Role of nitric oxide in the cerebral vasodilatory responses to vasopressin and oxytocin in dogs

バソプレッシン及びオキシトシンによる犬脳血管拡張作用に於けるnitric oxideの役割

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ABSTRACT

We angiographically assessed the vasodilatory effects of vasopressin and oxytocin on the basilar arteries in dogs. Intracisternal bolus injections of vasopressin (100 pmol and 1 nmol) and oxytocin (1 and 10 nmol) produced dose-dependent increases in the internal diameter of the basilar arteries without affecting mean arterial blood pressure. The maximal dilatations of the basilar arteries induced by 1 nmol vasopressin and 10 nmol oxytocin were 142.3 ± 19.9 % and 136.8 ± 25.5 % of the baseline, respectively. When the same peptides were injected into the vertebral artery, the maximal dilatations were similar, but the duration of response was shorter. Pretreatment with intracisternal injection of 10 μmol N^G-monomethyl-L-arginine (L-NMMA), which inhibits the synthesis of nitric oxide from L-arginine, suppressed the vasodilatory responses induced by intracisternal injection of vasopressin and oxytocin, and by intra-arterial injection of vasopressin. Calcitonin gene-related peptide also caused dilatation of the basilar artery when injected into the cisterna magna, but its effect was not blocked by L-NMMA. L-NMMA reduced the basal diameter of the basilar artery in a dose-dependent manner; L-arginine produced dose-dependent increases in diameter. The vasoconstriction induced by L-NMMA was reversed by high concentrations of L-arginine. These results suggest that vasopressin and oxytocin dilate the basilar arteries via the release of nitric oxide from both the intraluminal and extraluminal sides, and that synthesis and release of nitric oxide in the vascular wall contributes to maintenance of basal vascular tonus.

Key words: vasopressin, oxytocin, nitric oxide, N^G-monomethyl-L-arginine, L-arginine, canine cerebral arteries

Running title: Cerebral vasodilation by vasopressin

INTRODUCTION

Current evidence indicates that vasopressin and oxytocin, circulating vasoactive peptides released from the neurophypophysial gland, play a role in regulating cerebral, as well as peripheral, vascular tonus. Regional differences in sensitivity and responsiveness of the vasculature to vasopressin and oxytocin have been demonstrated in the cerebral and coronary arteries in different animal species (Faraci et al., 1988; Myers et al., 1989; Suzuki et al., 1992). These peptides reduce resistance of large vessels and increase resistance of small vessels. Vasopressin-immunoreactive nerve fibers have been identified in the cerebral pial arteries of guinea pigs (Itakura et al., 1988). Such nerve fibers suggest that vasopressin may regulate local cerebral blood flow not only as a circulating hormone, but also as a neurotransmitter.

The in vitro vasodilatory effects of vasopressin and oxytocin are mediated through V1 receptors connected to an endothelium-dependent relaxing mechanism (Katusic et al., 1984; Katusic et al., 1986). We confirmed angiographically that intra-arterial injections of vasopressin and oxytocin into the vertebral artery dilated the major cerebral arteries, including the vertebral, basilar arteries as well as the circle of Willis and its main branches(Suzuki et al., 1992). Nitric oxide or a closely related factor formed from L-arginine has been strongly implicated as an endothelium-derived relaxing factor (Ignarro et al., 1987; Palmer et al., 1987; Palmer et al., 1988). In this paper, we shall refer to endothelium-derived relaxing factor as nitric oxide. Analogs of L-arginine that inhibit the synthesis of nitric oxide from L-arginine have been developed (Hibbs et al., 1987; Rees et al., 1989; Moor et al., 1990). N^G-monomethyl-L-arginine (L-NMMA), N^G-nitro-L-arginine and N^G-amino-L-arginine are representative antagonists that are frequently used to elucidate the pharmacologic functions of nitric oxide.

In the present study, we investigated whether the intracisternal injection of vasopressin and oxytocin dilated the basilar arteries via the release of nitric oxide in vivo. We also investigated the differences in the vascular responses obtained by intracisternal and intra-arterial injection of vasopressin.

