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Dopamine constricts porcine pial veins

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Abstract

Dopamine has been shown to induce pial arterial relaxation and constriction in several species. Its mode of action on pial veins, however, remains unclarified. The vasomotor effect of dopamine on porcine pial veins was, therefore, examined using an in vitro tissue bath technique. The results indicated that dopamine constricted exclusively isolated ring segments of pial veins in the presence or absence of active muscle tone. The constriction induced by dopamine was not affected by N_{ω}-nitro-L-arginine (L-NNA, 2×10^{-5} M) or indomethacin (10^{-5} M). Only in few preparations was the constriction induced by maximum concentration of dopamine potentiated by L-NNA, suggesting that dopamine at high concentrations may release NO or a NO-related substance. In the presence of L-NNA (2×10^{-5} M), dopamine-induced constriction was inhibited by phentolamine and yohimbine (but not prazosin) in a concentration-dependent manner with maximum inhibition at 10^{-6} M. SKF38393 and 6-bromo-APB (selective dopamine D_1 receptor agonists) and LY171555 (a selective dopamine D_2 receptor agonist) also induced pial venous constriction exclusively in the presence of L-NNA. The constriction was not affected by phentolamine (10^{-6} M). The order of potency for these agonists in the presence of phentolamine, propranolol, guanethidine and L-NNA was: 6-bromo-APB > SKF38393 > dopamine > LY171555. The dopamine-induced constriction in the presence of phentolamine was further inhibited by both SCH23390 (a selective dopamine D_1 receptor antagonist) and sulpiride (a selective dopamine D_2 receptor antagonist), but was not affected by dopamine D_3 or D_4 receptor antagonists. These results indicate that dopamine at low and high concentrations induces exclusively constriction of isolated porcine pial veins. The constriction is mediated by postsynaptic α_2-adrenoceptors, and dopamine D_1 and D_2 receptors. © 1997 Elsevier Science B.V.

Keywords: Dopamine D_1 receptor; Dopamine D_2 receptor; α_2-adrenoceptors; Pial vein; (Constriction); (Porcine)

1. Introduction

Dopamine is known to play a significant role in regulating vascular function by binding to specific dopamine receptors, and non-dopamine receptors such as α-and β-adrenoceptors (Marin and Rivilla, 1982; Sharkey and McCulloch, 1986; Goldberg, 1984; Ricci et al., 1994). At least five different dopamine receptors have been identified and cloned (Sibley and Monsma, 1992; O'Dowd, 1993). Only two types of dopamine receptors with regard to their functional significance in the cardiovascular system, however, have been defined based on pharmacological and biochemical studies. The dopamine D_1 receptors, which are coupled to the G_s proteins, are found to be located on smooth muscle cell membrane and mediate arterial relaxation. The dopamine D_2 receptors which are probably coupled to the G_i proteins, have primarily prejunctional localization and mediate arterial relaxation indirectly by decreasing the sympathetic vasoconstrictor tone (Kebabian and Calne, 1979; Vallar and Meldolesi, 1989; Lokhandwala and Hedge, 1990; Civelli et al., 1993; Friedman et al., 1989; Ricci et al., 1994).

The dopamine-induced vascular responses are significantly variable among blood vessels from different regions and different species (Goldberg et al., 1978; Okamura et al., 1991; Hughes et al., 1988; Kelley, 1982; Toda, 1983a; Toda, 1983b). In general, most arteries relax via dopamine D_1 receptors while veins constrict in response to low concentration of dopamine, probably via α-adrenoceptors (Okamura et al., 1991).

