

## Relationship Between Alpha<sub>2</sub>-Adrenergic Function and Suicidal Behavior in Depressed Patients

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**Abstract.** The current main neurochemical theories of the biological correlates of suicidal behavior involve serotonergic and, to a lesser extent, dopaminergic systems. Few data are available about the possible implication of the noradrenergic function. In the present study, we assessed the growth hormone response to clonidine, a selective  $\alpha_2$ -adrenergic agonist, in 15 *DSM-III-R* major depressive inpatients with a history of suicide attempts, compared with 15 age- and gender-matched major depressive inpatients without a history of suicidal behavior. Mean ( $\pm$  SD) growth hormone peak responses to clonidine were significantly lower in the group of suicide attempters than in the control group:  $2.93 \pm 3.01$  ng/ml vs.  $8.28 \pm 8.15$  ng/ml. Therefore, these results suggest that a blunted growth hormone response to clonidine could be a biological correlate of suicidal behavior.

**Key Words.** Affective disorder, growth hormone, clonidine, norepinephrine.

The prevailing neurochemical theory about biological correlates of suicidal behavior focuses on the serotonergic system. In 1976, Åsberg et al. found a bimodal distribution of cerebrospinal fluid (CSF) concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in depression (Åsberg et al., 1976a). They showed that patients who attempted suicide before being hospitalized had low CSF 5-HIAA levels compared with those without a history of suicide attempt (Åsberg et al., 1976b). Several studies in different diagnostic categories confirmed that patients who attempted suicide had lower CSF 5-HIAA levels than control subjects (Brown et al., 1979, 1982; Ågren, 1980; Träskman et al., 1981; van Praag, 1982, 1983; Banki and Arató, 1983; Ninan et al., 1984). The role of serotonin in the biology of suicidality was also assessed in post-mortem (Mann et al., 1986a) and platelet studies (Meltzer and Arora, 1986) with controversial results.

A dopamine dysfunction could also be related to suicidal behavior. Indeed, some studies reported low CSF levels of the dopamine metabolite homovanillic acid in depressed patients with a history of suicide attempt (Ågren, 1980, 1983; Träskman et al., 1981; Montgomery and Montgomery, 1982; Roy et al., 1986). Recently, we showed

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that patients with a history of suicidal behavior exhibited a significantly lower growth hormone (GH) response to apomorphine, a selective dopaminergic agonist, than patients who had never attempted suicide (Pitchot et al., 1992). This finding suggested that a hyposensitivity of dopaminergic receptors could be related to suicidal behavior.

Few data are available about the implication of the noradrenergic system in suicidal patients. In 1976, Beskow et al. showed a decrease of norepinephrine levels in the putamen of suicide victims. In post-mortem studies,  $\beta$ -adrenergic receptor binding has been found significantly increased in the frontal cortex of suicide victims compared with controls (Zanko and Biegon, 1983; Mann et al., 1986b). Secunda et al. (1986) showed smaller urinary outputs of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and a lower plasma concentration of MHPG in suicide attempters compared with patients without a history of suicidal behavior. CSF studies have also provided additional but inconsistent data for the noradrenergic hypothesis of suicidal behavior. Brown et al. (1979) found higher levels of CSF MHPG in personality disordered patients with a history of suicide attempts than in control subjects. Ågren (1980) reported a negative correlation between measures of suicidal tendencies and CSF MHPG levels in depressed patients. However, Roy et al. (1989), who studied CSF, urinary, and plasma indices of noradrenergic function, did not find any relationship between norepinephrine and suicidal behavior.

In this context, the aim of the present study was to assess noradrenergic function in depressed suicide attempters by measuring the GH response to an intravenous clonidine challenge. Clonidine exhibits a highly specific  $\alpha_2$ -adrenergic agonistic activity and stimulates GH secretion through postsynaptic  $\alpha_2$ -adrenergic receptors in the hypothalamus (Lal and Martin, 1980; Siever et al., 1982). This clonidine-induced GH response appears to be blunted among major depressive patients (Matussek et al., 1980; Checkley et al., 1981, 1984; Charney et al., 1982; Siever et al., 1982; Siever and Uhde, 1984; Boyer et al., 1986; Anseau et al., 1988), supporting an  $\alpha_2$ -adrenergic receptor disturbance in major depressive disorders. Here, we postulated that blunted GH responses to clonidine might be related to suicidal behavior in depressed patients.

