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Adrenoceptors Mediating the Cardiovascular and Metabolic Effects of α-Methylnoradrenaline in Humans[1]

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ABSTRACT

α-Methylnoradrenaline is a widely used tool to study α_2-adrenoceptor function, but its selectivity for this receptor has not been validated in humans in vivo. To characterize the adrenoceptors mediating cardiovascular and metabolic effects of α-methylnoradrenaline in humans, we have performed graded i.v. infusions of α-methylnoradrenaline in a randomized, placebo-controlled crossover study in six young, healthy males in the absence and presence of the β-adrenoceptor antagonist propranolol, the α_1-adrenoceptor antagonist doxazosin, and the α_2-adrenoceptor antagonist yohimbine. α-Methylnoradrenaline dose-dependently increased heart rate, systolic blood pressure, cardiac output, blood glucose, serum insulin, free fatty acids, and gastrin, shortened the duration of heart rate-corrected electromechanical systole, and decreased diastolic blood pressure, total peripheral resistance, and plasma noradrenaline. Propranolol completely reversed the rise in heart rate and cardiac output, the fall in peripheral resistance, the shortening of electromechanical systole, and the rise in insulin; it blunted the increase in free fatty acids and gastrin. Yohimbine did not significantly influence most parameters but significantly potentiated the rise in insulin, blunted the increase in glucose, and prevented the fall in noradrenaline. Doxazosin was largely without effect on any of these parameters. We conclude that i.v. administered α-methylnoradrenaline primarily acts on β-adrenoceptors in the human cardiovascular and metabolic system, but an α_2-adrenergic component of the response is detectable for changes of plasma noradrenaline, blood glucose, and serum insulin. Whereas α-methylnoradrenaline is selective for α_2- over α_1-adrenoceptors, β-adrenoceptor blockade is required to unmask α-adrenoceptor-mediated vasoconstriction.

α_2-Adrenoceptors mediate many of the cardiovascular, metabolic, and endocrine functions of the endogenous catecholamines noradrenaline and adrenaline (Ruffolo et al., 1993). The quantitative responsiveness to α_2-adrenoceptor stimulation can vary considerably between and within individuals. Such variation is partly related to receptor regulation phenomena that have been demonstrated, e.g., in essential hypertension (Insel, 1996) and end-stage renal disease (Daul et al., 1987). Moreover, variability of α_2-adrenoceptor responsiveness also may relate to polymorphisms in the genes encoding these receptors (Freeman et al., 1995; Svetkey et al., 1996).

Because many physiological parameters are under a mixed control by multiple adrenoceptor types, in vivo studies on genetic or disease-induced alterations of human α_2-adrenoceptors require the administration of selective exogenous agonists. In this regard, most previous studies have relied on clonidine, azepexole (also known as B-HT 933), and α-methylnoradrenaline. The systemic use of clonidine is complicated by several factors. First, clonidine has central effects, e.g., blood pressure lowering, which may, at least partly, occur independent of α_2-adrenoceptors (Ernsberger and Haxhiu, 1997). Second, clonidine is only a partial agonist at α_2-adrenoceptors and may, in some cases, even act as an antagonist (Michel et al., 1989). Third, the selectivity of clonidine for α_2- over α_1-adrenoceptors is poor (Blöchl-Daum et al., 1991). Azepexole has been studied less intensively, but many of the above problems may apply because it is structurally related to clonidine (Ernsberger et al., 1987). In contrast, α-methylnoradrenaline is a catecholamine derivative; therefore, it is unlikely to cross the blood-brain barrier, and central effects have not been reported for this compound after systemic administration. In in vitro studies α-methylnoradrenaline consistently has been found to be selective for α_2- over α_1-adrenoceptors with selectivity factors ranging between 8- and 300-fold (Ruffolo et al., 1988). Therefore, α-methylnoradrenaline infusions have been used by several investigators to study human α_2-adrenoceptor function in vivo (FitzGerald et al., 1981; Elliott and Reid, 1983; Murphy et al., 1984; Schäfers et al., 1990; MacGilchrist et al., 1991; Krum et al., 1992). On the other hand, α-methylnoradrenaline has more

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ABBREVIATIONS: CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; QS_2c, heart rate-corrected duration of the electromechanical systole; TPR, total peripheral resistance.

pronounced effects on systolic than diastolic blood pressure (DBP) (Murphy et al., 1984; Schäfers et al., 1990), which is inconsistent with a claimed α_2-adrenoceptor-mediated vasoconstriction and points to a possible involvement of cardiac β-adrenoceptors.

The present study was designed to validate the use of α-methylnoradrenaline as a tool to study α_2-adrenoceptor responsiveness in human in vivo. Therefore, we have identified the adrenoceptor type mediating α-methylnoradrenaline responses on cardiac and vascular function and circulating concentrations of noradrenaline, free fatty acids, glucose, insulin, gastrin, and growth hormone by using selective antagonists. Additionally, we have determined the reproducibility of various hemodynamic and metabolic parameters that are under adrenergic control.

Materials and Methods

Study Protocol. Six young male volunteers (mean age, 25.6 ± 3.8 years; mean weight, 71.6 ± 4.7 kg) participated in this placebo-controlled, randomized, single-blind study after having given informed, written consent. All subjects were drug-free and were judged to be healthy on the basis of medical history, physical examination, electrocardiogram, and routine laboratory screening. The study protocol had been approved by the Ethics Committee of the University of Essen Medical School and was in accordance with the principles laid down in the Declaration of Helsinki.

