Pharmacological Analysis of Vasodilator Responses to Alpha₂-Adrenoceptor Agonists in Isolated Rat Common Carotid Arteries

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Abstract—Using the cannula inserting method, vasodilator responses to alpha₂-adrenoceptor agonists (clonidine, guanabenz, DJ7141 and xylazine) were investigated in isolated and perfused rat common carotid arteries. Alpha₂-adrenoceptor agonists dose-dependently induced a vasodilation in preparations preconstricted by noradrenaline. The potencies were in the order of clonidine > guanabenz > DJ-7141 > xylazine. Removal of the endothelium inhibited ACh-induced vasodilation, but not the alpha₂-agonist-induced dilation. Atropine treatment inhibited ACh-induced vasodilation, but not the alpha₂-agonist-induced dilation. Alpha₂-agonist-induced dilations were not modified by beta-blockade, which significantly suppressed isoprenaline-induced vasodilations. The potent alpha₂-adrenoceptor antagonist DG5128 did not influence the alpha₂-agonist-induced vasodilation. In preparations preconstricted by PGF₂α, clonidine and xylazine never induced a vasodilation, and clonidine frequently induced vasoconstrictions that were completely blocked by bunazosin. It is concluded that alpha₂-adrenoceptor agonist-induced vasodilation is independent from the existence of the endothelium, and that it is not related to vascular beta- and alpha₂-adrenoceptors and muscarinic receptors, suggesting that the alpha₂-adrenoceptor agonist-induced vasodilation is due to an antagonistic activity towards the vascular alpha₁-adrenoceptors.

Although the alpha₁-adrenoceptor subtype linked to vasoconstriction is the predominant postsynaptic receptor in vascular smooth muscle, the postsynaptic alpha₂-adrenoceptor subtype also mediates constriction of vascular smooth muscle as reviewed by several authors (1–4). However, it has been also reported that the alpha₂-adrenoceptor agonist produced a vasodilation in isolated dog coronary arteries (5–7), in precontracted preparations of the rat superior mesenteric artery (8), and in canine femoral and rat tail arteries (9). Nakane et al. (7) reported that xylazine- and clonidine-induced vasodilations are not mediated by alpha₁- and alpha₂-adrenoceptors, because of the absence of a blocking effect by bunazosin (a selective alpha₁-antagonist) and DG5128 (a selective alpha₂-antagonist). It was reported that the endothelium-dependent relaxation was mediated by alpha₂-adrenoceptors in dog coronary arteries (6, 10), in dog femoral and pulmonary arteries and veins (10, 11), and in rat tail arteries (9). However, Nakane et al. (7) showed that clonidine-induced vasodilations are not endothelium-dependent, because it was not influenced by removal of the endothelium.

Recently, Chiba and Tsukada (12) demonstrated that the isolated and perfused rat common carotid artery well-responded to noradrenaline (NA), and its action was long-lasting even when administered in a bolus injection by the cannula inserting method developed and modified by Hongo and Chiba (13) and Tsuji and Chiba (14). In the present study, we attempted to clarify pharmacologically the mechanisms underlying the antagonism of NA-induced tone by alpha₂-adrenoceptor agonists, clonidine, guanabenz, DJ7141 and xylazine, using the cannula in-
serting method.

**Materials and Methods**

Male or female Wistar rats weighing 200 to 300 g (aged 10 to 15 weeks) were used in this study. After treatment with sodium heparin (200 units/kg, i.v.), the rats were killed by rapid exsanguination, and the common carotid artery was excised and immersed immediately in cold Ringer solution at 4°C for marking the preparation. Isolated common carotid arteries that were 0.8 to 1.3 cm in length and 0.7 to 1 mm in outer diameter were selected for this study. A stainless steel cannula with small holes 2 mm from the distal sealed end (0.6 to 0.8 mm in outer diameter and 3 cm in length) was carefully inserted into each vessel segment to avoid injury of the intraluminal surface of the isolated vessel. Segments were set up in the bath for preparation as described by Tsuji and Chiba (14).

