Pharmacological Features of Vascular Responses of Isolated Dog and Monkey Lingual Arteries to Vasoactive Substances

Ranko Skrbic* and Shigetoshi Chiba

Department of Pharmacology, Shinshu University School of Medicine, Matsumoto 390, Japan

Received January 11, 1991 Accepted June 14, 1991

ABSTRACT — Using a perfusion technique of isolated vessels, vasoconstrictor responses to alpha-adrenoceptor agonists (norepinephrine [NE], phenylephrine [PE], clonidine, xylazine and tyramine) and KCl were investigated in isolated, perfused dog and monkey lingual arteries. A stainless steel cannula was inserted into the lingual artery segment and perfused with Krebs-Henseleit solution at a constant flow rate. In dog lingual arteries, the agonists induced vasoconstrictions with the following order of potency: NE > PE > tyramine >> clonidine > xylazine > KCl. In monkey preparations, the order was NE > PE >> clonidine >> tyramine > xylazine > KCl. In both preparations, NE- and PE-induced constrictions were blocked by bunazosin (an alpha-1 adrenoceptor antagonist), but not influenced by midaglizole (a potent alpha-2 antagonist). Diltiazem (a Ca entry blocker) significantly attenuated NE-induced vasoconstrictions in dog lingual arteries, but did not significantly influence these in monkey preparations. These results suggest that: [1] these arteries contain mostly alpha-1 but scarcely any alpha-2 adrenoceptors; [2] in dog preparations, tyramine induced a marked vasoconstriction which may contribute to investigation on the mechanisms of catecholamine releases from sympathetic nerve terminals; and [3] different blocking effects of diltiazem may indicate that extracellular Ca** influx may have varying degrees of importance in alpha-1 adrenoreceptor-mediated constrictions in different species, although participation of an intracellular mechanism might not be ruled out.

The rich vascularization of the tongue indicates that it has a more abundant blood supply than other muscular organs of the body. The tongue is an efficient heat exchanger in the open mouth panting animal, and specific vascular elements such as arteriovenous anastomoses (AVA) control blood flow and heat transfer from the blood perfusing the tongue to the mucous surfaces from which heat is removed by evaporation (1). Since the tongue is blood-supplied via the lingual artery, its vascular reactivity for active substances including nerve transmitters might be important in the regulation of tongue circulation.

It is generally accepted that alpha-adrenergic innervation of blood vessels provides the most important remote control of blood flow. It is also widely recognized that there are two distinct populations of postsynaptic adrenoreceptors, alpha-1 and alpha-2 receptors (2–7). The alpha-1 adrenoceptor subtype linked to a vasoconstriction is the
predominant postsynaptic receptor in vascular smooth muscle, while the postsynaptic alpha-2 adrenoceptor subtype also mediates constriction of several vascular smooth muscles (6, 8, 9) as well as vasodilation in isolated dog coronary arteries (10, 11), dog femoral arteries and rat tail arteries (12). Although there are many studies concerned with the vasomotor control of lingual blood flow, mainly on the level of AVA, in those mammals in whom the tongue contributes to respiratory evaporative heat loss during panting, there is still no available report on the vascular reaction of the isolated lingual artery. Thus, by using the system of perfused isolated vessels which was developed by Hongo and Chiba (13) and modified by Tsuji and Chiba (14), we investigated the functional characteristics of alpha-adrenoceptors involved in the contractile responses of the isolated and perfused dog and monkey lingual arteries.