We examined the cardiovascular and metabolic effects of α-methylnoradrenaline administered by i.v. infusion in four incremental dose steps of 0.1, 0.2, 0.4, and 0.8 $\mu g \times kg^{-1} \times min^{-1}$ for 10 min at each dose level. For safety reasons, infusions of α-methylnoradrenaline were terminated if systolic blood pressure rose by more than 50 mm Hg, DBP rose by more than 30 mm Hg, or heart rate increased by more than 50 beats/min (bpm) or fell (with propranolol pretreatment) below 40 bpm. During each study day i.v. infusions of α-methylnoradrenaline were performed after subjects had been given the following pretreatments: 1) placebo, given as 0.9% NaCl, 10 ml of loading dose, followed by a slow i.v. maintenance infusion, 2) α_1-adrenoceptor blockade with 2 mg of doxazosin p.o. (Cardular; Pfizer, Karlsruhe, Germany), 3) α_2-adrenoceptor blockade with yohimbine, given as a loading dose of 32 $\mu g \times kg^{-1}$ by slow i.v. injection over 10 min followed by an i.v. maintenance dose of 1 $\mu g \times kg^{-1} \times min^{-1}$, and 4) β-adrenoceptor blockade with propranolol (Dociton; Zeneca GmbH, Plankstadt, Germany) given as an i.v. loading dose of 62.5 $\mu g \times kg^{-1}$ over 10 min followed by a maintenance infusion of 0.45 $\mu g \times kg^{-1} \times min^{-1}$. For all i.v. treatments the infusions were started immediately after the administration of the loading dose and were maintained until the end of the α-methylnoradrenaline infusion. For all treatments the maintenance infusion was infused at an identical infusion rate of 20 ml $\times h^{-1}$. The chosen doses of propranolol and doxazosin have been shown previously in young healthy volunteers to suppress the effects of i.v. isoprenaline on blood pressure and heart rate and to abolish the effect of i.v. noradrenaline on DBP, respectively (Schäfers et al., 1997; Werner et al., 1997). The chosen dose of yohimbine effectively blocks α_2-adrenoceptors because it elevates resting blood pressure, enhances the blood pressure response to an isometric hand-grip test, and antagonizes the adrenaline-induced α_2-adrenoceptor-mediated aggregation of human platelets ex vivo (Goldberg et al., 1983); however, the exact degree of α_2-adrenoceptor blockade by this yohimbine dose is not known. The i.v. loading dose injections of placebo, yohimbine, and propranolol were administered 45 min before the start of the α-methylnoradrenaline infusion. The doxazosin tablet was given 120 min before the commencement of i.v. α-methylnoradrenaline so that the agonist infusion was done during the time of maximal plasma levels of doxazosin (Vincent et al., 1983).

During pretreatment with either placebo, doxazosin, or yohimbine, the preset safety limit of an increase in systolic blood pressure of 50 mm Hg was reached in most subjects during the highest dose of 0.8 $\mu g \times kg^{-1} \times min^{-1}$ so that infusions of α-methylnoradrenaline were terminated. With propranolol pretreatment, infusion of α-methylnoradrenaline resulted in an increase in DBP (see below) with a secondary reflex bradycardia. Therefore, with propranolol only two subjects received the dose of 0.8 $\mu g \times kg^{-1} \times min^{-1}$ and only three subjects completed the dose of 0.4 $\mu g \times kg^{-1} \times min^{-1}$. For these reasons ANOVA for the comparison between placebo and doxazosin and placebo and yohimbine, respectively, was restricted to the dose levels of 0.1, 0.2, and 0.4 $\mu g \times kg^{-1} \times min^{-1}$, and, for the comparison between placebo and propranolol, ANOVA was restricted to the doses of 0.1 and 0.2 $\mu g \times kg^{-1} \times min^{-1}$ only. Accordingly, all figures are restricted to the first three dose levels from 0.1 to 0.4 $\mu g \times kg^{-1} \times min^{-1}$.

To assess the between-day variability of the cardiovascular and metabolic responses induced by an i.v. infusion of α-methylnoradrenaline, placebo was administered on two different study days so that each subject participated in a total of 5 study days that were at least 1 week apart. Treatments were allocated randomly with the two placebo days always separated by 2 weeks.

Hemodynamic Measurements. Hemodynamics were assessed noninvasively with direct measurements of heart rate (HR), blood pressure, systolic time intervals, transthoracic impedance, and pulse transmission time. Stroke volume, cardiac output (CO), total peripheral resistance (TPR), and pulse-wave velocity were calculated from the directly measured parameters. For analysis purposes, TPR and DBP were chosen as the primary parameters for vasoconstrictor tone and pulse-wave velocity was chosen as the parameter for vascular compliance, whereas CO, stroke volume, systolic time intervals, and HR were used as the primary parameters of cardiac function, respectively. Blood pressure (mm Hg) was measured with a standard mercury sphygmomanometer, with the disappearance of Korotkow's sound defined as DBP. Systolic time intervals were measured according to standard techniques (Lewis et al., 1977; Li and Belz, 1993) from simultaneous recordings of an electrocardiographic lead, a phonocardiogram, and a carotid pulse tracing at high paper speed (100 mm $\times s^{-1}$) using a Siemens-Cardirex multichannel ink jet recorder (Siemens Medizintechnik, Erlangen, Germany) as described previously (Schäfers et al., 1994, 1997). From these recordings we determined the duration of the RR-interval, i.e. the duration between two R-waves of the electrocardiogram, from which HR was calculated, the duration of electromechanical systole, and the duration of left ventricular ejection time. The duration of the pre-ejection period was calculated by subtraction of left ventricular ejection time from electromechanical systole. The duration of the electromechanical systole was corrected for HR to yield QS_2c (Schäfers et al., 1994). Pulse transmission time was determined noninvasively from pressure tracings over the carotid and femoral artery as described previously (Breithaupt-Grögler et al., 1997). Aortic pulse-wave velocity then was calculated as the ratio between the distance traveled by the pulse wave and pulse transmission time (Breithaupt-Grögler et al., 1997). Stroke volume (ml) was measured by impedance cardiography, applying the standard approach with circular tape electrodes and graphical signal analysis according to Kubicek's equation (Kubicek et al., 1966). A "Kardio-Dynagraph" was used to record changes in transthoracic impedance (Heinz Diefenbach Elektromedizin, Frankfurt, Germany). CO ($l \times min^{-1}$) was calculated as CO = HR × stroke volume/1000. TPR (dyne $\times s \times cm^{-5}$) was calculated as mean arterial pressure divided by CO × 80, where mean arterial pressure was defined as DBP plus one-third of the pulse pressure.

