Naunyn-Schmiedeberg's Arch Pharmacol (2002) 366 : 104–109
DOI 10.1007/ s00210-002-0582-6

ORIGINAL ARTICLE

Christine Giessler · Thekla Wangemann
Rolf-Edgar Silber · Stefan Dhein · Otto-Erich Brodde

Noradrenaline-induced contraction of human saphenous vein and human internal mammary artery: involvement of different α-adrenoceptor subtypes

Received: 30 January 2002 / Accepted: 17 April 2002 / Published online: 14 June 2002

Abstract Although saphenous veins and internal mammary arteries are commonly used for coronary artery bypass grafting, only a very few comparative studies are available on α-adrenoceptor-mediated vasoconstriction in these vessels. Thus, we determined, in isolated rings from human saphenous vein and human internal mammary artery, contractile responses to noradrenaline (10^{-8}–10^{-4} M) in the absence and presence of the α-adrenoceptor antagonists yohimbine (α_2-adrenoceptor antagonist, 10^{-8}–10^{-6} M), prazosin (α_1-adrenoceptor antagonist, 10^{-9}–10^{-7} M), 5-methylurapidil (5-MU, α_{1A}-adrenoceptor antagonist, 10^{-8}–10^{-6} M), BMY 7378 (α_{1D}-adrenoceptor antagonist, 10^{-7}–10^{-6} M), and chloroethylclonidine (CEC, irreversible α_{1B}-adrenoceptor antagonist, 3×10^{-5} M for 30 min). All experiments were carried out in the presence of 10^{-7} M propranolol and 10^{-5} M cocaine. In both vessel types noradrenaline evoked concentration-dependent contractions. In saphenous veins yohimbine was a potent antagonist (pA_2-value 8.32) while prazosin, 5-MU and BMY exhibited only marginal antagonistic effects. CEC, however, significantly decreased noradrenaline-induced contractions. In contrast, in internal mammary arteries prazosin (pA_2-value 9.65) and 5-MU (pK_B-values 7.2–7.5) were potent antagonists, while yohimbine and BMY exhibited only weak antagonistic effects. CEC, however, significantly decreased noradrenaline-induced contractions. We conclude that in saphenous vein the contractile response to noradrenaline is mediated predominantly by α_2-adrenoceptors, while in internal mammary artery it is mediated (to a major part) by α_{1B}- and (to a minor part) by α_{1A}-adrenoceptors.

Keywords Human saphenous vein · Human internal mammary artery · Noradrenaline · α-Adrenoceptor subtype

C. Giessler · S. Dhein · O.-E. Brodde (✉)
Institute of Pharmacology, University of Halle,
Magdeburger Strasse 4, 06097 Halle/Saale, Germany
e-mail: otto-erich.brodde@medizin.uni-halle.de,
Tel.: +49-345-5571773, Fax: +49-345-5571835

T. Wangemann · R.-E. Silber
Clinic for Cardiothoracic Surgery, University of Halle,
Halle, Germany

O.-E. Brodde
Institute of Pathophysiology and Department of Nephrology,
University of Essen, School of Medicine,
Hufelandstr. 55, 45147 Essen, Germany

Introduction

Coronary artery bypass grafting is one important therapy for coronary heart disease. Typically, human saphenous veins or internal mammary arteries are used as bypass material. However, a clinical problem encountered with coronary artery bypass is development of vasospasms in the graft, which might be due to 5-hydroxytryptamine released from activated platelets, to catecholamines or to other factors. Thus, information on the receptors involved in these vasoconstrictions is necessary to provide strategies for prevention and therapy of these spasms. In order to allow a comparison of the two vessels, it is also necessary to study both vessels in the same bioassay system. While there are several studies on α-adrenoceptors in human saphenous veins (Docherty and Hyland 1985; Steen et al. 1986; Beckeringh et al. 1987; Gavin et al. 1997; Rizzo et al. 2001) or in internal mammary arteries (Bevilacqua et al. 1991; He et al. 1993; Rudner et al. 1999), there is to our knowledge only one comparative study in both vessel types (Weinstein et al. 1989). Thus, we decided to study noradrenaline-elicited contractions in rings of both human saphenous veins and human internal mammary arteries and to determine the α-adrenoceptor subtype(s) involved.

Materials and methods

All experiments were performed on vascular rings from human saphenous veins or mammary arteries obtained during coronary artery bypass from the Clinic for Cardiothoracic Surgery, University of Halle, Germany. The experiments were approved by the local ethical committee and were carried out in accordance to the German laws for clinical studies.

Patients and surgical procedure. We investigated saphenous veins from 23 patients without apparent heart failure undergoing coronary artery bypass grafting (age: 65.2±1.8 years; 19 men, 4 women; body weight: 82.4±3.4 kg; NYHA [angina pectoris]: II–III) and internal mammary arteries from 24 patients (age: 64±1.8 years; 14 men, 10 women; body weight: 81.5±2.9 kg; NYHA [angina pectoris]: II–III).