## Methods

**Subjects.** The study was performed in 15 *DSM-III-R* major depressive inpatients with a history of suicide attempts (American Psychiatric Association, 1987) during the current episode. The patients were consecutive admissions to the Psychiatric Unit of the University Hospital of Liège, Belgium. Most of the patients (13/15) have been included in another study (Pitchot et al., 1992). Table 1 presents individual characteristics of patients 1-15. The sample comprised nine male and six female patients with a mean age of 39.2 (SD = 9.7). These patients were individually matched for gender, age (within 3 years) and, in the case of women, menopausal status to 15 major depressive inpatients without a history of suicidal behavior (Table 1: patients 16-30). The two groups did not differ in mean age or weight. All patients had a score of at least 18 on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960) at the end of a drug-free period of at least 2 weeks. Moreover, there was no difference in washout periods between the two groups.

Past history of suicide attempt was based on interviews with the patients and their family members. Suicide attempts were classified as violent (hanging, drowning, deep cuts, and

shooting) or nonviolent (drug overdoses and superficial wrist cuts). All patients were free of medical illness as evidenced by history, medical examination, electrocardiogram, chest x-ray, electroencephalogram, and routine laboratory tests. The clonidine test was performed between days 3 and 12 of the menstrual cycle in premenopausal women (Tulandi et al., 1987). Patients with a basal systolic blood pressure < 100 mmHg were excluded from the study. Moreover, to be included, patients had to have a basal ( $t_0$ ) GH level < 5 ng/ml before the pharmacological challenge (Anseau et al., 1984). The exclusion of subjects with basal GH values > 5 ng/ml was recommended by Laakmann (1990) who demonstrated that "prestimulator" healthy volunteers responded significantly less to a noradrenergic challenge than healthy volunteers with low basal values. Finally, the protocol was approved by the Ethical Committee of the University of Liège Medical School, and all patients were fully informed of the study and gave their consent.

**Neuroendocrine Test Procedure.** The clonidine test was performed in all subjects at bed-rest after an overnight fast. At 7 a.m., an indwelling catheter was inserted in a forearm vein. Blood samples of 10 ml were collected at -20, 0, 20, 40, 60, and 120 minutes after injection at 8 a.m. of clonidine, 0.15 mg diluted in saline to obtain 20 cc intravenously in 10 minutes.

GH was measured with a double antibody radioimmunoassay (Franchimont, 1968), with intra-assay and interassay coefficients of variation of, respectively,  $13.3 \pm 4.7\%$  and  $14.8 \pm 9.6\%$  and a detection limit of 0.2 ng/ml.

**Data Analysis.** GH responses to clonidine were assessed by GH peak values following injection and by the area under the curve (AUC) between  $t_0$  and  $t_{120}$  minutes. Analyses were performed using absolute GH values as well as differences related to basal ( $t_0$ ) levels (relative values). Since the correlations between absolute and relative values were very high ( $r > 0.98$ ), only absolute values are reported here. The responses of patients with and without a history of suicide attempt as well as violent and nonviolent suicide attempters were compared by analysis of covariance (ANCOVA) for age and weight.

## Results

There was a significantly weaker GH response to the clonidine test in the group of suicide attempters than in the group without a history of suicidal behavior for the GH peak responses (mean  $\pm$  SD =  $2.93 \pm 3.01$  ng/ml vs.  $8.28 \pm 8.15$  ng/ml;  $F = 3.63$ ;  $df = 3, 26$ ;  $p = 0.026$ ) and for the log of AUC values ( $F = 2.0$ ;  $df = 2, 28$ ;  $p < 0.05$ ). GH responses to clonidine did not differ significantly between melancholic and nonmelancholic depressed patients ( $F = 1.22$ ;  $df = 3, 26$ ;  $p = 0.32$ ). There was no correlation between mean GH responses and scores on the Hamilton Rating Scale for Depression ( $r = -0.004$ ,  $p = 0.98$ ).

Mean GH responses to clonidine did not differ between nonviolent (mean  $\pm$  SD =  $3.4 \pm 3.08$  ng/ml) and violent (mean  $\pm$  SD =  $2.52 \pm 3.10$  ng/ml) attempters ( $F = 0.66$ ;  $df = 3, 11$ ;  $p = 0.59$ ). Moreover, the time between the suicide attempt and the neuroendocrine investigation was not correlated with GH responses ( $r = -0.41$ ,  $p = 0.12$ ).

