, we have reported that the periarterial nerve stimulation-induced vasoconstriction mediated by vascular adrenergic nerves is significantly potentiated after treatment with capsaicin (Kawasaki et al., 1990). Therefore, the present study was conducted to investigate further whether vasoconstriction mediated by vascular adrenergic nerves is modulated by endogenous CGRP in the rat mesenteric vascular bed. To this aim, we used CGRP-(8–37) to block CGRP receptors and capsaicin to produce endogenous CGRP dysfunction.

2. Materials and methods

2.1. Perfusion of the mesenteric vascular bed

Male Wistar rats (purchased from Charles River Japan, Shizuoka, Japan), weighing 320 and 380 g, were anesthetized with sodium pentobarbital (50 mg/kg i.p.). The mesenteric vascular bed was isolated and prepared for perfusion as described previously (Kawasaki and Takasaki, 1984). The mesenteric vascular bed was separated from the intestine by cutting close to the intestinal wall. Only four main arterial branches from the superior mesenteric trunk running to the terminal ileum were perfused with a modified Krebs–Ringer bicarbonate solution (Krebs' solution) at a constant flow rate of 5 ml/min with a peristaltic pump (SJ-1215; ATTO, Tokyo, Japan). The preparation was also superfused with the same solution at a rate of 0.5 ml/min to prevent drying. Modified Krebs' solution of the following composition (mM) was used: NaCl (120.0), KCl (5.0), $CaCl_2$ (2.4), $MgSO_4$ (1.2), $NaHCO_3$ (25.0), disodium EDTA (0.027) and dextrose (11.0) (pH 7.4). The Krebs' solution was bubbled with a mixture of 95% O_2–5% CO_2 before passage through a warming coil maintained at 37°C. Changes in the perfusion pressure were measured with a pressure transducer (MPU-0.5A; Nihon Kohden) and recorded on a polygraph (RM-25; Nihon Kohden).

2.2. Periarterial nerve stimulation and bolus injection of noradrenaline

The perfused mesenteric vascular bed was subjected to periarterial nerve stimulation or a bolus injection of nor-

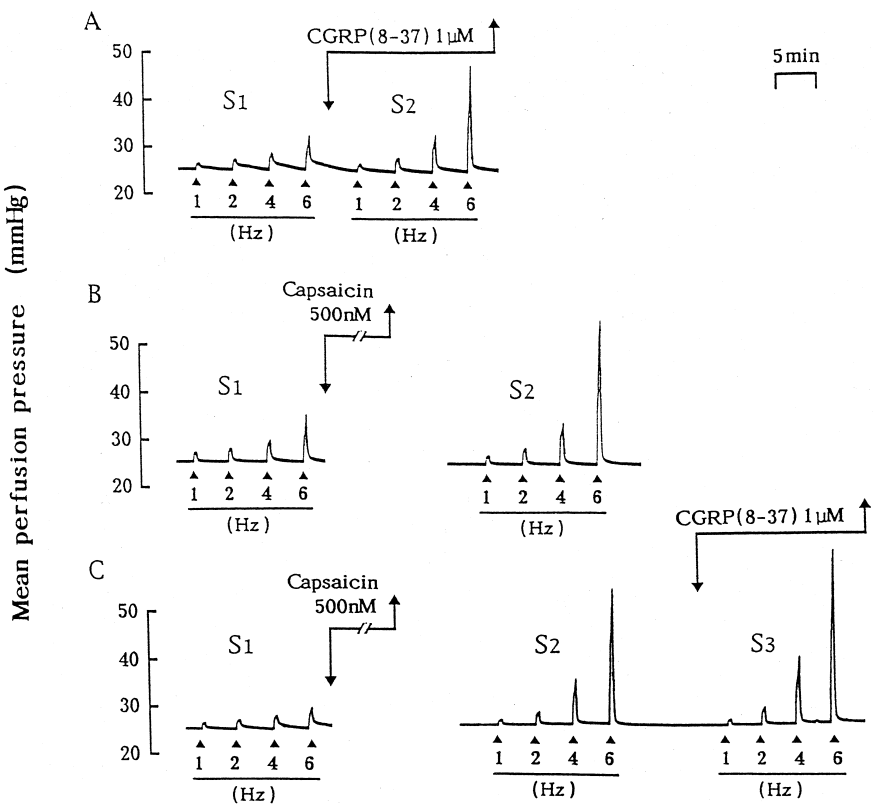

Fig. 1. Typical records showing pressor responses to periarterial nerve stimulation (PNS; 1–6 Hz) after treatment with CGRP-(8–37) (1 μM) (A and C) and capsaicin (500 nM) (B and C) in perfused mesenteric vascular beds of the rat. S_1, control responses; S_2, responses after capsaicin treatment or during CGRP-(8–37) perfusion; S_3, responses during CGRP-(8–37) perfusion after capsaicin treatment.