None of the patients had been treated with sympathomimetics for at least 3 weeks before surgery. However, patients were treated with nitrates, calcium antagonists, β-adrenoceptor antagonists and angiotensin-converting enzyme inhibitors (alone or in combination) and statins for lipid lowering.

Premedication typically consisted of 2 mg flunitrazepam given orally the evening before or on the morning of surgery. Anaesthesia during operation was performed under modified neuroleptic anaesthesia with flunitrazepam and fentanyl and controlled ventilation with 1:1 mixture of oxygen and N_2O with addition of up to 1.0% (v.v.) isoflurane. Pancuronium was used for muscle relaxation. Saphenous veins and internal mammary arteries were obtained during cardiopulmonary bypass. Immediately after excision, all specimens were placed in autologous heparinized whole blood (Zerkowski et al. 1993) and kept overnight in the refrigerator.

Measurement of contractile force. The preparation of vascular rings was performed in oxygenated Krebs-Henseleit solution (composition see below) at room temperature. Ring preparations (cylinders of 2–4 mm diameter and 3–4 mm length) were placed into oxygenated modified Krebs-Henseleit buffer containing (mM): NaCl 119, KCl 4.75, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, $CaCl_2$ 2.25, D-glucose 10, EDTA 0.03, ascorbic acid 0.1, equilibrated with carbogen at 37°C. Adhering fat and connective tissue were removed. These rings were placed in 10-ml organ baths containing Krebs-Henseleit solution with constant oxygenation (carbogen) at 37°C. The contractile force was measured isometrically using force transducers connected to amplifiers and recorders (Föhr Medical Instruments, Germany). The resting tension of the vessels was adjusted to 9.81 mN and the developed force was recorded via a strain gauge on a Hellige recorder (Hellige, Freiburg, Germany). The strips were allowed to equilibrate for 60 min (bath fluid was replaced every 20 min during this period). Following equilibration contractile response of the preparations to 50 mM KCl was measured. Only preparations that responded adequately to the KCl challenge were used for further experiments. After washout, preparations were contracted by 10^{-6} M noradrenaline (NA) and, after washout, contractions were repeated until stable reproducible contractions were obtained (usually 2–3 times). After careful washout, the cumulative concentration-response curve for NA (10^{-10}–10^{-4} M) was assessed in absence or presence of yohimbine (α_2-adrenoceptor antagonist, 10^{-8}–10^{-6} M), prazosin (α_1-adrenoceptor antagonist, 10^{-9}–10^{-7} M), 5-methyl-urapidil (5-MU, α_{1A}-adrenoceptor antagonist, 10^{-8}–10^{-6} M; Gross et al. 1988; Hanft and Gross 1989), BMY 7378 (α_{1D}-adrenoceptor antagonist, 10^{-7}–10^{-6} M; Goetz et al. 1995) and after pre-treatment with chlorethylclonidine (CEC, irreversible α_{1B}-adrenoceptor antagonist, 3×10^{-5} M, CEC was washed out 30 min before the NA concentration-response curve was assessed; Michel et al. 1993). All experiments were carried out in presence of propranolol (10^{-7} M) and cocaine (10^{-5} M). In order to exclude desensitization phenomena, only one concentration-response curve for NA was obtained on each strip. Antagonists (except CEC, see above) were added 1 h before constructing a concentration-response curve for NA. Effects of antagonists on NA-induced contraction were compared with those obtained simultaneously in a ring not incubated with the antagonist.

Affinities of antagonists for human saphenous vein or internal mammary artery α-adrenoceptors were assessed by Schild-plot analysis (Arunlakshana and Schild 1959) and expressed as pA_2-values. Alternatively – if Schild plots were not possible or revealed slopes significantly less than unity – K_B-values for antagonists were calculated using the formula (Jenkinson et al. 1995):

$$K_B = \frac{[B]}{[CR - 1]} \quad (1)$$

where [B] is the concentration of antagonist used, and CR is the agonist EC_{50} in the presence of antagonist divided by the agonist EC_{50} in the absence of antagonist.

Statistical evaluation. Data given are means ± SEM of *n* experiments. Experimental data were analyzed by computer-supported iterative non-linear regression analysis using the Prism program (GraphPad Software, San Diego, Calif., USA). Sigmoid curves were fitted to the data for NA-induced contraction; in these calculations the bottom of the curves was fixed at 0 (i.e. 0% contraction over basal); the Hill slopes were kept variable.

Statistical significance of differences in maximal contraction evoked by noradrenaline in the absence and presence of CEC was analyzed by paired two-tailed Student's *t*-test. A *P*-value <0.05 was considered to be significant. All statistical calculations were performed with the Prism program.

