Psychopharmacology (2007) 190:181–188
DOI 10.1007/s00213-006-0597-7

ORIGINAL INVESTIGATION

Cardiovascular reactivity to mental stress is not affected by alpha2-adrenoreceptor activation or inhibition

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Received: 2 May 2006 / Accepted: 20 September 2006 / Published online: 17 November 2006

Abstract
Rationale It has been postulated that cardiovascular reactivity to mental stress varies with tonic central sympathetic nervous system activity, but pharmacological evidence is missing.
Objective To test whether modulation of central sympathetic nervous system activity by alpha2-adrenergic agonism and antagonism affects cardiovascular reactivity to mental stress.
Materials and methods On three five-stepped dose/concentration–response study days, 12 healthy male volunteers received intravenous infusions of dexmedetomidine (alpha2-agonist, target plasma concentrations: 0.04–0.32 ng/ml), yohimbine (alpha2-antagonist, doses: 0.016–0.125 mg/kg), and placebo, respectively. During each dose step, subjects performed a 5-Choice Reaction Time Task (CRTT) and a Paced Auditory Serial Addition Task (PASAT) to induce moderate mental stress. Prestress baseline, as well as stress-induced responses of heart rate, and noninvasive finger arterial blood pressure (Finapres) were assessed.
Results Prestress baseline heart rate and blood pressure decreased with increasing doses of dexmedetomidine and increased with increasing doses of yohimbine. However, dexmedetomidine and yohimbine did not affect stress-induced heart-rate and blood-pressure changes.
Conclusions Cardiovascular reactivity to mental stress is not related to pharmacologically manipulated tonic central sympathetic nervous system activity by alpha2-adrenergic agonists and antagonists. These results do not support the assumption that cardiovascular reactivity is an index of tonic central sympathetic nervous system activity.

Keywords Sympathetic nervous system · Mental stress · Cardiovascular reactivity · Alpha2-adrenoreceptors

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Introduction

There is a long history of mental stress testing in clinical psychophysiology (Fahrenberg et al. 1983), psychosomatic medicine (Carroll et al. 2003), and psychopharmacology (Back et al. 2005). Psychological stressors are able to activate the main components of the stress system, the corticotropin-releasing hormone and the locus coeruleus–norepinephrine/autonomic systems and their peripheral effectors, the pituitary–adrenal axis, and the limbs of the autonomic system (Chrousos and Gold 1992). Among the many physiological variables which change in response to stress, the cardiovascular parameters, heart rate and blood pressure, are the most widely used indices of mental stress reactivity (Lovallo 2005). Those cardiovascular responses are easily and reliably assessable and occur as fast as within seconds or minutes.

Mental stress may induce acute severe cardiovascular consequences (Goldberg et al. 1996; Kario et al. 2003), and chronic hyperreactivity to mental stress may lead to cardiovascular pathology, as suggested by the finding that enhanced reactivity to mental stress predicts future hypertension (Carroll et al. 2003; Tuomisto et al. 2005), and other chronic cardiovascular diseases (Matthews et al. 2006).

Cardiovascular reactivity is mediated by the autonomic nervous system. Parasympathetic withdrawal may occur

during stress and may explain some of the cardiovascular changes, such as mild tachycardia (Buchholz et al. 2003; Langewitz et al. 1994). However, the dominant source of stress-induced cardiovascular stress reactivity is increased sympathetic nervous system activity (Hjemdahl et al. 1989).

Alpha2-adrenergic receptors play a dominant role in central and peripheral sympathetic neurotransmission in the way that they inhibit the release of norepinephrine from the locus coeruleus and peripheral nerve terminals (Hein 2001). Alpha2-adrenergic receptors located in the ventrolateral medulla reduce tonic sympathetic activity, while alpha2-adrenergic receptors within the dorsovagal nucleus activate parasympathetic pathways (Unnerstall et al. 1984). Alpha2-adrenergic receptors may therefore play a crucial role as a modulator of the cardiovascular stress response.

