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Anxiogenic Properties of Yohimbine

I. Behavioral, Physiological and Biochemical Measures

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Summary. The anxiogenic effects of yohimbine, a specific alpha-2-receptor antagonist were examined by administering 20 mg yohimbine orally to 8 panic patients on placebo treatment, 7 panic patients on alprazolam treatment and 12 controls using a double-blind randomized design, instructions that minimized the expectancy of experiencing a panic attack and two additional structured situations. Yohimbine induced more pronounced increases in anxiety and panicky ratings, norepinephrine secretion, maximum heart rate and high heart rate variability and decreases in skin temperature in panic patients compared with controls. However, possibly owing to an instructional set and experimental design that distracted patients from unpleasant bodily sensations no panic attacks were observed.

Key words: Cortisol – Electrodermal activity – Heart rate – Norepinephrine – Panic disorder – Yohimbine

Introduction

Considerable progress has been made in recent years in elucidating the psychobiology of panic disorder. Various biological theories of panic disorder have been derived from studies showing that several pharmacological and physiological agents can cause panic anxiety in vulnerable individuals [Shader et al. 1982; Carr and Sheehan 1984; Teicher 1988; Uhde and Tancer 1990]. Substances acting on different systems have shown anxiogenic potencies: caffeine [Uhde et al. 1984a; Charney et al. 1985a], which acts mainly on the adenosine receptor, the serotonin-receptor agonist metachlorophenylpiperazine (mCPP) [Charney et al. 1987a; Kahn et al. 1988], the beta-receptor agonist isoproterenol [Frohlich et al. 1969; Easton and Sherman 1976; Freedman et al. 1984; Rainey et al. 1984; Pohl et al. 1988], sodium lactate [Liebowitz et al. 1985; Dillon et al. 1987] and carbon dioxide [Gorman et al. 1984; Woods et al. 1986; Gorman et al. 1988; van den Hout and Griez 1984; Griez et al. 1990; Gorman et al. 1989] have been shown to induce anxiogenic effects in patients with panic disorder.

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The first observations that yohimbine, a specific alpha-2-receptor antagonist, may be anxiogenic came from studies with i.v. application performed on a variety of psychiatric patients [Holmberg et al. 1962; Garfield et al. 1967]. Subsequent studies showed that 20 mg yohimbine orally induced profound anxiety in panic disorder patients [Uhde et al. 1984b]. Patients with frequent panic attacks had significantly greater 3-Methoxy-4-Hydroxyphenyläthylenglykol (MHPG) increases and greater anxiety than control subjects after yohimbine administration [Charney et al. 1984], and yohimbine provoked panic attacks in 54% of panic patients in contrast to 5% of healthy subjects [Charney et al. 1987b]. Patients reporting a panic attack had significantly larger increases in plasma MHPG, cortisol and heart rate than the healthy controls [Charney et al. 1987b]. From this work it has been hypothesized that panic attacks are triggered by an impaired presynaptic regulation of the release of norepinephrine in the locus ceruleus [Charney et al. 1984, 1987b]. While treatment with diazepam appears to have little effect on alpha-2-adrenoceptor sensitivity [Charney et al. 1983], the triazolobenzodiazepine alprazolam seems to have significant effects on alpha-2-adrenoceptor mediated responses [Charney and Heninger 1985b; Charney et al. 1986]. Alprazolam significantly reduced baseline cortisol [Charney and Heninger 1985b] and plasma MHPG [Charney et al. 1986] and blunted the yohimbine-induced increases in plasma MHPG, anxiety, and nervousness. The most robust effect of alprazolam was an almost complete antagonism of the anxiogenic actions of yohimbine [Charney and Heninger 1985b].