Chemicals. (-)-Noradrenaline bitartrate, cocaine hydrochloride and (±)-propranolol hydrochloride were purchased from Sigma (Deisenhofen, Germany). 5-Methyl-urapidil hydrochloride, chloroethylclonidine hydrochloride and BMY 7378 dihydrochloride (8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4,5]decane-7,9-dione dihydrochloride) were purchased from Research Biochemicals International (Natick, Mass., USA). All other chemicals were of the highest purity grade commercially available.

Results

Saphenous vein

In rings of human saphenous vein NA (10^{-8}–10^{-4} M) caused concentration-dependent contractions; the EC_{50}-value was 0.18±0.02 μM (Fig. 1a). The α_2-adrenoceptor antagonist yohimbine (10^{-8}–10^{-6} M) caused a concentration-dependent rightward shift of the concentration-response curve for NA without affecting the maximum effect. Schild analysis of these data revealed a pA_2-value for yohimbine of 8.32±0.1 (Fig. 1a).

In contrast to yohimbine, the α_1-adrenoceptor antagonist prazosin (10^{-9}–10^{-7} M) affected the concentration-response curve for NA (Fig. 2a) only marginally; only at higher NA concentrations (>10^{-6} M) a small rightward shift was observed. Similar to prazosin the α_{1A}-adrenoceptor-selective antagonist 5-MU (10^{-8} M and 10^{-7} M; Fig. 3a) and the α_{1D}-adrenoceptor antagonist BMY 7378 (10^{-7} M and 10^{-6} M; Fig. 4a) affected the concentration-response curve for NA only marginally; 10^{-6} M 5-MU, however, caused a significant rightward shift of the NA concentration-response curve; this resulted in a pK_B-value of 7.13±0.22 (Fig. 3a). Chloroethylclonidine (3×10^{-5} M for 30 min) shifted the concentration-response curve for NA to the right and significantly decreased maximum effect (Fig. 4a).

Internal mammary artery

In rings of internal mammary artery NA (10^{-8}–10^{-4} M) caused concentration-dependent contraction; the EC_{50}-value was 0.56±0.04 μM (Fig. 1b). In contrast to saphenous vein, however, yohimbine at 10^{-8} M did not shift the concentration-response curve for NA to the right, but

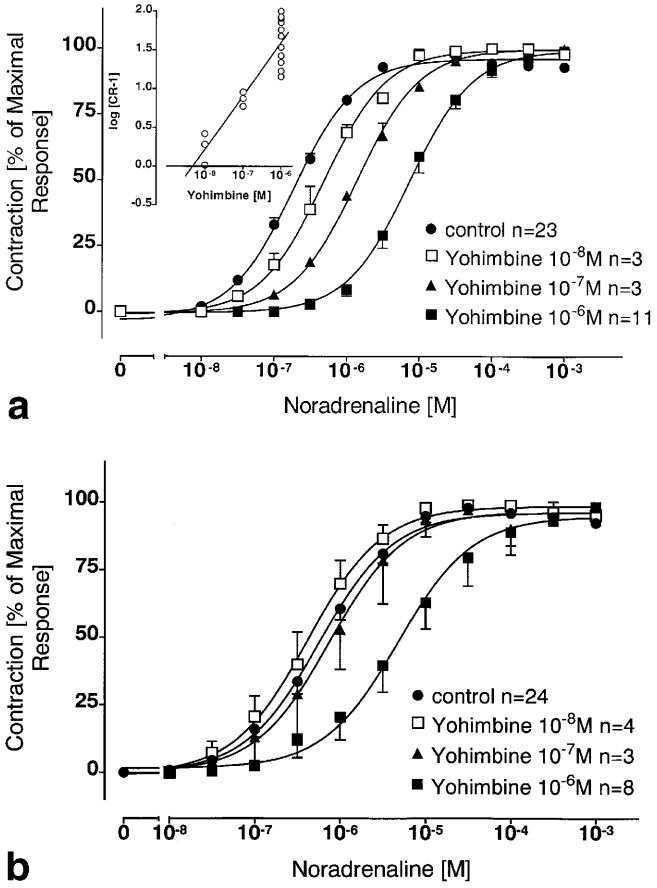

Fig. 1 Effects of yohimbine (10^{-8}–10^{-6} M) on noradrenaline-induced contraction in rings of **a** human saphenous vein and **b** human internal mammary artery. *Ordinates:* noradrenaline-induced contraction in % of maximal response. *Abscissae:* molar concentrations of noradrenaline. The *inset* in **a** shows Schild-plot analysis of the yohimbine antagonism. Means ± SEM; *n*= number of experiments (preparations). Maximal contraction evoked by noradrenaline was 5.9±0.7 mN (*n*=23) in **a** and 5.45±0.6 mN (*n*=24) in **b**

