Alpha2-Adrenoreceptor Status in Obsessive-Compulsive Disorder

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Ten patients with obsessive-compulsive disorder (OCD) and 13 normal control subjects received intravenous infusions of 2×10^{-6} g/kg of clonidine and normal saline on separate days. Responses to the drug relating to plasma growth hormone (GH), 3-methoxy-4-hydroxyphenylglycol (MHPG), heart rate, blood pressure, and several symptoms were determined. Additionally, platelet alpha2-adrenoreceptor binding was measured in most of the subjects. GH, MHPG, blood pressure, and heart rate responses to clonidine did not differ between groups. As expected, patients reported more symptoms than normal subjects, and clonidine was sedating for both groups. Patients did not differ from normal subjects in the symptom response to clonidine. The maximum number of binding sites (B_{max}) for tritiated clonidine was significantly greater in OCD patients than in normals. This pattern of alpha2-adrenoreceptor status is different than the patterns in major depression and panic anxiety.

Introduction

Obsessive-Compulsive disorder (OCD) has been considered to be a rare and treatment-refractory disorder. However, a recent epidemiological study (Karno et al. 1988) has reported that OCD is one of the more prevalent psychiatric disorders (1.2%-2.4%). Serotonergic drugs, such as clomipramine (Insel et al. 1983; Zak et al. 1988), fluvoxamine (Goodman et al. 1989), and fluoxetine (Turner et al. 1985; Jenike et al. 1989), have been reported to be effective in the treatment of OCD. The effectiveness of serotonergic drugs has led to the serotonergic hypothesis of OCD (Zohar et al. 1987). Other biological studies also support the significant role of serotonin in OCD (Zohar and Insel. 1987; Zohar et al. 1987; Hollander et al. 1988).

Prior studies have indicated that adrenergic abnormalities, including alpha adrenoreceptor (Cameron et al., 1984; Roy-Byrne and Uhde. 1985; Albus et al. 1986; Charney

et al. 1989; Sevy et al. 1989) and beta adrenoreceptor (Lima and Turner 1983; Albus et al. 1986; Brown et al. 1988) binding abnormalities, as well as abnormal responses to infusions of alpha$_2$ adrenergic drugs (Charney et al. 1984; Siever et al. 1985; Charney and Heninger 1986; Uhde et al. 1986; Nutt 1989) and beta adrenergic drugs (Nesse et al. 1984), may be present in panic anxiety and generalized anxiety disorder; however, not all studies have observed differences (Nutt and Fraser 1987; Norman et al. 1987; Stein and Uhde 1988; Schittecatte et al. 1988; Uhde et al. 1989). Similar abnormalities of beta adrenoreceptor binding parameters (Extein et al. 1979; Pandey et al. 1979; Mann et al. 1985; Wood et al. 1986; Carstens et al. 1987) and responses to adrenergically active drugs (Matussek et al. 1980; Checkley et al. 1981; Charney et al. 1982; Siever and Uhde 1984; Siever et al. 1985; Nutt and Cowan 1987; Amsterdam et al. 1989), but not of alpha$_2$ adrenoreceptor binding (Cameron et al. 1984; Katona et al. 1987; Sevy et al. 1989), have been observed in major depressive disorder. Individuals with both depression and panic appear to have alpha$_2$-adrenoreceptor binding similar to panic patients (Grunhaus 1988; Grunhaus et al. in press). Thus, there is evidence of adrenergic dysfunction in some of the anxiety disorders as well as in major depression.

Unlike studies of serotonergic activity in OCD, and in contrast to studies in other anxiety disorders, studies of adrenergic function in OCD are few and results are conflicting. Siever et al. (1983) have reported blunted plasma growth hormone (GH) responses to clonidine, an alpha$_2$-adrenoreceptor agonist. As clonidine appears to increase GH release via postsynaptic receptor stimulation (Eriksson et al. 1982), the results of Siever et al. (1983) suggest that postsynaptic alpha$_2$-adrenoreceptor sensitivity is decreased in OCD. In addition, Hollander et al. (1988) have reported a significant reduction in obsessions in response to clonidine infusion. However, Rasmussen et al. (1987) reported no significant effect of yohimbine, an alpha$_2$-adrenoreceptor antagonist, on OCD symptoms, and no difference in the plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) response to yohimbine between OCD patients and normal subjects.