## Discussion

The results of the present study suggest an involvement of the noradrenergic system, particularly  $\alpha_2$ -adrenergic function, in the expression of suicidal behavior. Indeed, suicide attempters exhibited smaller GH responses to clonidine than patients without a history of suicide attempts. Thus, a hyposensitivity of  $\alpha_2$ -adrenergic receptors

**Table 1. Individual characteristics of the sample and neuroendocrine results**

| Patient | Sex   | Age  |      | HRSD | Tsa  | Nsa | Diagnosis               | History of suicide attempt | Clonidine GH peak: ng/ml |
|---------|-------|------|------|------|------|-----|-------------------------|----------------------------|--------------------------|
|         |       | (yr) | (kg) |      |      |     |                         |                            |                          |
| 1       | F     | 23   | 62   | 20   | 3    | 4   | MDD, nonmelancholic, UP | Drug overdose              | 8.2                      |
| 2       | M     | 26   | 64   | 25   | 3.5  | 2   | MDD, nonmelancholic, UP | Drug overdose              | 1.0                      |
| 3       | M     | 27   | 83   | 29   | 3    | 3   | MDD, nonmelancholic, UP | Drug overdose              | 0.7                      |
| 4       | F     | 33   | 73   | 18   | 6    | 2   | MDD, nonmelancholic, UP | Drug overdose              | 1.7                      |
| 5       | M     | 34   | 76   | 25   | 3    | 1   | MDD, nonmelancholic, UP | Hanging                    | 3.0                      |
| 6       | M     | 36   | 66   | 38   | 7    | 1   | MDD, melancholic, UP    | Defenestration             | 0.3                      |
| 7       | M     | 38   | 60   | 24   | 3    | 2   | MDD, melancholic, UP    | Hanging                    | 6.5                      |
| 8       | M     | 41   | 70   | 35   | 150  | 1   | MDD, melancholic, UP    | Hanging                    | 0.1                      |
| 9       | M     | 42   | 79   | 18   | 4    | 1   | MDD, nonmelancholic, UP | Drowning                   | 8.0                      |
| 10      | F     | 44   | 69   | 25   | 3    | 3   | MDD, melancholic, BP    | Drug overdose              | 2.1                      |
| 11      | F     | 46   | 63   | 35   | 24   | 1   | MDD, melancholic, UP    | Drug overdose              | 7.4                      |
| 12      | M     | 49   | 83   | 33   | 100  | 1   | MDD, nonmelancholic, UP | Shooting                   | 1.7                      |
| 13      | M     | 55   | 87   | 20   | 48   | 1   | MDD, nonmelancholic, UP | Hanging                    | 0.3                      |
| 14      | F     | 39   | 70   | 18   | 8    | 1   | MDD, nonmelancholic, UP | Drug overdose              | 2.7                      |
| 15      | F     | 55   | 71   | 25   | 100  | 1   | MDD, melancholic, UP    | Shooting                   | 0.3                      |
| Mean    | 9M,6F | 39.2 | 71.7 | 25.8 | 31.0 |     |                         |                            | 2.93                     |
| SD      |       | 9.7  | 8.3  | 6.7  | 47.2 |     |                         |                            | 3.01                     |

| Patient | Sex   | Age  |      | HRSD | Tsa | Nsa | Diagnosis               | History of<br>suicide attempt | Clonidine<br>GM peak: ng/ml |
|---------|-------|------|------|------|-----|-----|-------------------------|-------------------------------|-----------------------------|
|         |       | (yr) | (kg) |      |     |     |                         |                               |                             |
| 16      | F     | 26   | 67   | 18   | —   | —   | MDD, nonmelancholic, UP | —                             | 16.1                        |
| 17      | M     | 29   | 70   | 26   | —   | —   | MDD, melancholic, UP    | —                             | 27.7                        |
| 18      | M     | 29   | 70   | 26   | —   | —   | MDD, melancholic, UP    | —                             | 1.0                         |
| 19      | F     | 36   | 49   | 35   | —   | —   | MDD, nonmelancholic, UP | —                             | 12.8                        |
| 20      | M     | 37   | 87   | 29   | —   | —   | MDD, melancholic, BP    | —                             | 0.8                         |
| 21      | M     | 34   | 84   | 28   | —   | —   | MDD, nonmelancholic, UP | —                             | 2.5                         |
| 22      | M     | 36   | 74   | 30   | —   | —   | MDD, nonmelancholic, UP | —                             | 0.5                         |
| 23      | M     | 41   | 88   | 23   | —   | —   | MDD, nonmelancholic, UP | —                             | 0.2                         |
| 24      | M     | 45   | 103  | 18   | —   | —   | MDD, nonmelancholic, UP | —                             | 3.4                         |
| 25      | F     | 42   | 52   | 21   | —   | —   | MDD, nonmelancholic, UP | —                             | 12.7                        |
| 26      | F     | 44   | 52   | 25   | —   | —   | MDD, melancholic, UP    | —                             | 2.8                         |
| 27      | M     | 48   | 72   | 24   | —   | —   | MDD, nonmelancholic, UP | —                             | 6.9                         |
| 28      | M     | 57   | 72   | 27   | —   | —   | MDD, nonmelancholic, UP | —                             | 8.3                         |
| 29      | F     | 36   | 74   | 33   | —   | —   | MDD, nonmelancholic, UP | —                             | 19.6                        |
| 30      | F     | 55   | 75   | 35   | —   | —   | MDD, melancholic, BP    | —                             | 8.9                         |
| Mean    | 9M,6F | 39.6 | 72.6 | 26.5 |     |     |                         |                               | 8.28                        |
| SD      |       | 9.07 | 14.5 | 5.4  |     |     |                         |                               | 8.15                        |