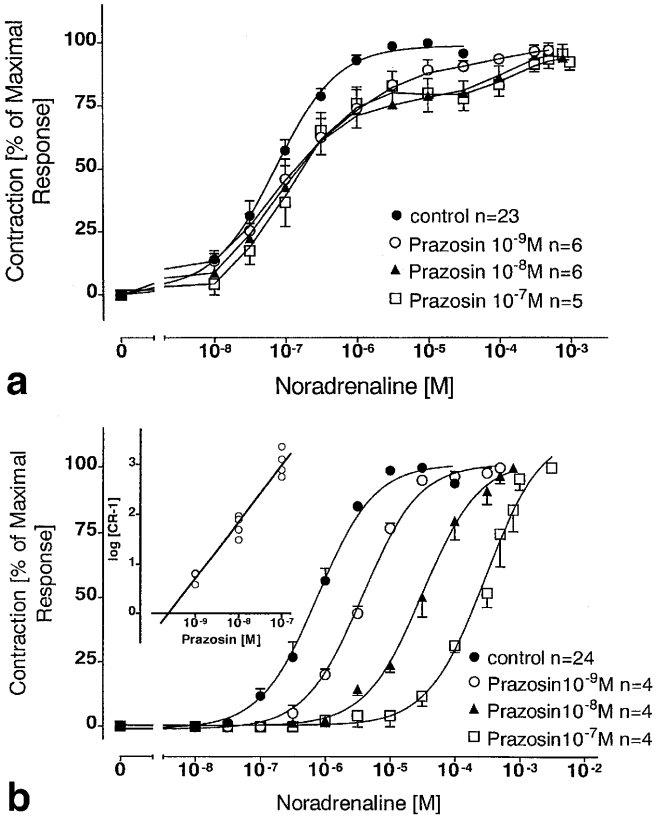

Fig. 2 Effects of prazosin (10^{-9}–10^{-7} M) on noradrenaline-induced contraction in rings of **a** human saphenous vein and **b** human internal mammary artery. *Ordinates:* noradrenaline-induced contraction in % of maximal response. *Abscissae:* molar concentrations of noradrenaline. The *inset* in **b** shows Schild-plot analysis of the prazosin antagonism. Means ± SEM; *n*= number of experiments (preparations)

shifted it slightly to the left (EC_{50}-value decreased significantly to 0.29±0.04 μM). Only at the rather high concentration of 10^{-6} M, yohimbine caused a rightward shift of the NA concentration-response curve; this resulted in a pK_B-value of 6.65±0.27 (Fig. 1b).

On the other hand, prazosin was a potent antagonist of NA-induced contraction of human internal mammary artery (Fig. 2b): Schild-plot analysis of these data revealed a pA_2-value of 9.65±0.09.

5-MU (10^{-7}–10^{-6} M) concentration-dependently shifted the concentration-response curve for NA to the right; however, NA curves in the presence of 10^{-7} M and 3×10^{-7} M were biphasic thus preventing Schild analysis of these data (Fig. 3b). Calculation of pK_B-values according to Jenkinson et al. (1995) revealed pK_B-values of 7.36±0.53 (at 10^{-7} M), 7.49±0.21 (at 3×10^{-7} M) and 7.22±0.27 (at 10^{-6} M). On the other hand, BMY, only at the high concentrations of 3×10^{-7} M and 10^{-6} M, significantly shifted the NA concentration-response curve to the right (Fig. 4b); this resulted in pK_B-values of 7.00±0.15 (at 3×10^{-7} M) and 7.42±0.23 (at 10^{-6} M). CEC (3×10^{-5} M) shifted the concentration-response curve for NA to the right and significantly decreased maximum effect in the internal mammary artery (Fig. 4b).

Discussion

The main finding of this study was that NA-induced contraction is mediated by different α-adrenoceptor subtypes in human saphenous vein and human internal mammary artery, human vascular tissue often used for coronary artery bypass grafting. In saphenous vein the α_2-adrenoceptor antagonist yohimbine was a potent antagonist of NA-induced contraction whereas the α_1-adrenoceptor antagonist prazosin had only marginal effects. In contrast, in internal mammary artery prazosin was a potent antagonist of NA-induced contraction whereas yohimbine showed only marginal effects. Thus, these data clearly demonstrate that in saphenous vein predominantly α_2-adrenoceptors, in internal mammary artery mainly α_1-adrenoceptors mediate NA-induced contraction.