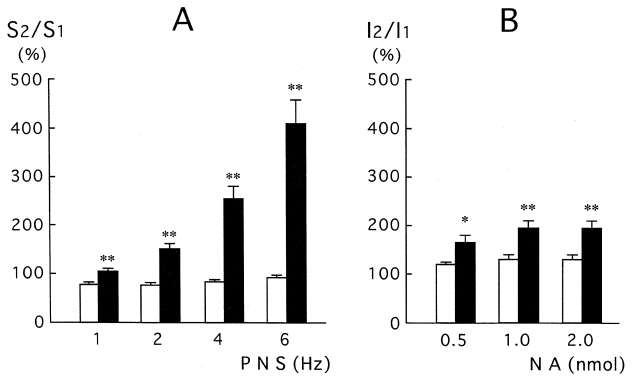

Fig. 2. Effect of CGRP-(8–37) (1 μM) on pressor responses to periarterial nerve stimulation (PNS; A) and a bolus injection of noradrenaline (NA; B) in perfused mesenteric vascular beds of the rat. The ordinate indicates a percentage (%) of responses induced by the first PNS (S_1) or injection (I_1). S_1 and I_1, the first PNS and injection; S_2 and I_2, the second PNS and injection during vehicle or CGRP-(8–37) perfusion. Open column, vehicle control ($n = 5$); solid column, CGRP-(8–37) perfusion ($n = 5$). $* P < 0.05$, $** P < 0.01$, compared with vehicle control (unpaired *t*-test).

adrenaline after the basal perfusion pressure had been allowed to stabilize. Periarterial nerve stimulation was given for 30 s at 5-min intervals using bipolar platinum ring electrodes placed around the superior mesenteric artery. Rectangular pulses of 1 ms in duration and supramaximum voltage (60 V) were applied at 1, 2, 4 and 6 Hz using an electronic stimulator (SEN 3301, Nihon Kohden). Noradrenaline (0.5, 1 and 2 nmol) was infused directly into the perfusate proximal to the arterial cannula using an injection pump (model 975, Harvard). The volumes of injection were 100 μl over 10 s.

2.3. Experimental protocols

After pressor responses to periarterial nerve stimulation were obtained as controls, the preparation was perfused with Krebs' solution containing 500 nM capsaicin for 20 min. After discontinuation of capsaicin perfusion, the preparation was rinsed with capsaicin-free Krebs' solution for 90 min and subsequently, periarterial nerve stimulation was started. To examine the effect of CGRP-(8–37) on the pressor responses to either periarterial nerve stimulation or a bolus injection of noradrenaline, periarterial nerve stimulation or noradrenaline injection was performed before and during perfusion with Krebs' solution containing CGRP-(8–37) at a concentration of 1 μM that abolished the CGRP-nerve mediated or exogenously applied CGRP-induced vasodilation (Han et al., 1990a,b). CGRP-(8–37) perfusion began 5 min before and throughout periarterial nerve stimulation or noradrenaline injection. In the preparation treated with capsaicin, periarterial nerve stimulation was performed before and during perfusion with Krebs' solution containing CGRP-(8–37) (1 μM) or CGRP (0.1, 0.3, and 1 nM). CGRP-(8–37) or CGRP perfusion began 5 min before and throughout periarterial nerve stimulation, respectively. Thereafter, to determine denervation of NANC nerves by capsaicin, the preparation was contracted with continuous perfusion of methoxamine at a submaximal concentration of 7 μM in the presence of 5 μM guanethidine which was added to block adrenergic neurotransmission, and then periarterial nerve stimulation was applied. As a control, Krebs' solution containing no capsaicin was perfused with the same schedule as capsaicin treatment. For each preparation, the results were evaluated by comparing the perfusion pressure responses with either periarterial nerve stimulation or noradrenaline injection before and during perfusion of CGRP-(8–37) or vehicle (S_2/S_1 or I_2/I_1 ratio), or before and after capsaicin or vehicle treatment (S_2/S_1 ratio), or before and during the perfusion of the drugs (S_3/S_2 ratio) after capsaicin treatment.