Recent research indicated that stress during the early postnatal period reduces central alpha2-adrenergic receptor density, a mechanism that would lead to basal, as well as stress-induced central sympathetic nervous system hyperreactivity in adult life (Caldji et al. 1998; Francis et al. 1999). Stress in later life also reduces receptor binding of the alpha2-receptor agonist clonidine (U'Prichard and Kvetnansky 1980) and the alpha2-adrenergic antagonist ^{3}H-rauwolscine (Nukina et al. 1987). Animals with a downregulation of alpha2-receptor function show a chronic activation of the sympathetic nervous system (Flügge 1999; Flügge et al. 2001). However, ongoing psychosocial stress may also result in a persistent upregulation of alpha2-adrenergic receptors accompanied by behavioral consequences comparable to a state of depression (Flügge et al. 2004).

Several pathological states, all being associated with chronic cardiovascular disease, have been reported to be characterized by both increased tonic central sympathetic nervous system activity during resting baseline conditions and enhanced phasic stress responsiveness. Depression has been associated with increased basal sympathetic nervous system tone (Guinjoan et al. 1995), as well as increased vascular (Matthews et al. 2005) and cardiac (Kibler and Ma 2004) stress reactivity. Several anxiety disorders are associated with an increased baseline sympathetic nervous system activity (Cohen et al. 2000), as well as increased sympathetic responsiveness to standing (Coupland et al. 2003), and an increased reactivity of vasoconstricting sympathetic nerves (Lambert et al. 2002). Increased central sympathetic tone has been found in borderline hypertension (Smith et al. 2004), which is characterized by increased cardiovascular reactivity to mental stress (Julius and Nesbitt 1996).

Given all this evidence, it seems reasonable to suggest that enhanced cardiovascular reactivity may occur as a result of increased sympathetic tone induced by altered alpha2-adrenergic receptor function. However, this hypothesis has never been tested systematically in pharmacological experiments.

Alpha2-adrenergic drugs are well known to influence tonic central sympathetic nervous system activity (Hein et al. 1999). The imidazoline derivate clonidine, an apha2-adrenergic agonist, has a long tradition in clinical medicine and is used to inhibit sympathetic nervous system activity in pathological states such as hypertensive crisis (Varon and Marik 2000), agitation, and delirium (Stanley et al. 2005). Recently, the new highly selective alpha2-adrenergic agonist dexmedetomidine, an imidazoline derivate as well, has been introduced to human application. Dexmedetomidine has the advantage of a short half-life, which makes it especially suitable for intravenous administration. Indeed, computer-controlled (STANPUMP) infusion pump setups have been developed (Dyck et al. 1993), and several studies have shown that these devices validly control dexmedetomidine plasma concentrations during different circumstances in humans (Talke et al. 2003). Some studies indicated excellent concentration–response associations of dexmedetomidine with plasma catecholamines (Scheinin et al. 1998) and psychomotor reaction time (Angst et al. 2004). Unfortunately, no such procedure is available to study alpha2-adrenergic antagonists. At the moment, the alkaloid yohimbine is the only substance available for human clinical application. Yohimbine has been used to increase central sympathetic nervous system activity in pathological states such as orthostatic hypotension (Biaggioni et al. 1994), erectile dysfunction, and impotence (Tam et al. 2001). It has the potential of clinical beneficial effects after a loss of adrenergic hypoglycemic counter-regulation (Moberg et al. 1996) and may induce panic attacks in vulnerable subjects (Sullivan et al. 1999). Dose–response characteristics have been established for plasma catecholamines and cardiovascular parameters (Goldberg et al. 1983; Grossman et al. 1991; Grunhaus et al. 1989; Hedner et al. 1992; Sullivan et al. 1999).