MATERIALS AND METHODS

Mature mongrel dogs of either sex, weighing 8 to 20 kg, were used in these experiments. All procedures were performed under general anesthesia with intravenous pentobarbital (25 mg/kg). Dogs were intubated, and respiration was controlled through tracheal tubes with room air delivered by a respirator (Igarashi Ika Kogyo Co., Model B2, Tokyo, Japan). The ventilation rate (approximately 12 cycles/min) and tidal volume (20 ml/kg) were adjusted to maintain arterial blood gas and pH within physiological limits. In this series, the mean baseline value of PaO_2 was 90.0 ± 18.8 mmHg, $PaCO_2$ was 33.0 ±7.1 mmHg and pH was 7.36 ±0.08. A catheter was placed in the left femoral artery to monitor mean arterial blood pressure. To prevent dehydration, which elevates the endogenous plasma vasopressin, a slow intravenous infusion of saline solution was maintained during the procedure.

Measurement of vascular diameter by angiography

The internal diameter of the basilar artery was determined by vertebral angiography. A catheter for angiography was inserted directly into the right vertebral artery just before the foramen of the transverse process of the cervical vertebra (C6) at the base of the neck. A control angiogram was performed using 3.0 ml of 65% iothalamate meglumine at a fixed magnification before the injection of the control or test solutions. Then, angiograms

were continued periodically (5, 10, 15, 20, 30, 45, 60, 90, 120 min) after the control or test solutions were injected through a No. 22 spinal needle into the cisterna magna or the vertebral artery. Volume of 1.5 ml of physiological saline was used as a control solution, and all injected substances, vasopressin, oxytocin, calcitonin gene-related peptide(CGRP), L-NMMA, or L-arginine, were dissolved in the same amount of physiological saline just before use. The pH of all test solutions except for L-arginine, an alkaline amino acid, was almost the same as the control solution. The vasodilatory effect induced by L-arginine solution which had been neutralized by HCl did not differ from the original effect.

In the investigation of the modulating effects of L-NMMA or/and L-arginine on the vasodilation induced by vasopressin, oxytocin, or CGRP, these substances were intracisternally injected 30 min before the administration of each peptide. Injection of solutions into the cisterna magna was done after withdrawing gently the same amount of cerebrospinal fluid to preserve the intracranial pressure as constant as possible. Care was taken to keep the animals in a head-down position, which enhanced the contact of preparations with the basilar artery.

The middle third of the basilar artery was chosen for quantitative evaluation and the internal diameters of the basilar arteries were measured by means of a computerized image analysis system (Macintosh IIcx, Image 1.27, Apple Computer Inc., Cupertino, CA, USA), as previously reported (Harada et al., 1990; Satoh et al., 1991; Suzuki et al., 1992). The differences in the internal diameter after injection of peptides and nitric oxide-related substances were compared to determine the effects of these substances on vascular activity.

Data are expressed as a percentage of the diameter of the arterial segment before the injection of test substances (defined as 100 %).

Materials

Synthetic Arg-vasopressin, oxytocin and human calcitonin gene-related peptide α (CGRPα) were purchased from Peptide Institute Inc., Osaka, Japan. L-NMMA was

obtained from Calbiochem , La Jolla, CA , USA. L-arginine and all other chemicals were reagent grade.

Statistical analysis

Data are expressed as mean ± S.D. Differences were analyzed by analysis of variance and Dunnett's test, and Student's t-test. P values less than 0.05 were considered statistically significant.

RESULTS

Intracisternal injection of vasopressin, oxytocin, and CGRP

The intracisternal injection of saline solution as a control did not produce a significant change in the internal diameter of the basilar arteries (1.7 ± 0.2 mm, n=5) on the angiogram over 120 min period. After bolus injections of vasopressin (100 pmol and 1 nmol), oxytocin (1 and 10 nmol), and CGRP (100 pmol and 1 nmol), dose-dependent increases in the internal diameter of the basilar arteries were clearly observed (Fig. 1). We selected the the middle third of the basilar artery for representative quantitative evaluation.

The maximal dilation induced by 1 nmol of vasopressin, 10 nmol of oxytocin, and 1 nmol of CGRP were 142.3 ± 19.9 %, 136.8 ± 25.5 %, and 139.8 ± 31.5 % of the baseline, respectively. Significant dilation persisted for 30, 15, and 20 min, respectively.

There were no significant differences in mean arterial blood pressure among treatment groups or between control baseline and treatment groups (Table 1).