In order to clarify the role of adrenergic mechanisms in OCD, we attempted to replicate the previously reported abnormal GH response to clonidine in these patients. We also evaluated the MHPG, heart rate, blood pressure, and symptom responses to clonidine in the same individuals. Finally, we determined platelet alpha$_2$-adrenoreceptor binding in some of the same subjects who received the clonidine challenge.

Methods

Subjects

Ten patients with OCD (5 men, 5 women, mean age 33.6 ± 10.0 years, mean duration of illness 8.1 ± 16.6 years) and 13 normal subjects (7 men, 6 women, mean age 32.7 ± 10.0 years) were studied. All patients met DSM-III criteria (American Psychiatric Association, 1980) for OCD. None had other Axis I diagnoses known to be associated with a blunted GH response to clonidine, including major depression (Matussek et al. 1980; Checkley et al. 1981; Charney et al. 1982; Siever and Uhde 1984), panic disorder (Charney and Heninger 1986; Uhde et al. 1986; Nutt 1989), or alcohol dependence (Matussek et al. 1984). No normal subject reached criteria for any DSM-III Axis I disorder. A semistructured psychiatric interview was used for diagnostic evaluation of all subjects. Medical history, physical examination, and screening laboratory studies were used to insure that all subjects were medically healthy and were drug free for at least 2 weeks before testing. Female subjects were studied within the first 10 days of the menstrual

cycle; no menopausal women were studied. Only one of the patients was hospitalized at the time of study. Subjects with regular alcohol consumption equivalent to, or greater than, an average of four cans of beer per week were excluded. All subjects gave written informed consent.

Procedure

All subjects were studied twice on separate days; no more than 7 days separated the first and second infusions for any subject. On one of the days an active drug was administered, on the other, a saline "placebo." Subjects were told that the infusion order was random. However, to avoid "breaking the blind" (intravenous clonidine is very sedating), all subjects except one received the saline infusion first.

All subjects were admitted to the University of Michigan Medical Center Clinical Research Center the night before each study day, and remained in bed after midnight other than for brief bathroom use. All subjects fasted from midnight. At 8 AM, a 21-gauge "heparin lock" needle was inserted into an antecubital vein. Baseline blood samples were collected 60 and 75 min after needle insertion. After the 75-min blood sample, either 2 μg/kg (2 × 10⁻⁶ g/kg) of clonidine in 10 ml of normal saline, or 10 ml of saline ("placebo") was administered intravenously over 10 min. Additional blood samples were collected at 15, 30, 45, 60, 90, 120, and 180 min after infusion. Blood pressure, heart rate, and symptom ratings were obtained at the times of each blood sample. Symptom ratings were analog measures, from 0 ("none") to 9 ("most ever"). The symptoms rated included "sad," "confused," "worried," "tense," "tired," "feeling good," "panic," "drowsy," "fatigue," "dizzy," "headache," "dry mouth," and "nausea"; the state portion of the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al. 1969) was also completed at each of these times. Ratings for "obsessions" and "compulsions" would have been highly desirable, but we were not convinced that analog scales for such complex symptomatology would be valid or even reliable; thus, they were not included. For 8 of the OCD patients and 7 of the normal controls, blood samples for platelet alpha₂-adrenoreceptor binding assays were obtained at the time of the 60-min baseline sample.

Biochemical Assays

For measurement of plasma GH and MHPG, 7-ml blood samples were collected into tubes containing heparin and EDTA. Plasma was separated and frozen at −80°C until assay. Plasma GH was measured by radioimmunoassay, and plasma MHPG was measured by HPLC with our previously published method (Hariharan et al. 1989).

Platelet membrane alpha₂-adrenoreceptor binding assays were performed by our previously published method (Garcia-Sevilla et al. 1981). The maximum number of binding sites (B_{max}) and apparent dissociation constant (K_D) were determined for the specific binding of tritiated clonidine, a specific partial agonist, and for tritiated yohimbine, a specific antagonist, to fresh (never-frozen) platelet membranes. Specific binding was approximately 85% for clonidine and 90% for yohimbine.