2.4. Statistical analysis

The results, expressed as the means ± S.E.M, were analyzed statistically using an unpaired *t*-test and One-way analysis of variance followed by Dunnett's test. A *P* value less than 0.05 was considered statistically significant.

2.5. Drugs

The following drugs were used: capsaicin (Sigma, St. Louis, MO, USA), guanethidine sulfate (Tokyo Kasei, Tokyo, Japan), human CGRP-(8–37) (Peptide Institute, Osaka, Japan), L-noradrenaline HCl (Sigma), methoxamine HCl (Nihon Sinyaku, Kyoto, Japan), prazosin HCl (Pfizer, Tokyo, Japan), rat CGRP (Peptide Institute) and

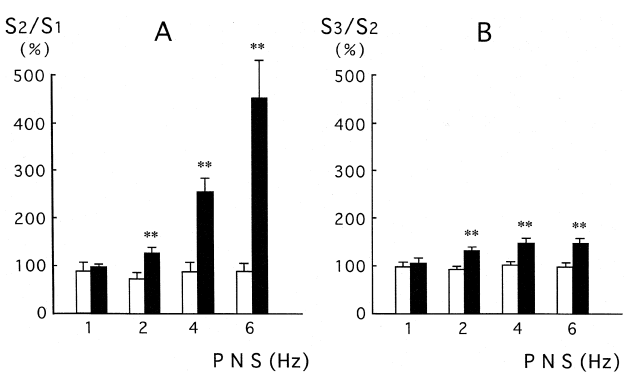

Fig. 3. Effects of treatment with capsaicin (500 nM) (A) or CGRP-(8–37) (1 μM) (B) after capsaicin treatment on pressor responses to periarterial nerve stimulation (PNS; 1–6 Hz) in perfused mesenteric vascular beds of the rat. The ordinate of A and B indicates a percentage (%) of responses induced by the first PNS (S_1) and the second PNS (S_2), respectively. (A) S_1, the responses without treatment; S_2, the responses after vehicle or capsaicin treatment. Open and solid columns indicate vehicle control ($n = 5$) and capsaicin treatment ($n = 5$), respectively. (B) S_2, the second PNS-induced responses after capsaicin treatment; S_3, the third PNS-induced responses during vehicle or CGRP-(8–37) perfusion after capsaicin treatment. Open and solid columns indicate vehicle control ($n = 5$) and CGRP-(8–37) perfusion ($n = 5$), respectively. $** P < 0.01$, compared with vehicle control (unpaired *t*-test).

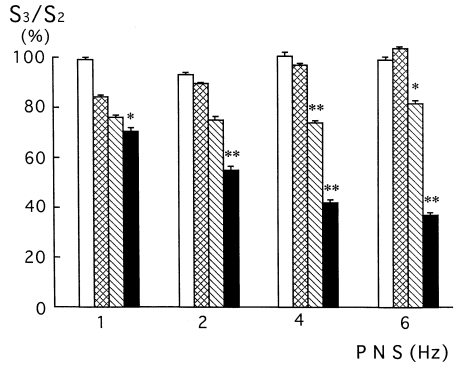

Fig. 4. Effect of exogenous CGRP (0.1–1 nM) perfusion on pressor responses to periarterial nerve stimulation (PNS; 1–6 Hz) after treatment with capsaicin in perfused mesenteric vascular beds of the rat. The ordinate indicates a percentage (%) of the response induced by the second (S_2) PNS. S_2, the second PNS-induced responses after capsaicin treatment; S_3, the third PNS-induced response during vehicle or exogenous CGRP perfusion after capsaicin treatment. Open column, vehicle control ($n = 5$); cross-hatched column, 0.1 nM CGRP perfusion ($n = 5$); hatched column, 0.3 nM CGRP perfusion ($n = 5$); solid column, 1 nM CGRP perfusion ($n = 5$). $*\ P < 0.05$; $**\ P < 0.01$, compared with vehicle control (Dunnett's test).

tetrodotoxin (Sigma). All drugs, except noradrenaline and capsaicin, were dissolved in distilled water and diluted with Krebs' solution. Noradrenaline was dissolved in 0.9% saline containing 0.1% ascorbic acid and stocked in a freezer. On the day of the experiment, final dilutions of noradrenaline were made with Krebs' solution just before being injected. Capsaicin was dissolved in 50% ethanol and diluted with Krebs' solution (final alcohol concentration is 0.4 μg/ml).

