Vascular Responsiveness of Isolated and Perfused Simian Metacarpal Veins to Several Vasoconstrictor Substances

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Abstract—Using the cannula inserting method, vascular responses to 7 vasoconstrictor substances were investigated on isolated, perfused simian metacarpal veins. The vein was markedly constricted by an intraluminal administration of norepinephrine, phenylephrine and 5-hydroxytryptamine with a maximal increase in perfusion pressure of over 100 mmHg. Clonidine and xylazine induced only a slight vasoconstriction, but tyramine produced no significant constriction. A large dose of KCl induced a strong vasoconstriction. In this study, it was demonstrated that the simian metacarpal vein has a specific characteristic of vascular reactivity.

Characteristics of the vascular responsiveness to various vasoactive agents are quite different in many aspects, and the different responsiveness between arteries and veins has widely been studied in various organs. Using the cannula inserting method (1), we previously reported that the simian digital artery is a useful in vitro model for investigating the pharmacological responses of skin supplying arteries (2). In the present study, to obtain a much clearer understanding of the pharmacological characteristics of the skin circulation, we attempted to investigate the responsiveness of the simian metacarpal vein to various vasoconstrictor substances in comparison to that of the simian digital artery.

Japanese monkeys (Macaca fuscata) of either sex, weighing 3-9 kg, were anesthetized with ketamine hydrochloride (10 mg/kg, i.m.). After treatment with sodium heparin (200 units/kg, i.v.), monkeys were sacrificed by rapid exsanguination from the right common carotid artery. Palmar proper digital arteries and metacarpal veins were then carefully isolated from both forelimbs, and segments (without large branches, 0.4-0.7 mm and 0.6-0.9 mm outer diameter for arteries and veins, respectively, and 4-6 mm in length) were cut from each isolated vessel. Each segment was inserted with a stainless steel cannula with one small hole at a 5 mm distance from the distal blind end (27 gauge, and outer diameter of 0.4 mm and 3 cm in length). The cannula with vascular segment was placed in a cup-shaped glass container and perfused with a constant flow rate (1.0-2.0 ml/min) by means of a peristaltic pump (Harvard Apparatus, model 505-1210). The perfusate contained NaCl, 118; KCl, 4.7; CaCl₂, 2.5; KH₂PO₄, 1.3; MgCl₂, 1.2; NaHCO₃, 25; and glucose, 5.6 in millimolar composition, and it was bubbled with 95% O₂ and CO₂ and maintained at a constant temperature of 37°C with a circulator pump (Haake FE2). The perfusion rate was adjusted at the beginning of the experiments to obtain a control perfusion pressure of approximately 100 mmHg for arteries and 5-15 mmHg for veins, respectively. The perfusion pressure was measured with an electronic manometer (Nihon Kohden Co. AP621G), and the vascular responses were recorded as changes of perfusion pressure.

Drugs used were tyramine hydrochloride (Tokyo Kasei), serotonin creatinin sulfate (5-hydroxytryptamine, 5-HT, Sandoz), dlnorepinephrine hydrochloride (NE, Sankyo), phenylephrine hydrochloride (PE, Kowa), clonidine hydrochloride (CL, Boehringer
Ingelheim), xylazine hydrochloride (XY, Bayer) and potassium chloride (KCl). The drugs were dissolved in saline. Each drug solution was intraluminally administered into the perfusion line close to the cannula in a volume of 0.01–0.03 ml over 4 sec by use of a microinjector (Terumo Co.). The data are shown as means±S.E.M.

Histologic examination of arterial and venous preparations after the experimental procedures revealed that the endothelial cells remained almost intact and the muscular cells consisted of 6–8 layers in both vessels (preliminary observations).

The injection of KCI or NE temporarily induced an immediate increase in perfusion pressure in the venous preparation in a dose-related manner, and good reproducibility was obtained by repetitive injections of KCl (3 mg) or NE (0.1 µg) as shown in Fig. 1. The responsiveness to KCl or NE was consistently induced for over 6 hr during the experiments. Among the vasoconstrictor agents used, NE, 5-HT and PE were potent and they produced strong contractile responses of the vein. Threshold doses for inducing vasoconstrictions were 0.003–0.01 µg for NE or 5-HT and 0.01–0.03 µg for PE; 0.3 µg of each agent caused an increase in perfusion pressure of over 100 mmHg. XY and CL produced dose-dependent constrictions, but the maximal responses were much smaller even at larger doses, i.e., increases in perfusion pressure of 25±18 and 23±16 mmHg, respectively. Tyramine, even when applied at a large dose of 30 µg, induced only a weak vasoconstriction. KCl also produced a strong contractile response in a dose-related manner, but usually at extremely large doses of over 300 µg. Summarized data are shown as dose-response curves in Fig. 2. Responses of digital arteries isolated from the same monkey were examined to compare them with the responses in the veins, and the results were as follows: in the arteries, KCl (3 mg) produced 168±37 mmHg increase and NE (0.01 µg) produced 190±31 mmHg increase in perfusion pressure, and in the veins, KCl (3 mg) produced 94±26 mmHg increase and NE (0.1 µg) produced 101±23 mmHg increase in perfusion pressure (n=6–9).