In saphenous vein yohimbine antagonized NA-induced contraction with a pA_2-value of 8.32 which is well in its range of affinity at the α_2-adrenoceptors (Starke 1981;

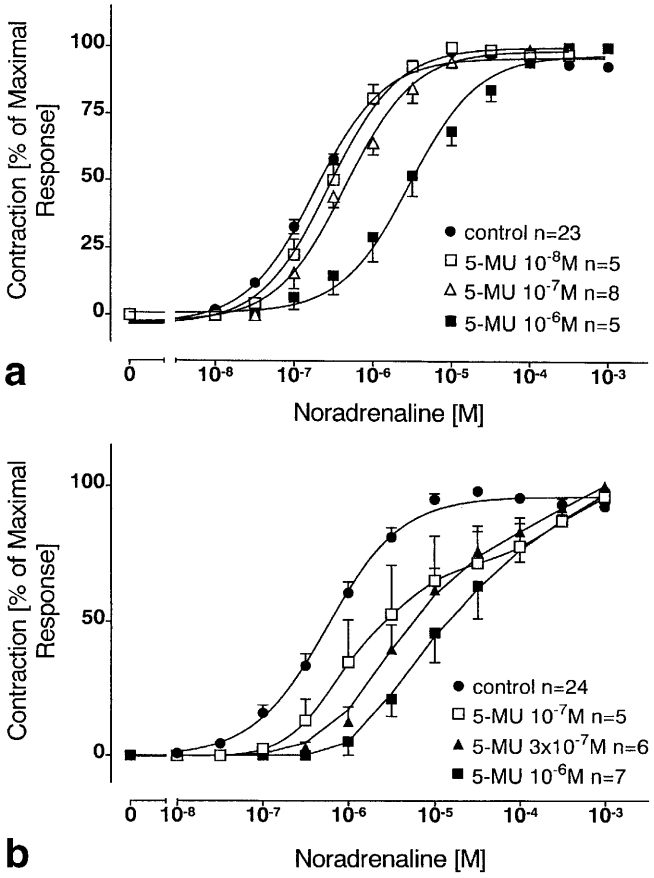

Fig. 3 Effects of 5-methyl-urapidil (*5-MU*; 10^{-8}–10^{-6} M) on noradrenaline-induced contraction in rings of **a** human saphenous vein and **b** human internal mammary artery. *Ordinates:* noradrenaline-induced contraction in % of maximal response. *Abscissae:* molar concentrations of noradrenaline. Means ± SEM; *n*= number of experiments (preparations)

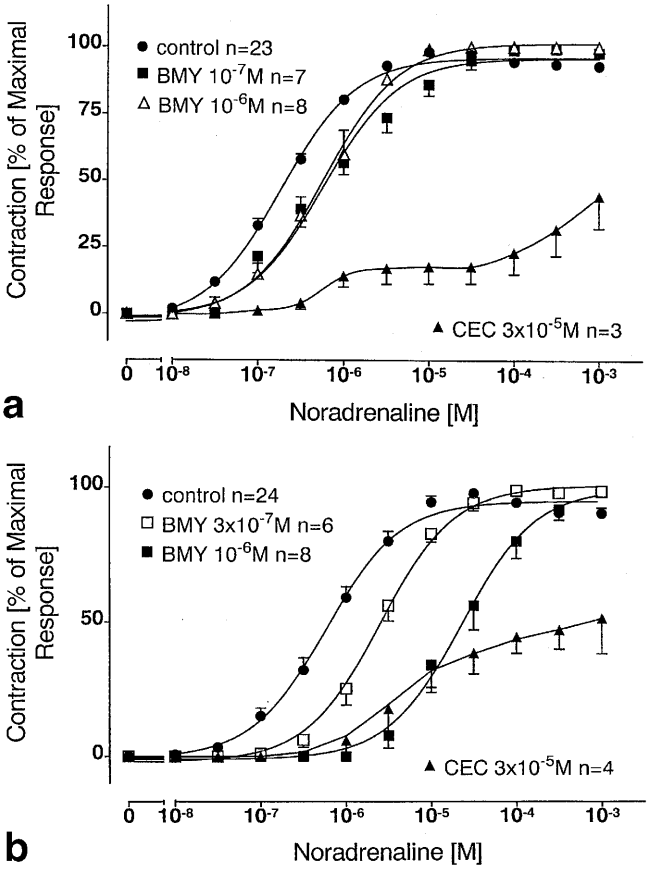

Fig. 4 Effects of BMY 7378 (10^{-7}–10^{-6} M) and of pretreatment with chloroethylclonidine (*CEC*; 3×10^{-5} M for 30 min at 37°C) on noradrenaline-induced contraction in rings of **a** human saphenous vein and **b** human internal mammary artery. *Ordinates:* noradrenaline-induced contraction in % of maximal response. *Abscissae:* molar concentrations of noradrenaline. Means ± SEM; *n*= number of experiments (preparations). Maximal contraction evoked by noradrenaline in the presence of CEC was 2.9±1.0 mN (n=3, P<0.05) in **a** and 2.9±1.6 mN (n=4, P<0.05) in **b**