The significance of dopamine involved in mediating cerebral vascular and neuronal functions has been demonstrated (Sharkey and McCulloch, 1986; Nau et al., 1992; Dawson et al., 1992; Kao et al., 1994). Several reports have indicated that dopamine relaxes pial arteries in several species particularly in the presence of α-adrenoceptor antagonist (Toda, 1976; Edvinsson and MacKenzie, 1977;

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Oudart et al., 1981; Forster et al., 1983; Toda, 1983a; Toda, 1983b). The effect of dopamine on pial veins, however, has not been clarified. The vasomotor effect of dopamine on porcine pial veins was, therefore, examined using an in vitro tissue bath technique. The results indicated that the porcine pial veins constricted exclusively upon application of dopamine. The constriction was mediated by the dopamine D_1 and D_2 receptors and α_2-adrenoceptors.

2. Materials and methods

Fresh heads of adult pigs of either sex were obtained from a local packing company. Immediately following sacrifice, the brains were removed and pial veins from the temporal lobes were excised under a dissecting microscope.

The following chemicals were used: propranolol hydrochloride (Ayerst Laboratories, New York, NY), guanethidine sulfate and phentolamine hydrochloride (CIBA, Summit, NJ), 3-hydroxytyramine hydrochloride, yohimbine hydrochloride and N_ω-nitro-L-arginine (L-NNA) (Sigma, St. Louis, MO), *R*(+)-SKF-38393 hydrochloride, (−)-quinpirole hydrochloride (LY171555), *R*(+)-SCH-23390 hydrochloride, *R*(+)-6-bromo-APB hydrobromide, U-101958 and U99194A, (+)butaclamol HCl, and *S*(−)-sulpiride (all from Research Biochemicals, Natick, MA), prazosin hydrochloride (Pfizer, Brooklyn, NY).

2.1. In vitro tissue bath technique

Ring segments (4 mm in length) of pial veins were cannulated with a stainless steel rod and a marlebile wire (Lee et al., 1994), mounted horizontally and placed in Krebs–bicarbonate solution (31°C, pH 7.4) equilibrated with 95% O_2 and 5% CO_2. The composition of Krebs–bicarbonate solution was (mM): Na^+ 144.2; K^+ 4.9; Ca^{2+} 1.6; Mg^{2+} 1.2; Cl^- 126.7; SO_4^{2-} 1.19; HCO 25.0; dextrose 11.1; ascorbic acid 0.1; and calcium disodium ethylenediamine tetraacetate (EDTA) 0.023 (Lee et al., 1994). A resting tension of 100 mg was applied to the venous segments and a period of 60 min was allowed for equilibration. Unless otherwise stated, phentolamine (10^{-6} M), propranolol (10^{-6} M), L-NNA (2×10^{-5} M) and guanethidine (10^{-6} M) were administered 20 min before and remained throughout the entire experiment in order to eliminate the possible influence of α-adrenergic, β-adrenergic, nitric oxidergic, and neuronal uptake components, respectively. Constrictions of porcine pial veins were elicited by cumulative applications of dopamine or dopamine agonists in the presence or absence of active muscle tone induced by U-46619 (0.1 μM). After a full concentration–response relationship was completed, the veins were washed with prewarmed fresh Krebs–bicarbonate solution. After 40 min of equilibration, a full dopamine or dopamine agonist concentration–response relationship was repeated in the presence of a given receptor antagonist. In some experiments three consecutive dopamine or dopamine agonist concentration–response curves were obtained from each tissue preparation. The first served as a control curve. The second and the third were in the presence of a single concentration of receptor antagonists. The antagonist was added to the tissue bath 20 min before applications of dopamine or dopamine agonist. Accordingly, each tissue preparation serves as its own control. Constrictions induced by dopamine agonists were calculated as percent of the maximum constriction induced by dopamine. All drug concentrations reported were the final concentrations in the tissue baths.

2.2. Data analysis

Results were computed as the mean ± S.E.M. and were evaluated using Student's *t*-test for paired or unpaired samples as appropriate. Two-way or three-way analysis of variance was also performed. $P < 0.05$ was accepted as significant. EC_{50} values were determined for each ring preparation and the geometric means were calculated (Fleming et al., 1972).