Both substances, dexmedetomidine and yohimbine, are suitable to modulate tonic central sympathetic nervous system activity. The main research question of the current study is whether pharmacological modulation of central sympathetic nervous system activity via alpha2-adrenergic agonism (dexmedetomidine) and antagonism (yohimbine) affects cardiovascular stress responsiveness. To answer this question, repetitive stress testing is mandatory. A description of the effects of test repetition will also be provided to inform future research in this field.

Materials and methods

Participants

Twelve healthy male subjects (age mean: 26 years; age range: 20–36 years) participated in the investigation. They were

recruited via e-mail and posters and received monetary incentive for their participation. All subjects were non-smokers. Physical history and examination (including blood-pressure reading and routine ECG) were normal, as was blood hematology and chemistry. All subjects were medication-free and did not self-report any drug abuse. Lifetime psychopathology was assessed according to a medical and psychological checklist. The study was approved by the local ethic committee, and an informed consent was collected before the study entry from each participant.

Procedure

All participants were tested on three experimental days with 1 week intervals when placebo, yohimbine, and dexmedetomidine were given intravenously in single blinded fashion. The sequence of drugs was strictly counterbalanced to control for potential sequence effects. Subjects were randomly allocated to the sequence of the drugs. Participants were asked to refrain from alcohol or caffeine the night before and during each experimental day.

On each experimental day, subjects entered the psychophysiological laboratory at 8 a.m., where a small venous line was placed at the left forearm for drug infusions. Drug infusions started 60 min after entering the laboratory. Each experimental day included five infusion periods, all lasting exactly 60 min. The first period was always without drug administration. Steady-state plasma concentrations were achieved about 15 min after drug infusion. At that time, prestress baseline cardiovascular data were recorded for 5 min. Subjects were instructed to relax and to neither move nor speak. Afterward, the 5-Choice Reaction Time Task (CRTT) occurred for 3 min followed by 3 min of Paced Auditory Serial Addition Task (PASAT). Other tests not specified here were performed to fill the 60-min time. During the experimental procedures, subjects remained seated in a semirecumbent position and performed mental tasks. One study day lasted about 10 h and included a clinical observation period from 3 to 6 p.m.

Drug administration

Dexmedetomidine (Abbott), yohimbine (Pharmaceutical Division, University Hospital Basel), and placebo were administered by a Harvard Apparatus 22 infusion pump (Harvard Apparatus, South Natick, MA, USA).

For dexmedetomidine, the infusion pump targeted plasma dexmedetomidine concentrations of 0.04, 0.08, 0.16, and 0.32 ng/ml (Talke et al. 2003). The pump was controlled by STANPUMP software (generously provided by Steven Shafer, M.D., Department of Anesthesia, Stanford University, Palo Alto, CA, USA) based on pharmacokinetic data of dexmedetomidine (Dyck et al. 1993) so that steady-state plasma concentrations were achieved almost instantaneously. Pharmacokinetic data for yohimbine HCL have been explored (Hedner et al. 1992; Le Corre et al. 1999; Tam et al. 2001). However, no computer-controlled infusion protocols have been established as to achieve steady-state plasma concentrations. Yohimbine HCL (Pharmaceutical Division, University Hospital Basel) was administered in four dose steps (16, 32, 64, and 128 μg/kg) (Goldberg et al. 1983). Half of the doses were administered as 5-min injections. The remaining dose was constantly infused over 55 min so that each infusion step lasted exactly 60 min. Placebo was continuously infused. No external cues indicated which drug was administered.

Cardiovascular assessments

During each single dose step, cardiovascular beat-to-beat data were assessed at prestress baseline (5 min) and during two mental stress tests (3 min each). ECG (lead II) and continuous finger arterial blood pressure (Finapres system, Ohmeda, Englewood, USA) were recorded. After the data were edited for outliers due to artifacts or ectopic myocardial activity, the mean finger systolic and diastolic blood pressure and heart rate were calculated per person and condition.