Data Analysis

Values for each dependent variable at each time point on the clonidine day minus the same values on the saline "placebo" day (difference scores) were used for data analysis of the clonidine challenge data. A profile analysis, a multivariate analog of a between-
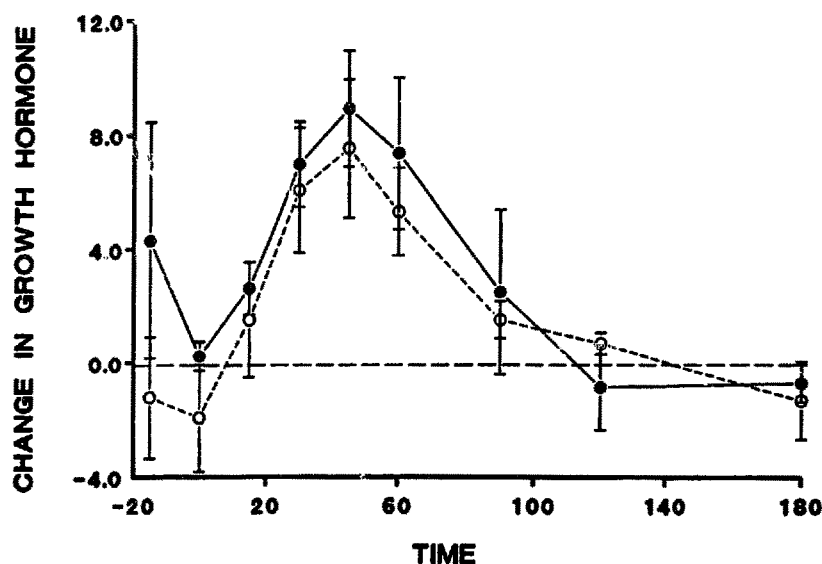
Figure 1. Means and standard errors of the means for plasma growth hormone (GH) levels (ng/ml) at 15 and 0.5 min before, and 15, 30, 45, 60, 90, 120, and 180 min after intravenous infusion of 2 μg/kg (2 × 10^{-6} g/kg) of clonidine, for patients with obsessive-compulsive disorder (OCD) and for normal subjects. GH data were calculated for each subject at each time point as the difference between the GH level after clonidine minus the GH level obtained at the same time after administration of a saline "placebo" infusion, given on a separate day. The solid line represents normal subjects and the dotted line represents patients. Both groups demonstrated a significant GH increase in response to clonidine; no difference between groups was observed.

within repeated-measures analysis of variance (ANOVA) (Harris 1975), was performed for each dependent variable for OCD patients versus normal subjects. For clarity of interpretation of results, the heart rate, and the symptom data, separate profile analyses of the actual values on the two study days were also performed and reported if significant. Receptor binding data from OCD patients were compared with normal subjects with the Kruskal-Wallis ANOVA for ranked data. Pearson product-moment correlations were performed among the physiological and receptor-binding data. Student's t-tests were also used.