3. Results

3.1. Constriction induced by dopamine, dopamine D_1 and D_2 receptor agonists

About 40% of pial venous rings (99 of 250) with or without active muscle tone (induced by U-46619, 0.1 μM) constricted exclusively upon application of dopamine in a concentration-dependent manner. Subsequent studies were performed in the absence of active muscle tone. The constriction induced by dopamine was not affected by indomethacin (10^{-5} M, $n = 7$) or L-NNA (2×10^{-5} M, $n = 5$). However, in few occasions ($n = 5$), the constriction induced by dopamine at 10^{-3} M was enhanced in the presence of L-NNA (2×10^{-5} M). Accordingly, in the subsequent studies, L-NNA (2×10^{-5} M) was included in the bath throughout the experiment. Thus, in the presence of phentolamine (10^{-6} M), propranolol (10^{-6} M), L-NNA (2×10^{-5} M) and guanethidine (10^{-6} M), dopamine (10^{-7} M–10^{-3} M) induced concentration-dependent constrictions of porcine pial veins (Fig. 1).

Similarly, dopamine D_1 receptor agonists SKF38393 and 6-bromo-APB and dopamine D_2 receptor agonist LY171555 (Nagahama et al., 1986; Trugman and James, 1993; Neumeyer et al., 1992) induced exclusively concentration-dependent constrictions of the pial veins in the presence of phentolamine (10^{-6} M), propranolol (10^{-6} M), L-NNA (2×10^{-5} M) and guanethidine (10^{-6} M) (Fig. 1). The pial veins, however, are more sensitive to SKF38393, dopamine and 6-bromo-APB than to

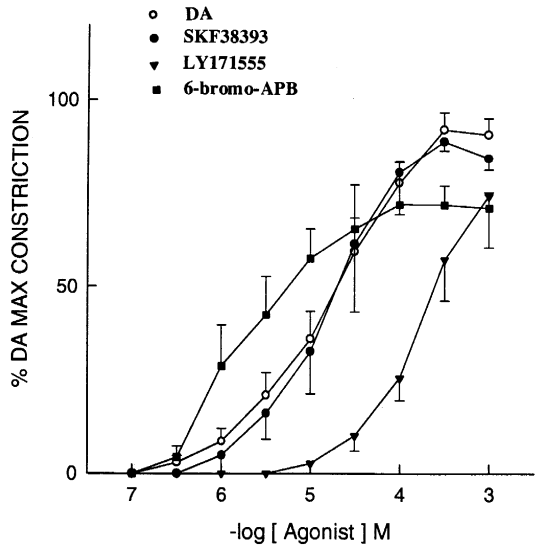

Fig. 1. Dopamine, 6-bromo-APB, SKF38393 and LY171555 induced concentration-dependent constrictions in the presence of phentolamine (10^{-6} M), propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M). Each point represents mean ± S.E.M. of 5 experiments.

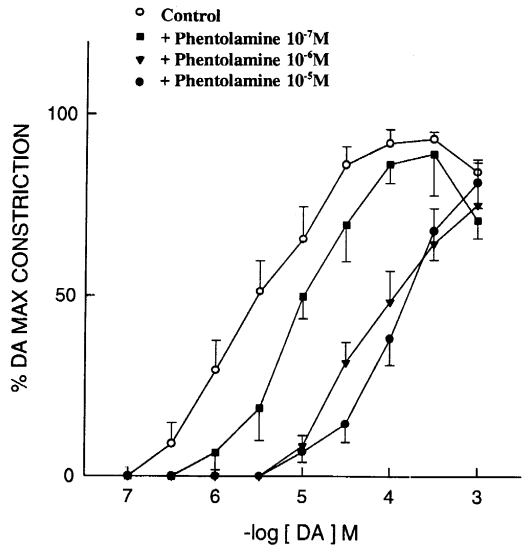

Fig. 2. Effects of phentolamine on dopamine-induced pial venous constriction in the presence of propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M). Phentolamine in a concentration-dependent manner shifted the dopamine concentration–response curves parallelly to the right. Each point represents mean ± S.E.M. of 6 experiments.