Mental stress testing

The CRTT can be used to test visual attention and cognitive-motor speed, as well as to induce stress (Langewitz et al. 1994; Schachinger et al. 2000). The test is well implemented in our laboratory to induce stress and to assess global cognitive function. Subjects were requested to respond to colored lights (red, blue, green, yellow, and white) presented in random order as accurately and fast as possible by pressing a button of the same color. Stimuli and buttons were presented by a response box. The interstimulus interval was adapted to the subject's performance, leading to a constant false response rate of 50%. The total test time was 3 min. The order of lights was completely randomized in each trial so that learning effects over the dose steps and over the experimental days were excluded. Reaction times were recorded by a computer. Detailed descriptions of the test are published elsewhere (Schachinger et al. 2000, 2003; Szinnai et al. 2005).

The PASAT has also frequently been used in our working group as a stress test and to measure cognitive functions. It can be used either as a test of divided attention and working memory or as an instrument to induce stress (Mathias et al. 2004). The participants were presented with one digit numbers through headphones via a computer. They were asked to add each number to the previous one and to tell the sum aloud. Numbers were administered in

2.5-s intervals. The total task took 3 min. Five parallel versions of the PASAT were used so that each subject worked on five different versions per day to exclude learning effects also over the experimental days. Subjects' answers were recorded on a PC and were rectified and integrated later. Verbal reaction time and accuracy of the answers were analyzed via computer after visual artifact control. Detailed descriptions of the test procedure are published elsewhere (Schachinger et al. 2003).

Data reduction and statistical analysis

The impact of pharmacological manipulation was evaluated by adjusting all data to the initial drug-free period, as well as individual placebo data. Drug effects were tested by repeated measures ANOVA with drug (dexmedetomidine vs yohimbine) and dose steps (0 to 4) as independent within factors, the interaction of both factors indicating a significant dose-dependent association to pharmacological manipulation of alpha2-adrenoreceptors. Reactivity scores (Δ) were derived for heart rate and systolic and diastolic blood pressure. They were calculated as simple differences between stress and baseline values. Drug effects were also tested by repeated measures ANOVA with drug (dexmedetomidine vs yohimbine) and dose steps (0 to 4) as independent within factors.

To control for differences of initial values, a repeated measures ANOVA was calculated over the initial drug-free periods with drug (placebo, dexmedetomidine, yohimbine) as within factor.

However, initial drug-free data and placebo data are reported, too. This will allow for the recalculation of original mean data. Prestress baseline data and the habituation of the stress response over the five placebo sessions were analyzed with another repeated measures ANOVA with time (sessions 1–5) as within factor. For post hoc analyses, simple *t* test was used.

Data are reported as mean±SE. Exact two-tailed *p*-values are reported, with $p<0.05$ signifying statistical significance. All statistical calculations were performed with SAS software (release 9.1, WinNT, SAS Institute, Cary, NC, USA).

A-priori power analysis

A pilot test–retest (7 days interval) of 16 healthy nonsmokers revealed mean PASAT HR reactivity scores of 10 bpm. The test–retest correlations of PASAT reactivity scores were $r=0.83$, $p=0.0001$. Test–retest differences between day 1 and day 2 were −0.6±3.6 bpm. Power estimation was based on a one-sided paired *t* test model. When treatment is assumed to induce a 50% change in reactivity scores, power is estimated to be 0.98 for a sample of $n=12$. A conservative assumption (treatment effect of a 30% change in reactivity scores) would still yield a power estimation of 0.76.

Results

The mean age, weight, and height of participants were 26 years (range 20–36 years), 75.6 kg (range 62.5–90 kg), and 179.4 cm (range 168–186 cm), respectively. Reaction times in the stress tasks (not specified in this study) indicated that all subjects complied with task instructions.