MATERIALS AND METHODS

Twenty-three mongrel dogs of either sex, weighing 6–20 kg, and seventeen Japanese monkeys (Macaca fuscata) weighing 2–16 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and ketamine hydrochloride (10 mg/kg, i.m.), respectively. After treatment with sodium heparin (200 units/kg, i.v.), the animals were sacrificed by rapid exsanguination. The tongue was cut out at the level of the papillae vallate, and the lingual artery, which is the largest collateral branch of the external carotid artery (Fig. 1), was carefully isolated and dissected into several segments (10–15 mm in length and 0.5–2.0 mm in outer diameter). Then, each segment was cannulated and set up for perfusion as described previously (13, 14). Briefly, a stainless steel cannula (17–25 gauge, 0.4–1.6 mm in outer diameter and 3–4 cm in length), with one or three small holes at a distance of 5 mm from the distal blind end, was carefully inserted into each vessel segment. The segment was fixed to the cannula by a thin thread distal from the hole, and thus the stream from the hole of the cannula passed only through the intraluminal surface of the vascular segment. The interval required for the preparation of arterial segments was about 60 min. The procedure before perfusion was performed in the cold perfusion solution at a temperature of 4–10°C. The isolated, cannulated artery was placed into a 100-ml tissue bath, which was maintained at a temperature of 37°C, with a circulator thermopump (Haake FE2), and was perfused with Krebs-Henseleit solution of the following composition: 118 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl₂, 1.2 mM MgCl₂, 1.2 mM KH₂PO₄, 25 mM NaHCO₃, and 11 mM glucose by means of a peristaltic pump (Eyela MP-3), and gassed with 95% O₂ and 5% CO₂ to maintain the pH level at 7.2–7.4. The flow rate (1.5–2.0 ml/min) was adjusted at the beginning of the experiments to obtain a basal perfusion pressure between 50–100 mmHg, and then it was kept constant throughout the experiment. The perfusion pressure was measured with an electromanometer (Nihon Kohden, MPU-0.5 A) and recorded by a rectigraph (Nihon Kohden WT-685G). The constritor response was, therefore, observed as an increase in perfusion pressure. The arteries were equilibrated for about 90 min until the perfusion pressure reached a stable baseline condition. The drug solution (10–30 μl) was administered into the rubber tube connecting the needle cannula by a microsyringe (Terumo Co.), and the injection time was about 3 sec. The interval between drug administrations was greater than 4 min in order to prevent tachyphylaxis.

Drugs used were dl-norepinephrine hydrochloride (NE; Sankyo, Tokyo), phenylephrine hydrochloride (PE; Kowa Co., Ltd., Nagoya), clonidine hydrochloride (CLO; Boehringer Ingelheim), xylazine hydrochloride (XYL; Bayer A.G., Osaka), tyramine hydrochloride (TYR; Tokyo Kasei), potassium chloride (Wako, Tokyo), bunazosin hydrochloride (Eisai, Tokyo), midaglizole (DG-5128) (2-[2-(4,5-dihydro-1H-imidazol-2-yl)-1 phenylethyl] pyridine dihydrochloride sesquihydrate; Daiichi, Tokyo) and diltiazem hydrochloride (Tanabe, Tokyo).
Fig. 1. A schematic illustration of vascular distribution of the dog lingual artery. 1, a. carotis externa; 2, a. lingualis; 3, a. sublingualis; 4, m. genioglossus (cut); 5, m. hyoglossus; 6, m. styloglossus; 7, mandibula; 8, basihyoid bone; 9, stylohyoid bone. Dotted lines show the part of the lingual artery used in this study.

Results are expressed as the mean ± S.E.M. The two-way analysis of variance (ANOVA) was used for the statistical analysis of multiple comparisons of each dose-response curve. Statistical differences between two means were determined by Student’s t-test for unpaired observations. A P value of less than 0.05 was used as the criterion for statistical significance.

RESULTS

Control responses to alpha-adrenoceptor agonists

The injection of NE and PE induced an immediate and transient increase in perfusion pressure in both dog and monkey lingual arteries, and the durability and repetitiveness of NE- and PE-induced constrictor responses were examined preliminary. When NE (1 μg) or PE (3 μg) was intraluminally injected repetitively at 4–5 min intervals in an isolated dog lingual artery, the vasoconstrictor responses were almost the same degree for each injection. The responsiveness to NE or PE was not greatly altered for over 12 hr after the beginning of the experiments (data not shown). The same observations were found in monkey lingual arteries.