Baseline measurements of hemodynamic parameters were performed after 30 min of supine rest (baseline 1 recordings). Immediately before the start of the α-methylnoradrenaline infusion another measurement was performed to determine the effects of the antagonist treatments; these values also served as baseline for the subsequent infusion of α-methylnoradrenaline (baseline 2 recordings).

Blood pressure was measured five times each at baseline, immediately before α-methylnoradrenaline infusion, and during the last 5 min of each dose step of the agonist infusion, i.e., throughout minute 5 to 10. Recordings of systolic time intervals, transthoracic impedance, and pulse transmission time were always performed after the last blood pressure measurement. At each time point five cardiac cycles were analyzed, and the mean of these five cycles and of the five blood pressure recordings was taken for the analysis of the dose-response curve.

Neurohumoral Measurements. At baseline 1 and 2 and at the end of the 0.1- and 0.4-$\mu g \times kg^{-1} \times min^{-1}$ doses of the α-methylnoradrenaline infusion, blood was drawn from an antecubital vein for the measurement of blood glucose, plasma concentrations of noradrenaline and adrenaline, gastrin, free fatty acids, and serum concentrations of insulin and growth hormone. Plasma catecholamines were analyzed by HPLC with electrochemical detection; measurements of concentrations of free fatty acids, insulin, gastrin, and growth hormone were performed with commercially available kits obtained from Wako (Neuss, Germany), Biochem Immunosystems (Freiburg, Germany), IBL (Hamburg, Germany), and Nichols Institute (San Juan Capistrano, CA), respectively.

Chemicals. α-Methylnoradrenaline was obtained from Research Biochemical International (Natick, MA) and prepared by our hospital pharmacy as a sterile stock solution of 1 $mg \times ml^{-1}$ in physiological saline using sodium pyrophosphate as preservative. The α-methylnoradrenaline stock solution was stable for at least 2 weeks with recovery rates of 95 to 99%. The solutions for i.v. administration were freshly prepared on each study day by dilution in 0.9% saline. Yohimbine was obtained from Caelo (Hilden, Germany) and prepared as a stock solution of 2 $mg \times ml^{-1}$ in 0.9% saline by our hospital pharmacy. Solutions for i.v. administration were freshly prepared on each study day.

Data Analysis. The intraday variability of test parameters under resting conditions was assessed by the coefficient of variation of a total of six measurements obtained at regular intervals over a period of 75 min during the first placebo day within each subject. The interday variability of resting parameters was assessed by calculation of the coefficient of variation of the baseline 1 measurements, i.e., the baseline after 30 min of complete rest immediately before administration of the antagonists, of the 5 study days.

Because there were only 2 placebo days, calculation of a coefficient of variation was not meaningful for calculation of the interstudy-day reproducibility of α-methylnoradrenaline responses. Therefore, this variability was assessed by calculating the mean difference between the responses to 0.4 $\mu g \times kg^{-1} \times min^{-1}$ α-methylnoradrenaline during the two placebo days ± the S.D. of this mean difference. Additionally, the responses during the 2 placebo days were compared by paired t test.

The antagonist-induced alterations of baseline parameters were compared with the mean alterations of both placebo days by paired, two-tailed t tests. Possible effects of antagonists on the α-methylnoradrenaline-induced changes were analyzed by two-way ANOVA of the entire dose-response curve range from 0.1 to 0.4 $\mu g \times kg^{-1} \times min^{-1}$, comparing each antagonist treatment against placebo. Multiple comparison corrections for the three different treatments (doxazosin, propranolol, and yohimbine) were not performed; therefore, the resulting P values are to be interpreted in a descriptive manner. $P < .05$ (two-tailed) was considered statistically significant. All quoted P values for comparison by ANOVA refer to main treatment effects. Serum insulin data during α-methylnoradrenaline were log-transformed before statistical analysis to achieve homogeneity of variances. All values are shown as mean ± S.E.M. if not stated otherwise.

Results

Data Reproducibility. Under supine resting conditions, the intraday coefficient of variation for cardiovascular parameters ranged from 0.7% for QS_2c to 6.6% for TPR (Table 1). Coefficients of variation for intraday variability were not calculated for the hormonal and metabolic parameters because only two measurements were available for each study day. The interday coefficient of variation for the baseline 1 measurements of the five study days ranged from 1.2% for QS_2c to 6.9% for cardiac output (Table 1). The interday coefficient of variation for the metabolic and hormonal parameters generally were larger, ranging from 11.8% for glucose to 41.5% for noradrenaline (Table 1).