The ANOVA showed significant interactions between drug and dose step for baseline resting (prestress) heart rate ($F_{4,44}=13.2$, $p<0.0001$) and systolic ($F_{4,44}=20.5$, $p<0.0001$) and diastolic ($F_{4,44}=12.7$, $p<0.0001$) blood pressure (see Fig. 1, upper row), indicating an influence of the pharmacological manipulation on alpha2-adrenergic receptors on cardiovascular parameters.

Heart-rate reactivity scores to CRTT and PASAT were not affected by pharmacological manipulation of alpha2-adrenoreceptors nor was systolic and diastolic blood pressure ($p>0.19$) (see Fig. 1, middle and lower rows).

The initial drug-free periods did not differ systematically in heart rate and systolic or diastolic blood pressure ($p>0.42$) (see Table 1a–c).

During placebo experiments, there was a trend of increasing baseline blood-pressure values from the first measurement to the four following measurements in systolic ($F_{4,44}=2.64$, $p=0.12$) and diastolic ($F_{4,44}=2.92$, $p=0.09$) blood pressure; heart rate did not change significantly ($F_{4,44}=1.52$, $p=0.24$) (see Table 1a–c).

During placebo testing, there was a trend toward a habituation of the stress effects of PASAT in systolic blood pressure ($F_{4,44}=5.07$, $p=0.08$) and a significant effect of habituation in diastolic ($F_{4,44}=11.9$, $p<0.001$) blood pressure over time. Habituation was constant, and post hoc tests showed that the difference from the first to the third dose step reached significance. Also, the CRTT effect tended to decrease over the placebo sessions in diastolic ($F_{4,44}=5.89$, $p=0.06$) blood pressure. The reactivity of systolic blood pressure to CRTT did not change over time ($F_{4,44}=1.63$, $p=0.21$). Heart rate remained rather stable in reaction to PASAT and CRTT ($p>0.37$) over the five sessions of placebo testing (see Table 1a–c).

Discussion

This placebo-controlled dose/concentration–response study of 12 male volunteers indicated that cardiovascular reactivity to mental stress did not vary with agonism (dexmedetomidine) or antagonism (yohimbine) of alpha2-adrenoreceptors. Thus, the data do not support the assumption that cardiovascular reactivity to mental stress is an index of tonic central sympathetic nervous system activity.

Our results are in accordance with the previous reports indicating that the alpha2-adrenoreceptor agonist clonidine