The results of the above cited challenge studies seem to fulfill to a greater or lesser extent the requirements for a chemical model of anxiety [Guttmacher et al. 1983; Gorman et al. 1987]. However, there seem to be several intervening variables mitigating behavioral responses to a challenge drug. Although studies on sleep panic and relaxation-induced panic suggest that panic can emerge from diminished levels of arousal [Mellmann and Uhde 1989a, 1989b; Adler et al. 1987], it also appears that the degree of arousal at baseline plays a significant role in terms of behavioral sensitivity. In challenge paradigms increased base levels of behavioral ratings and somatic

Table 1. Characteristics of controls, patients under placebo (Plac. Pat.) and patients under alprazolam medication (Alpr. Pat.). p.a. = panic attacks, STAI-X1 = Spielberger state anxiety scale, HAS = Hamilton anxiety scale, BECK = Beck depression inventory, ZUNG = Zung anxiety status inventory

	Controls ($n = 12$)	Plac. Pat. ($n = 8$)	Alpr. Pat. ($n = 7$)
Age (years)	34.5 ± 5.84	36.0 ± 7.3	37.0 ± 6.7
Gender	4 m, 8 f	2 m, 6 f	2 m, 5 f
mg Alprazolam/day	–	–	3.88 ± 2.01
p.a./week	–	1.75 ± 2.25	1.71 ± 2.4
Diagnosis (DSM III)	–	4 Panic disorder 4 Agoraph. + p.a.	3 Panic disorder 4 Agoraph. + p.a.
Duration of illness (years)	–	9.13 ± 6.48	9.43 ± 4.54
STAI-X1	27.64 ± 5.64	49.44 ± 7.37	42.43 ± 6.64
HAS	–	20.31 ± 4.14	18.47 ± 5.89
ZUNG	3.31 ± 1.60	12.42 ± 7.30	9.35 ± 5.6

symptoms make the occurrence of panic attacks more likely [Woods et al. 1986; Margraf et al. 1986].

Moreover, instructional set and the experimental design have been shown to affect the response to anxiogenic agents in several studies. Administration of sodium lactate led to considerable anxiety in subjects given anxiety instructions, whereas pleasant, low tension instructions resulted in little or no change in anxiety [van der Molen et al. 1987]. The degree of anxiety and panic experienced during CO_2 inhalations could be manipulated by providing explicit or minimal information [Rapee et al. 1986]. Another study showed that the likelihood of experiencing a panic attack during inhalation of CO_2 is influenced by a sense of control over the inhalation and the resulting somatic symptoms [Sanderson et al. 1989].

The purpose of this study was to evaluate further a possible interaction between biological and experimental factors in a challenge paradigm. Therefore we did not apply a single blind [Uhde et al. 1984b] or double blind design with a fixed sequence [Charney et al. 1984, 1987b]. Instead, we chose a more conventional design with randomized presentation, since a fixed sequence does not control for adaptation effects to the experimental condition. This design seems the most appropriate one to balance out expectancy factors that are considered to increase base levels in behavioral ratings and somatic symptoms [Clark 1986; Margraf et al. 1986]. The instructions were designed to minimize anticipatory anxiety and expectancies of experiencing a panic attack so as to better study "pure" yohimbine effects on behavioral, physiological and biological measures. Moreover, two structered situations were included to test if these tasks distract patients from unpleasant bodily changes induced by yohimbine and thus reduce its anxiogenic effects.

Methods

Subjects

All patients (4 males, 11 females) were treated as outpatients at the anxiety disorder clinic of the National Institute of Mental Health. Only patients who met DSM-III criteria for agoraphobia with panic attacks or for panic disorder without concomitant depression were included in the study (APA, 1980). Eight patients were under placebo medication for at least 2 weeks prior the first test day, seven patients were treated with alprazolam over a period of 6 to 8 weeks and were under a stable alprazolam dosage for at least 1 week prior the first test day. In spite of alprazolam treatment, patients were not free of panic attacks. Their frequency of panic attacks was comparable to the placebo patient group. Patients stayed under placebo or under the identical dosage of alprazolam until the second test day.