In the present study, it was shown that the isolated and perfused simian metacarpal vein is a useful model for investigating vascular responsiveness of the skin area as well as the simian digital artery (2) i.e., the venous preparation showed good reproducibility and durability in the responses to NE and KCl.

Vascular postjunctional alpha-2 adrenoceptors are usually considered to be observed more readily in veins than in arteries, especially when functional alpha-2 adrenoceptors are examined in vitro (3, 4). In the present experiments, however, the simian metacarpal vein showed only a weak vasoconstriction to XY or CL (selective alpha-
2 adrenergic agonists) in spite of its strong constrictor response to NE (a non-selective alpha-adrenergic agonist) or PE (a selective alpha-1 adrenergic agonist). The alpha-1 dominant responsiveness is in contrast to that of the simian digital artery which was markedly constricted by either alpha-1 or -2 adrenergic agonists (2). Stevens and Moulds (5, 6), using the human digital artery and metacarpal vein, reported similar results, i.e., the former vessel was constricted by both alpha-1 and -2 adrenergic agonists, but in the latter vessel, PE produced much greater contractile response than CL. The physiologic and pathologic roles of postjunctional alpha-2 adrenoceptors in the skin circulation are not yet established sufficiently. We previously reported that the canine intermediate auricular artery and the simian digital artery, both arteries supply blood flow mainly to the skin tissue, were markedly constricted via both alpha-1 and -2 adrenoceptors, and suggested the possible important role of alpha-2 adrenoceptors in the regulation of skin circulation associated with body temperature, especially in cold exposure (2, 7). The different sensitivities of simian digital artery and metacarpal vein to alpha-2 adrenergic agonists raise a further possibility that these receptors may have some important roles in the regulation of the skin circulation.

The effect of 5-HT as a potent vasoconstricting agent on the metacarpal vein indicates that 5-HT, mainly released from aggregated platelets (8), might have some roles in vascular obstructive diseases not only in skin arteries but also in skin veins (2, 9).

Tyramine is a well-known agent which acts on sympathetic nerve terminals and releases catecholamines. We reported previously that the canine intermediate auricular and the simian digital arteries were strongly constricted by tyramine and that skin supplying arteries might have a rich labile store of tyramine-sensitive catecholamines (2, 10). In the present study, the simian metacarpal vein revealed only a weak contractile response, suggesting that sympathetic innervation and/or catecholamine pool in sympathetic nerve terminals might be different between skin arteries and veins. However, since we did not examine the responsiveness of the vein to electrical nerve stimulation, we can not make conclusions about the mechanisms involved in the different sensitivities between the vein and the artery to tyramine; this remains for further investigations.

References
1 Hongo, K. and Chiba, S.: A new method for measuring vascular responsiveness of relatively larger arteries of dogs. J. Pharmacol. Methods 9, 83–91 (1983)
2 Ito, T. and Chiba, S.: Vascular responsiveness of simian digital artery to various vasoactive substances. J. Invest. Dermatol. 86, 678–682 (1986)
3 De Mey, J.D. and Vanhoutte, P.M.: Uneven distribution of postjunctional alpha_1 and alpha_2-like adrenoceptors in canine arterial and venous smooth muscle cells. Circ. Res. 48, 875–884 (1981)
4 Van Zwieten, P.A. and Timmermans, P.B.M.W.M.: Cardiovascular α_2-receptors. J. Mol. Cell. Cardiol. 15, 717–733 (1983)
5 Stevens, M.J. and Moulds, R.F.W.: Pharmacological comparison of human isolated digital arteries and metacarpal veins. Clin. Exp. Pharmacol. Physiol. 9, 129–138 (1982)
6 Stevens, M.J. and Moulds, R.F.W.: Are the pre- and post-synaptic α-adrenoceptors in human vascular smooth muscle atypical. J. Cardiovasc. Pharmacol. 4, S129–S133 (1982)
7 Ito, T. and Chiba, S.: Existence of two types of post-junctional α-adrenoceptors in the isolated canine intermediate auricular artery. J. Pharmacol. Exp. Ther. 234, 698–702 (1985)
8 Moulds, R.F.W., Iwanov, V. and Medcalf, R.L.: The effect of platelet-derived contractile agents on human digital arteries. Clin. Sci. 66, 443–451 (1984)
9 Arnelklo-Nobin, B., Novin, A., Owman, C. and Tornebrandt, K.: Serotonergic mechanisms in isolated human peripheral arteries and veins. J. Cardiovasc. Pharmacol. 7, S52–S55 (1985)
10 Chiba, S. and Ito, T.: Predominant sensitivity to tyramine in the isolated intermediate auricular artery of the dog. J. Auton. Pharmacol. 5, 109–114 (1985)