The perfusion solution contained 118 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl2, 25 mM NaHCO3, 1.2 mM MgSO4, 1.2 mM KH2PO4 and 11 mM glucose; and it was bubbled with 95% O2 and 5% CO2, which maintained the pH of the solution at 7.2-7.4. The bath and perfusion circuit were warmed at 37°C with a thermopump (Haake, Model FE2, Karlsruhe, F.R.G.). The speed of the perfusion flow was initially adjusted so that the perfusion pressure was maintained at 50-70 mmHg and kept constant throughout the experiments. The perfusion flow rate was usually 1 ml/min in the majority of the cases. The vasoconstriction was therefore observed as an increase in perfusion pressure, which was continuously measured with an electric manometer. Drugs in this study were noradrenaline hydrochloride (NA; Sankyo, Tokyo, Japan), clonidine hydrochloride (Boehringer Ingelheim, F.R.G.), xylazine hydrochloride (Bayer A.G., Osaka, Japan), guanabenz acetate (Nihon Shoji, Tokyo, Japan), DG5128 (2-[2-(4,5-dihydro-1H-imidazol-2-yl)-1-phenyl]pyridine dihydrochloride sesquihydrate; Daiichi, Tokyo, Japan), bunazosin hydrochloride (Eisai, Tokyo, Japan), atropine sulphate (Takeda, Osaka, Japan), isoprenaline hydrochloride (ICl Pharm., Osaka, Japan), acetylcholine chloride (ACh; Daiichi, Tokyo, Japan), prostaglandin F2α (PGF2α; Ono, Osaka, Japan), potassium chloride (Wako, Tokyo, Japan) and saponin (Kanto Chem., Tokyo, Japan). The drug solution was injected intraluminally into the isolated vessel from the rubber tubing close to the cannula in a volume of 0.01-0.03 ml for a period of 4 sec. In the cases for inducing preconstrictions by PGF2α, 1 μg/ml of PGF2α was continuously infused, because a bolus injection of PGF2α did not produce a stable long-lasting vasoconstriction.

The results are expressed as the mean±S.E.M. Statistical differences between two means and two curves (P<0.05) were determined by Student's t-test for unpaired observations and analysis of variance, respectively.

**Results**

Effects of alpha2-adrenoceptor agonists on preconstricted vessels induced by NA: When a relatively large dose of NA was injected into the isolated and perfused common carotid artery of the rat, a long-lasting vasoconstriction was readily obtained as reported previously (12). NA (3 to 10 μg) induced long-lasting vasoconstrictions (30-60 min) with an increase of approximately 30 mmHg in perfusion pressure. In 38 experiments, NA (5.76±0.56 μg, n=38) induced an increase of 43±3 mmHg in perfusion pressure. After induced long-lasting vasoconstriction by NA, vascular responses to 4 alpha2-adrenoceptor agonists, clonidine, xylazine, guanabenz and DJ7141, were investigated. Each alpha2-adrenoceptor agonist induced vasodilations in a dose-related manner, showing transient decreases in perfusion pressure for 1 to 5 min in a dose range of 0.01-10 μg. Summarized data are shown in Fig. 1. The rank order of vasodilatory potencies was clonidine>guanabenz>DJ7141>xylazine.

Effects of propranolol on isoprenaline-and alpha2-adrenoceptor agonist-induced vasodilations in preparations preconstricted by NA: When isoprenaline was administered, a vasodilation was induced in a dose-related manner in preparations preconstricted by NA. Isoprenaline-induced vasodilations were readily inhibited by treatment with propranolol. Figure 2 shows that the isopre-
naline-induced dilation is inhibited, but the xylazine-induced dilation is not blocked by 1 μg propranolol. Propranolol by itself induced slight increases in perfusion pressure (9±2 mmHg at 0.1 μg, n=15; 4±2 mmHg at 1 μg, n=15; 2±2 mmHg at 10 μg, n=15). As shown in Fig. 3, 1 μg propranolol significantly shifted the isoprenaline-induced vasodilation to the right, but 10 μg propranolol did not modify clonidine-, xylazine-, guanabenz- or DJ7141-induced vasodilations.