LY171555. The sensitivity of pial veins to 6-bromo-APB, SKF38393 and dopamine was not significantly different (Fig. 1 and Table 1). The order of potency is 6-bromo-APB > SKF38393 > dopamine > LY171555. The constrictions induced by dopamine and its agonists (SKF38393, 6-bromo-APB and LY171555) were blocked by butaclamol (10^{-5} M) which, however, did not affect the constriction induced by KCl (60 mM) ($n = 3$, data not shown).

3.2. Effects of α-adrenoceptor antagonists on constrictions induced by dopamine, and dopamine D_1 and D_2 receptor agonists

In the presence of propranolol (10^{-6} M), LNNA (2×10^{-5} M) and guanethidine (10^{-6} M), the dopamine-induced venoconstriction was inhibited by phentolamine in a concentration-dependent manner, as indicated by a parallel rightward shift of concentration–response curves without changing the maximum constriction (Fig. 2; Table 2). The maximum inhibition was reached at 10^{-6} M of phentolamine. The pA_2 value for phentolamine against dopamine is 6.78 ± 0.14 ($n = 6$). Phentolamine at 10^{-6} M, however, did not significantly affect SKF38393- or LY171555-induced constrictions (Fig. 3A, B). In parallel studies, SKF38393-induced constriction was blocked by SCH23390 (3×10^{-5} M) but not by sulpiride (Fig. 4). Yohimbine (10^{-6}–10^{-5} M), a selective α_2-adrenoceptor antagonist, mimicked the inhibitory effect of phentolamine as indicated by parallel shift of dopamine concentration–response curve to the right (Fig. 5A), while prazosin (10^{-7}–10^{-5} M), a selective α_1-adrenergic receptor antagonist, did not affect the contraction induced by dopamine (Fig. 5B).

Table 1
The EC_{50} values and the maximum constriction induced by dopamine agonists

Agonists	EC_{50} (M) [a]	Maximum constriction (%)	*n*
Dopamine	$6.0\ (2.8–13.0)\times10^{-5}$	91.73 ± 4.68	15
SKF38393	$1.2\ (0.6–2.2)\times10^{-5}$	88.30 ± 8.30	5
6-bromo-APB	$8.1\ (4.6–14.0)\times10^{-6}$	71.83 ± 11.40	5
LY171555	$1.5\ (1.3–1.8)\times10^{-4}$ [b]	74.72 ± 13.77	5

All experiments were performed on porcine pial veins in the presence of phentolamine (10^{-6} M), propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M).
[a] Geometric means with 95% confidence interval.
[b] $P < 0.05$ indicates significant difference from dopamine values (paired Student's *t*-test).

Table 2
The effect of phentolamine on EC_{50} values and the maximum constriction induced by dopamine

Antagonists	EC_{50} (M) [a]	Maximum constriction (%)	*n*
Control	$3.3\ (1.2–9.5)\times10^{-6}$	93.24 ± 2.00	10
Phentolamine (10^{-7} M)	$1.2\ (0.6–2.2)\times10^{-5}$	89.18 ± 11.38	5
Phentolamine (10^{-6} M)	$6.3\ (2.1–18.8)\times10^{-5}$ [b]	75.20 ± 11.62	5
Phentolamine (10^{-5} M)	$1.1\ (0.7–1.8)\times10^{-4}$ [b]	81.28 ± 6.90	5

All experiments were performed on porcine pial veins in the presence of propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M)
[a] Geometric means with 95% confidence interval.
[b] $P < 0.05$ indicates significant difference from control values (paired Student's *t*-test).