Results

Clonidine Challenge

In all subjects, plasma GH increased significantly in response to clonidine (profile analysis of difference scores, $F = 5.59$, $p = 0.004$). Peak responses to 2 μg/kg of intravenous clonidine for both groups occurred at 45 min postinfusion; levels returned to baseline within 120 min. For all subjects, clonidine increased GH an average of 8.5 ng/ml above the average baseline level of 2.7 ng/ml. This increase was approximately 120% of the increase (approximately 7.0 ng/ml) reported in 22 normal subjects in response to 1.5 μg/kg of intravenous clonidine (Nutt and Glue 1988). There was no difference in GH response in patients versus normal subjects (Figure 1). Peak GH response (highest level attained at any post-clonidine sampling time) and mean GH level at 30, 45, and 60 min post-clonidine for OCD patients, but not for normal subjects, were significantly negatively
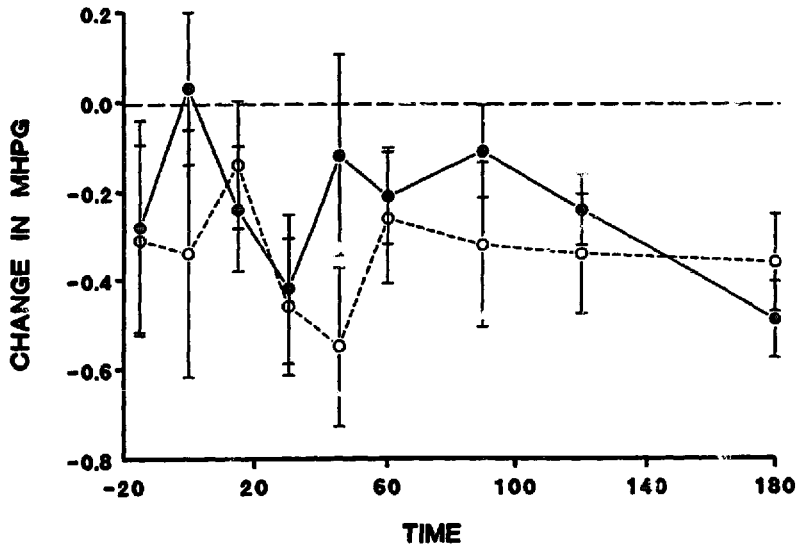
Figure 2. Means and standard errors of the means for plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) (ng/ml) after clonidine. Details are the same as in Figure 1. No significant group difference was observed. There was a strong trend ($p = 0.06$) for clonidine to produce a significant decrease in MHPG.

correlated with a subjective rating of perceived stress for the 6 months prior to study ($r = -0.84$, $t = 4.15$, $p = 0.004$, and $r = -0.83$, $t = 3.93$, $p = 0.006$, respectively). In other words, higher stress ratings were associated with greater blunting of the GH response.

There was a trend towards a significant decrease in MHPG in response to clonidine for both groups (profile analysis of difference scores, $F = 2.69$, $p = 0.06$). No difference between groups was observed (Figure 2)

By profile analysis of difference scores, large and significant decreases in response to clonidine were observed for both systolic ($F = 10.5$, $p = 0.0001$) and diastolic ($F = 6.85$, $p = 0.001$) blood pressures (not shown); the average maximum decreases were 17.3 mm Hg systolic at 90 min postinfusion ($t = 5,12$, $p < 0.0001$) and 13.5 mm Hg diastolic at 45 min postinfusion ($t = 6.27$, $p < 0.0001$). For both systolic and diastolic pressures, substantial decreases were observed within 15 min postinfusion, which persisted throughout the 3-hr session. No difference between groups was observed.

Normal subjects had a lower mean heart rate than patients with OCD by approximately six beats per min on both days (not shown); this was significant for the saline placebo day (profile analysis of placebo data, $F = 3.01$, $p = 0.03$). Clonidine produced small mean decreases in heart rate of less than four beats per min at each time point for both groups. Patients and normal subjects were equally sensitive to the clonidine effect on heart rate.

Normal subjects had low mean symptom levels (less than 2.0 for all symptom variables at all time points), except for "feeling good" (>7.0) and the STAI (<28, range of possible scores is 20–80), on the placebo day; levels were comparably low on the clonidine day for all variables except "tired" (<3.0), "drowsy" (<4.5), "fatigue" (<2.5), and "dry mouth" (<3.0). On the placebo day, symptom scores were significantly higher (profile analyses of placebo data) for patients than for normal subjects for "sad" (peak