The variability of the agonist-induced changes in hemodynamic, hormonal, and metabolic parameters was assessed by a comparison of the data obtained with 0.4 $\mu g \times kg^{-1} \times min^{-1}$ α-methylnoradrenaline on the 2 placebo days (Table

TABLE 1
Intra- and interday variability of cardiovascular, metabolic, and hormonal parameters under resting conditions and during α-methylnoradrenaline infusion

	Resting Intraday Variability	Resting Interday Variability	Interday Variability of α-Methylnoradrenaline Response
	%	%	
Systolic blood pressure	1.2	1.7	1.8 ± 3.6 mm Hg
DBP	2.0	2.5	2.2 ± 9.1 mm Hg
Mean arterial pressure	1.3	1.7	−0.5 ± 5.6 mm Hg
HR	3.0	5.7	−0.6 ± 2.1 min^{-1}
QS_2	0.8	1.6	−2.5 ± 8.5 ms
QS_2c	0.7	1.2	−2.8 ± 9.6 ms
Left ventricular ejection time	1.5	2.2	−3.8 ± 7.4 ms
Pre-ejection period	4.2	3.2	1.3 ± 9.8 ms
Stroke volume	5.5	6.7	6.3 ± 6.9 ml
CO	5.8	6.9	0.4 ± 0.4 $l \times min^{-1}$
TPR	6.6	6.8	−47 ± 161 dyne $\times s^{-1} \times cm^{-5}$
Pulse-wave velocity	3.8	6.1	−0.3 ± 0.5 $m \times s^{-1}$
Noradrenaline		41.5	−10 ± 49 pg $\times ml^{-1}$
Glucose		11.8	−6.9 ± 14.4 mg $\times dl^{-1}$
Insulin		39.7	−1.6 ± 2.7 μU $\times ml^{-1}$
Free fatty acids		36.5	2.3 ± 7.3 mg $\times dl^{-1}$
Gastrin		10.3	−2.8 ± 20.7 pg $\times ml^{-1}$

The variability of resting parameters is given as coefficient of variation (%) as calculated from six and five measurements in each subject for intra- and interday variability, respectively. The variability of α-methylnoradrenaline responses is given as the mean difference between the response on the first and second placebo day ± S.D.; these values are based on the comparison of the responses observed at the 0.4 $\mu g \times kg^{-1} \times min^{-1}$ dose during the 2 placebo days. All values are based on six subjects being studied. QS_2 and QS_2c, duration of electromechanical systole and its heart rate-corrected form.

1). There was no significant difference between the 2 placebo days in the response to α-methylnoradrenaline for any of the parameters. For example, the mean differences of QS_2 and plasma noradrenaline were −2.5 ± 8.5 ms and −10 ± 49 pg × ml^{-1}, respectively.

Antagonist Effects on Baseline Parameters. Baseline 1 measurements, i.e., values after 30 min of supine rest immediately before administration of the study treatments, are shown in Table 2. On the placebo days, none of the parameters was altered significantly at baseline 2, i.e., relative to baseline 1 (data not shown). The α_1-adrenoceptor antagonist, doxazosin, did not cause statistically significant changes in resting hemodynamics or hormonal and metabolic parameters (Table 2). In contrast, the α_2-adrenoceptor antagonist, yohimbine, significantly increased systolic blood pressure (10.3 mm Hg), pulse-wave velocity (0.71 m × s^{-1}), HR (4.6 bpm), plasma noradrenaline (121 pg × ml^{-1}), and serum insulin (2.2 μU × ml^{-1}) and shortened QS_2c (8.1 ms). The β-adrenoceptor antagonist, propranolol, significantly lowered heart rate (4.7 bpm) and systolic blood pressure (1.5 mm Hg). This was associated with a prolongation of pre-ejection period, but this difference failed to reach statistical significance with the given number of observations. None of the antagonists affected baseline values for free fatty acids or gastrin (Table 2). For plasma adrenaline and serum growth hormone 46 and 64% of all baseline measurements were below the limits of detection of 10 pg × ml^{-1} and 0.5 ng × ml^{-1}, respectively. Therefore, the influence of adrenoceptor antagonists on these parameters was not analyzed.

Antagonist Effects on α-Methylnoradrenaline-Induced Changes. Intravenous infusion of α-methylnoradrenaline dose-dependently increased HR (Fig. 1), systolic blood pressure (Fig. 2), pulse pressure (data not shown), pulse-wave velocity (data not shown), and CO (Fig. 3); shortened QS_2c (Fig. 4) and pre-ejection period (data not shown); and reduced DBP (Fig. 5) and TPR (Fig. 6). α-Methylnoradrenaline also increased serum insulin (Fig. 7), whole blood glucose (Fig. 8), serum free fatty acids (Fig. 9), and serum gastrin (Fig. 10) and decreased plasma noradrenaline (Fig. 11). In the three subjects, where serum growth hormone levels were above the limits of detection (i.e., >0.5 ng × ml^{-1}) during at least one of the two placebo days at baseline 2, α-methylnoradrenaline reduced serum growth hormone (data not shown).