3. Results

3.1. Effect of CGRP-(8–37) on pressor response to periarterial nerve stimulation and noradrenaline injection

Periarterial nerve stimulation (1, 2, 4 and 6 Hz) of perfused mesenteric vascular beds with resting tone produced a frequency-dependent increase in perfusion pressure due to vasoconstriction (Fig. 1A). These pressor responses to periarterial nerve stimulation were abolished by 300 nM tetrodotoxin, 5 μM guanethidine and 50 nM prazosin (data not shown), indicating that they were produced by endogenous transmitter noradrenaline released from vascular adrenergic nerves.

In perfused mesenteric vascular beds without active tone, perfusion of 1 μM CGRP-(8–37) did not alter the resting mean perfusion pressure. The pressor responses to periarterial nerve stimulation at 1, 2, 4 and 6 Hz were significantly potentiated during 1 μM CGRP-(8–37) perfusion as compared with control responses (Fig. 1A and Fig. 2A). The potentiation of the periarterial nerve stimula-

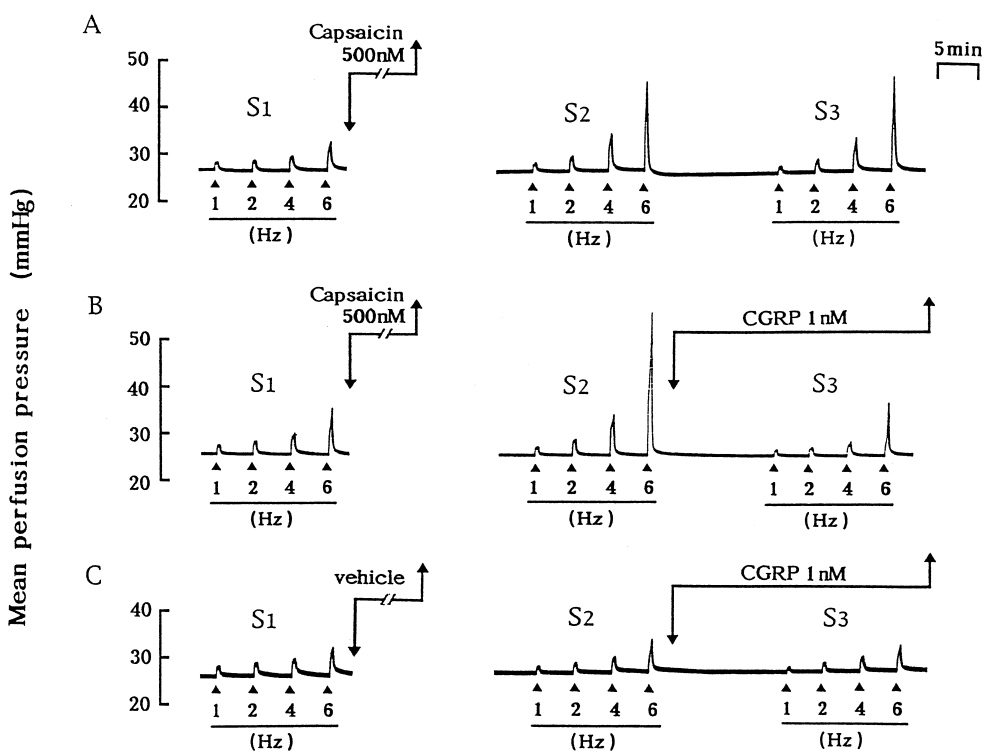

Fig. 5. Typical records showing the effect of exogenous CGRP (1 nM) perfusion on pressor responses to periarterial nerve stimulation (PNS) in perfused mesenteric vascular beds treated (B) and untreated (C) with capsaicin. (A) Control responses. S_1, the responses before treatment; S_2, the responses after capsaicin or vehicle treatment; S_3, the responses during vehicle or CGRP perfusion.

tion-induced response by CGRP-(8–37) was frequency-dependent.