When a mixed alpha-adrenoceptor agonist, NE, and an alpha-1 adrenoceptor agonist, PE, were intraluminally administered into the isolated dog lingual artery, an increase in perfusion pressure was induced in a dose-related manner. Threshold doses for inducing a vasoconstriction were 0.01 to 0.03 μg for NE and 0.03 to 0.1 μg for PE, and the largest increase in pressure recorded were about 250 mmHg for both NE and PE at doses of 1 and 3 μg, respectively. Almost the same increase in perfusion pressure was observed after administration of tyramine an indirect sympathomimetic amine, at a dose of 300 μg. The threshold dose for tyramine was approximately 0.3 μg. On the other hand, alpha-2 adrenoceptor agonists, clonidine and xylazine, produced only a slight increase in perfusion pressure even in very large doses such as 300 and 1000 μg, respectively. KCl produced a vasoconstriction in a dose-related manner, but the threshold dose was highest among the agents used in this study, and the increase of perfusion pressure was usually less than 150 mmHg even at the extremely high dose of 10 mg. The order of potencies for inducing vasocontriction was NE > PE > tyramine >> clonidine > xylazine > KCl. Figure 2 (upper panel) shows the summarized data of dose-response curves for 5 different alpha-adrenoceptor agonists and KCl in the isolated dog lingual artery preparation. The ED_{50} values are shown in Table 1.
Fig. 2. Dose-response curves for 5 adrenoceptor agonists and KCl on isolated dog (upper panel) and monkey (lower panel) lingual arteries. Responses are expressed as values of absolute increases from the control level. Points represent the mean value and vertical bars represent ± S.E.M. Numbers of experiments were as follows: NE: norepinephrine (n = 38), PE: phenylephrine (n = 39), TYR: tyramine (n = 11), CLO: clonidine (n = 22), XYL: xylazine (n = 19), KCl: potassium chloride (n = 28), for dog lingual arteries; and NE (n = 30), PE (n = 31), TYR (n = 6–15), CLO (n = 6–19), XYL (n = 7–14), KCl (n = 20), for monkey lingual arteries.

Table 1. ED$_{50}$ of norepinephrine, phenylephrine, tyramine, clonidine and xylazine in isolated canine and simian lingual arteries

|                | ED$_{50}$ [Dog] |            | ED$_{50}$ [Monkey] |            |
|----------------|----------------|------------|--------------------|------------|
|                | µg (nmol)     | µg (nmol)  |                    |            |
| Norepinephrine | 0.22 (1.07)   | 0.078 (0.38)|                    |            |
| Phenylephrine  | 0.74 (3.63)   | 0.23 (1.13)|                    |            |
| Tyramine       | 15.69 (90.4)  | 23.42 (134.9)|                    |            |
| Clonidine      | 23.41 <       | 3.32 (12.4)|                    |            |
| Xylazine       | 86.05 <       | 406.1 < (1581.5 <)|                    |            |
Effects of alpha-adrenoceptor agonists and KCl on monkey lingual artery preparations

The summarized data of the dose-response curves for all used vasoactive substances are shown in Fig. 2 (lower panel). When NE and PE were added to the isolated arterial preparation, a vasoconstriction was induced in a dose-related manner. The threshold doses for inducing a vasoconstriction were approximately 0.001 to 0.003 μg for NE and 0.003 to 0.01 μg for PE, and they were smaller than those in the dog lingual artery, but maximum increases in perfusion pressure were almost the same as in the dog preparation. Tyramine produced a vasoconstriction in a dose-related manner, but the potency and efficacy were significantly smaller than those in the dog lingual artery. The maximum increase in perfusion pressure was less than 100 mmHg. In several preparations, clonidine induced a relatively potent vasoconstriction. The threshold dose was 0.03 to 0.1 μg, and the maximum response was approximately 75 to 100 mmHg at a dose of 300 μg. On the contrary, xylazine produced almost the same response as those in dog preparations. The duration of responses to clonidine and xylazine in extremely large doses was longer than that induced by other agents used in this study. As shown in dog preparations, in monkey preparations, KCl produced a small response even at the dose of 10 mg. The rank order of potency of vasoconstrictions was NE > PE >> clonidine > tyramine > xylazine > KCl.