Effects of L-NMMA and L-arginine on the responses to vasopressin, oxytocin and CGRP

Pretreatment with 10 μmol of L-NMMA injected intracisternally 30 min before injection of vasopressin and oxytocin suppressed the vasodilatory responses induced by intracisternal injections of vasopressin and oxytocin, but the response to CGRP was not inhibited by L-NMMA(Fig. 2). Typical vertebral angiograms are shown in Fig 3. Intracisternal injection of L-NMMA also inhibited the vasodilatory response to intra-arterial injection of vasopressin . When 10 μmol L-NMMA and 100 μmol L-arginine were administered simultaneously, the vasodilatory response to vasopressin was restored.

Effects of L-NMMA and L-arginine on basal diameter of cerebral arteries

Intracisternal injection of L-NMMA produced dose-dependent decreases in the internal diameter of the basilar arteries, while L-arginine produced dose-dependent increases(Fig. 4). For example, 10 μmol L-NMMA produced vasoconstriction that lasted more than 120 min with a maximal decrease in diameter of 75.7 ± 14.8 % of the baseline. A dose of 100 μmol L-arginine produced significant increases in the basilar arteries for 45 min, with a maximal increase of 135.8 ± 18.5 % of the baseline. The vasoconstriction induced by L-NMMA was reversed by the application of a 10-fold concentration of L-arginine. There were no significant changes in mean arterial blood pressure after the intracisternal injection of L-NMMA or L-arginine.

DISCUSSION

Our results showed that intracisternal injections of vasopressin and oxytocin in anesthetized dogs produced dose-dependent dilatations of the internal diameter of the basilar arteries, as demonstrated by angiography. Intracisternal injection of thses peptides in concentrations up to 1 and 10 nmol was not associated with any significant change in mean arterial blood pressure. The potency of oxytocin is less than one-tenth that of vasopressin, as determined by the measurement of vertebral blood flow (Suzuki et al., 1992). When compared with the results previously obtained by intra-arterial injection (Suzuki et al., 1992), the intracisternal injection of vasopressin or oxytocin produced vasodilation of a similar degree, but of a longer duration. These findings may explain the ease of diffusion of peptides from the extraluminal side into the vascular wall when there is no barrier such as a tight junction of the endothelium, or a slow degradation of peptides in the cerebrospinal fluid as compared with their degradation in serum.

Previous reports suggest that the vasodilatory effects of vasopressin and oxytocin are mediated through the endothelium and V_1- receptors, as has been shown in the canine basilar artery in vitro and in vivo(Katusic et al., 1984; Suzuki et al., 1992). The intracisternal injection of L-NMMA, an arginine analog that inhibits the activity of the nitric oxide synthase, suppressed the vasodilatory effects of vasopressin and oxytocin. The suppressive effect of L-NMMA on vasopressin's action was reversed by a high concentration of L-arginine, a substrate for the formation of nitric oxide. These observations suggest that nitric oxide may be responsible for the vasodilation induced by vasopressin and oxytocin in the major cerebral arteries. However, the vasodilation induced by the intracisternal injection of CGRP, which has a potency similar to that of vasopressin, was not affected by pretreatment with L-NMMA. CGRP, a potent vasodilatory neuropeptide involved in the sensory fibers innervating brain vessels (McCulloch et al., 1986; Saito et al., 1989), directly stimulates adenylate cyclase of vascular smooth muscle

leading to the accumulation of cAMP (Edvinsson et al., 1985) and to increases in local cerebral blood flow(Ikegaki et al, 1989; Suzuki et al., 1989). Our results confirmed our earlier in vitro findings(Ikegaki et al. 1989) which indicated that the cerebral vasodilatory response to CGRP was independent of the formation of nitric oxide.