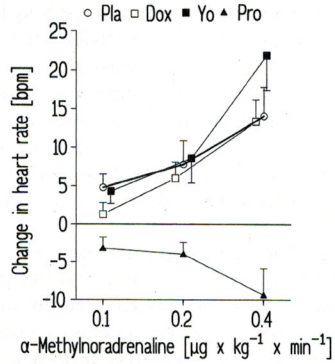

Fig. 1. Effects of i.v. infusion of α-methylnoradrenaline on heart rate after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

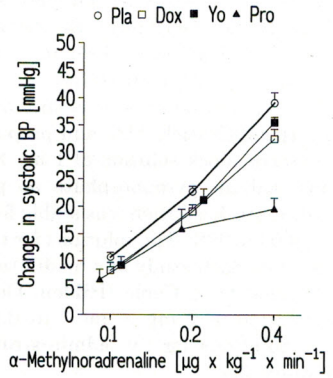

Fig. 2. Effects of i.v. infusion of α-methylnoradrenaline on systolic BP after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

The α_1-adrenoceptor antagonist, doxazosin, slightly but significantly blunted the increase in systolic blood pressure ($P < .05$; Fig. 2). Doxazosin treatment did not significantly affect the α-methylnoradrenaline-induced changes of HR (Fig. 1), CO (Fig. 3), QS_2c (Fig. 4), DBP (Fig. 5), pulse pres-

TABLE 2
Effects of placebo and adrenoceptor antagonists on cardiovascular, metabolic, and hormonal parameters under resting conditions

	Placebo Baseline 1	Placebo	Doxazosin	Yohimbine	Propranolol
DBP (mm Hg)	71.2 ± 1.2	0.5 ± 0.1	0.0 ± 1.0	3.3 ± 1.5	2.9 ± 1.3
SBP (mm Hg)	110.7 ± 1.8	0.6 ± 0.3	0.7 ± 0.3	10.3 ± 1.2***	−1.5 ± 0.6*
TPR (dyne × s × cm^{-5})	1299 ± 143	56 ± 19	−73 ± 87	49 ± 43	177 ± 68
SV (ml)	100.3 ± 6.9	−3.0 ± 2.1	1.2 ± 6.4	−6.0 ± 5.2	−3.3 ± 5.2
CO (liter × min^{-1})	5.53 ± 0.62	−0.2 ± 0.1	0.3 ± 0.3	0.1 ± 0.2	−0.6 ± 0.2
HR (bpm)	54.6 ± 3.5	−0.7 ± 1.1	1.9 ± 2.7	4.6 ± 1.8*	−4.7 ± 1.2*
QS_2 (ms)	429.0 ± 4.2	0.5 ± 1.6	−4.2 ± 7.6	−13.8 ± 2.6**	6.3 ± 3.6
QS_2c (ms)	495.0 ± 3.5	−0.4 ± 1.0	−1.8 ± 4.6	−8.1 ± 1.6*	0.7 ± 2.8
LVET (ms)	326.6 ± 4.0	0.1 ± 2.6	−4.5 ± 6.1	−8.5 ± 2.8*	−3.2 ± 4.8
PEP (ms)	102.4 ± 2.2	0.4 ± 1.5	0.4 ± 3.1	−5.2 ± 2.2	9.5 ± 3.6
PWV (m × s^{-1})	5.33 ± 0.15	0.10 ± 0.08	−0.02 ± 0.11	0.71 ± 0.15*	−0.09 ± 0.08*
Noradrenaline (pg × ml^{-1})	313 ± 82.6	31.4 ± 19.5	85.7 ± 25.7	121.2 ± 21.6**	−0.8 ± 36.9
Free fatty acids (mg × dl^{-1})	8.5 ± 1.2	0.1 ± 0.9	0.3 ± 1.5	1.9 ± 2.9	0.7 ± 2.6
Insulin (μU × ml^{-1})	5.7 ± 1.6	−0.7 ± 0.4	0.7 ± 0.8	2.2 ± 0.6***	−0.9 ± 0.6
Glucose (mg × dl^{-1})	82.3 ± 1.1	−4.2 ± 3.5	7.1 ± 6.1	−9.1 ± 5.4	−8.5 ± 4.6
Gastrin (pg × ml^{-1})	69.4 ± 13.5	4.3 ± 1.6	7.8 ± 4.5	7.0 ± 5.0	−0.8 ± 4.1

Changes in cardiovascular parameters and plasma catecholamines induced by the different study drugs are summarized as the difference between baseline 1 (i.e., baseline before administration of any drug) and baseline 2 (i.e., baseline before start of the i.v. α-methylnoradrenaline infusion), respectively. The baseline 1 values are shown as the average of the 2 placebo days. *,**, and *** P <.05, <.01, and <.001, respectively, versus placebo in a paired t test; $n = 6$. SBP, systolic blood pressure; SV, stroke volume; LVET, left ventricular ejection time; PEP, pre-ejection period, and PWV, pulse-wave velocity.

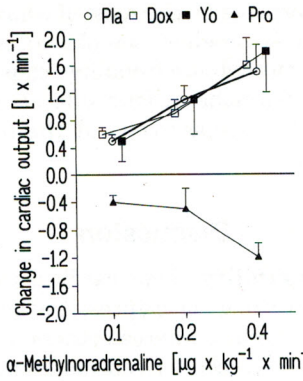

Fig. 3. Effects of i.v. infusion of α-methylnoradrenaline on CO after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

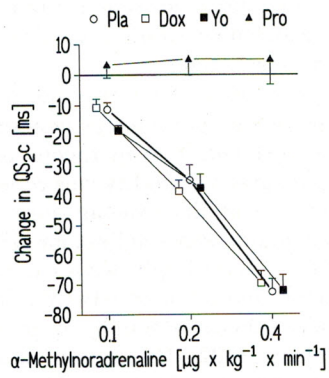

Fig. 4. Effects of i.v. infusion of α-methylnoradrenaline on the duration of QS_2c after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

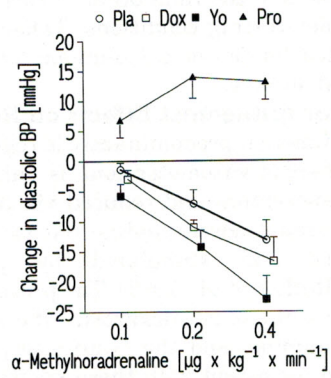

Fig. 5. Effects of i.v. infusion of α-methylnoradrenaline on diastolic BP after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