MacKinnon et al. 1994; Hieble et al. 1995). On the other hand, neither prazosin (10^{-9}–10^{-7} M) nor the α_{1A}-adrenoceptor-selective antagonist 5-MU (10^{-8} M and 10^{-7} M) nor the α_{1D}-adrenoceptor-selective antagonist BMY 7378 (10^{-7} M and 10^{-6} M) exhibited considerable antagonistic activity against NA-induced contraction although they were used in concentrations 10- to 100-fold higher than their affinities at α_1- (prazosin pK_B 8.5–10; Starke 1981; Hieble et al. 1995; Alexander and Peters 1999), α_{1A}- (5-MU pK_B 8.63; Michel et al. 1995) or α_{1D}-adrenoceptors (BMY pK_B 8.2–9.4; Dhein et al. 2001). Accordingly, a significant contribution of α_{1A}- or α_{1D}-adrenoceptors to the contractile action of NA in human saphenous vein is quite unlikely. On the other hand, 5-MU, at the rather high concentration of 10^{-6} M, significantly shifted the concentration-response curve of NA to the right yielding a pK_B-value of 7.13. This pK_B-value is in its range of the affinity at the α_{1B}-adrenoceptor (pK_B 6.93; Michel et al. 1995); thus, this could indicate some interaction with α_{1B}-adrenoceptors. However, the fact that prazosin was not effective (at least at lower NA concentrations) argues against a considerable involvement of α_{1B}-adrenoceptors. It is more likely that at a concentration of 10^{-6} M 5-MU interacts with α_2-adrenoceptors in the human saphenous vein because the affinity of 5-MU at α_2-adrenoceptors is in this range (pK_i-values from 6.1 to 6.9; Hieble et al. 1995; Daniel et al. 1996). Finally, the quite marked antagonistic effect of CEC on NA-induced contraction in the human saphenous vein could also indicate some α_{1B}-adrenoceptor effects; however, CEC is quite active as an antagonist at α_{2A}- or α_{2C}-adrenoceptors; thus, 10 μM CEC (i.e. a concentration three times less than that used in the present study) reduced the number of α_{2A}-adrenoceptors by 37% and that of α_{2C}-adrenoceptors by 53% (Michel et al. 1993). As discussed above, prazosin was not effective in the human saphenous vein; it is, therefore, very likely that the effects of CEC are mediated by inactivation of α_2-adrenoceptors.

Several studies from the literature have consistently shown that in human saphenous vein α_2-adrenoceptors mediate agonist-induced contraction (Docherty and Hyland 1985; Steen et al. 1986; Beckeringh et al. 1987; Weinstein

et al. 1989; Roberts et al. 1992; Smith et al. 1992; Gavin et al. 1997; Rizzo et al. 2001) while controversial data have been published on the existence of α_1-adrenoceptors mediating contraction, with some studies demonstrating their occurrence (Beckeringh et al. 1987; Weinstein et al. 1989; Roberts et al. 1992; Rizzo et al. 2001) while others failed to do so (Steen et al. 1986; Smith et al. 1992; Gavin et al. 1997). Although in our study the contribution of α_1-adrenoceptors appears to be only marginal, we cannot completely exclude it since in the presence of prazosin NA concentration-response curves became biphasic showing a small prazosin antagonism at high NA concentrations.

Studies from the literature have revealed that predominantly α_{2C}-adrenoceptors mediate contraction in human saphenous vein (Gavin et al. 1997; Rizzo et al. 2001). Subtype-selective antagonists for the α_{2A}-, α_{2B}- and α_{2C}-adrenoceptors are not available at present. We, therefore, did not further subclassify the α_2-adrenoceptor subtype present in human saphenous vein; however, the fact that 5-MU exhibited a pK_B-value of 7.13 (very close to its pK_i-value at α_{2C}-adrenoceptors [6.88] determined in radioligand binding studies; Hieble et al. 1995) and CEC (that inactivates α_2-adrenoceptor subtypes with an order of potency: $\alpha_{2C}>\alpha_{2A}>>>\alpha_{2B}$; Michel et al. 1993) markedly reduced NA-induced contraction might be taken as an indication that also in our preparations α_{2C}-adrenoceptors may predominate.

In human internal mammary artery, in contrast to saphenous vein, yohimbine at low concentrations did not antagonize NA-induced contraction. It did so only at the rather high concentration of 10^{-6} M yielding a pK_B-value of 6.6 that is about 100 times higher than its affinity at the α_2-adrenoceptor (see above). On the other hand, prazosin antagonized NA-induced contraction in the internal mammary artery with high potency (pA_2-value 9.65) indicating that in human internal mammary artery predominantly α_1-adrenoceptors mediate NA-induced contraction, in agreement with data from the literature (Weinstein et al. 1989; Bevilacqua et al. 1991; He et al. 1993; Rudner et al. 1999).