Recent studies suggest that nitric oxide is synthesized not only in blood vessels, but also in various tissues such as the central and peripheral nervous system, pituitary gland, adrenal gland, platelets or fibroblasts (Salvemini et al., 1989; Bredt et al., 1990; Radomski et al., 1990; Kuhn et al., 1991). It has also been suggested that nerve fibers in the vascular wall and smooth muscle cells in blood vessels are able to synthesize and release nitric oxide(Bredt et al., 1990; Wood et al., 1990; Benjamin et al., 1991; Mollace et al., 1991). In an immunohistochemical study, dense staining for nitric oxide synthase was observed in the endothelium and the anterior cerebral artery of the rat (Bredt et al, 1990), suggesting that nitric oxide can influence the tonus of smooth muscle from different sites such as the endothelium and nerve endings in the adventitia. L-NMMA induced contraction of the canine basilar artery even after the removal of the endothelium (Katusic 1991), and blocked the transient vasodilatory responses following transmural electrical stimulation of nonadrenergic noncholinergic nerves(Gonzalez and Estrada, 1991; Toda et al., 1990). When vasopressin is injected from the intraluminal side, nitric oxide release from the endothelium may be the main mediator of vasodilation, but it is unclear which of the sites that store nitric oxide in blood vessels are stimulated from the extraluminal side. Intracisternal injection of L-NMMA probably suppresses the synthesis of nitric oxide in both the endothelium and nerve endings, because it similarly inhibits the vasodilatory activity induced by intraluminal and extraluminal administration of vasopressin.

Our in vivo data revealed that the intracisternal injection of L-NMMA and L-arginine produced significant and long-lasting changes in the diameter of basilar arteries, probably leading to hemodynamic changes in cerebral blood flow. The alterations in the vascular diameter we observed in the canine basilar artery were greater than those observed

by Faraci (1990) in the rat basilar artery, but were relatively consistent with results obtained by the topical application of these substances to mouse and piglet pial arterioles (Rosenblum et al., 1990; Busija et al., 1989). Our findings are also similar to those of Tanaka et al (1991) who reported that the intravenous administration of L-NMMA inhibited nitric oxide synthesis, significantly reducing the regional blood flow in the cortex and deep brain structures accompanied by an elevation in systemic blood pressure. Our results demonstrated that the intracisternal injection of vasopressin and oxytocin dilated the canine basilar arteries in vivo. The activity of these peptides appeared to be mediated via the release of nitric oxide, because L-NMMA blocked the effects of vasopressin and oxytocin and this blocking effect was reversed by L-arginine. The synthesis and release of nitric oxide in vascular tissue including the endothelium, smooth muscle and nerve fibers, seem to be essential to the maintenance of the basal cerebral circulation. Further studies are needed to determine how the nitric oxide synthesized in different parts of the vascular tissue interacts, and how nitric oxide interacts with other vasoactive substances like vasopressin or acetylcholine.

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Table 1 Mean arterial blood pressure before and after the intracisternal injection of saline, vasopressin, oxytocin and CGRP.

Group	N	Control	Postinjection interval								
			5min	10min	15min	20min	30min	45min	60min	90min	120min
saline	5	108±13	108±13	105±15	110±15	107±13	109±18	110±18	112±18	113±18	112±18
vasopressin											
100pmol	5	105±11	106±11	104±10	104±13	104±13	104±14	105±12	101±15	98±13	101±14
1nmol	7	106±9	111±9	107±10	107±10	108±10	106±8	107±6	107±6	106±4	106±7
oxytocin											
1nmol	5	109±20	105±19	104±20	108±21	107±23	103±24	100±24	98±20	103±24	104±28
10nmol	7	111±27	108±28	108±30	106±28	109±27	109±26	109±31	105±28	106±34	106±36
CGRP											
100pmol	5	121±17	121±18	122±25	117±21	118±18	117±17	111±14	107±16	114±19	112±17
1nmol	6	104±11	103±13	105±15	106±9	107±13	103±14	100±9	103±6	98±8	99±8

Values are mean ± S.D. (mmHg)

N indicates the number of animals

No significant change is seen in each group.

FIGURE LEGENDS

Fig. 1 Percentage change in diameter of basilar arteries in response to intracisternal injections of vasopressin(A), oxytocin(B) and CGRP(C). Values are mean ± S.D. The number of animals is indicated in parentheses. The asterisks indicate significant difference from control (Dunnett's test)

Fig.2 Effects of L-NMMA and L-arginine on response of basilar arteries to vasopressin, oxytocin and CGRP. Values are mean ± S.D. The number of animals is indicated in parentheses. NS indicates no significant difference.

A: Effect of L-NMMA on response of basilar artery to intracisternal vasopressin in the absence and presence of L-arginine. 100 μmol L-arginine and/or 10 μmol L-NMMA was injected 30 minutes before intracisternal injection of 1 nmol vasopressin. Angiography was done 15 minutes after the application of vasopressin.