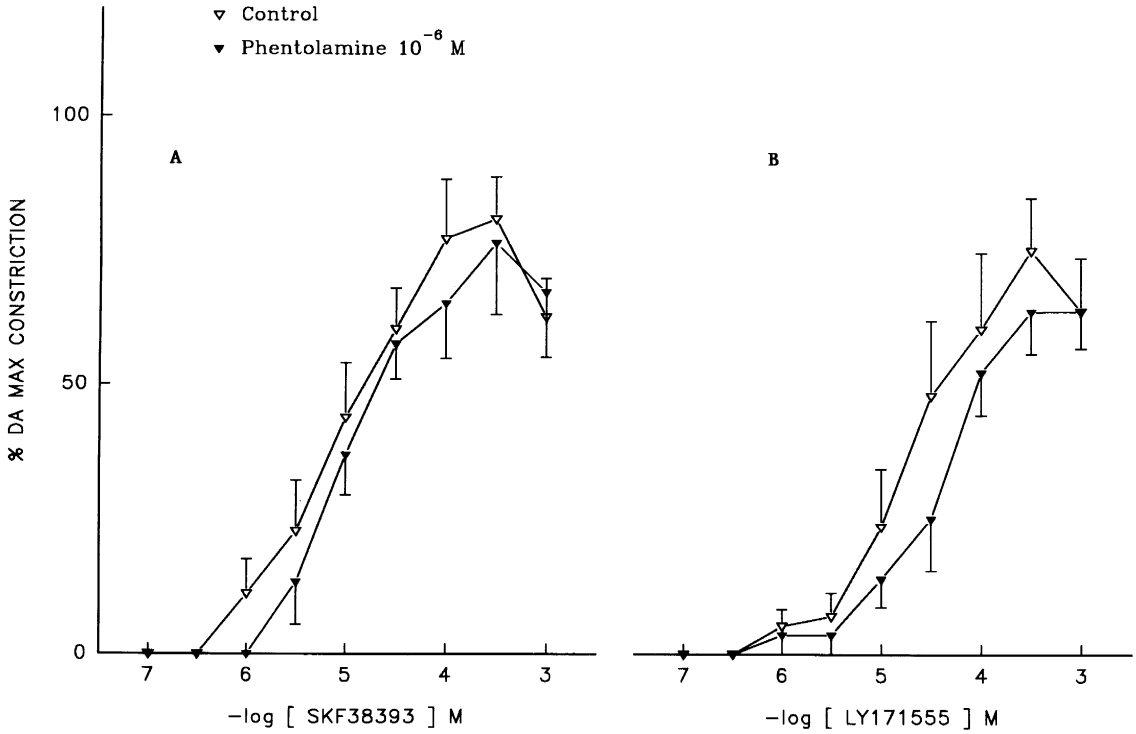

Fig. 3. Effects of phentolamine on SKF38393-induced (A) and LY17155-induced (B) pial venous constriction. Phentolamine (10^{-6} M) did not significantly affect constrictions induced by these two agonists. Propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M) were present in the bath throughout the entire experiments. Each point represents mean ± S.E.M. of 5 experiments.

3.3. Effects of dopamine receptor antagonists on dopamine-induced constriction

In the presence of phentolamine (10^{-6} M), propranolol (10^{-6} M), L-NNA (2×10^{-5} M) and guanethidine (10^{-6} M), the dopamine-induced pial venoconstriction was significantly inhibited by both SCH23390, a dopamine D_1 receptor antagonist, and sulpiride, a dopamine D_2 receptor antagonist (Castellano et al., 1991), in a concentration-dependent manner (Fig. 6; Table 3). Both receptor antagonists shift the dopamine concentration–response curves parallelly to the right without changing maximum constriction ($p > 0.05$). On the other hand, in the presence of phentolamine, dopamine-induced constriction was not affected by U-9919A (a dopamine D_3 receptor antagonist, $n = 4$) or U-101958 (a dopamine D_4 receptor antagonist, $n = 4$) (data not shown). SCH23390 and sulpiride, on the