**Effects of a potent alpha<sub>2</sub>-adrenoceptor antagonist, DG5128, on alpha<sub>2</sub>-agonist-induced vasodilations:** When the potent alpha<sub>2</sub>-adrenoceptor antagonist DG5128 was injected into the perfused artery, the perfusion pressure was temporarily increased 17±2 mmHg (n=11) by 100 μg. After pretreatment with 100 μg DG5128, each agonist was examined. The clonidine-induced vasodilations were slightly inhibited but not significantly in the majority of the cases. Xylazine-, guanabenz- and DJ7141-induced vasodilations were never influenced by DG5128 treatment. Summarized data are shown in Fig. 4.

**Effects of removal of the endothelium on ACh-, isoprenaline- and alpha<sub>2</sub>-adrenoceptor agonist-induced vasodilations:** As reported previously, 1 to 3 mg saponin administered as a bolus, intraluminally, readily produced a disappearance of the endothelium in the isolated and cannulated vessel preparations (15-17). In the present study, 3 mg saponin induced a temporary increase in perfusion pressure (14±2 mmHg, n=17), which gradually returned to a slightly higher level than the control value. Intraluminal bolus injections of ACh dose-dependently induced a vasodilation in preparations preconstricted by NA. After treatment with 3 mg saponin, ACh-induced vasodilations were completely

**Propranolol**

1 μg

![Graph showing the effects of propranolol on isoprenaline- and xylazine-induced vasodilations.]
suppressed. However, isoprenaline-induced vasodilations were not modified by an absence of the endothelium. Moreover, each alpha2-adrenoceptor agonist-induced vasodilation was not influenced by saponin treatment. Summarized data are shown in Fig. 5.

**Effects of atropine on ACh- and clonidine-induced vasodilations:** ACh-induced vasodilations were readily inhibited by atropine treatment. On the other hand, clonidine-induced vasodilations were not modified by atropine treatment. Summarized data are shown in Fig. 6. Xylazine-induced vasodilations were also not influenced by 10 μg atro-
Effects of ACh, isoprenaline, clonidine and xylazine on preconstricted preparations produced by an infusion of PGF$_{2\alpha}$: In almost half of the preparations used, an infusion of PGF$_{2\alpha}$ caused a fluctuation of perfusion pressure, i.e., rhythmic vasoconstrictions were consistently observed. Thus, such cases of unstable perfusion pressure were omitted in these experiments. During an infusion of 1 µg/min...
of PGF<sub>2α</sub>, ACh and isoprenaline consistently induced a vasodilation in a dose-related manner under such conditions as well as in NA-preconstricted preparations. On the other hand, xylazine did not induce any change in perfusion pressure. Clonidine did not induce a vasodilation in all 12 preparations used, but it frequently produced a vasoconstriction in doses of 0.1–10 μg. Summarized data are shown in Fig. 7. The vasoconstrictions induced by 0.1–10 μg of clonidine were completely inhibited by 10 μg bunazosin (a potent selective alpha<sub>1</sub>-adrenoceptor antagonist) in 3 experiments (data not shown).

**Discussion**

It is well-known that stimulation of postsynaptic alpha<sub>2</sub>-adrenoceptors can initiate not only a vasoconstriction (18, 19, 20–25), but also a relaxation (6, 10, 11). The release of endothelial-derived relaxing factors mediates a vasodilation in vessels in response to ACh and many vasoactive substances (26–28). There have been several reports that the vasodilation induced by alpha<sub>2</sub>-agonists is due to an endothelium-dependent dilatory mechanism (9, 11). Moreover, a number of reports have indicated that removal of the endothelium enhances contractile responses to alpha<sub>2</sub>-agonists (9, 29, 30). In the present study, we showed alpha<sub>2</sub>-agonist-induced vasodilations in isolated rat common carotid arteries preconstricted by NA. Matsuda et al. (9) reported that extraluminal application of alpha<sub>2</sub>-agonists induced vasoconstrictions in isolated rat tail arteries; the preconstricted arteries were readily dilated by intraluminal application of an alpha<sub>2</sub>-agonist, and this effect disappeared by removal of the endothelium. Since the existence of alpha<sub>2</sub>-adrenoceptors on cultured endothelial cells was suggested on the basis of increased levels of intracellular cyclic nucleotides after exposure of the culture to agonists (31, 32), several groups have suggested that alpha<sub>2</sub>-adrenoceptors might exist on endothelial cells, and the activation of such receptors would lead to a relaxation of the artery. However, in this study, alpha<sub>2</sub>-agonist-induced vasodilations were not influenced by the absence of the endothelium, although ACh-induced vasodilations were completely abolished, indicating that the vasodilation by alpha<sub>2</sub>-agonists is not mediated by dilatory factors from the endothelial cells.