The bolus injection of noradrenaline (0.5, 1 and 2 nmol) also induced a concentration-dependent increase in perfusion pressure. The pressor response to bolus injection of noradrenaline (0.5–2 nmol) was also potentiated significantly in the presence of CGRP-(8–37) (Fig. 2B). However, the potentiation of the noradrenaline-induced response was much smaller than that of the periarterial nerve stimulation-induced response and was not dose-dependent.

3.2. Effect of capsaicin treatment on pressor responses to periarterial nerve stimulation

In perfused mesenteric vascular beds without active tone, perfusion of 500 nM capsaicin did not alter the resting mean perfusion pressure. As shown in Fig. 1B and Fig. 3, pressor responses to periarterial nerve stimulation at 2, 4 and 6 Hz, but not at 1 Hz, were potentiated significantly after treatment with 500 nM capsaicin for 20 min. The potentiation was greater with higher frequencies than with lower frequencies.

In the perfused mesenteric vascular bed with active tone produced by methoxamine (7 μM) and guanethidine (5 μM), periarterial nerve stimulation at 2, 4 and 6 Hz produced a frequency-dependent decrease in perfusion pressure which resulted from vasodilation and was abolished by 1 μM CGRP-(8–37). After treatment with capsaicin, periarterial nerve stimulation did not cause vasodilation (data not shown).

3.3. Effect of CGRP-(8–37) on pressor response to periarterial nerve stimulation after capsaicin treatment

Pressor responses to periarterial nerve stimulation at 1, 2, 4 and 6 Hz were significantly potentiated after capsaicin treatment. In preparations treated with capsaicin, pressor responses to periarterial nerve stimulation at 2, 4 and 6 Hz, but not 1 Hz, were further potentiated by 1 μM CGRP-(8–37) perfusion (Fig. 1C and Fig. 3). However, the potentiation by CGRP-(8–37) of the periarterial nerve stimulation-induced responses was smaller than that of CGRP-(8–37) alone and was not frequency-dependent (Fig. 3).

3.4. Effect of exogenous CGRP on pressor response to periarterial nerve stimulation

In preparations with or without capsaicin treatment, the resting mean perfusion pressure was not altered by CGRP perfusion (0.1, 0.3 and 1 nM). In preparations treated with capsaicin, the augmented pressor responses to periarterial nerve stimulation were attenuated in a concentration-dependent manner by addition of CGRP (0.1, 0.3 and 1 nM) (Fig. 4). Exogenously applied CGRP at a concentration of 1 nM markedly reduced the pressor responses to periarterial nerve stimulation to levels similar to those of control responses before capsaicin treatment (Fig. 5B and Fig. 6D). However, in preparations not treated with capsaicin, exogenous CGRP at a concentration of 1 nM did not attenuate significantly the pressor responses to periarterial nerve stimulation (Fig. 5C and Fig. 6B).

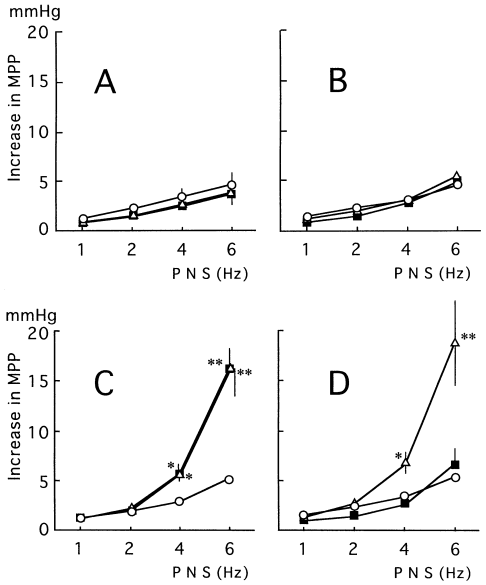

Fig. 6. Effect of exogenous CGRP (1 nM) perfusion on pressor responses to periarterial nerve stimulation (PNS) in perfused mesenteric vascular beds untreated (A and B) and treated (C and D) with capsaicin. The ordinate indicated pressor response (mm Hg). Open circles, the first PNS-induced responses before the capsaicin or vehicle treatment; open triangles, the second PNS-induced responses after capsaicin or vehicle treatment; closed squares, the third PNS-induced responses during vehicle or CGRP perfusion after capsaicin or vehicle treatment. (A) Vehicle perfusion without capsaicin treatment ($n = 5$). (B) CGRP perfusion without capsaicin treatment ($n = 5$). (C) Vehicle perfusion after capsaicin treatment ($n = 5$). (D) CGRP perfusion after capsaicin treatment ($n = 5$). $*\ P < 0.05$, $**\ P < 0.01$, compared with the first PNS-induced responses in each frequency (Dunnett's test).