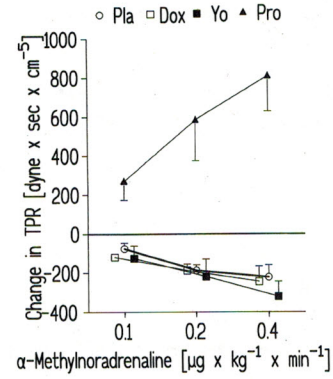

Fig. 6. Effects of i.v. infusion of α-methylnoradrenaline on TPR after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

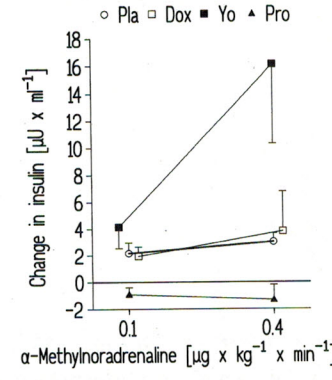

Fig. 7. Effects of i.v. infusion of α-methylnoradrenaline on serum insulin after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

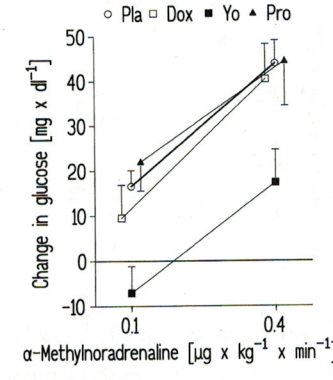

Fig. 8. Effects of i.v. infusion of α-methylnoradrenaline on blood glucose after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

sure (data not shown), pulse-wave velocity (data not shown), TPR (Fig. 6), or any of the hormonal and metabolic parameters (Figs. 7–11).

The α_2-adrenoceptor antagonist, yohimbine, significantly enhanced the α-methylnoradrenaline-induced fall in DBP ($P < .05$; Fig. 5) but did not significantly affect the fall in TPR (Fig. 6) or the changes of other hemodynamic parameters (Figs. 1–4). Although neither yohimbine nor doxazosin significantly affected the α-methylnoradrenaline-induced elevation of HR, this increase was significantly greater during yohimbine than during doxazosin treatment in a direct, pairwise comparison ($P < .01$; Fig. 1). Yohimbine significantly blunted the increase in glucose ($P < .01$; Fig. 8), prevented the fall in plasma noradrenaline ($P < .05$; Fig. 11), and enhanced the rise in serum insulin ($P < .05$; Fig. 7). In a direct comparison between the α-adrenoceptor antagonists, α-methylnoradrenaline increased glucose significantly more during doxazosin than during yohimbine treatment ($P < .05$; Fig. 8). Moreover, α-methylnoradrenaline decreased plasma noradrenaline during doxazosin and increased it during yohimbine treatment ($P < .05$ for direct comparison of doxazosin versus yohimbine; Fig. 11).

The β-adrenoceptor antagonist, propranolol, completely prevented the shortening of QS_2c ($P < .001$; Fig. 4) and pre-ejection period ($P < .05$; data not shown) by α-methylnoradrenaline and converted the fall in DBP ($P < .01$; Fig. 5)

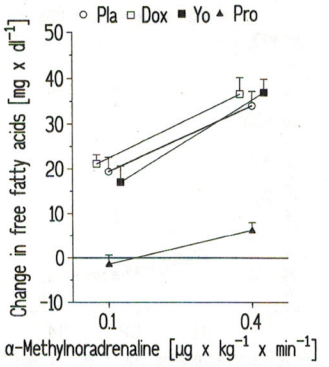

Fig. 9. Effects of i.v. infusion of α-methylnoradrenaline on free fatty acids after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

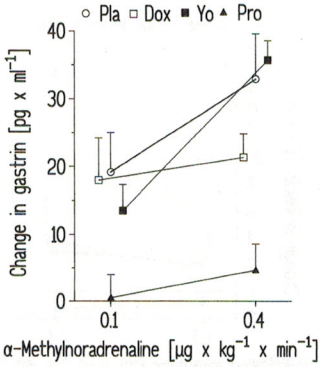

Fig. 10. Effects of i.v. infusion of α-methylnoradrenaline on serum gastrin after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

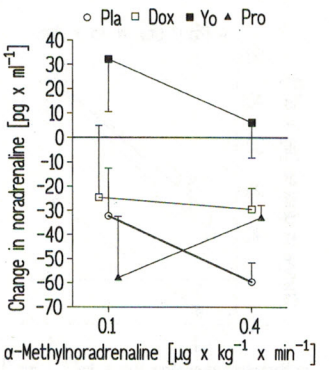

Fig. 11. Effects of i.v. infusion of α-methylnoradrenaline on plasma noradrenaline after pretreatment with placebo (Pla), doxazosin (Dox), yohimbine (Yo), and propranolol (Pro). Means ± S.E.M.; $n = 6$ for each treatment.

and TPR ($P < .05$; Fig. 6) into increases. Similarly, the increases in HR ($P < .01$; Fig. 1) and CO ($P < .001$; Fig. 3) were reversed to decreases after β-adrenoceptor blockade, and the increase in pulse pressure was markedly reduced ($P < .0001$; data not shown). Propranolol treatment prevented the rise in serum insulin ($P < .01$; Fig. 7) and blunted the increase in free fatty acids ($P < .01$; Fig. 9) and gastrin ($P < .05$; Fig. 10) but had no significant effect on glucose (Fig. 8) and noradrenaline (Fig. 11) during α-methylnoradrenaline infusion.