In the present experiments, alpha<sub>2</sub>-adrenoceptor agonist-induced vasodilations were not inhibited by the potent alpha<sub>2</sub>-adrenoceptor antagonist DG5128, which is a preferential and specific alpha<sub>2</sub>-adrenoceptor antagonist in the dog mesenteric artery and the rat vas deferens (33). The present study indicates that the alpha<sub>2</sub>-adrenoceptor agonist-induced dilation is not mediated by activation of alpha<sub>2</sub>-adrenoceptors in the rat common carotid artery.

In this study, alpha<sub>2</sub>-adrenoceptor agonist-induced vasodilations were not modified by atropine in doses which completely blocked ACh-induced vasodilations. Therefore, alpha<sub>2</sub>-adrenoceptor agonist-induced dilations do not involve cholinergic mechanism.

As alpha<sub>2</sub>-adrenoceptor agonist-induced dilations were not influenced by propranolol in doses that significantly suppressed the isoprenaline-induced vasodilations, the dilation is not mediated by beta-adrenoceptors.

In preconstricted preparations induced by PGE<sub>2α</sub>, xylazine did not induce any vasodila-
tions. Clonidine also did not produce any vasodilation in PGE$_2$-preconstricted vessels, but rather frequently produced vasoconstrictions. Since the clonidine-induced vasoconstrictions were suppressed by the potent alpha$_1$-antagonist bunazosin, it might be due to the alpha$_1$-agonistic action of clonidine, indicating that clonidine is a partial alpha$_1$-adrenoceptor agonist, but xylazine is not. Previously, Ruffolo et al. (18, 19) indicated the existence of alpha$_2$-adrenoceptors by use of clonidine which mediated vasoconstrictions in the rat aorta, but we did not obtain such evidence in the rat common carotid artery. This may be to regional differences and/or different procedures, because we used intraluminal perfusion preparations but they used spiral preparations.

Agrawal and Daniel (8) reported that alpha$_2$-adrenoceptor agonists exhibited their antagonistic activity at the alpha$_1$-adrenoceptors in ring preparations of rat mesenteric arteries preconstricted by alpha$_1$-adrenoceptor agonists but not in those preconstricted by alpha$_2$-adrenoceptor agonists, suggesting that alpha$_1$-adrenoceptor activation is counteracted by alpha$_2$-adrenoceptor agonists in the rat mesenteric artery. In the present study, because each alpha-adrenoceptor agonist dose-dependently induced clear vasodilations in preparations preconstricted by NA but not in those preconstricted by PGF$_2$-alpha, each alpha$_2$-adrenoceptor agonist may interact through alpha-adrenergic mechanisms. As each alpha$_2$-adrenoceptor agonist did not produce a clear vasoconstriction by itself and NA-induced vasoconstrictions were readily suppressed by bunazosin, NA-induced vasoconstrictions are due to activation of alpha$_1$-adrenoceptors. Thus, it is strongly indicated that alpha$_2$-adrenoceptor agonist-induced vasodilations in preconstricted preparations by NA might be due to its antagonistic action for activated alpha$_1$-adrenoceptors.

It was reported that two independent binding sites for [3H]prazosin and [3H]yohimbine have been observed in the plasma membrane vesicles of the rat mesenteric artery (34), suggesting the presence of subtypes of postsynaptic alpha-adrenoceptors in the rat mesenteric artery. However, they also suggested that alpha$_2$-adrenoceptor agonists elicit the responses through their interactions with the alpha$_1$-adrenoceptors since the pA$_2$ values of prazosin against constrictions to either selective alpha$_1$- or alpha$_2$-agonists are similar (8). Previously, alpha$_2$-adrenoceptor agonists have been reported to behave as an antagonist at alpha$_1$-adrenoceptors in the isolated and perfused hindquarter of the rat (35) and in rabbit aorta (36). Agrawal and Daniel (8) proposed a model for the postsynaptic alpha-adrenoceptors in which the receptor is a common macromolecule in which the antagonists selective for the alpha$_1$ and alpha$_2$ subtypes bind independently, but alpha-adrenoceptor agonists probably occupy both the sites.