Controls were obtained from responses to advertisements and for the most part were not familiar with laboratory studies. They were confirmed to have no personal or family history of panic attacks and to be free of mental disorder on the basis of a structured psychiatric interview. None of the controls reported taking any psychoactive medication. However, this was not confirmed by drug analyses and relied only on the subjects' (Ss) reports. All Ss were instructed to adhere to a low monoamine diet for at least 3 days prior to the test. Patients and controls were found to be free of significant medical problems on the basis of a complete medical and neurological evaluation including electrocardiogram.

Table 1 lists the age, gender, dosage of alprazolam, panic attacks per week, DSM-III diagnosis, duration of illness, STAI-X1 [Spielberger et al. 1970], HAS [Hamilton 1969] and ZUNG anxiety status inventory [Zung 1971] for patients and controls.

Procedure

The study was conducted at the Laboratory of Psychology and Psychopathology at the National Institute of Mental Health, Bethesda. All subjects participated in two test days during which they were randomly assigned to either 4 tablets of placebo or 4 tablets of 5 mg yohimbine on the first day and the other substance on the second test day. The interval between test days ranged from 1 to 3 weeks. The subjects arrived at the laboratory by 8:45 a.m. of each test day after fasting overnight and remained in the fasting state during the test until approximately 1 p.m. Throughout the study, Ss were seated in a comfortable armchair in a quiet room. At around 9:15 a.m. an IV cannula was inserted in a forearm vein and kept patent with a 0.9% sodium chloride solution. Yohimbine or placebo tablets were administered at around 10:15 a.m.

The instructions were designed to minimize expectancies of experiencing a panic attack. Ss were told that yohimbine in the dosage administered is not very likely to induce panic attacks. Moreover, they were assured that a substance that immediately relieves panicky feelings would be available in case of panic and that the investigator would be sitting in the adjacent room and could be called for assistance whenever Ss wanted it.

Rest periods and two structured situations were included before and after tablet intake: a mental arithmetic task (MA) and a continuous performance task [CPT; Rosvold et al. 1956]. A flow sheet of the study is in Albus et al. (this issue).

Behavioral ratings were administered 35 minutes before and 75 min following the yohimbine or placebo dose. A visual analogue scale completed by the subject was used to evaluate the changes of

5 different symptoms related to anxiety (panicky feelings, anxiety, nervousness, apprehension, muscle tension). The subject marked the point on a 100 mm line corresponding to his feelings at that time. Therefore, the score could range from 0 (not at all) to 100 (extremely). Additionally, once during the baseline period subjects filled out the anxiety status inventory [Zung 1971] and the Spielberger state anxiety scale [Spielberger et al. 1970].

Every 15 minutes after tablet intake Ss were asked if they could identify if they had received yohimbine or placebo and how sure they felt about that. To determine whether a patient had a panic attack during the procedure two criteria had to be satisfied: 1) a crescendo of extreme anxiety or fear and an increase in the severity of four or more DSM-III physical symptoms for a panic attack, 2) patients must have reported that the symptoms they experienced were similar to those during spontaneous panic attacks.

Physiological Recording

Physiological recordings were made continuously during the period from −20 to 0 minutes before tablet intake and again from +90 to +110 minutes after tablet intake on a Grass polygraph, the output of which was digitized and stored for offline analyses by a computer.

Electrodermal activity was recorded from the distal phalanges of the middle and ring fingers of each hand using a constant voltage (0.5 V) method, Ag/AgCl electrodes and electrode collars punched to a diameter of 8 mm with 0.5% KCl electrode paste. The signal was coupled to a low level DC preamplifier through a circuit described by Lykken and Venables [1971]. Heart rate was recorded by a tachograph from an EKG signal. Skin temperature was recorded from the medial phalanx of the ring finger of the left hand. Respiration rate was measured by means of a mercury strain gauge.

Biochemical Methods

Blood was sampled for norepinephrine (NE) and cortisol (COR) 30 and 20 minutes prior to yohimbine or placebo intake and 90 min after tablet intake. NE samples were placed into tubes containing ethylenglycol tetraacetic acid. Tubes were kept on ice, a maximum of 30 minutes before separation of plasma in a refrigerated centrifuge. Then plasma specimens were frozen at −70°C until assay. NE was assayed by a modification of high pressure liquid chromatography and electrochemical detection [Caliguri and Mefford 1984; Seppala et al. 1984]. Plasma cortisol was determined by a antibody radioimmunassay. To reduce the variance in method, plasma specimens were assayed in duplicate.

