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Intravascular substance P dilates cerebral parenchymal vessels through a specific tachykinin NK_1 receptor in cats

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Abstract

The role of substance P in the cerebral parenchymal circulation was examined in 19 anesthetized cats. The local cerebral blood volume in the temporoparietal cortex was measured by our photoelectric method. Cerebral blood volume reflects the cumulative dimensions of the parenchymal microvessels. Intravenous injection of 0.01, 0.1, and 1 mg/kg FK888 (N^2-[(4*R*)-4-hydroxy-1-(1-methyl-1*H*-indol-3-yl)carbonyl-L-prolyl]-*N*-methyl-*N*-phenylmethyl-3-(2-naphthyl)-L-alaninamide), a selective tachykinin NK_1 receptor antagonist, had no significant effects (compared to the vehicle, ethanol) on cerebral blood volume and mean arterial blood pressure. Intracarotid injection of 1, 10, 100 pmol/kg, and 1 nmol/kg substance P increased cerebral blood volume ($P < 0.01$) in a dose-dependent manner (maximal increase of 6.5% at 5 min). Following injection of 1 nmol/kg substance P, cerebral blood volume was initially reduced, possibly due to the marked fall in mean arterial blood pressure ($P < 0.01$). The cerebral blood volume increase elicited by 1 nmol/kg substance P was strongly blocked ($P < 0.05$) by prior injection of 1 mg/kg FK888. However, the depressor effect of 1 nmol/kg substance P (-24 ± 4 mm Hg at 30 s, $P < 0.01$) was partially inhibited ($P < 0.01$) by FK888. We conclude that endogenous substance P may not have a significant role in the maintenance of resting tone of cerebral parenchymal vessels. Intravascular substance P, however, dilates the small microvessels through a specific tachykinin NK_1 receptor and could be involved in the development of pathologic processes such as migraine headache.

Keywords: Cerebral blood volume; Cerebral vessel; FK888; Photoelectric method; Substance P; Tachykinin NK_1 receptor antagonist

1. Introduction

Mammalian tachykinins consist of three major peptides, substance P, neurokinin A, and neurokinin B, which share the common C-terminal sequence -Phe-X-Gly-Leu-Met-NH_2 (Maggio, 1988). The biological activities of tachykinins are mediated through three tachykinin receptors, NK_1, NK_2, and NK_3. Substance P, neurokinin A, and neurokinin B exhibit their highest affinity for tachykinin NK_1, NK_2, and NK_3 receptors, respectively (Watling, 1992).

In the periphery, substance P is present in the small-diameter, unmyelinated C fibers that constitute primary sensory neurons, and is involved in the transmission of nociceptive information (Hökfelt et al., 1975). Substance P is also demonstrated in the perivascular nerve fibers of the major cerebral arteries, trigeminal ganglia, and upper cervical dorsal root ganglia (Edvinsson et al., 1981; Liu-Chen et al., 1983; Suzuki et al., 1989). Substance P-containing fibers of the large cerebral arteries originate mainly from the ipsilateral trigeminal ganglion (Liu-Chen et al., 1983; Uddman et al., 1985; McCulloch et al., 1986). In the neurons of the trigeminal ganglia and perivascular nerve fibers, substance P is colocalized with neurokinin A and calcitonin gene-related peptide (CGRP) (McCulloch et al., 1986; Edvinsson et al., 1988; Suzuki et al., 1989).

It has been shown that substance P relaxes precontracted cerebral arteries in vitro (Edvinsson et al., 1981, 1988; Edvinsson and Jansen, 1987; Mejia et al., 1988). Perivascular application of substance P and other tachykinins dilated pial arteries and veins of the brain surface (Edvinsson et al., 1981, 1982b; McCulloch et al., 1986; Beattie et al., 1993b; Rosenblum et al., 1993). However, there are few studies concerning the effects of

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circulating substance P on the cerebral vessels, especially on the parenchymal microvessels (Beattie et al., 1993a).

Although there is not enough evidence, substance P has been implicated in the pathogenesis of migraine (Moskowitz and Macfarlane, 1993), vasospasm after subarachnoid hemorrhage, and postischemic hyperemia (Macfarlane et al., 1991). In migraine headache, orthodromic activation of the trigeminovascular pathway seems to convey pain sensation to the brain, while antidromic impulses induce the release of neurotransmitters, CGRP and substance P. In addition to cerebral vasodilation, substance P increases plasma protein extravasation in the dura (Markowitz et al., 1987), thereby aggravating the inflammatory process associated with migraine headache (Moskowitz and Macfarlane, 1993).