After placebo and α-adrenoceptor blockade by doxazosin and yohimbine, α-methylnoradrenaline did not increase plasma growth hormone levels (most of which were below the limit of detection at baseline; see above). After propranolol pretreatment, α-methylnoradrenaline caused minor increments of growth hormone in four subjects of 1.0, 10.3, 0.8, and 0.2 ng × ml^{-1}, respectively, at the 0.4-µg × kg^{-1} × min^{-1} dose level.

Discussion

Data Reproducibility. Some cardiovascular parameters are assessed directly (e.g., blood pressure) but represent complex physiological events, whereas others (e.g., TPR) are obtained indirectly, i.e., are derived mathematically from directly measured parameters, but are presumed to represent primary physiological events. Thus, TPR and QS_2c are primary indicators of vascular and cardiac function, respectively, whereas blood pressure represents the integration of inotropic and chronotropic events, vascular compliance, and vascular smooth muscle tone.

Under resting conditions the intra- and interday variability of the cardiovascular parameters generally was smaller than that of the hormonal and metabolic parameters, and, expectedly, the intraday variability was consistently smaller than the interday variability. Among the hemodynamic parameters the variability was smallest for QS_2c as an indicator of cardiac effects. Accordingly, QS_2c can detect changes of systolic performance more sensitively than M-mode echocardiography, Doppler echocardiography, or impedance cardiography (de Mey et al., 1992). Under stimulated conditions, a quantitative assessment of data variability was more difficult, but there was no systematic change in the responses to 0.4 µg × kg^{-1} × min^{-1} α-methylnoradrenaline between the two placebo days, and the rank order of variability was similar to that under resting conditions. Taken together these data can be used for power calculations for future clinical pharmacological studies.

Adrenoceptor Antagonist Effects on Resting Parameters. Cardiac function predominantly is regulated via β-adrenoceptors, whereas vasomotor tone is enhanced via both α_1- and α_2-adrenoceptors and reduced via β-adrenoceptors. In contrast, neuronal noradrenaline release is inhibited by α_2-adrenoceptors and stimulated by β-adrenoceptors (Langer, 1977; Ruffolo et al., 1993). The present effects of the α_1-adrenoceptor antagonist, doxazosin, the α_2-adrenoceptor antagonist, yohimbine, and the β-adrenoceptor antagonist, propranolol, are consistent with these known functions.

In the present and previous studies (Goldberg et al., 1983; Schäfers et al., 1997) yohimbine predominantly increased systolic blood pressure with only little effect on DBP and TPR. This can be explained by an increase in stroke volume, a reduction in vascular compliance, or both. Because yohimbine had no significant effect on stroke volume or CO, a reduced vascular compliance appears to be more likely. This hypothesis is supported by the significant acceleration of pulse-wave velocity, suggesting a decrease in vascular compliance (Belz, 1995). Whether yohimbine affects vascular compliance directly or, e.g., via central mechanisms, remains to be determined.

Only little is known regarding the adrenoceptor types that control glucose, insulin, free fatty acid, growth hormone, and gastrin levels in humans in vivo. In mice and rats, pancreatic insulin release can be inhibited by α_2-adrenoceptor stimula-

tion (Angel et al., 1990; Niddam et al., 1990). Our yohimbine data indicate that this mechanism is operative and tonically activated by endogenous catecholamines in humans. On the other hand, our propranolol data indicate that β-adrenoceptors involved in the control of insulin release are not tonically active in human. Whereas previous studies have demonstrated adrenergic modulation of lipolysis (Burns et al., 1981; Wright and Simpson, 1981; Tarkovacs et al., 1994), growth hormone secretion (Brown et al., 1985, 1988), and gastrin release (Intorre et al., 1994), our data indicate that none of the parameters is tonically controlled by endogenous catecholamines under resting conditions. Thus, multiple adrenoceptor types are involved in the control of cardiovascular, metabolic, and hormonal function in humans in vivo, some of which appear to be tonically active under resting conditions. The relative contributions of adrenoceptor types differ considerably between parameters.

α-Methylnoradrenaline Effects. α-Methylnoradrenaline is a standard tool to assess human peripheral α_2-adrenoceptor function in humans in vivo (see Introduction). In contrast to clonidine (Brown et al., 1988), α-methylnoradrenaline lacked consistent effects on plasma growth hormone levels in the present study, confirming that α-methylnoradrenaline does not cross the blood-brain barrier. Although α-methylnoradrenaline is a potent and efficacious α_2-adrenoceptor agonist in vitro, the assumption that it is selective for α_2-adrenoceptors in human in vivo has not been validated to our knowledge. Our study confirms that α-methylnoradrenaline increases systolic blood pressure more than DBP (Murphy et al., 1984; Schäfers et al., 1990), indicating a cardiac rather than a vascular effect. The use of primary indicators of cardiac and vascular function and of selective antagonists has allowed us to investigate the underlying mechanisms in more detail.

α-Methylnoradrenaline markedly shortened QS_2c and increased CO, indicating enhanced cardiac systolic performance because of a positive inotropic effect (Lewis et al., 1977; Johnson et al., 1981). Both changes were fully suppressed by the β-adrenoceptor antagonist, propranolol, but were not affected by the α-adrenoceptor antagonists. Thus, α-methlynoradrenaline markedly stimulates cardiac β-adrenoceptors. This stimulation is quantitatively similar to that of the full β-adrenoceptor agonist, isoprenaline, as determined under similar conditions in our laboratory (Schäfers et al., 1994). Although these data clearly demonstrate β-adrenoceptor stimulation by α-methylnoradrenaline, they do not allow conclusions about selectivity over α_2-adrenoceptors because the latter do not contribute to inotropy.