Data Reduction

The digitized ANS data were edited and analysed by computer as described by Zahn et al. (1986). The electrodermal variables included the number of nonspecific skin conductance responses (SCR) per minute (NS/min), their mean amplitude and recovery rate, and the maximum, mean, and slope of skin conductance level during the rest and task periods. For all of these, data from the two hands were averaged. For heart rate (HR), each period was divided into 10 s epochs, and for each epoch the mean, maximum and minimum HR was computed. The variables analysed were the mean and standard deviation (SD) of these mean, high, and low points, and the maximum and minimum HR for the whole period. Skin temperature was digitized every 10 s and averaged for each period. Respiration rate was the number of complete cycles during the first minute of each period without movement artifacts or aperiodic breathing.

Data Analysis

The data were analysed using standard statistical analysis systems (SAS) and biomedical programs (BMDP). The effects of yohimbine on plasma cortisol, NE, physiological measures and behavioral ratings were initially evaluated using analyses of variance (ANOVA) with independent dimensions: a) group (controls, patients taking alprazolam, patients taking placebo); b) order (yohimbine or placebo on the first test day); c) drug (Yohimbine or placebo); d) time (predrugs vs. postdrug), and e) condition (rest and task periods) when appropriate. The central questions of the overall effects of yohimbine vs. placebo on the dependent variables and the group differences in these effects were tested by the drug × time and drug × time × group interactions, respectively.

Separate ANOVAs were done for the controls and for the two patient groups, permitting evaluation of the effects of alprazolam treatment on the dependent variables and on their response to yohimbine.

Results

No significant order effects and no significant differences in baseline values for physiological and biochemical parameters between the three groups were observed. With one exception, reported below, alprazolam treatment affected neither the overall mean nor the drug × time interaction of any dependent variable significantly. Variations among conditions (rest, mental arithmetic and CPT) will be reported in a companion article (Albus et al. this issue).

Subjective Effects of Yohimbine

93% (13 out of 14) of the patients were able to correctly identify yohimbine in contrast to only 50% (6 out of 12) of the controls (Chi-square = 4.05; $p < .05$). Moreover, patients were able to differentiate between yohimbine and placebo intake within a significantly shorter time (× patients = 27.7 min; × controls = 80 min; VA: $dF = 1,22$; $F = 28.71$; $P < 0.001$)

Yohimbine increased all items on the analog scale compared with placebo as shown by the significant

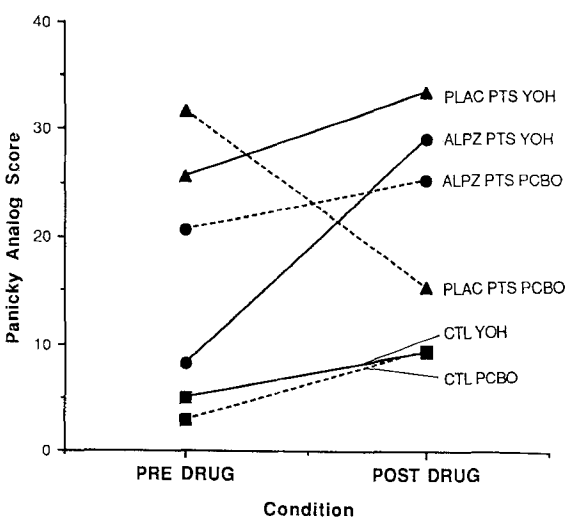

Fig. 1. Panicky ratings. Effects of yohimbine (YOH) and placebo (PCBO) on self ratings of panicky in controls (CTL), patients under placebo (PLAC PTS) and patients under alprazolam (ALPZ PTS) medication.