Recently, a number of selective tachykinin NK_1 receptor antagonists, such as CP96345, RP67580, and GR82334, have been synthesized (Watling, 1992; Beattie et al., 1993b). FK888 (N^2-[(4*R*)-4-hydroxy-1-(1-methyl-1*H*-indol-3-yl)carbonyl-L-prolyl]-*N*-methyl-*N*-phenylmethyl-3-(2-naphthyl)-L-alaninamide) is a novel potent, competitive, and selective dipeptide antagonist for the tachykinin NK_1 receptor (Fujii et al., 1992; Aramori et al., 1994). By inhibiting vasodilation or the increase in vascular permeability mediated by substance P, it is possible that substance P receptor antagonists may ameliorate the pathologic processes associated with migraine headache and other substance-P-related disorders.

The aim of the present study was to determine the role of substance P in the cerebral parenchymal microcirculation. We examined the effects of substance P and a tachykinin NK_1 receptor antagonist, FK888, on the cerebral microvessels using our photoelectric technique (Tomita et al., 1978, 1983).

2. Materials and methods

Adult cats weighing 1.5–4.3 kg (mean weight 3.0 kg) were anesthetized by intraperitoneal injection of 50 mg/kg α-chloralose and 500 mg/kg urethane. Small amounts of 1% procaine hydrochloride were used for local anesthesia. The body temperature of the animals was maintained at 37–37.5°C by a heated blanket. After endotracheal intubation, respiration was kept constant with a volume-controlled respirator (Harvard, model 662). The left lingual artery and the femoral vein were cannulated and were used for injecting agents into the carotid artery and systemic circulation, respectively. Systemic arterial blood pressure was monitored through a catheter inserted into the femoral artery.

The head of each animal was fixed in a stereotaxic head holder. The local cerebral blood volume was measured continuously by the photoelectric method, the details of which have been reported previously (Tomita et al., 1978, 1983). Briefly, the photoelectric apparatus consists of a micro-lamp of 1 mm in diameter (Hamai Electric) and a silicon photodiode (Sharp Electric) covered with a band pass filter. Through a small cranial hole made in the left temporoparietal region, the micro-lamp was inserted into the brain tissue to approximately 5 mm below the surface. The photodiode, which was attached to the skull just above the inserted lamp, continuously measured the intensity of transmitted light passing through a 5 mm layer of cerebral cortex. The intensity of light was calibrated to the cerebral blood volume (expressed in ml/100 ml brain, or vol.%) according to the equation described in our previous paper (Tomita et al., 1978).

FK888 (Fujisawa Pharmaceutical, Osaka, Japan) was dissolved in 100% ethanol. First, in ten animals, the effects of intravenous administration of 0.2 ml ethanol (vehicle), and 0.01, 0.1 and 1 mg/kg FK888 on cerebral blood volume and arterial blood pressure were sequentially

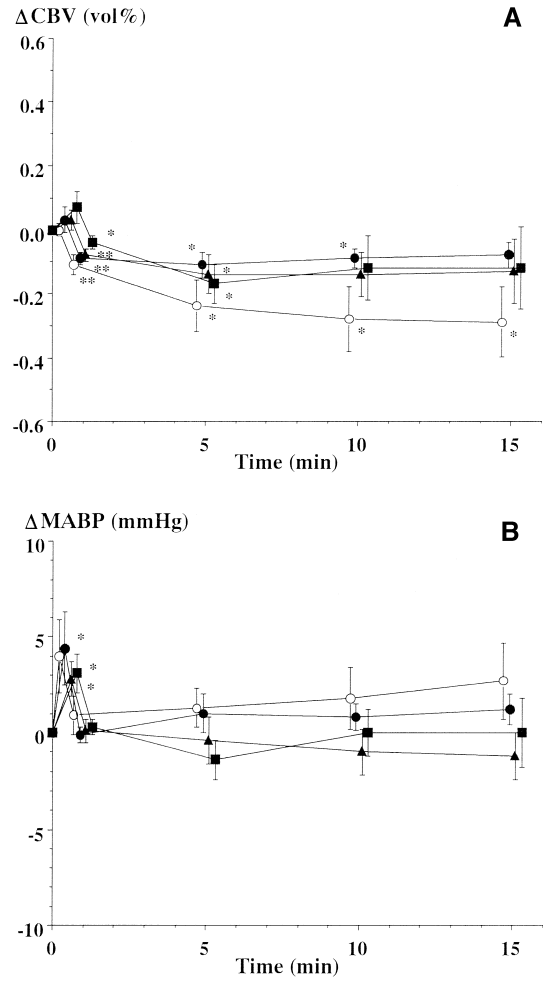

Fig. 1. Time course of (*A*) cerebral blood volume (CBV) and (*B*) mean arterial blood pressure (MABP) following intravenous administration of ethanol (○), and 0.01 (●), 0.1 (▲), and 1 (■) mg/kg FK888. Values are means ± S.E.M. (*) $P < 0.05$ and (**) $P < 0.01$ vs. 0 min. The changes in cerebral blood volume and MABP after injection of each dose of FK888 were not significantly different from the effect of vehicle (ethanol).