Effect of bunazosin and midaglizole on NE-induced responses

When bunazosin, a potent and selective alpha-1 adrenoceptor antagonist, was injected into the perfusion line at doses of 0.1–1 μg, the perfusion pressure did not change significantly. Bunazosin (0.1 μg), injected by bolus injection, inhibited the constrictor response to repeated injections of 0.3 μg of NE at a similar degree for 15 to 20 min after injection. Thus, the dose-response curves were made within 20 min after an injection of each dose of bunazosin in both dog and monkey vascular preparations. The effect of bunazosin on the dose-response curve for NE is shown in Fig. 3 for dogs (upper panel) and monkeys (lower panel), respectively and Table 2. Bunazosin significantly shifted the dose-response curve for NE to the right in a parallel manner in dog arteries. The dose-response curve for NE in monkey arteries was also shifted to the right to the same extent. On the other hand, midaglizole (100 μg), a potent alpha-2 adrenoceptor antagonist (15), did not significantly reduce the NE-induced constrictions in dog and monkey lingual arteries (Fig. 4). Bunazosin also significantly shifted the dose-response...
curve for PE to the right in dog preparations, and it suppressed the contractile response to clonidine in monkey lingual arteries (data not shown). In several experiments, in both species vasoconstrictor responses to 1–3 µg of tyramine were completely inhibited by 1 µg bunazosin (data not shown). Midaglizole failed to affect any of these responses (data not shown).

**Effects of diltiazem on NE-induced responses**

After intraluminal pretreatment of the preparation with diltiazem, a potent calcium antagonist, basal perfusion pressure was not changed significantly. Diltiazem (10–100 µg) reduced the maximum effects and shifted the dose-response curve for NE in dog lingual arteries to the right in a non-competitive manner (Fig. 5, upper panel), but in monkey lingual arteries, the NE-induced vasoconstriction was not affected significantly even by a very large amount of diltiazem (100 µg) as shown in Fig. 5 (lower panel). Diltiazem also reduced the maximum effects and shifted to the right the dose response-curve for PE in dog lingual arteries (data not shown).

### Table 2. ED$_{50}$ values of norepinephrine (NE) after 0.1 µg and 1 µg bunazosin in isolated canine and simian lingual arteries

|                      | ED$_{50}$ of NE (µg) | $K_B$ (nmol) |
|----------------------|----------------------|--------------|
| **[Dog]**            |                      |              |
| Control              | 0.38                 | 1.09 × 10$^{-10}$ |
| after 0.1 µg bunazosin | 1.22               | 1.01 × 10$^{-10}$ |
| after 1.0 µg bunazosin | 9.50               |              |
| **[Monkey]**         |                      |              |
| Control              | 0.11                 | 0.49 × 10$^{-10}$ |
| after 0.1 µg bunazosin | 0.63               |              |
| after 1.0 µg bunazosin | 5.14               | 0.51 × 10$^{-10}$ |

**Fig. 4.** Effects of midaglizole on NE-inducing vasoconstrictions in the isolated, perfused dog (upper panel) and monkey (lower panel) lingual arteries. Data are expressed as changes in the perfusion pressure and shown as means ± S.E.M. ○: Control, ■: Midaglizole, 100 µg.
DISCUSSION

In this study, we demonstrated that the order of vasoconstrictor responses of alpha-adrenoceptor agonists in isolated dog lingual arteries was almost the same as those shown to occur in dog mesenteric arteries (16), dog femoral arteries (17) and branches of the skeletal muscle area of dog femoral arteries (18). NE (a mixed alpha-1 and alpha-2 agonist) and PE (an alpha-1 agonist) produced a strong vasoconstriction in a dose-dependent manner. On the other hand, a selective alpha-2 adrenoceptor agonist, xylazine, and a relatively selective alpha-2 agonist, clonidine, produced very weak vasoconstrictions even at relatively large doses. The relative order of potency for inducing vasoconstrictions by agonists was NE > PE > tyramine > clonidine > xylazine, indicating that the dominating postjunctional alpha-adrenoceptor type in dog lingual arteries is the alpha-1 type.

In isolated monkey lingual arteries, the vasoconstrictor responses to the alpha-adrenoceptor agonists were usually more potent than those in dog lingual arteries, although their efficacies were not so different. Differing from the dog lingual artery, clonidine occasionally induced a significant vasoconstriction in the monkey lingual artery, while xylazine, as in the dog lingual artery, failed to induce any significant response except at the maximum dose used in this study (1 mg). The relative order of potency for inducing vasoconstrictions was NE > PE >> clonidine > tyramine > xylazine.

