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# Noradrenergic Response to Intravenous Yohimbine in Patients with Depression and Comorbidity of Depression and Panic

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*Adrenergic response following infusions of yohimbine or normal saline was evaluated in 9 control subjects, 8 patients suffering from a major depressive episode (MDE), and 12 patients suffering from concurrent MDE and panic disorder (MDE + P). Blood was drawn at -20, 0, 5, 10, 20, 45, and 90 min following the infusions, and assayed for norepinephrine (NE) and 3-methoxy-4-hydroxy-phenyl glycol (MHPG). Although the patient groups exhibited higher baseline NE concentrations, and a greater NE area under the plasma concentration versus time curve ( $AUC_{0-90}$ ) during the yohimbine infusion, the differences were not statistically significant. Baseline NE was significantly correlated with the NE  $AUC_{0-90}$  in all three groups, suggesting that, although the NE system may be dysregulated in the MDE and MDE + P patients, the NE system still appears to respond somewhat predictably following a challenge, even though the actual magnitude of response may vary.*

**Key Words:** Comorbidity, depression, panic, norepinephrine, MHPG, yohimbine

## Introduction

Dysfunction of  $\alpha_2$ -adrenergic receptors has been implicated in both major depressive illness and panic disorder (Price et al 1986; Charney and Heninger 1985). Yohimbine, an  $\alpha_2$  receptor antagonist, has been used as a probe to investigate the functioning of the norepinephrine (NE) system. When administered to individuals suffering from panic disorder, yohimbine precipitates a panic attack in the majority of these individuals (Charney et al 1992), and causes significant increases in 3-methoxy-4-hydroxy-phenylglycol (MHPG). However, when yohimbine is administered to depressed persons it does not cause a sig-

nificantly greater MHPG response when compared with controls (Price et al 1986).

Comorbidity of depression and panic is found in a proportion of patients with either disorder but studies exploring  $\alpha_2$ -adrenergic function in patients with comorbidity have not been published. We have used a yohimbine challenge paradigm to compare NE system functioning among individuals suffering from major depressive illness with (MDE + P) or without (MDE) panic disorder and healthy control subjects, to test the hypothesis that NE response to yohimbine is more prominent in the comorbid (MDE + P) patients.

## Methods

Twenty-nine individuals received a yohimbine challenge, including: Nine control subjects, eight depressed subjects (MDE), and 12 persons suffering from concurrent depression and panic disorder (MDE + P). All subjects received

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sion and panic disorder (MDE + P). All subjects received a physical examination, blood chemistry, complete blood count, and electrocardiogram, as well as a low monoamine diet beginning 72 hr prior to, and lasting throughout, the study period.

The nine, medication-free control subjects (7 women, 2 men, 26 to 56 years old) were found to be free of psychiatric illness. Eight inpatients (6 women, 2 men, 18 to 48 years old) who met DSM-III diagnostic criteria for major depressive episode were included. Twelve additional inpatients (9 women, 3 men, 25 to 52 years old) met the DSM-III diagnostic criteria for panic disorder as well as for major depressive episode. All subjects were drug-free for 14 days prior to the study and all women were studied during the first 10 days of their menstrual cycle.

Subjects participated in two study sessions; at 7 AM all subjects were placed at bed rest while an intravenous catheter was placed in the arm and bed rest was maintained throughout the procedure. At approximately 8:30 AM on the first day all subjects received a double-blind, bolus intravenous injection of either normal saline (20 ml) or 0.15 mg/kg (maximum 10 mg) of yohimbine HCl (0.45 mg/ml solution). We concluded that this dose was likely to induce an increase in sympathetic outflow (Grossman et al 1991; Goldstein et al 1991), while maintaining specificity for  $\alpha_2$  receptors (Johnston and File 1989, Ramage and Tomlinson 1985). Blood samples were drawn at -20, 0, 5, 10, 20, 45, and 90 min following yohimbine administration. Plasma NE was determined using a modification of a previously published method (Eisenhofer et al 1986) and MHPG was determined by the method developed in our laboratory (Hariharan et al 1989).

The baseline values for NE and MHPG on the placebo day and on the yohimbine day were compared using an unpaired *t*-test, and comparisons among the three groups

of subjects (control, MDE, MDE + P) were accomplished using an analysis of variance (ANOVA) for repeated measures. The areas under the concentration versus time curves for both NE (NE AUC<sub>0-90</sub>) and MHPG (MHPG AUC<sub>0-90</sub>) were calculated using the trapezoidal method, adjusting for the baseline value. On the yohimbine day the NE and MHPG baseline values were correlated with NE AUC<sub>0-90</sub> and MHPG AUC<sub>0-90</sub>, respectively. Natural log transformation of all NE and MHPG values was performed prior to statistical comparisons.

## Results

Baseline NE and MHPG values were not significantly different between the yohimbine and placebo study days (Table 1). Neither of these baseline values differ among the three groups on either the placebo or yohimbine days.

All three groups showed significantly ( $p < 0.01$ , for each) higher NE AUC<sub>0-90</sub> following yohimbine, when compared with the placebo day (Figure 1). The mean NE AUC<sub>0-90</sub> following yohimbine in the MDE + P and the MDE groups did not differ significantly from the control group. Nor did the group differences in MHPG AUC<sub>0-90</sub> achieve statistical significance. The interindividual variability in all groups was very large, and probably contributed to the lack of statistically significant differences.