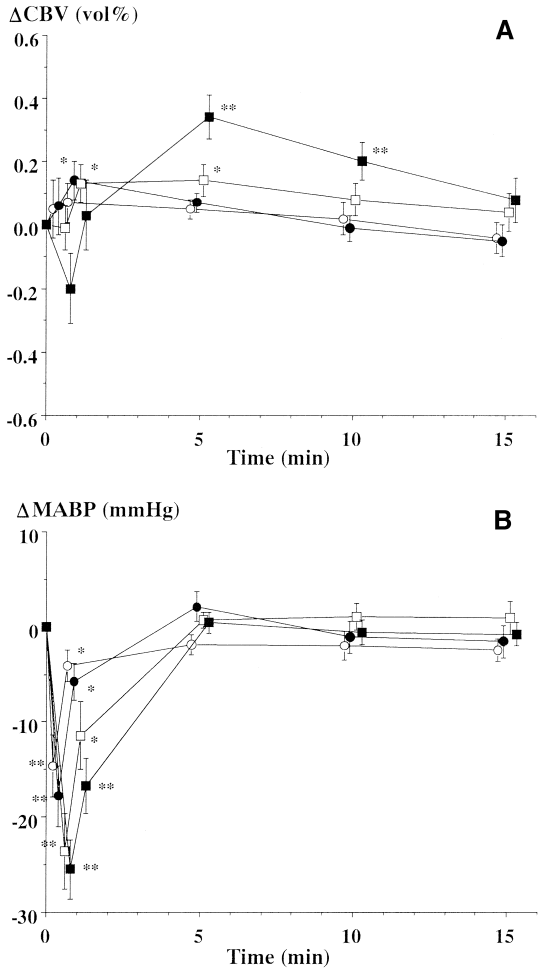

Fig. 2. Changes in (*A*) cerebral blood volume (CBV) and (*B*) mean arterial blood pressure (MABP) following intracarotid injection of 1 (○), 10 (●), 100 pmol/kg (□), and 1 nmol/kg (■) substance P. Values are means ± S.E.M. (∗) $P < 0.05$ and (∗∗) $P < 0.01$ vs. 0 min. Substance P increased cerebral blood volume in a dose-dependent manner. The initial reduction in cerebral blood volume following injection of 1 nmol/kg substance P possibly reflected the marked fall in MABP.

recorded for 15 min. There was a 20-min interval between each dose. According to our preliminary study, the effect of FK888 was not long-lasting (less than 20 min). Secondly, 1 ($n = 8$), 10 ($n = 9$), 100 pmol/kg ($n = 10$) and 1 nmol/kg ($n = 17$) substance P (Peptide Institute, Osaka, Japan), prepared as 1 ml volumes with saline, were injected sequentially into the carotid artery over approximately 10 s. The alterations in cerebral blood volume and arterial blood pressure were observed for 15 min after administration of each dose. Finally, the changes in cerebral blood volume and arterial blood pressure following intracarotid injection of 1 nmol/kg substance P, given before and 2 min after intravenous injection of 1 mg/kg FK888, were compared in 11 animals.

The experimental protocols conformed to the guiding principles of the American Physiological Society. The data are presented as means ± S.E.M. Statistical analysis was performed by using Student's *t*-test.

3. Results

As summarized in Fig. 1A, the cerebral blood volume changes elicited by intravenous administration of FK888 were not significantly different from the effect of vehicle (ethanol), although the vehicle induced a mild reduction in cerebral blood volume. Thus, FK888 per se does not seem to have a significant effect on cerebral blood volume. Further, FK888 itself does not have a significant effect on arterial blood pressure, since the changes in mean arterial blood pressure following FK888 injection were not significantly different from those following injection of vehicle (ethanol) (Fig. 1B).