In the present study, bunazosin, a potent and highly selective alpha-1 antagonist (19, 20), dose-dependently inhibited NE- and PE-induced vasoconstrictions in both dog and monkey lingual arteries. However, NE- and PE-induced responses were not suppressed by midaglizole, which is a preferential and specific alpha-2 antagonist (15). These results suggest that NE and PE produced vasoconstrictions mediated via alpha-1 adrenoceptors but not alpha-2 adrenoceptors in both dog and monkey lingual arteries. Moreover, we also found that the clonidine-induced vasoconstrictor response in monkey lingual arteries was readily blocked by bunazosin, and it was unaffected after pretreatment with midaglizole, suggesting that the effectiveness of clonidine must be ascribed partially to its alpha-1 agonistic component in these preparations, showing that clonidine has not only alpha-2 but also alpha-1 adrenoceptor stimulating properties (21–23). In order to study the role of Ca++ movement on alpha-1 adrenoceptor-induced constrictions, we used diltiazem, a selective Ca++ entry blocker; and it suppressed and shifted the dose-response curve for NE to the right in dog lingual arteries, while in
monkey lingual arteries, the dose-response curve for NE was not significantly affected after treatment with diltiazem. The differential effect of diltiazem suggests that the constriction mediated by NE in dog lingual arteries required mainly Ca$^{++}$ influx, while that in monkey lingual arteries did not. Since the Ca-sensitizing action of NE and different Ca stores in different tissues were reported, we need additional experiments to clarify the different sensitivities of diltiazem on NE-induced vasoconstrictions between dog and monkey lingual arteries in future.

In both preparations, KCl produced the smallest response among other vasoconstrictors even at a dose of 10 mg. Compared with other blood vessels which have been investigated in this laboratory using the same method, the lingual arteries from both species showed the lowest sensitivity to KCl. Sinanovic and Chiba (24) proposed that a relatively small vasoconstriction response to KCl in skeletal muscle arteries may indicate the resistance of the cell membrane to the KCl depolarizing effect and consequently, less Ca$^{++}$ influx from the extracellular space, or an existence of relatively voltage insensitive Ca$^{++}$ channels.

It is well-recognized that most blood vessels are innervated by postganglionic sympathetic nerves. The density of innervation varies widely and probably reflects the contribution of the individual vessels to centrally controlled responses (25). In 1985, Chiba and Ito (26) reported that tyramine exerted its strong vasoconstrictor action in the dog intermediate auricular artery but only a weak response in the dog mesenteric artery. In monkey digital arteries tyramine also produced a very strong vasoconstriction (27), while in dog and monkey femoral arteries (17, 18, 24) tyramine produced only a slight vasoconstriction. In this study we found that tyramine produced a very strong vasoconstriction in the dog lingual artery, although in relatively high doses of 100 and 300 $\mu$g, but in the monkey lingual artery, the same doses of tyramine induced only a weak response. The mechanism of different tyramine action is unknown yet.

It is concluded that: 1) isolated lingual arteries have abundant alpha-1 adrenoceptors and 2) alpha-1 adrenoceptor-induced constriction may involve different importance of extracellular Ca influx between dog and monkey lingual arteries, although the participation of intracellular Ca mobilization and Ca sensitivity might be not ruled out.

REFERENCES

1. Pleschka, K.: Control of tongue blood flow in regulation of heat loss in mammals. Rev. Physiol. Biochem. Pharmacol. 100, 75 – 120 (1984)

2. Drew, G.M. and Whiting, S.B.: Evidence for two distinct types of postsynaptic $\alpha$-adrenoceptor in vascular smooth muscle in vivo. Br. J. Pharmacol. 67, 207 – 215 (1979)

3. Langer, S.Z.: Presynaptic regulation of the release of catecholamines. Pharmacol. Rev. 32, 337 – 362 (1981)

4. Starke, K.: $\alpha$-Adrenoceptor subclassification. Rev. Physiol. Biochem. Pharmacol. 88, 199 – 236 (1981)

5. Timmermans, P.B.M.W.M. and van Zwieten, P.A.: $\alpha_2$ Adrenoceptors: Classification, localization, mechanisms and targets for drugs. J. Med. Chem. 25, 1389 – 1401 (1982)

6. McGrath, J.C.: Evidence for more than one type of post-junctional $\alpha$-adrenoceptor. Biochem. Pharmacol. 31, 467 – 484 (1982)