B: Effect of L-NMMA on response of basilar artery to intra-arterial vasopressin. Intracisternal 10 μmol L-NMMA was injected 30 minutes before the intra-arterial injection of 1 nmol vasopressin. Angiography was done 2 minutes after the injection of vasopressin.

C: Effect of L-NMMA on response of basilar artery to intracisternal injection of oxytocin. Intracisternal 10 μmol L-NMMA was injected 30 minutes before the intracisternal injection of 10 nmol oxytocin and 1 nmol CGRP. Angiography was done 10 minutes after the injection of oxytocin and 10 minutes after the injection of CGRP.

D: Effect of L-NMMA on response of basilar artery to intracisternal injection of CGRP

Fig. 3 Representative vertebral angiograms showing the effects of vasopressin and L-NMMA on the internal diameter of the canine basilar artery

A. Control (before injection of vasopressin)

B. 15 minutes after intracisternal injection of 1 nmol vasopressin

C. Control (before injection of L-NMMA)

D. 30 minutes after intracisternal injection of 10 μmol L-NMMA

E. 15 minutes after intracisternal injection of 1 nmol vasopressin following injection of 10 μmol L-NMMA

Fig. 4 Percentage change in diameter of basilar artery in response to intracisternal injection of L-NMMA (A), L-arginine(B), and L-arginine after L-NMMA(C).

C. 100 μmol L-arginine was injected intracisternally 30 minutes after intracisternal injection of 10 μmol L-NMMA.

Values are mean ± S.D. The number of animals is indicated in the parentheses.

The asterisks indicate significant difference from control (Dunnett's test)

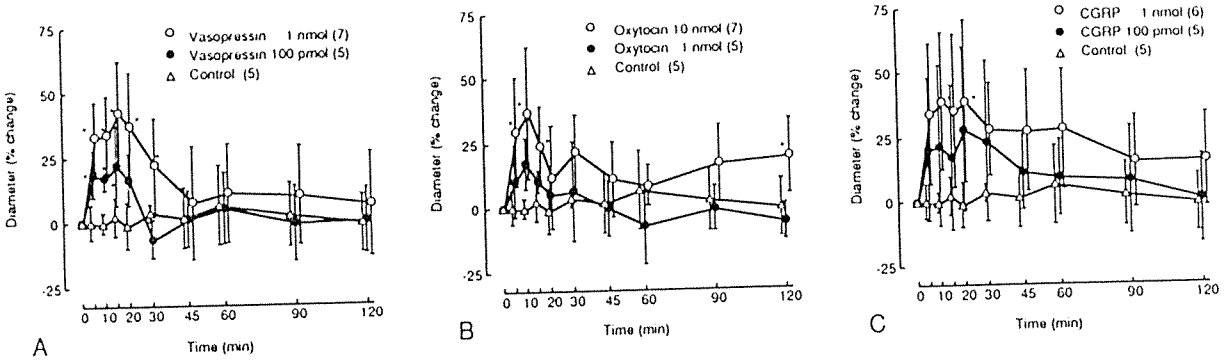
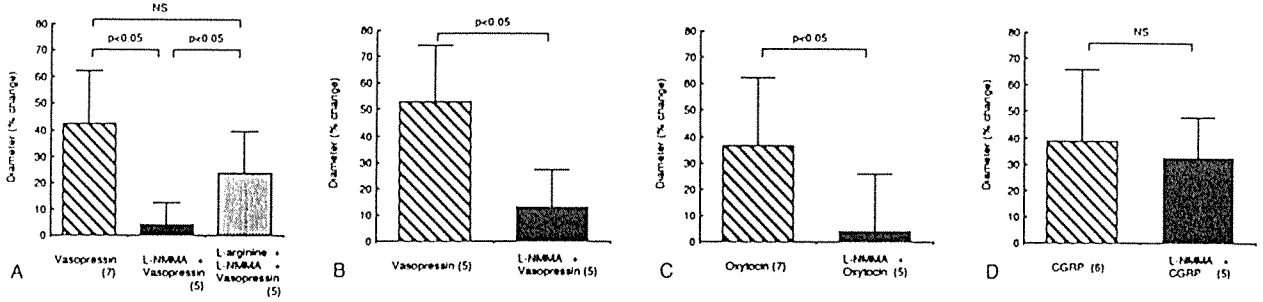