As shown in Fig. 2A, intracarotid injection of substance P increased cerebral blood volume in a dose-dependent

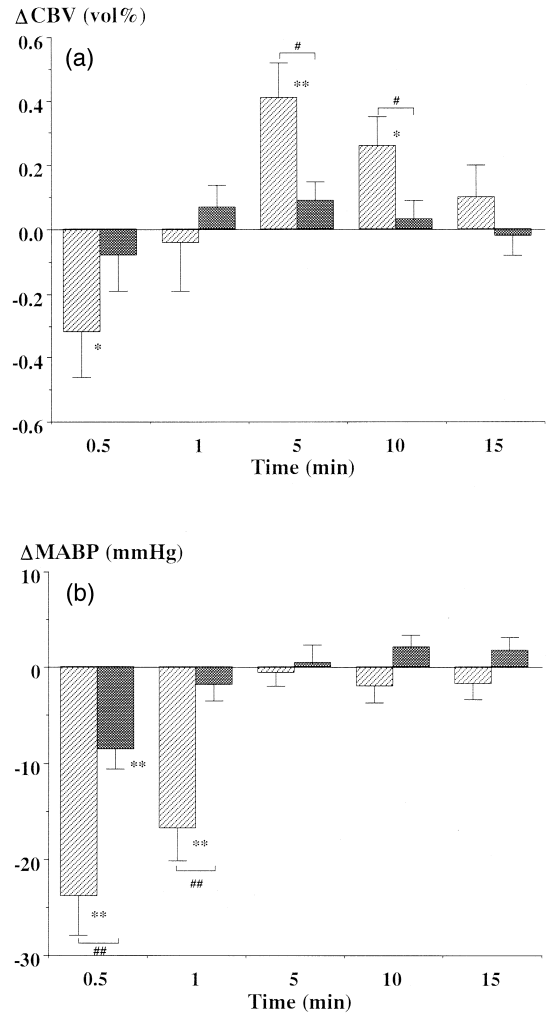

Fig. 3. Changes in (a) cerebral blood volume (CBV) and (b) mean arterial blood pressure (MABP) elicited by intracarotid injection of 1 nmol/kg substance P, before (hatched column) and after (dark hatched column) intravenous administration of 1 mg/kg FK888. Values are means ± S.E.M. (∗) $P < 0.05$ and (∗∗) $P < 0.01$ vs. 0 min. (#) $P < 0.05$ and (##) $P < 0.01$ between the two groups. The cerebral blood volume increases and MABP reductions following injection of substance P were inhibited by preinfusion of FK888.

manner. The initial cerebral blood volume reduction following infusion of 1 nmol/kg possibly reflected the marked fall in mean arterial blood pressure seen with this dose (Fig. 2B). The cerebral blood volume increase following administration of 1 nmol/kg substance P was inhibited ($P < 0.05$) by preinfusion of 1 mg/kg FK888 (Fig. 3a).

The initial mean arterial blood pressure values for the groups administered 1, 10, 100 pmol, and 1 nmol/kg substance P were 122 ± 8, 123 ± 8, 114 ± 9, and 118 ± 7 mm Hg, respectively. As shown in Fig. 2B, intracarotid injection of substance P induced a transient but marked reduction of arterial blood pressure in a dose-dependent manner. Mean arterial blood pressure recovered to the initial level within 5 min, and remained constant thereafter. The depressor effect of 1 nmol/kg substance P was attenuated ($P < 0.01$) by preinjection of 1 mg/kg FK888 (Fig. 3b).

Physiological parameters, such as Pa_{O_2}, Pa_{CO_2}, and pH of the animals were normal at the beginning of the experiment and did not show any significant changes during the study.

4. Discussion

The photoelectric method permits continuous and quantitative monitoring of the cerebrocortical microcirculation. Cerebral blood volume represents the cumulative dimensions of the parenchymal microvasculature, which includes arterioles, capillaries, and venules. The precise degree of contribution by these vascular components is not known. The validity and technical details of the method have been discussed previously (Tomita et al., 1978, 1983). The measurements of hemodynamic parameters obtained by this method correlate well with those determined by other standard techniques, such as hydrogen gas clearance (Tomita et al., 1988). Insertion of the micro-lamp into the brain tissue does not affect the physiological responses of the cerebral microvessels (Tomita et al., 1978). In the chronic stage, only mild gliosis is observed around the inserted lamp.

In the present study, intravenous administration of the specific tachykinin NK_1 receptor antagonist FK888 elicited no significant changes in cerebral blood volume and arterial blood pressure, when compared to the vehicle. Edvinsson et al. (1982a) found no appreciable changes in pial artery diameter following perivascular microapplication of a substance P receptor antagonist, [D-Pro^2,D-Trp^{7,9}]substance P, in cats. Intrathecal infusion of anti-substance P γ-globulin also did not affect cerebral artery diameter in squirrel monkeys (Shiokawa et al., 1993). These observations and ours indicate that local production of substance P and its action mediated by the tachykinin NK_1 receptor are not important for maintaining the tone of small parenchymal as well as large pial vessels.