On the yohimbine day correlations between baseline NE and NE AUC<sub>0-90</sub>, were significant in the control ( $r = 0.77$ ,  $p = 0.014$ ), the MDE ( $r = 0.79$ ,  $p = 0.021$ ), and the MDE + P ( $r = 0.75$ ,  $p = 0.005$ ) groups. The correlation between baseline MHPG and MHPG AUC<sub>0-90</sub> following yohimbine was not significant in any of the groups.

Table 1. Norepinephrine and MHPG Baseline and AUC<sub>0-90</sub> Values (X ± SD)

	Normal saline day				Yohimbine day			
	baseline NE (pg/ml)	baseline MHPG (pg/ml)	NE AUC <sub>0-90</sub> (pg/ml × min)	MHPG AUC <sub>0-90</sub>	baseline NE (pg/ml)	baseline MHPG (pg/ml)	NE AUC <sub>0-90</sub> (pg/ml × min)	MHPG AUC <sub>0-90</sub>
Controls	247.4	3.23	1857	6.4	201.8	3.17	41077 <sup>a</sup>	80.9 <sup>a</sup>
± SD	132.5	0.69	3638	27.2	83.9	0.69	28122	53.5
(n)	9	9	8	9	9	9	9	9
MDE	295.5	2.68	3782	45.0	299.6	2.66	40773 <sup>a</sup>	61.3
± SD	93.1	1.11	11297	78.1	122.2	1.08	28763	36.6
(n)	8	8	8	6	8	8	8	8
MDE + P	295.0	3.11	3031	-12.9	305.8	3.03	61099 <sup>a</sup>	78.5 <sup>a</sup>
± SD	151.7	0.87	6252	19.6	158.4	0.81	40727	38.3
(n)	12	12	12	12	12	12	12	12

<sup>a</sup> $p < 0.05$ , using paired *t*-tests. Normal saline day compared with Yohimbine day.

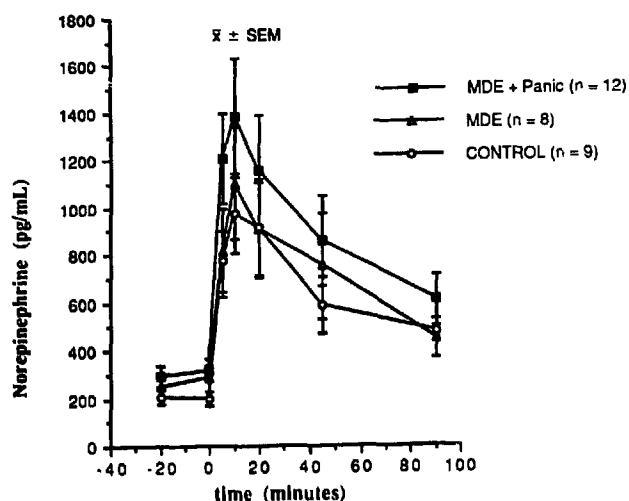


Figure 1. Norepinephrine response following yohimbine administration in MDE + P, MDE, and control groups. There were no statistically significant intergroup differences among the groups.

## Discussion

Panic disorder may be concurrently present in approximately 30% of patients suffering from MDE (Leckman et al 1983; Fawcett and Kravitz 1983). This subgroup of depressed patients may exhibit a more severe disease course and respond less well to treatment (Leckman et al 1983; Grunhaus et al 1986), so there is reason to suspect that this subgroup may exhibit a unique response to a noradrenergic challenge. Although response of MDE + P to a yohimbine challenge has not previously been reported, Price et al (1986) reported that the MHPG response following yohimbine did not differ when patients suffering

from depression were compared with controls. Similarly, we found no significant difference in MHPG  $AUC_{0-90}$  between the control and MDE groups. We also found no significant difference in MHPG  $AUC_{0-90}$  between the MDE + P and the control (or MDE alone) groups. This was unexpected because Charney et al (1992, 1987) has documented significantly greater MHPG concentrations at 2, 3, and 4 hr following yohimbine in patients suffering from panic disorder. In our patients the comorbidity of depression and panic may have attenuated the response that would have been seen if patients were suffering from panic alone.

The relationship of baseline NE to NE  $AUC_{0-90}$  following the yohimbine challenge was determined by correlating baseline NE with NE  $AUC_{0-90}$ . In all groups a significant correlation was found between the baseline NE and the NE  $AUC_{0-90}$  following yohimbine, suggesting that, although the relationship may differ among the different groups, the NE output following  $\alpha_2$  blockade is directly related to the baseline NE tone. This implies that, although the NE system may be dysregulated in MDE and MDE + P patients, the system is still working in synchrony, such that it can respond somewhat predictably following a challenge, even though the actual magnitude of the response may vary depending on the patient population.

Overall, we found that all groups exhibited increases in NE and MHPG following yohimbine, but the large interindividual variability precludes any firm conclusions regarding a differential response among our groups. Although a slightly higher mean NE response to yohimbine in our patient groups, compared with controls, suggests that, while significant differences may exist, a larger sample size would be necessary to exhibit such a difference.

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