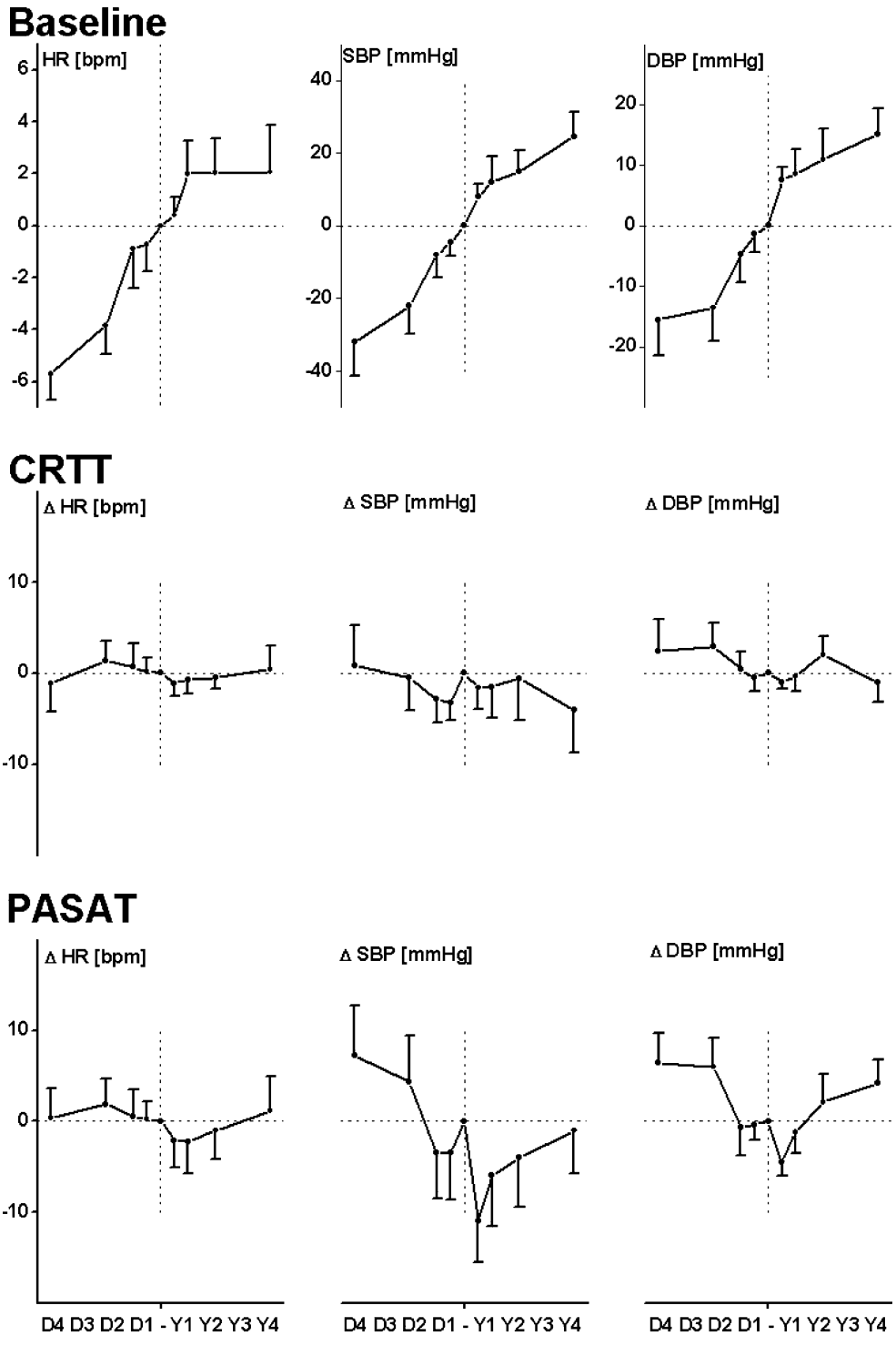

Fig. 1 Effects of dexmedetomidine (D4–D1) and yohimbine (Y1–Y4) on heart rate and systolic and diastolic blood pressure (*D4* highest dose of dexmedetomidine, *D1* lowest dose of dexmedetomidine, *Y1* lowest dose of yohimbine, *Y4* highest dose of yohimbine). Data were adjusted to the initial drug-free period, as well as individual placebo data. *Upper row* baseline data, *middle row* reactivity scores (Δ) to CRTT, *lower row* reactivity scores (Δ) to PASAT. *Bars* represent means and SE

did not affect cardiovascular responses to mental arithmetic stress (Ruddel et al. 1988; Weder et al. 1989). However, our data are in contrast to the recent data indicating that cardiovascular responses to aversive stimulation may be decreased by dexmedetomidine (Ebert et al. 2000; Hogue et al. 2002). This discrepancy may be explained by the types of stressors. The latter studies used thermal stressors, such as local cold (Ebert et al. 2000) or heat (Hogue et al. 2002), which activate heterogeneous neurochemical responses, different from other stressors (Pacak et al. 1998).