Substance P induced a short-lasting, but marked fall in arterial blood pressure. The depressor effect of substance P was inhibited to approximately one-third by preinjection of FK888. Thus, the tachykinin NK_1 receptor predominantly mediates the vasodilator action of substance P in the peripheral circulation of cats. The incomplete blockade by FK888 may be due to an insufficient amount of FK888 used, or to an additional contribution by tachykinin receptors other than the NK_1 type.

In addition to the documented dilatation of large cerebral vessels by abluminal substance P (Edvinsson et al., 1981; McCulloch et al., 1986; Beattie et al., 1993b; Rosenblum et al., 1993), we demonstrated that blood-borne substance P also dilates cerebral vessels, especially the parenchymal microvessels. The initial reduction in cerebral blood volume following infusion of a large dose of substance P was possibly caused by the rapid and marked fall in arterial blood pressure (Kobari et al., 1992; Barzó et al., 1993). The problem remains of how intravascular substance P gains access to its receptors. As with other neuropeptides, we assume that substance P may partly cross the blood-brain barrier, may change the permeability of the blood-brain barrier, or may act directly on the vascular endothelium (Kobari et al., 1994a).

Early studies have shown that intravenous infusion of substance P increases carotid blood flow, as measured with an electromagnetic flowmeter, in dogs (Hallberg and Pernow, 1975), but not in humans (Samnegård et al., 1978). However, carotid blood flow cannot be used as an estimate of the brain circulation per se. Recently, Beattie et al. (1993a) reported that intracarotid administration of substance P did not change cerebral blood flow measured by laser Doppler flowmeter in guinea-pigs. The reason for the discrepancy between their result and ours is not clear, but it may be explained by the differences in the vascular segments that were studied, in the amounts of substance P used, and in the species. The possibility that the blood-brain barrier might be damaged with our method cannot be ruled out.

The maximal increase in cerebral blood volume of approximately 6.5% after substance P injection was rather modest when compared to those induced by CGRP (approximately 10%) and other vasodilator neuropeptides (Kobari et al., 1994a,1995). The vasodilator potency of substance P was calculated to be approximately one-half that of CGRP, which was consistent with the observations of others (McCulloch et al., 1986). Further, perivascular application of substance P (Edvinsson et al., 1981; McCulloch et al., 1986; Beattie et al., 1993b) seems to induce greater vasodilation than intravascular infusion.

Since the increase in cerebral blood volume elicited by substance P was completely blocked by preadministration of a selective tachykinin NK_1 receptor antagonist, FK888, the vasodilator action of substance P on the cerebral parenchymal vessels is mediated by the tachykinin NK_1 receptor in cats. The presence of the tachykinin NK_1 receptor has been suggested in isolated cerebral arteries in vitro (Edvinsson and Jansen, 1987; Stubbs et al., 1992) and

in the superficial pial arteries in situ (Beattie et al., 1993b). The present study demonstrated the participation of the tachykinin NK_1 receptor in substance P-induced dilatation of the cerebral parenchymal microvessels.

Cerebral vasodilation by substance P is dependent on the presence of an intact endothelium (Edvinsson et al., 1985; Edvinsson and Jansen, 1987; Mejia et al., 1988; Rosenblum et al., 1993). Since substance P-induced vasodilation is inhibited by N^G-monomethyl-L-arginine (an inhibitor of nitric oxide synthesis), but not by indomethacin (an inhibitor of prostacyclin synthesis) (Rosenblum et al., 1993), nitric oxide or related compounds may be the endothelium-derived relaxing factor (EDRF) for substance P. The role of nitric oxide has been demonstrated in the cerebral vasodilation caused by a number of neuropeptides (Kobari et al., 1994a,b).

Although still controversial, there are reports on dilatation of cerebral vessels and increased cerebral blood flow during attacks of migraine headache (Sakai and Meyer, 1978; Kobari et al., 1989, 1990). Release of CGRP and substance P following activation of the trigeminovascular pathway (Moskowitz and Macfarlane, 1993) may lead to cerebral hyperperfusion. In this context, substance P antagonists could have a therapeutic role.

We conclude that endogenous substance P does not seem to modulate the resting tone of cerebral parenchymal vessels, but circulating substance P dilates the cortical microvessels through a specific tachykinin NK_1 receptor. These data are in keeping with the possibility that substance P may contribute to the evolution of various pathologic processes such as migraine headache.

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