7. Van Zwieten, P.A. and Timmermans, P.B.M.W.M.: Cardiovascular $\alpha$-receptors. J. Mol. Cell Cardiol. 15, 717 – 733 (1983)

8. Langer, S.Z. and Hicks, P.E.: Alpha-adrenoceptor subtypes in blood vessels: physiology and pharmacology. J. Cardiovasc. Pharmacol. 6, Supp. 4, S547 – S558 (1984)

9. Ito, T. and Chiba, S.: Existence of two types of postjunctional alpha adrenoceptors in the isolated canine intermediate auricular artery. J. Pharmacol. Exp. Ther. 234, 698 – 702 (1985)

10. Cocks, T.M. and Angus, J.A.: Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. Nature 305, 627 – 630 (1983)

11. Nakane, T. and Chiba, S.: Postjunctional $\alpha$-adrenoceptor subtypes in isolated and perfused canine epicardial coronary arteries. J. Cardiovasc. Pharmacol. 10, 651 – 657 (1987)

12. Matsuda, H., Kuon, E., Holtz, J. and Busse, R.: Endothelium-mediated dilations contribute to the polarity of the arterial wall in vasomotion induced
by α₂-adrenergic agonists. J. Cardiovasc. Pharmacol. 7, 680–688 (1985)

13 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)

14 Tsuji, T. and Chiba, S.: Potentiating effect of methysergide on norepinephrine-induced constriction of the isolated internal carotid artery of the dog. Japan. J. Pharmacol. 34, 95–100 (1984)

15 Muramatsu, I., Oshita, M. and Yamanaka, K.: Selective alpha-2 blocking action of DG-5128 in the dog mesenteric artery and rat vas deferens. J. Pharmacol. Exp. Ther. 227, 194–198 (1983)

16 Chiba, S. and Tsukada, M.: Vasoconstrictor responses of isolated and perfused canine mesenteric arteries to alpha-adrenoceptor agonist. Arch. Int. Pharmacodyn. Ther. 271, 241–248 (1984)

17 Kawai, K. and Chiba, S.: Vascular responses of isolated canine and simian femoral arteries and veins to α-adrenoceptor agonist. Arch. Int. Pharmacodyn. Ther. 284, 201–211 (1986)

18 Sinanovic, O. and Chiba, S.: Responsiveness of skeletal muscle arteries of the dog femoral artery to α-adrenoceptor agonists before and after cold storage. Arch. Int. Pharmacodyn. Ther. 287, 146–157 (1987)

19 Shoji, T.: Comparison of pre- and postsynaptic α-adrenoceptor blocking effects of E-643 in the isolated vas deferens of the rat. Japan. J. Pharmacol. 31, 361–368 (1981)

20 Hata, F., Kondo, E., Kondo, S., Kagawa, K. and Ishida, H.: Characteristics of [³H]E-643-binding to alpha adrenoceptors. Japan. J. Pharmacol. 32, 181–187 (1982)

21 Kobinger, W. and Pichler, L.: α-Adrenoceptor subtypes in cardiovascular regulation. J. Cardiovasc. Pharmacol. 4, S81–S85 (1982)

22 Holck, M.I., Jones, C.H.M. and Haeusler, G.: Differential interactions of clonidine and methoxamine with the postsynaptic α-adrenoceptor of rabbit main pulmonary artery. J. Cardiovasc. Pharmacol. 5, 240–248 (1983)

23 Agrawal, D.K. and Daniel, E.E.: Agonists interaction with radiolabeled α-adrenoceptor antagonists binding sites in rat mesenteric artery. J. Cardiovasc. Pharmacol. 7, Supp. 6, S66–S75 (1985)

24 Sinanovic, O. and Chiba, S.: Responsiveness of monkey skeletal muscle arteries to vasoconstrictor substances before and after cold storage. Japan. J. Pharmacol. 46, 237–246 (1988)

25 Vanhoutte, P.M., Verbeuren, T.J. and Webb, R.C.: Local modulation of adrenergic neuroeffector interaction in the blood vessel wall. Physiol. Rev. 61, 151–247 (1981)

26 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)

27 Ito, T. and Chiba, S.: Vascular responsiveness of simian digital artery to various vasoactive substances. J. Invest. Dermatol. 86, 678–682 (1986)