On the other hand, α-methylnoradrenaline surprisingly decreased DBP and TPR, indicating a vasodilating rather than the expected vasoconstricting action on vascular smooth muscle, and this was blocked by propranolol. Thus, even in the vasculature, where α- and β-adrenoceptors coexist, β-adrenoceptor stimulation dominated the overall functional response to α-methylnoradrenaline. Indeed, α-methylnoradrenaline-induced vasoconstriction was detected only in the presence of propranolol, although vasoconstriction is the prototypical vascular response to stimulation of both α_1- and α_2-adrenoceptors (Jie et al., 1987b; Ruffolo et al., 1993). Because, in contrast to yohimbine, α_1-adrenoceptor blockade by doxazosin had hardly any effect on the hemodynamic, metabolic, and hormonal responses to α-methylnoradrenaline, we suggest that the vasoconstriction observed in the presence of propranolol was mediated by stimulation of vascular α_2-adrenoceptors. The contribution of α_2-adrenoceptors to the control of vascular tone in humans in vivo clearly has been shown by previous studies (Jie et al., 1987b). Although we are fully aware that our data do not provide conclusive evidence for this suggestion, it is supported by the following observations. First, the significant potentiation of the fall in DBP in the presence of yohimbine is consistent with blockade of vasoconstricting α_2-adrenoceptors. Second, prototypical α_1-adrenoceptor agonists such as noradrenaline and phenylephrine cause vasoconstriction even without concomitant β-adrenoceptor blockade upon systemic i.v. administration (Schäfers et al., 1997, 1999).

A different situation appears to exist for the prejunctional regulation of noradrenaline release, which can be inhibited by α_2-adrenoceptors and stimulated by β-adrenoceptors (Langer, 1977; Brown et al., 1985; Jie et al., 1987a; Ruffolo et al., 1993). Despite the dominance of β-adrenoceptor effects postjunctionally in the vasculature, α-methylnoradrenaline lowered plasma noradrenaline, and this was blocked by yohimbine but not affected significantly by propranolol. Thus, α-methylnoradrenaline behaves as a predominant β-adrenoceptor agonist at postjunctional cardiac and vascular receptors but as a predominant α_2-adrenoceptor agonist at prejunctional receptors. We speculate that vastly different receptor reserves for the two pre- and postjunctional pathways may explain this differential action of α-methylnoradrenaline.

The metabolic and endocrine parameters also exhibited a complex regulation pattern. Thus, α-methylnoradrenaline-induced increases of serum insulin were enhanced by yohimbine and fully suppressed by propranolol, demonstrating a dual control by stimulatory β- and inhibitory α_2-adrenoceptor pathways. On the other hand, in the absence of adrenoceptor blockade, α-methylnoradrenaline elevated blood glucose despite increased insulin concentrations. This indicates that additional mechanisms may be involved in the elevation of blood glucose by α-methylnoradrenaline, e.g., stimulation of glucagon or activation of glycogenolysis. Irrespective of the nature of the underlying physiological mechanisms, this rise in blood glucose did not involve α_1- or β-adrenoceptors because blockade of α_1- or β-adrenoceptors had no effect. In contrast, yohimbine antagonized the increase in blood glucose, indicating involvement of α_2-adrenoceptors possibly by their effect on insulin release, which was enhanced in the presence of yohimbine.

α-Methylnoradrenaline increased free fatty acids and gastrin. Both effects were blunted by propranolol but not affected by doxazosin or yohimbine, indicating mediation solely via β-adrenoceptors. Taken together, these data demonstrate that some metabolic and hormonal responses to i.v. α-methylnoradrenaline are controlled mostly, if not exclusively, by α_2-adrenoceptors, e.g., plasma noradrenaline and blood glucose; some are controlled by β-adrenoceptors, e.g., free fatty acids and gastrin; whereas others depend on the balance between inhibitory α_2- and stimulatory β-adrenoceptors, e.g., insulin. Interestingly, none of the metabolic responses to α-methylnoradrenaline in vivo appears to involve α_1-adrenoceptors, although this adrenoceptor type is well expressed, e.g., in the human liver (Garcia-Sainz et al., 1995).

Conclusions. Taken together, our data indicate that α-methylnoradrenaline is selective for α_2- over α_1-adrenoceptors, but its overall effects on hemodynamic and metabolic parametery, with the exception of plasma noradrenaline and glucose levels, are mediated largely via β-adrenoceptors. For most parameters that are under dual α_2- and β-adrenoceptor control, e.g., DBP, TPR, and insulin, α-methylnoradrenaline behaves as a predominant β-adrenoceptor agonist. However, for the regulation of plasma noradrenaline, which is also under dual α_2- and β-adrenoceptor control, the α_2-adrenoceptor actions of α-methylnoradrenaline dominate. This profile of α-methylnoradrenaline resembles that of the endogenous catecholamine, adrenaline, which has predominant inotropic and vasodilator properties. Because the DBP response to noradrenaline involves mainly α_1-adrenoceptors (Schäfers et al., 1997), we propose that α-methylnoradrenaline may be selective for α_2- relative to α_1-adrenoceptors in humans in vivo. However, its α_2-adrenoceptor-stimulating effects on the cardiovascular system can be revealed only during concomitant β-adrenoceptor blockade. With these precautions, it may be the agonist of choice for studies of peripheral α_2-adrenoceptor function in humans in vivo.

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