Fig. 1 Oyama et al ↑



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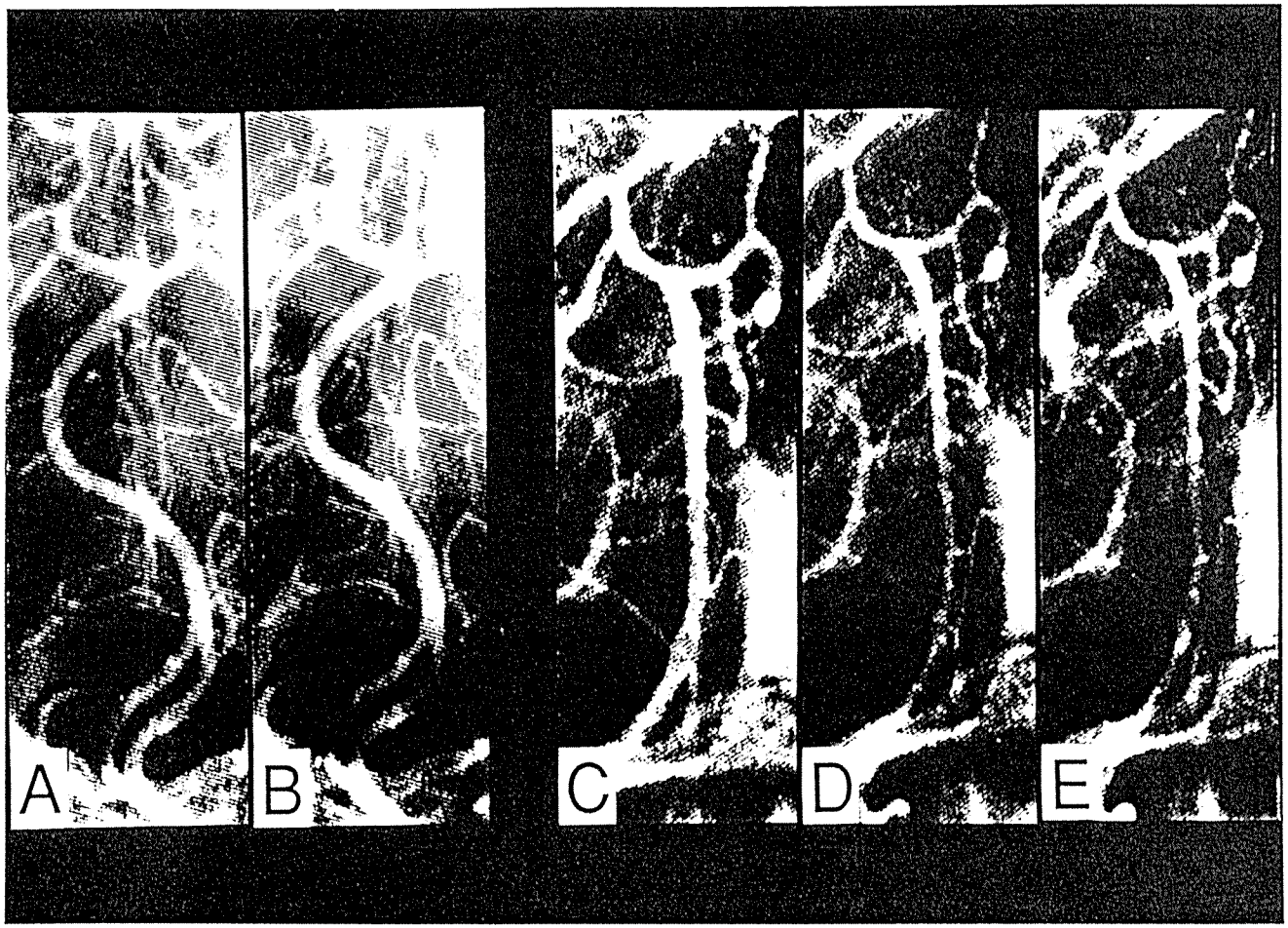