For further subclassification of the α_1-adrenoceptor subtype we used the rather subtype-selective antagonists 5-MU (α_{1A}), BMY 7378 (α_{1D}) and CEC (α_{1B}). 5-MU (10^{-7}–10^{-6} M) concentration-dependently shifted the concentration-response curve for noradrenaline to the right; however, noradrenaline concentration-response curves in the presence of 10^{-7} M and 3×10^{-7} M 5-MU were biphasic indicating interaction with more than one α_1-adrenoceptor subtype. From these experiments pK_B-values for 5-MU were calculated ranging from 7.2 to 7.5 which are between its affinity at α_{1A}- (8.63; Michel et al. 1995) and α_{1B}- and α_{1D}-adrenoceptors (6.97 and 7.31; Michel et al. 1995). Involvement of α_{1D}-adrenoceptors seems to be unlikely because BMY 7378 exhibited only at the rather high concentrations of 3×10^{-7} M and 10^{-6} M antagonistic effects against NA-induced contraction with pK_B-values of 7.0–7.4 which are by far lower than the affinity of BMY 7378 at the α_{1D}-adrenoceptor (8.2–9.4; Dhein et al. 2001). On the other hand, CEC (30 μM, i.e. a concentration about 30 times higher than its EC_{50}-value for the α_{1B}-adrenoceptor-alkylating effect; Michel et al. 1993) markedly decreased NA-induced contraction in internal mammary artery which is in favor of the idea that α_{1B}-adrenoceptors are involved. Taken together, the fact that in the presence of 5-MU NA concentration-response curves were biphasic indicating interaction with more than one α_1-adrenoceptor subtype, the pK_B-values of 7.2–7.5 for 5-MU, the rather low potency of BMY 7378 and the marked effect of CEC are in favor of the idea that, in the human internal mammary artery, NA-induced contraction is mediated (to a major part) by α_{1B}-adrenoceptors and (to a minor part) by α_{1A}-adrenoceptors; α_{1D}-adrenoceptors appear not to be involved. These data are in good agreement with recently published data from Rudner et al. (1999) who observed that, in human internal mammary artery, phenylephrine-induced contraction is mediated by α_{1A}- and α_{1B}-adrenoceptors; α_{1D}-adrenoceptors were not involved. It is interesting to note that this group described that in human internal mammary artery α_{1B}-adrenoceptor expression increased with increasing age of the patients. Thus, in patients <55 years of age α_{1A}-adrenoceptors were the major subtype, whereas in patients >65 years of age α_{1B}-adrenoceptors were the major subtype (Rudner et al. 1999). In our study patients were about 65 years old; this might explain why in our study mainly α_{1B}-adrenoceptors mediate NA-induced contraction in the internal mammary artery.

In conclusion: NA-induced contraction of the two common bypass grafts for coronary artery bypass grafting, saphenous vein and internal mammary artery, is brought about by different α-adrenoceptor subtypes. While in saphenous vein NA-induced contraction is mediated predominantly by α_2-adrenoceptors (α_{2C}-adrenoceptors?), in internal mammary artery it is mediated by α_{1B}- and α_{1A}-adrenoceptors whereby it appears to be dependent on the age of the patients which subtype predominates (Rudner et al. 1999). Thus, the data of this study, i.e. a more detailed characterization of the α-adrenoceptor subtypes involved in NA-induced contraction, might be helpful for a better understanding of the pathophysiology of vasospasms of coronary artery bypass grafts.

Acknowledgements This work was supported by a grant of the Deutsche Forschungsgemeinschaft (SFB 598-02 to O.-E.B.).

References

Alexander SPH, Peters JA (1999) Trends Pharmacol Sci receptor and ion channel nomenclature supplement, 10th edn. Elsevier Trends Journals, Cambridge, pp 11–14

Arunlakshana O, Schild HO (1959) Some quantitative uses of antagonists. Br J Pharmacol 14:48–58

Beckeringh JJ, Zerkowski H-R, Rohm N, Brodde O-E (1987) α-Adrenoceptors in preparations of the human saphenous vein. J Cardiovasc Pharmacol 10 [Suppl 4]:S91–S93

Bevilacqua M, Vago T, Monopoli A, Baldi G, Forlani A, Antona C, Biglioli P, Scrofani R, Norbiato G (1991) α_1-Adrenoceptor subtype mediates noradrenaline induced contraction of the human internal mammary artery: radioligand and functional studies. Cardiovasc Res 25:290–294

Daniel EE, Low AM, Gaspar V, Lu-Chao H, Green J, Akrong J, Duerksen S, Soyka C, Chen CK, Boyd J, Kwan CY (1996) Unusual α-adrenoceptor subtype in canine saphenous vein: comparison to mesenteric vein. Br J Pharmacol 117:1535–1543