level 3.6, $F = 16.0$, $p = 0.0006$), "worried" (peak 4.7, $F = 20.79$, $p < 0.0002$), "tense" (peak 3.3, $F = 16.3$, $p = 0.0005$), "tired" (peak 4.8, $F = 10.1$, $p = 0.004$), "fatigue" (peak 4.1, $F = 8.28$, $p = 0.009$), "headache" (peak 3.0, $F = 4.72$, $p = 0.04$), and the STAI (peak 49, $F = 79.7$, $p < 0.0001$), and significantly lower for "feeling good" (peak 4.9, $F = 22.1$, $p = 0.0001$). On the clonidine day, levels for patients remained significantly higher (by profile analyses of clonidine data) for "worried" (peak 2.6, $F = 10.6$, $p = 0.004$), "tense" (peak 2.0, $F = 6.51$, $p = 0.02$), "tired" (peak 5.3, $F = 4.95$, $p = 0.04$), and for the STAI (peak 45, $F = 38.8$, $p = 0.006$), and remained lower for "feeling good" (peak 5.8, $F = 9.12$, $p = 0.006$), but was no longer significantly different for "sad," "fatigue," or "headache." Additionally, after clonidine, but not after placebo, "confused" was significantly higher for patients (peak 2.4, $F = 5.09$, $p = 0.03$). Based on all subjects (profile analyses of difference scores), clonidine produced increases in "tired" ($F = 4.34$, $p = 0.008$) and "drowsy" ($F = 5.08$, $p = 0.004$). For patients, on the placebo day, "worried" and "tense" demonstrated a pattern of monotonic decrease over time, whereas on the clonidine day there was a pattern first of increasing then decreasing scores; thus, despite the sedative effects, clonidine demonstrated no clear tension-reducing effect. (Results of profile analyses for the difference scores for the symptom variables agreed with the above results.) In summary, OCD patients reported substantial symptomatology on both days, and clonidine produced the expected sedative effect in both subject groups; normal subjects reported few symptoms other than sedation, and there was no clear-cut difference between patients and normal subjects in the effects of clonidine on symptom levels. Clonidine did not produce tension reduction in the patients.

The mean scores for the Carroll Rating Scale for Depression were significantly higher for the patients than for the normal subjects on both the placebo day (14.8 versus 1.3, Kruskal-Wallis statistic $= 11.4$, $p = 0.0007$) and the clonidine day (13.2 versus 1.1, Kruskal-Wallis statistic $= 6.48$, $p = 0.01$). These scores, however, are substantially lower than those observed in people with primary depression (Carroll et al. 1981; Feinberg et al. 1981; Nasr et al. 1984). The mean scores for the trait portion of the STAI, for normal subjects and patients respectively, were 29.2 versus 54.4 (Kruskal-Wallis statistic $= 12.6$, $p = 0.0004$) on the placebo day, and 26.5 versus 47.5 (Kruskal-Wallis statistic $= 9.71$, $p = 0.002$) on the clonidine day. These scores are comparable with the published levels for nonpatient populations and for psychiatric outpatients (Spielberger et al. 1969).

Platelet Membrane Binding

Age and gender ratios did not differ significantly between the patients and normal subjects who had the receptor assays. The maximum number of binding sites (B_{max}) for the binding of the agonist tritiated clonidine to platelet alpha$_2$-adrenoreceptors was significantly greater (Kruskal-Wallis statistic $= 4.10$, $p = 0.04$) in patients with OCD than in normal subjects (Table 1). The B_{max} for binding of the antagonist tritiated yohimbine was also greater in patients, but this difference did not reach statistical significance. Clonidine and yohimbine dissociation constants (K_D) did not differ between groups.

Correlations were performed, including the various physiological dependent variables in the clonidine challenge protocol and the platelet-binding parameters. No robust correlations or patterns of correlations among variables emerged.

Table 1. Platelet Alpha$_2$-Adrenoreceptor Binding Results in Patients with Obsessive-Compulsive Disorder (OCD) and in Normal Controls

	OCD (n = 8)	Normals (n = 7)
Clonidine B$_{max}$ (fmol/mg protein)[a]	41.3 ± 17.2	29.1 ± 9.48
Yohimbine B$_{max}$ (fmol/mg protein)	146 ± 87.3	111 ± 39.4
Clonidine K$_D$ (nM)	8.90 ± 6.80	5.17 ± 2.34
Yohimbine K$_D$ (nM)	2.32 ± 0.45	2.36 ± 0.78

[a]p = 0.04 for OCD patients versus normal subjects by Kruskal-Wallis ANOVA for ranked data.

Discussion

Patients had higher scores than normal subjects on several of the symptom ratings on both of the study days. Nevertheless, none of the physiological dependent variables in the clonidine challenge protocol (GH, MHPG, heart rate, and systolic and diastolic blood pressure) differentiated patients with OCD from normal subjects on either study day, and there was no difference in the symptom response to clonidine between patients and normal subjects. In contrast to the lack of difference between groups for the clonidine infusion protocol variables, the maximum number of platelet binding sites (B$_{max}$) for the alpha$_2$-adrenoreceptor partial agonist tritiated clonidine was significantly greater in patients than in normal subjects, and there was a nonsignificant increase for the B$_{max}$ for the antagonist tritiated yohimbine. Because of the sample size, the binding data results should be considered preliminary.