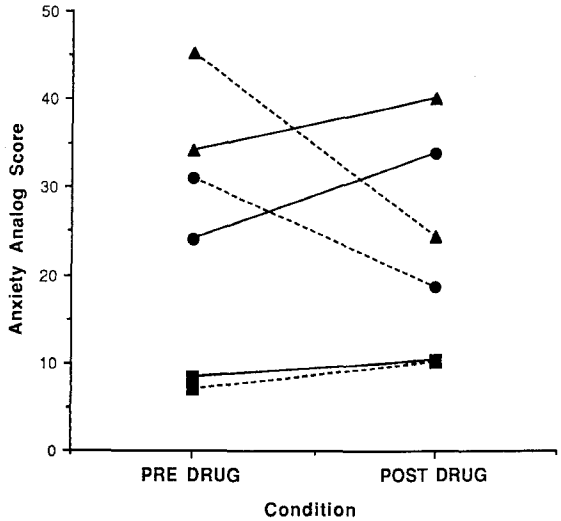

Fig. 2. Anxiety ratings. Effects of yohimbine (YOH) and placebo (PCBO) on self ratings of anxiety in controls (CTL), patients under placebo (PLAC PTS) and patients under alprazolam (ALPZ PTS) medication. Symbols see Fig. 1

D × T interactions in Table 3. However this was almost entirely due to the patients who were significantly more affected by yohimbine than were controls on 'panicky' and 'anxiety' ratings as indicated by the D × T × G interactions (Table 3, Fig. 1). Separate ANOVAs for the patients and controls showed significant D × T interactions for the patients, but not for the controls, on all scales. The overall analog ratings of these anxiety symptoms were higher in patients than in controls except for 'panicky'. This is due in part to a low predrug value in the alprazolam patients rather than to greater within-group variability on this measure.

Incidence of Panic Attacks After Yohimbine Adminstration

In spite of higher levels of anxiety, nervousness and panicky feelings none of the patients experienced a panic attack according to the required criteria.

Physiological and Biochemical Effects of Yohimbine

Several heart rate variables were affected significantly by yohimbine for the subjects as a whole as shown by D × T interactions (Table 3). The most significant effects are for variables that reflect high peak HR levels (maximum HR, SD high HR). Although the D × T × G interactions for these HR variables were not significant, separate ANOVAs for patients and controls confirm the impression given by Table 2 that the overall effects obtained are due to significant effects for the patients. There were no significant effects of yohimbine on resting HR in controls. There were no yohimbine effects in the low HR points. Yohimbine significantly lowered skin temperature for the patients ($P < 0.001$ for patients only), more so in the alprazolam group (D × T × Medi-

Table 2. Effect of yohimbine and placebo on mean heart rate, maximum heart rate, high heart rate variability (SD high heart rate) and skin temperature in controls (n = 12), patients under placebo (Plac. Pat. n = 8) and patients under alprazolam (Alpr. Pat. n = 7) medication (* $P < 0.05$)