Dhein S, Giessler C, Becker K, Pönicke K, Brodde O-E (2001) Inositol-phosphate formation in thoracic and abdominal rat aorta following $G_{q/11}$-coupled receptor stimulation. Naunyn Schmiedebergs Arch Pharmacol 363:322–329

Docherty JR, Hyland L (1985) Evidence for neuroeffector transmission through postjunctional α_2-adrenoceptors in human saphenous vein. Br J Pharmacol 84:573–576

Gavin KT, Colgan MP, Moore D, Shanik G, Docherty JR (1997) $Alpha_{2C}$-adrenoceptors mediate contractile responses to noradrenaline in the human saphenous vein. Naunyn Schmiedebergs Arch Pharmacol 355:406–411

Goetz AS, King HK, Ward SDC, True TA, Rimele TJ, Saussy DL Jr (1995) BMY 7378 is a selective antagonist of the D subtype of α_1-adrenoceptors. Eur J Pharmacol 272:R5–R6

Gross G, Hanft G, Rugevics C (1988) 5-Methylurapidil discriminates between subtypes of the α_1-adrenoceptor. Eur J Pharmacol 151:333–335

Hanft G, Gross G (1989) Subclassification of α_1-adrenoceptor recognition sites by urapidil derivatives and other selective antagonists. Br J Pharmacol 97:691–700

He GW, Shaw J, Hughes CF, Yang CQ, Thomson DS, McCaughan B, Hendle PN, Baird DK (1993) Predominant $alpha_1$-adrenoceptor-mediated contraction in the human internal mammary artery. J Cardiovasc Pharmacol 21:256–263

Hieble JP, Bondinell WE, Ruffolo RR (1995) α- and β-Adrenoceptors: from the gene to the clinic. 1. Molecular biology and adrenoceptor subclassification. J Med Chem 38:3415–3444

Jenkinson DH, Barnard EA, Hoyer D, Humphrey PPA, Leff P, Shankley NP (1995) International Union of Pharmacology committee on receptor nomenclature and drug classification. IX. Recommendations on terms and symbols in quantitative pharmacology. Pharmacol Rev 47:255–266

MacKinnon AC, Spedding M, Brown CM (1994) α_2-Adrenoceptors: more subtypes but fewer functional differences. Trends Pharmacol Sci 15:119–123

Michel MC, Kerker J, Branchek TA, Forray C (1993) Selective irreversible binding of chloroethylclonidine at α_1- and α_2-adrenoceptor subtypes. Mol Pharmacol 44:1165–1170

Michel MC, Kenny B, Schwinn DA (1995) Classification of α_1-adrenoceptor subtypes. Naunyn Schmiedebergs Arch Pharmacol 352:1–10

Rizzo CA, Ruck LM, Corboz MR, Umland SP, Wan Y, Shah H, Jakway J, Cheng L, McCormick K, Egan RW, Hey JA (2001) Postjunctional α_{2C}-adrenoceptor contractility in human saphenous vein. Eur J Pharmacol 413:263–269

Roberts SP, Kelly J, Cawthorne MA, Sennitt MV (1992) SK&F 104078, a post-junctionally selective α_2-adrenoceptor antagonist in the human saphenous vein in vitro. Naunyn Schmiedebergs Arch Pharmacol 345:327–332

Rudner XL, Berkowitz DE, Booth JV, Funk BL, Cozart KL, D'Amico EB, El-Moalem H, Page SO, Richardson CD, Winters B, Marucci L, Schwinn DA (1999) Subtype specific regulation of human vascular alpha(1)-adrenergic receptors by vessel bed and age. Circulation 100:2336–2343

Smith K, Connaughton S, Docherty JR (1992) Investigations of the subtype of α_2-adrenoceptor mediating contractions of the human saphenous vein. Br J Pharmacol 106:447–451

Starke K (1981) α-Adrenoceptor subclassification. Rev Physiol Biochem Pharmacol 88:199–236

Steen S, Castenfors J, Sjoberg T, Skarby T, Andersson KE, Norgen L (1986) Effects of alpha-adrenoceptor subtype-selective antagonists on the human saphenous vein. Acta Physiol Scand 126:15–19

Weinstein JS, Grossman W, Weintraub RM, Thurer RL, Johnson RG, Morgan KG (1989) Differences in alpha-adrenergic responsiveness between human internal mammary arteries and saphenous veins. Circulation 79:1264–1270

Zerkowski HR, Knocks M, Konerding MA, Doetsch N, Roth G, Hakim K, Reidemeister JC (1993) Endothelial damage of the venous graft in CABG. Influence of solutions used for storage and rinsing on endothelial function. Eur J Cardiothorac Surg 7:376–382