4. Discussion

In the perfused mesenteric vascular bed with resting tone, periarterial nerve stimulation produced a frequency-dependent increase in perfusion pressure due to vasoconstriction, which was abolished by tetrodotoxin, guanethidine and prazosin. We have reported that vasoconstriction in response to periarterial nerve stimulation in the mesenteric artery was abolished by tetrodotoxin, guanethidine, prazosin and 6-hydroxydopamine (Kawasaki and Takasaki, 1984; Kawasaki et al., 1987). Therefore, it is very likely that this pressor response to periarterial nerve stimulation was mediated by noradrenaline released from periarterial sympathetic, adrenergic nerves. Furthermore, the present and previous studies (Kawasaki et al., 1988) demonstrated that periarterial nerve stimulation of the perfused mesenteric vascular bed contracted by an α_1 adrenergic agonist

(methoxamine), in the presence of adrenergic neuron blocker (guanethidine), produces a frequency-dependent decrease in perfusion pressure due to vasodilation. This vasodilation is mediated by NANC vasodilator nerves, because the response is abolished by tetrodotoxin, but not by an anticholinergic drug or a β-adrenoceptor antagonist (Kawasaki et al., 1988). In addition, periarterial nerve stimulation in the perfused mesenteric vascular bed causes the tetrodotoxin-sensitive release of CGRP associated with the vasodilation (Fujimori et al., 1989). Moreover, the results obtained with a periarterial nerve stimulation-induced NANC vasodilation with CGRP-(8–37) (Han et al., 1990b), CGRP receptor desensitization (Han et al., 1990b) and antiserum against CGRP (Han et al., 1990a) have confirmed that the NANC vasodilation is mediated by endogenous CGRP released from CGRP-containing nerves. Thus, periarterial nerve stimulation of the mesenteric vascular bed produces excitation of both adrenergic vasoconstrictor nerves and CGRP-containing vasodilator nerves. Therefore, pressor responses induced by periarterial nerve stimulation in the mesenteric vascular bed with resting tone are the net result of actions mediated by both vasoconstrictor and vasodilator nerves.

In the present study, capsaicin treatment of the rat mesenteric vascular bed caused potentiation of the vasoconstriction in response to periarterial nerve stimulation, in accord with previous reports (Kawasaki et al., 1990; Li and Duckles, 1992). Capsaicin has been shown to deplete neuropeptides including tachykinins (substance P, neurokinin A, neurokinin B), and CGRP (Kawasaki et al., 1990; Holzer, 1991), from sensory neurons. In the rat mesenteric artery, neither neurokinin A, neurokinin B (Kawasaki et al., 1988; Kawasaki et al., 1990) nor substance P (Kawasaki et al., 1988; Li and Duckles, 1992) causes a vasodilator response. The periarterial nerve stimulation-induced NANC vasodilation mediated by endogenous CGRP is markedly attenuated in the preparation treated with capsaicin (Kawasaki et al., 1990). Thus, it is likely that the potentiation of pressor responses to periarterial nerve stimulation after capsaicin treatment is due mainly to a diminution of function of CGRP-containing nerves.