In the present functional study, we demonstrated that alpha$_2$-adrenoceptor agonist might have an antagonistic property for alpha$_1$-adrenoceptor activation. However, we could not obtain any evidence that there are alpha$_2$-adrenoceptors in the isolated rat common carotid artery. Thus, we need to investigate whether alpha$_2$-agonists influence post-receptor mechanisms.

References
1. Timmermans, P.B.M.W.M. and van Zwieten, P.A.: The postsynaptic alpha$_2$-adrenoceptor. J. Auton. Pharmacol. 1, 171–183 (1981)
2. McGrath, J.C.: Evidence for more than one type of postjunctional alpha adrenoceptor. Biochem. Pharmacol. 31, 467–484 (1982)
3. Starke, K. and Docherty, J.R.: Types and functions of peripheral alpha-adrenoceptors. J. Cardiovasc. Pharmacol. 4, Supp. 1, S3-S7 (1982)
4. 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)
5. Rimele, T.J., Rooke, T.W., Aarhus, L.L. and Vanhoutte, P.M.: Alpha$_1$ adrenoceptors and calcium in isolated canine coronary arteries. J. Pharmacol. Exp. Ther. 226, 668–672 (1983)
6. Cocks, T.M. and Angus, J.A.: Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. Nature 305, 627–630 (1983)
7. Nakane, T., Itoh, N. and Chiba, S.: Postsynaptic alpha-adrenoceptor subtypes in isolated and perfused canine epicardial coronary arteries. J. Cardiovasc. Pharmacol. 10, 651–657 (1987)
8. Agrawal, D.K. and Daniel, E.E.: Agonists interaction with radiolabeled alpha-adrenoceptor antago-
nists binding sites in rat mesenteric artery. J. Cardiovasc. Pharmacol. 7, Supp. 6, S66–S75 (1985)
9 Matsuda, H., Kuon, E., Holtz, J. and Busse, R.: Endothelium-mediated dilations contribute to the polarity of the arterial wall in vasomotion induced by $\alpha_2$-adrenergic agonists. J. Cardiovasc. Pharmacol. 7, 680–688 (1985)
10 Angus, J.A., Cock, T.M. and Satoh, K.: $\alpha_2$-Adrenoceptors and endothelium-dependent relaxation in canine large arteries. Br. J. Pharmacol. 88, 767–777 (1986)
11 Miller, V.M. and Vanhoutte, P.N.: Endothelium $\alpha_2$-adrenoceptors in canine pulmonary and systemic blood vessels. Eur. J. Pharmacol. 118, 123–129 (1985)
12 Chiba, S. and Tsukada, M.: Pharmacological features of vascular responses of isolated rat common carotid arteries to vasoactive substances by the cannula inserting method. Tohoku J. Exp. Med. 157, 199–204 (1989)
13 Hongo, K. and Chiba, S.: A new method for measuring vascular responsiveness of relatively larger arteries of dogs. J. Pharmacol. Methods 9, 83–90 (1983)
14 Tsuji, T. and Chiba, S.: Potentiating effect of methysergide on norpaminephrine-induced constriction of the isolated internal carotid artery of the dog. Jpn. J. Pharmacol. 34, 95–100 (1984)
15 Chiba, S. and Tsukada, M.: Vasoconstrictor responses induced by $\alpha$-adrenoceptor agonists before and after removal of the endothelial cells of dog mesenteric arteries. J. Auton. Pharmacol. 4, 257–260 (1984)
16 Chiba, S., Itoh, N. and Tsuji, T.: Vascular responses to intraluminal acetylcholine in isolated, perfused canine and simian basilar arteries. J. Auton. Pharmacol. 6, 101–107 (1986)
17 Nakane, T., Itoh, N. and Chiba, S.: Responses of isolated and perfused dog coronary arteries to acetylcholine, norpaminephrine, KCl, and di-tiazem before and after removal of the endothelial cells by saponin. Heart Vessels 2, 221–227 (1986)