The results of this study differ from those of Siever et al. (1983). In their study, the GH response to the same dose of clonidine was blunted in OCD patients. Additionally, in the prior study, pre-clonidine MHPG levels showed a trend to be greater for patients than for normal subjects; this increase was not observed in the present study. Finally, in the prior study, pre-clonidine norepinephrine levels (which were not measured in the present study) were also higher in the patient group.

It is not certain why there were differences between the results of our study and that of Siever et al., but some possibilities are apparent. First, even though the difference was not significant, the mean pre-clonidine GH level for patients in the prior study was 180% of the mean for normal subjects, a difference that did not occur in the present study. Second, subjects in the prior study had only one experimental session, whereas all subjects in the present study had the experience of having the experimental procedure twice; with the exception of one subject, the first of these sessions was with saline and the second was with clonidine. It is possible that a novelty and/or anxiogenic effect of the first experimental session interacted with the effects of the clonidine infusion to produce a blunted response in the prior study (in the present study, by paired t-tests in the patient group, only there were trends for the symptom variables "worried" and "tense" to be higher immediately prior to infusion on the first study day—for both, $0.05 < p < 0.10$). Third, although the prior investigators did exclude subjects with depressive disorder, they do not state whether or not subjects were excluded for the presence of other anxiety disorders or for moderate alcohol use. Fourth, it is not known what drug-free time period is actually necessary to guarantee that residual psychotropic drug effects are not occurring; possibly, unidentified differences between the studies in the drug-free period could have had an effect on outcome. And, last, as noted above, in this study, patients who rated

themselves as most "stressed" during the previous 6 months demonstrated the most blunting of the GH response. Thus, even though the OCD patients as a group did not demonstrate a blunted GH response, it is possible that a subgroup of highly "stressed" patients (the most symptomatic with OCD?) do show some blunting. If the patients in the study by Siever et al. were more "stressed," a difference in study outcome could be accounted for. Resolution of these questions awaits further study. Our results appear to be in agreement with those of Rasmussen et al. (1987) who found no difference between normal subjects and OCD patients in MHPG changes in response to challenge with the antagonist yohimbine, and with Hollander et al. (1989) who reported no blunting of the GH response to clonidine in OCD patients.

As described above, blunted GH responses to clonidine are well documented in both major depression and panic anxiety. Additionally, the GH response to growth hormone-releasing factor is blunted in panic patients (Rapaport et al. 1989). In major depression, the number of platelet $alpha_2$-adrenoreceptor binding sites is normal or increased, depending at least in part on whether an agonist or an antagonist ligand is used (Cameron et al. 1984; Katona et al. 1987; Sevy et al. 1989). In panic anxiety, the number of sites, as measured with tritiated clonidine or yohimbine, is normal or decreased (Cameron et al. 1984; Albus et al. 1986; Nutt and Fraser 1987; Charney et al. 1989). Based on these prior studies, and assuming that the results of the present study are correct (i.e., the GH and MHPG responses to clonidine infusion are normal, and tritiated clonidine binding is increased), it appears that the status of the $alpha_2$-adrenoreceptor is different in OCD than in either of these other disorders.

Differences in the patterns of abnormalities in the GH response to clonidine versus in the magnitude of platelet binding across different diagnostic groups (depressed, anxious, and normal individuals) suggests that the platelet and the hypothalamus have different populations of $alpha_2$-adrenoreceptors, as has been suggested previously (Hamilton and Reid 1986). Alternatively, another abnormality (instead of, or in addition to, the presumptive $alpha_2$-adrenoreceptor abnormality) might be present at some other point(s) in the central nervous system (CNS)—pituitary pathway(s) mediating the clonidine-stimulated GH response. The meaning of the platelet and the hypothalamic $alpha_2$-adrenoreceptor abnormalities for the pathophysiologies of these psychiatric disorders is not yet known.

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