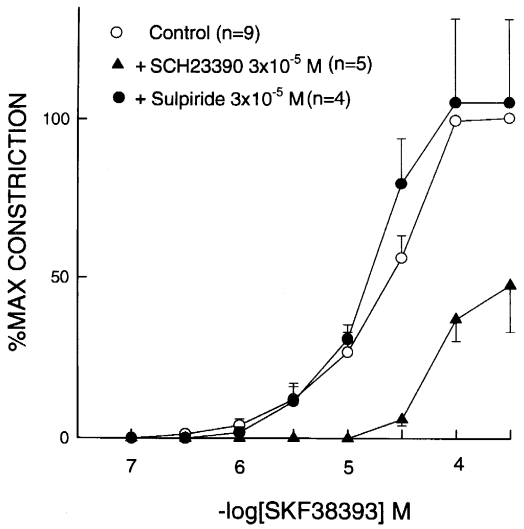

Fig. 4. Effects of SCH23390 and sulpiride on SKF38393-induced constriction in pial veins in the presence of propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M). SKF38393-induced concentration-dependent constriction was blocked by SCH23390 but was not affected by sulpiride. n = number of experiments.

Table 3
The EC_{50} values and the maximum constriction induced by dopamine in the presence of SCH23390 and sulpiride

Antagonists	EC_{50} (M) [a]	Maximum constriction (%)	n
Control	$2.3\ (1.1–4.9) \times 10^{-5}$	91.94 ± 3.63	10
SCH23390 (10^{-5} M)	$6.3\ (3.3–12.0) \times 10^{-5}$	82.17 ± 9.4	5
SCH23390 (10^{-4} M)	$3.9\ (1.5–10.5) \times 10^{-4}$ [b]	90.35 ± 11.61	5
Sulpiride (10^{-5} M)	$4.6\ (1.9–11.2) \times 10^{-5}$	100.62 ± 8.13	5
Sulpiride (10^{-4} M)	$5.2\ (1.9–14.3) \times 10^{-4}$ [b]	80.16 ± 10.52	5

All experiments were performed on porcine pial veins in the presence of phentolamine (10^{-6} M), propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M).

[a] Geometric means with 95% confidence interval.

[b] $P < 0.05$ indicates significant difference from control values (paired Student's t-test).