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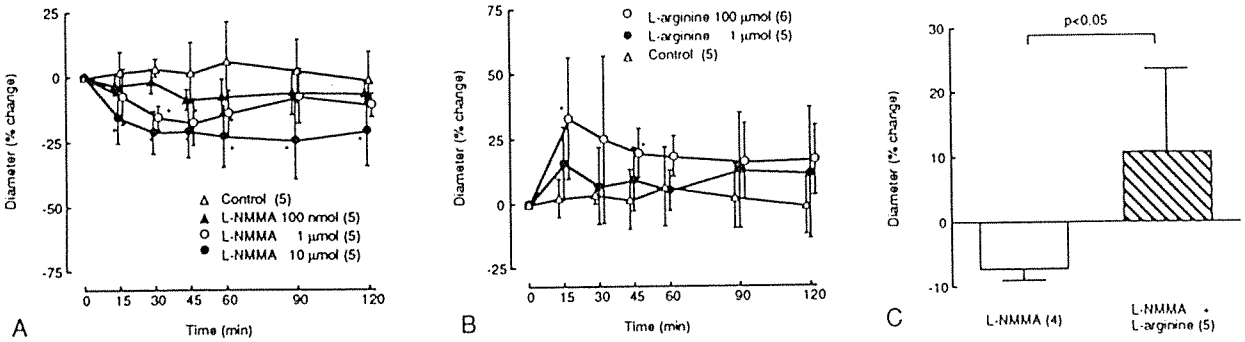

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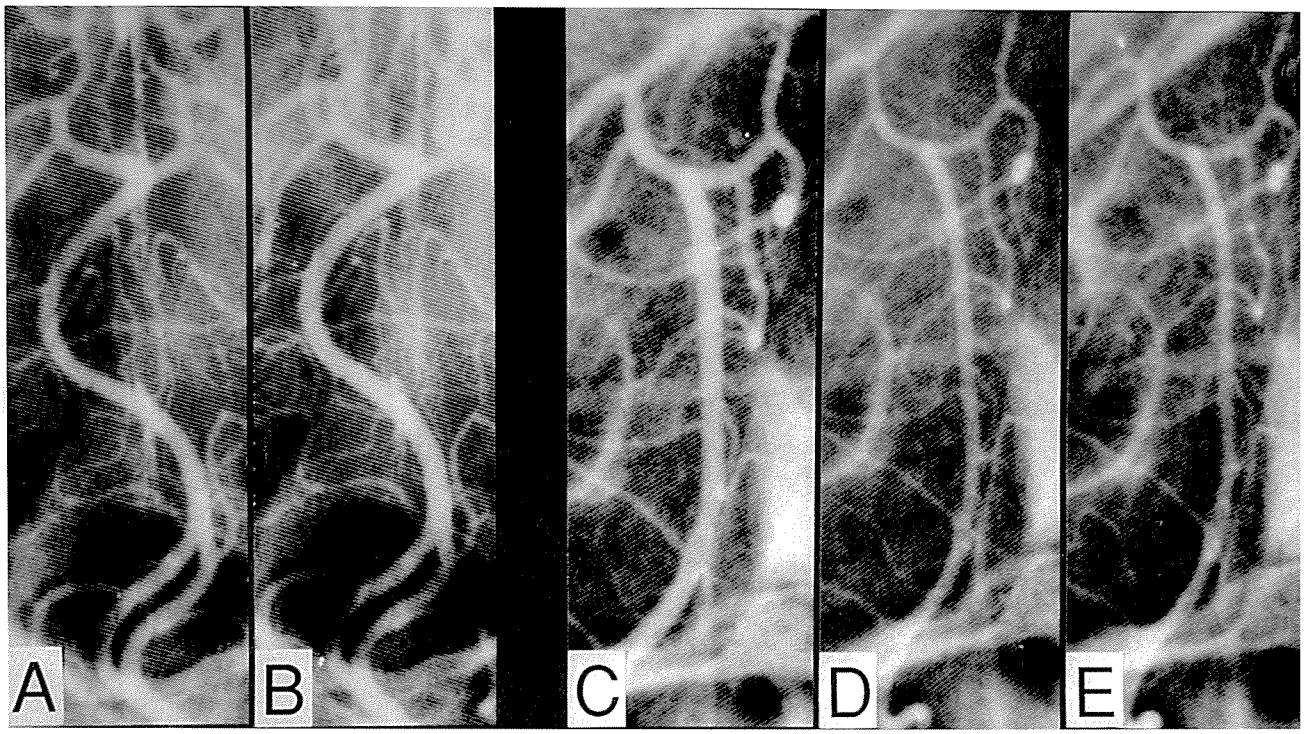

Fig. 3