	Controls		Plac. Pat.		Alpr. Pat.	
	Placebo (Mean ± SD)	Yohimbine (Mean ± SD)	Placebo (Mean ± SD)	Yohimbine (Mean ± SD)	Placebo (Mean ± SD)	Yohimbine (Mean ± SD)
Mean heart rate						
Mean baseline	66.8 ± 6.3	71.2 ± 5.6	68.1 ± 8.3	67.1 ± 9.2	67.8 ± 6.5	68.9 ± 7.1
Mean 90 min	61.0 ± 5.7	65.7 ± 5.3	64.5 ± 9.1	66.2 ± 7.9	67.2 ± 6.9	69.2 ± 7.2
Change from baseline	−5.8	−5.8	−3.6	−0.9	−0.6	0.3
Yohimbine-placebo difference	0.0		2.7		0.9	
Maximum heart rate						
Mean baseline	77.2 ± 8.4	81.4 ± 6.8	87.4 ± 12.8	79.5 ± 11.9	77.8 ± 7.6	79.5 ± 9.7
Mean 90 min	73.8 ± 8.9	81.7 ± 8.2	81.1 ± 8.3	84.2 ± 9.3	76.1 ± 7.9	84.5 ± 7.6
Change from baseline	−3.4	0.3	−6.3	4.7	−1.7	5.0
Yohimbine-placebo difference	3.7		11.0*		6.7	
SD high heart rate						
Mean baseline	2.7 ± 0.9	2.8 ± 1.3	4.8 ± 3.3	3.3 ± 1.4	2.7 ± 0.9	2.7 ± 0.9
Mean 90 min	4.6 ± 1.7	5.5 ± 2.4	4.6 ± 2.0	5.5 ± 3.0	3.3 ± 1.1	4.8 ± 1.9
Change from baseline	1.9	2.7	−0.2	2.2	0.6	2.1
Yohimbine-placebo difference	0.8		2.4		1.5	
Skin temperature						
Mean baseline	33.59 ± 1.20	32.36 ± 2.43	29.25 ± 2.36	30.78 ± 1.98	30.16 ± 4.19	32.06 ± 2.94
Mean 90 min	30.59 ± 2.69	30.45 ± 3.43	28.68 ± 2.88	27.96 ± 2.62	29.38 ± 3.04	27.17 ± 2.39
Change from baseline	−3.00	−1.91	−0.57	−2.82	−0.78	−4.89
Yohimbine-placebo difference	1.09		−2.25		−4.11	

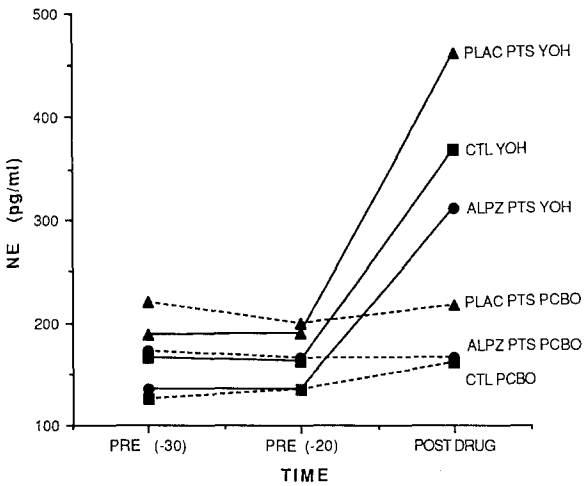

Fig. 3. Plasma NE. Effects of yohimbine (YOH) and placebo (PCBO) on norepinephrine (NE) secretion in controls (CTL), patients under placebo (PLAC PTS) and patients under alprazolam (ALPZ PTS) medication

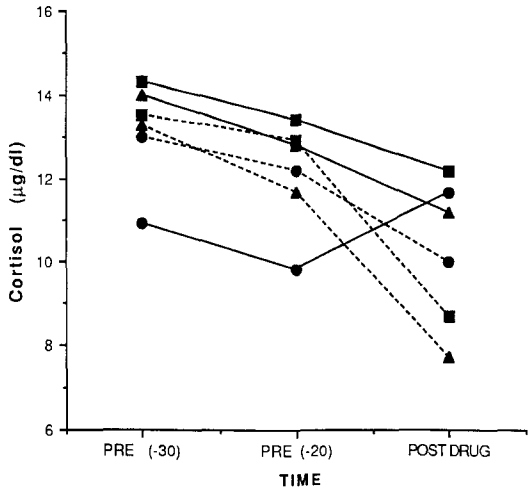

Fig. 4. Cortisol. Effects of yohimbine (YOH) and placebo (PCBO) on cortisol secretion in controls (CTL), patients under placebo (PLAC PTS) and patients under alprazolam (ALPZ PTS) medication. Symbols see Fig. 3

cation interaction, $P < 0.05$). The opposite effect for the controls only approached significance ($P = 0.07$).