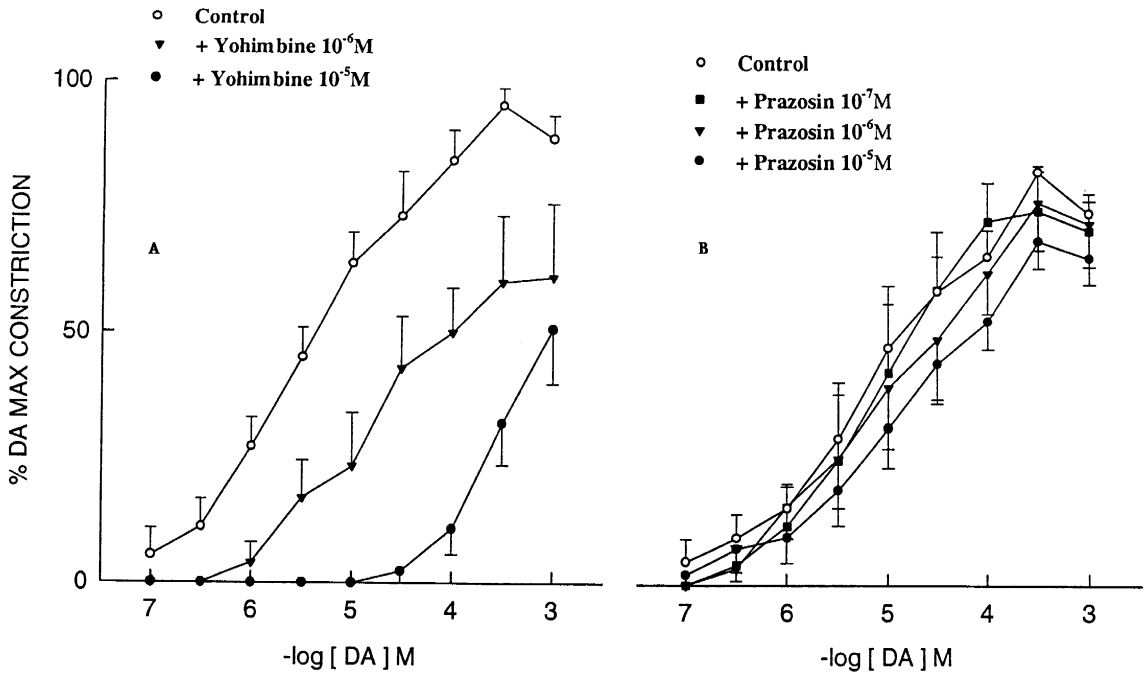

Fig. 5. Effects of yohimbine (A) and prazosin (B) on dopamine-induced pial venous constriction in the presence of propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M). Yohimbine, but not prazosin significantly shifted the dopamine concentration–response curves to the right. Each point represents mean ± S.E.M. of 5 experiments.

other hand, did not affect the constriction induced by KCl (60 mM) in the presence of phentolamine (10^{-6} M) (data not shown).

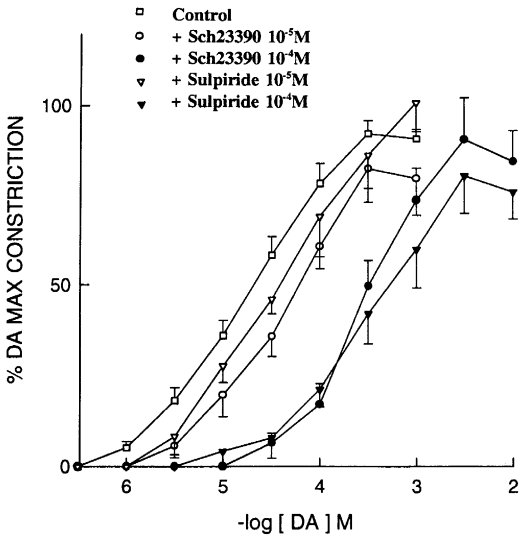

Fig. 6. Effects of SCH23390 and sulpiride on dopamine-induced venous constriction. SCH23390 and sulpiride shifted the dopamine concentration–response curves parallelly to the right without affecting the maximum constriction. Each point represents mean ± S.E.M. of 5 experiments. Phentolamine (10^{-6} M), propranolol (10^{-6} M), guanethidine (10^{-6} M) and L-NNA (2×10^{-5} M) were present in the bath throughout the entire experiment.

4. Discussion

Results of the present study demonstrated that in the presence or absence of active muscle tone induced by U-46619 (0.1 μM), the porcine pial veins constricted exclusively upon application of dopamine. The pial venous constriction induced by dopamine appeared to be mediated by α_2-adrenoceptors and dopamine D_1 and D_2 receptors on the vascular smooth muscle cells.

Unlike pial arteries, the thin porcine pial veins contain one or two layers of smooth muscle cells (Asada and Lee, 1992). Thus, it is extremely difficult to denude the endothelial cells. We have reported that endothelium in porcine pial veins plays a minimum role in regulating the venous tone (Lee et al., 1994; Ueno et al., 1995). This is supported by results of the present studies that the constriction induced by dopamine was not affected by L-NNA or indomethacin. Only in some veins was constriction induced by maximum concentration of dopamine enhanced by L-NNA, suggesting that endothelium-derived NO may be involved in constriction induced by dopamine at high concentrations.