18 Ruffolo, R.R., Jr., Waddell, J.E. and Yaden, E.L.: Postsynaptic alpha adrenergic receptor subtypes differentiated by yohimbine in tissues from the rat. Existence of alpha-2 adrenergic receptors in rat aorta. J. Pharmacol. Exp. Ther. 217, 235–240 (1981)
19 Ruffolo, R.R., Jr., Waddell, J.E. and Yaden, E.L.: Heterogeneity of postsynaptic alpha adrenergic receptors in mammalian aortas. J. Pharmacol. Exp. Ther. 221, 309–314 (1982)
20 Van Meel, J.C.A., De Jonge, S., Timmermans, P.B.M.W.M. and Van Zwieten, P.A.: Selectivity of some alpha adrenocceptor agonists for peripheral alpha-1 and alpha-2 adrenocceptors in the normotensive rat. J. Pharmacol. Exp. Ther. 219, 760–767 (1981)
21 Godfraind, T., Miller, R.C. and Lima, J.S.: Selective alpha_1 and alpha_2 adrenocceptor agonist-induced contractions and $^{45}$Ca fluxes in the rat isolated aorta. Br. J. Pharmacol. 77, 597–604 (1982)
22 Weiss, R.J., Webb, C.R. and Smith, C.B.: Alpha-2 adrenoceptors on arterial smooth muscle: Selective labeling by $[^{3}H]$clonidine. J. Pharmacol. Exp. Ther. 225, 599–605 (1983)
23 Scarborough, N.L. and Carrier, G.O.: Nifedipine and alpha adrenoceptors in rat aorta. I. Role of extracellular calcium in alpha-1 and alpha-2 adrenoceptor-mediated contraction. J. Pharmacol. Exp. Ther. 231, 597–602 (1984)
24 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)
25 Haniuda, M., Itoh, N. and Chiba, S.: Time-dependent enhancement of xylazine-induced, alpha-2 adrenoceptor-mediated vasoconstriction in isolated and perfused canine pulmonary veins. J. Pharmacol. Exp. Ther. 249, 340–347 (1989)
26 Furchgott, R.F. and Zawadzki, J.V.: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288, 273–276 (1980)
27 Furchgott, R.F.: Role of endothelium in responses of vascular smooth muscle. Circ. Res. 53, 557–573 (1983)
28 Furchgott, R.F.: The role of endothelium in the responses of vascular smooth muscle to drugs. Annu. Rev. Pharmacol. Toxicol. 24, 175–197 (1984)
29 Egleme, C., Godfraind, T. and Miller, R.C.: Enhanced responsiveness of isolated rat aorta to clonidine after removal of the endothelial cells. Br. J. Pharmacol. 81, 16–18 (1984)
30 Carrier, G.O. and White, R.E.: Enhancement of alpha-1 and alpha-2 adrenergic agonist-induced vasoconstriction by removal of endothelium in rat aorta. J. Pharmacol. Exp. Ther. 232, 682–687 (1985)
31 Buonassissi, V. and Venter, J.C.: Hormone and neurotransmitter receptors in an established vascular endothelial cell line. Proc. Natl. Acad. Sci. U.S.A. 73, 1612–1616 (1976)
32 Karnushina, I.L., Spatz, M. and Bembry, J.: Cerebral endothelial cell culture. I. The presence of $p_2$- and $\alpha_2$-adrenoceptors linked to adenylate cyclase
activity. Life Sci. 30, 849–858 (1982)

33 Muramatsu, I., Ohshita, M. and Yamanaka, K.: Selective alpha-2 blocking action of DG5128 in the dog mesenteric artery and rat vas deferens. J. Pharmacol. Exp. Ther. 227, 194–198 (1983)

34 Agrawal, D.K. and Daniel, E.E.: Radioligand binding studies of alpha-adrenoceptors in the plasma membrane vesicles of rat mesenteric artery. Fed. Proc. 42, 636 (1983)

35 Kobinger, W. and Pichler, L.: $\alpha_1/\alpha_2$ Selectivity ratio in a series of agonists and their relation to pre/postsynaptic activity ratios. Eur. J. Pharmacol. 91, 129–133 (1983)

36 Lues, I. and Schumann, H.-J.: BHT-920 acts as an $\alpha_1$-adrenoceptor agonist in the rabbit aorta under certain in vitro conditions. Naunyn Schmiedebergs Arch. Pharmacol. 325, 42–46 (1984)