Although two electrodermal variables (NS/min and maximum SCL) were higher on yohimbine sessions than on placebo sessions, this was true of predrug as well as postdrug levels. There were no D × T or D × T × G interactions that were significant or near significant for any electrodermal variable in either the overall analyses or separate ANOVAs for each group. Therefore we can conclude that yohimbine did not affect electrodermal activity in any group. Also, yohimbine exerted no effects on respiration rates in patients and controls.

Yohimbine induced a significant increase in NE in all three groups. This increase was significant for both patients and controls and most pronounced in the placebo group compared to the alprazolam group and controls but not significantly so. As shown in Fig. 2, cortisol declined over the course of the session on the placebo days, probably due to normal circadian variation. This decline was significantly antagonized (and even reversed in the alprazolam patients) by yohimbine as shwon by the significant D × T interaction (Table 3).

Discussion

Behavioral Effects of Yohimbine

Although none of the subjects experienced a panic attack meeting our criteria, there was evidence of greater subjective sensitivity to yohimbine in the patients than in controls. Our data show that in spite of higher baseline values yohimbine increased subjective ratings of panicky and anxiety more in panic patients than in controls. This

Table 3. ANOVA summaries (3-way analysis of variance ANOVAs) with repeated measures: Controls (n = 12) vs Plac. Pat. (n = 8) vs Alpraz. Pat. (n = 7)

	Pat. vs Contr. (dF 2; 24)		Interaction drug × time (dF 1; 24)		Interaction drug × time × group (dF 2; 24)	
	F	P	F	P	F	P
Panicky			12.34	0.01	5.17	0.01
Anxiety	3.45	0.05	11.97	0.01	3.65	0.05
Nervousness	3.64	0.05	6.92	0.01		
Apprehension	4.34	0.05	7.69	0.05		
Muscle tension	5.00	0.05	6.94	0.05		
Mean heart rate			5.03	0.05		
SD mean heart rate			7.57	0.01		
Maximum heart rate			13.76	0.001		
SD high heart rate			12.74	0.01		
SCR-NS/min maximum SCL						
Skin temperature			8.68	0.01	7.17	0.01
NE			11.20	0.001		
Cortisol			7.38	0.01		

finding is in line with those reported in other investigations [Charney et al. 1984, 1987b; Uhde et al. 1984b] and shows that yohimbine is a potent anxiogenic compound. The earlier identification of yohimbine application in the patients groups is another indication of stronger yohimbine effects in panic patients. This finding suggests both a more pronounced and more sudden yohimbine effect as well as a learned sensitization to changes in NE release and cardiac functioning in the patients [Clark 1986].

In contrast to the other yohimbine challenge studies [Uhde et al. 1984b; Charney et al. 1984, 1987b], the identical dosage of yohimbine failed to induce panic attacks in any of the patients. The discrepancy with the study of Uhde et al. (1984b) can be partially explained by their assessing behavioral responses to yohimbine in terms of both severe anxiety and panic.

Since half of our patients were treated with alprazolam it can be assumed that although it did not alter subjective anxiety responses to yohimbine, alprazolam exerted antipanic efficacy [Charney and Heninger, 1985b]. In the Charney (1984) study about half of the patients had more than 2.5 panic attacks/week. It was these patients who had larger increases in anxiety than the patients with fewer panic attacks. Since only one of the Ss in our placebo group had more than 2.5 panic attacks/week, we can conclude that yohimbine does not necessarily induce panic attacks in patients with only a few panic attacks/week.

Alprazolam Effects on Behavioral Ratings

The finding that alprazolam did not alter anxiety responses to yohimbine contrasts with the findings of Charney and Heninger (1985b). Again, differences in the patient samples investigated may explain this divergent result. While the patients in Charney's study were treated successfully with alprazolam our patient sample still suffered from panic attacks, suggesting that alprazolam reveals its anxiety blocking effects only in patients treated to the point of being free of panic.