The two stress tests used in this research have been previously validated. Both are challenging tasks which are frequently used to measure cognitive-motor functioning (Au Duong et al. 2005; Diamond et al. 1997; Dirette 2004; Shucard et al. 2004). They have been used successfully to induce stress (Langewitz et al. 1994; Mathias et al. 2004;

Table 1 Placebo data and initial drug-free data at baseline and in reaction to CRTT and PASAT

	Baseline	Δ CRTT	Δ PASAT
(a) Heart rate (bpm)			
Placebo 0[a]	60.07±1.90	7.90±1.95	10.40±2.82
Placebo 1[b]	57.68±1.58	6.81±1.52	8.72±2.14
Placebo 2[b]	57.11±1.74	6.23±1.32	7.74±1.48
Placebo 3[b]	57.91±1.94	6.46±1.20	7.29±1.48
Placebo 4[b]	58.13±1.92	7.40±2.10	7.41±1.57
Yohimbine 0[a]	62.18±1.86	7.30±1.20	11.25±2.94
Dex[c] 0[a]	61.69±1.91	8.21±1.44	10.44±1.48
(b) Systolic blood pressure (mmHg)			
Placebo 0[a]	133.71±5.41	12.38±3.04	20.48±2.65
Placebo 1[b]	142.97±4.84	7.71±2.04	14.90±3.74
Placebo 2[b]	142.13±4.91	6.58±1.86	12.08±1.42
Placebo 3[b]	144.06±5.18	8.30±0.98	10.15±2.13
Placebo 4[b]	141.43±5.87	8.74±1.94	7.17±3.21
Yohimbine 0[a]	131.73±6.33	11.14±2.16	24.14±2.74
Dex[c] 0[a]	130.84±4.32	12.68±1.99	19.35±2.88
(c) Diastolic blood pressure (mmHg)			
Placebo 0[a]	73.83±4.72	10.16±1.62	15.98±2.01
Placebo 1[b]	81.63±3.39	5.51±1.48	10.27±2.39
Placebo 2[b]	81.40±3.42	4.50±1.02	8.28±1.02
Placebo 3[b]	82.89±3.58	4.20±0.89	6.14±1.58
Placebo 4[b]	78.43±3.84	6.56±1.21	6.09±2.05
Yohimbine 0[a]	71.61±3.86	9.90±1.34	16.54±1.57
Dex[c] 0[a]	71.59±2.58	8.78±1.58	13.88±1.99

Values represent means and SE.
[a] No drug infused
[b] Dose steps of placebo
[c] Dexmedetomidine

Schachinger et al. 2000), and the range of cardiovascular reactions is comparable to that of other standard mental stress tests (Becker et al. 1996; Hoshikawa and Yamamoto 1997). The reactivity of heart rate remained stable also when the tests were presented repeatedly. Blood-pressure reactivity scores showed a tendency of habituation and reached significance only in diastolic blood pressure during the PASAT. This habituation pattern makes these tests suitable for pharmacological studies.

However, we were able to replicate that prestress baseline of heart rate and arterial blood pressure decreased with increasing doses of dexmedetomidine and increased with increasing doses of yohimbine. This has been suggested by previous research (Goldberg et al. 1983; Grossman et al. 1991; Penttila et al. 2004; Talke et al. 2003). Such changes can also be found when administering alpha2-adrenergic drugs directly into the central nervous system (Eisenach et al. 1994). Thus, although peripheral alpha2-adrenergic receptors may have been affected in the current research (Talke et al. 2003), the effects seen are clearly attributable to central alpha2-adrenergic activation or inhibition.

Our results are limited to young healthy male subjects, of whom none had evidence of altered autonomic nervous system function. However, gender differences in cardiovascular reactivity to stress have been found (Allen et al. 1993; Lawler et al. 1995; Traustadottir et al. 2003), and it is also known that autonomic dysfunction may lead to altered reactivity to mental stress (Forst et al. 1996). Thus, we cannot exclude the possibility that females, very old subjects, or patient groups with altered autonomic nervous system function would have shown other results.

In conclusion, cardiovascular reactivity to mental stress is not related to pharmacologically manipulated tonic central sympathetic nervous system activity or altered alpha2-adrenergic function. These results do not support the assumption that cardiovascular reactivity is an index of tonic central sympathetic nervous system activity.

Acknowledgement This work was supported by the German National Research Foundation (DFG grant SCHA 12372-1).

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