Dopamine-induced constrictions in most peripheral arteries and veins and cerebral arteries have been shown to be due to dopamine activation of α-adrenoceptors (Brodde, 1982; Toda, 1983a; Toda, 1983b; Kohli and Goldberg, 1987; Toda et al., 1989). Thus, in the presence of phentolamine, vasoconstriction induced by dopamine is decreased, or reversed to vasodilation which is suggested to

be mediated by dopamine D_1 receptors (Okamura et al., 1991). In the present experiments, the dopamine-induced pial venoconstriction was blocked by phentolamine in a concentration dependent manner. The response in the presence of phentolamine, however, was never reversed to a relaxation. Furthermore, the dopamine-induced constriction was blocked by yohimbine but was not affected by prazosin. These results suggest that dopamine-induced pial venous constriction is in part mediated by α_2-adrenoceptors. This is consistent with our previous report that the predominant adrenoceptors in the porcine pial veins are α_2-subtype (Asada and Lee, 1992).

Although the phentolamine inhibition of dopamine-induced constriction is concentration dependent, phentolamine at 10^{-5} M did not produce further inhibition on dopamine-induced constriction than that in the presence of 10^{-6} M phentolamine (Fig. 2). This result suggests that phentolamine at the concentration of 10^{-6} M already maximally blocks α-adrenoceptor-mediated response. The residual constriction induced by dopamine in the presence of phentolamine appears to be mediated by dopamine receptors. Firstly, the dopamine D_1 receptor agonists (SKF38393 and 6-bromo-APB) and dopamine D_2 receptor agonist (LY171555), like dopamine, induced constriction of porcine pial veins exclusively. The constriction, which was blocked by non-specific dopamine receptor antagonist, was not affected by phentolamine at the concentration that maximally shifted the dopamine concentration–response curve to the right (Figs. 2 and 3). Secondly, the dopamine-induced constriction in the presence of phentolamine (10^{-6} M) was blocked competitively by both dopamine D_1 (SCH23390) and D_2 (sulpiride) receptor antagonist, as indicated by parallel rightward shift of the concentration response curves while these receptor antagonists did not affect KCl-induced constriction. Taken together, the results indicated that both postsynaptic dopamine D_1 and D_2 receptors also mediate dopamine-induced constriction of porcine pial veins.

The dopamine D_1 receptors and α_2-adrenoceptors appear to be more sensitive than dopamine D_2 receptors to dopamine. De Keyser et al. (1988) reported based on radioligand binding studies that bovine pial vessels contain α_2-adrenoceptors and dopamine D_1 receptors: a result consistent to the present findings. These authors, however, did not observe dopamine D_2 receptor bindings using [^{3}H]spiroperidol as a ligand. This latter finding is different from the result of the present pharmacological study. This difference may be due to species variation. The possibility of the involvement of postsynaptic dopamine D_3 and D_4 receptors in mediating dopamine-induced venous constriction is not likely, since dopamine-induced constriction in the presence of phentolamine was not affected by dopamine D_3 or D_4 receptor antagonists.

The finding that dopamine induced exclusively constriction of porcine pial veins is consistent to that found in many peripheral veins from other species (Okamura et al., 1991). Constrictions induced by dopamine in most peripheral veins, however, were reversed by phentolamine to relaxations, which were suggested to be mediated by postsynaptic dopamine D_1 receptors (Okamura et al., 1991). In the present study, phentolamine never reversed dopamine-induced pial venous constriction to a relaxation even in the presence of active muscle tone induced by U-46619. Furthermore, SKF38393-induced pial venous constriction was blocked by SCH23390 (a dopamine D_1 receptor antagonist) but not by sulpiride (a dopamine D_2 receptor antagonist), further indicating that the dopamine D_1 receptors mediate constriction in porcine pial veins.

In summary, the porcine pial veins constricted exclusively upon application of dopamine. The constriction was mediated by not only α_2-adrenoceptors but also dopamine D_1 and D_2 receptors. The finding that dopamine induced exclusively constriction of porcine pial veins is consistent to that found in the peripheral veins from other species. Thus, dopamine may decrease pial venous capacitance. This is in line with the increasing evidence that dopamine tends to increase venous return and cardiac output by constricting veins and dilating arteries (Okamura et al., 1991). The finding that postsynaptic dopamine D_1 receptors mediates constriction of porcine pial veins, however, differs from current knowledge and, therefore, deserves further investigation.

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