Yohimbine Effects on Physiological and Biochemical Parameters

Similar to its effects on behavioral ratings, yohimbine induced increases in physiological and biochemical measures that are comparable with those reported in the other yohimbine challenge studies [Charney et al. 1984, 1987b]. While yohimbine administration had no effect on electrodermal activity in either patients or controls, it exerted pronounced effects on heart rate and heart rate variability in patients but generally not in controls. Since high heart rate changes are most influenced by yohimbine it is not surprising that Charney et al. (1984, 1987b), who report only overall heart rate, did not find differences in response to yohimbine. Changes specifically in high HR and in HR variability could be secondary to increases in tidal volume such as those that would occur in hyperventilation. It was not possible to investigate this hypothesis because the strain gauge method of measuring respiration does not permit reliable comparisons of predrug and postdrug amplitudes. Because of the known noradrenergic control of HR increases [Moore and Bloom 1979], the hypothesis that yohimbine increases the cardiovascular sensitivity to such influences cannot be ruled out.

In skin temperature an actual reversal of yohimbine effects in panic patients and controls occurred with yohimbine potentiating the vasoconstriction that occurred over time in the patients but not in the controls. These data support the assumption of a higher liability in noradrenergic functioning in panic patients.

In contrast to the skin temperature and HR data, yohimbine effects on NE-secretion were comparable in patients and controls. This finding is in line with Charney's (1984; 1987b) results which also did not show greater MHPG increases after yohimbine in patients as a whole compared to controls, but only in those that panicked (1987b) or in the subgroup with more than 2.5 pa/week (1984). Thus one can assume that increased noradrenergic activity in patients compared with controls is secondary to an actual panic attack and is not evidence for altered sensitivity in alpha-2-receptor function per se in panic patients.

In concordance with Charney's results (1984, 1987b) we found greater yohimbine-induced increases in cardiovascular and subjective parameters in panic patients as a whole than in controls despite the absence of difference in NE-secretion. Therefore we can conclude that panic patients are more sensitive in their cardiovascular and subjective reactions to alpha-2 blockade but not in their noradrenergic reactions.

Impact of Base Levels and Experimental Design on Yohimbine Response

Since yohimbine induced changes in physiological, biochemical and behavioral responses that are comparable with those reported in the other yohimbine challenge studies [Charney et al. 1984, 1987b; Uhde et al. 1984b], the finding of no panic attacks in our patient sample requires further explanation. Since base levels in behavioral ratings and somatic symptoms influence the occurrence of panic attacks [Woods et al. 1986; Margraf et al. 1986], lower base levels could account for the diverging results. This does not hold for base levels in behavioral ratings, since, like in other challenge studies [Nesse et al. 1984, Charney et al. 1984, 1985b, 1987b; Pohl et al. 1988; Dillon et al. 1987; Gorman et al. 1987, 1988; Woods et al. 1985], patients showed higher ratings in panicky feelings, anxiety and nervousness at baseline. The use of a double-blind randomized design together with an instructional set which was intended to minimize anticipatory anxiety and expectancies of experiencing a panic attack may have lowered autonomic arousal compared with the findings of studies without a separate placebo challenge [Uhde et al. 1984b; Liebowitz et al. 1985; Gorman et al. 1984, 1987, 1988; Fyer et al. 1984]. This is supported by the findings of no differences in base levels of MHPG, heart rate and cortisol in the total patient groups of the other double-blind yohimbine chal-

lenge studies [Charney et al. 1984, 1987b]. That the conditions of this study were more benign than those of Charney et al. (1987b) is suggested by the fact that the baseline heart rate of the panic patients in the present study was considerably lower (67–69 bpm; see Table 2) than the patients who panicked from yohimbine (80 bpm) and even from the controls in Charney's study (74 bpm). Since higher base levels may increase the likelihood of the occurrence of panic attacks [Woods et al. 1986; Margraf et al. 1986], this could account for the difference in the incidence of panic attacks.

Nevertheless, the earlier and correct identification of yohimbine indicates that patients perceived a more sudden and a more pronounced yohimbine effect. The inclusion of two structured situations which presumably distracted patients from unpleasant bodily sensations induced by yohimbine may have also decreased the likelihood of panic attacks after yohimbine. The data on these situations will be reported in a companion article (Albus et al. this issue).

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