Moreover, the present study showed that CGRP-(8–37) potentiated significantly the pressor responses to periarterial nerve stimulation, similar to the effect of capsaicin treatment. CGRP-(8–37), a C-terminal fragment of human α-CGRP, has been reported to cause a dose-dependent displacement of ^{125}I-[Tyr^{0}]rat CGRP binding and inhibition of CGRP-induced activation of adenylate cyclase in rat liver plasma membrane (Chiba et al., 1989). In vitro studies have shown that CGRP-(8–37) antagonizes the inotropic effect of CGRP in the guinea-pig isolated atria (Maggi et al., 1991) and the activation of adenylate cyclase in rat isolated intracerebral arterioles (Edwards et al., 1991). Moreover, the periarterial nerve stimulation-induced NANC vasodilation in the rat mesenteric vascular bed is antagonized by CGRP-(8–37) (Han et al., 1990b; Foulkes et al., 1991). In in vivo studies, CGRP-(8–37) attenuates exogenous CGRP-induced vasodilation in rabbit dorsal skin (Hughes and Brain, 1991), the cardiovascular responses in conscious rat (Gardiner et al., 1991), and exogenous CGRP and spinal cord stimulation-induced vasodilation in the pithed rat (Taguchi et al., 1992). However, no inhibitory effect of CGRP-(8–37) on the action of other agonists including adrenaline (Chiba et al., 1989; Bartho et al., 1991; Gardiner et al., 1992), glucagon (Chiba et al., 1989), isoprenaline (Gardiner et al., 1990; Han et al., 1990b; Maggi et al., 1991), neurokinin A (Franco-Cereceda, 1991), bradykinin (Donoso et al., 1990; Gardiner et al., 1992), VIP (Chakder and Rattan, 1991; Hughes and Brain, 1991), substance P (Donoso et al., 1990; Franco-Cereceda, 1991), histamine (Donoso et al., 1990) or prostaglandin E_1 (Hughes and Brain, 1991) has been shown in various experimental test objects. These data show that CGRP-(8–37) acts as a relatively specific antagonist for CGRP receptors. In the present study, CGRP-(8–37) also potentiated the vasoconstriction in response to exogenous noradrenaline injection. However, the potentiation was much smaller than that of the periarterial nerve stimulation-induced response. Therefore, potentiation of periarterial nerve stimulation-induced vasoconstriction by CGRP-(8–37) is due mainly to inhibition of the effect of endogenous CGRP which was released from perivascular CGRP-containing nerves in response to periarterial nerve stimulation.

The cause of the slight potentiation by CGRP-(8–37) of the noradrenaline-induced response is not clear. However, this may be due to inhibition of endogenous CGRP spontaneously released from CGRP-containing nerves in the resting state. This notion is supported by studies of the spontaneous release of CGRP (Fujimori et al., 1989) and the direct vasoconstrictor activity of CGRP-(8–37) (Han et al., 1990b). However, potentiating effect of CGRP-(8–37) itself on adrenergic function also seems likely. In addition, CGRP-(8–37) potentiated pressor responses to periarterial nerve stimulation after capsaicin treatment, but the effect of potentiation by CGRP-(8–37) in the capsaicin-treated preparation was also less than that in the absence of capsaicin treatment. In the capsaicin-treated preparation, endogenous CGRP function is largely inhibited, so that periarterial nerve stimulation produces excitation of adrenergic vasoconstrictor nerves and not of vasodilator nerves, to cause potentiation of the periarterial nerve stimulation-induced pressor response. Therefore, a possible cause of the further potentiation by CGRP-(8–37) seen after capsaicin treatment may be: (1) there exists an undetermined vasodilator factor which is antagonized by CGRP-(8–37); (2) CGRP-(8–37) by itself potentiates the adrenergic function as described before.

The present study showed that exogenously applied CGRP markedly attenuated the potentiated pressor responses to periarterial nerve stimulation in the capsaicin-

treated preparation in a concentration-dependent manner, suggesting that the endogenous CGRP suppresses the vasoconstriction mediated by adrenergic nerves. However, CGRP perfusion at a concentration of 1 nM, which induced a marked decrease in the response of the capsaicin-treated preparation, did not affect significantly the periarterial nerve stimulation-induced pressor response in the preparation without capsaicin treatment. Since CGRP (1 nM) causes vasodilation of the mesenteric artery with or without capsaicin treatment (Kawasaki et al., 1988; Kawasaki et al., 1990) and capsaicin does not affect the penetration through endothelium, it is unlikely that exogenous CGRP could not reach postsynaptic CGRP receptors. Thus, it is presumable that vasoconstriction mediated by adrenergic nerve stimulation in the intact preparation is maximally inhibited by endogenous CGRP released by CGRP nerve stimulation. Therefore, exogenous CGRP seems not to cause further inhibition. This indicates that the estimated local concentration of CGRP released at the neuro-effector junction is more than 1 nM.

In conclusion, the present results suggest that endogenous CGRP, which is released from CGRP-containing nerves at rest and in response to periarterial nerve stimulation, suppresses adrenergic nerve function in the regulatory mechanism of tone of peripheral resistant blood vessels.

Acknowledgements

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