Note. MDD = major depressive disorder. UP = unipolar. BP = bipolar. Tsa = time in weeks between the suicide attempt and the investigation. Nsa = number of suicide attempts. HRSD = Hamilton Rating Scale for Depression. GH = growth hormone. M = male. F = female.

could be a determinant of suicidal behavior in depressed patients. Moreover, the lack of correlation between GH responses and the time between suicide attempt and neuroendocrine investigation suggests that the clonidine test might be a "trait marker" for suicidal behavior. This interpretation is consistent with previous reports that considered a blunted GH response to clonidine as an indicator of higher vulnerability to endogenous depressive illness (Checkley et al., 1984; Siever and Uhde, 1984; Hoehe et al., 1986; Siever et al., 1986; Anseau et al., 1987; Mitchell et al., 1988). However, longitudinal studies are needed to determine if a persistent hyposensitivity of  $\alpha_2$ -adrenergic receptors might be a predictor of suicide.

Our results are in agreement with previous studies showing a trend for a decrease of noradrenergic activity in depressed patients with a history of suicidal behavior. In 1982, Ostroff et al. found a lower 24-hour urinary norepinephrine-to-epinephrine ratio in three depressive patients with a history of severe suicide attempts compared with depressed control subjects without a history of suicidal behavior. Secunda et al. (1986) reported low urinary and plasma MHPG measures in suicide attempters compared with control subjects. CSF MHPG levels exhibited a similar trend only in bipolar patients (Secunda et al., 1986). Ågren (1980) showed a negative correlation between CSF MHPG concentrations and measures of suicidality in depressed patients. However, these results were not confirmed in a recent study by Roy et al. (1989) who did not find any relationship between CSF, urinary, and plasma indices of noradrenergic activity and history of suicide attempt. In fact, these studies measured a generalized noradrenergic underactivity. In the present study, we specifically assessed postsynaptic  $\alpha_2$ -adrenergic receptor sensitivity in the hypothalamic-pituitary axis.

No significant difference in GH responses was found between violent and non-violent suicide attempters suggesting that disturbances in the sensitivity of  $\alpha_2$ -adrenergic receptors are not related to impulsive autoaggression. This observation is somewhat at variance with a recent report by Coccaro et al. (1992), who found a positive correlation between GH responses to clonidine and the Buss-Durkee Hostility Inventory "irritability" subscale, but not the "assault" subscale, in personality disordered patients and healthy volunteers. Here, in depressed patients, an  $\alpha_2$ -adrenergic receptor hyposensitivity seems more related to suicidality as such than to a dysfunction in the regulation of aggression. However, our sample size is too small to exclude definitively a role for the noradrenergic system in the type of suicide attempt.

A pitfall in this study is that the 2-week drug-free washout period may have been insufficient. Indeed, several reports have suggested that tricyclic antidepressants may impair the GH response to clonidine for periods longer than 3 weeks following their discontinuation (Corn et al., 1984; Schittecatte et al., 1989). Moreover, the difference between depressed patients with or without a history of suicidal behavior is rather weak, and our results should obviously be confirmed in further studies with larger numbers of patients. It would also be interesting to investigate the GH responses to clonidine in nondepressed suicidal patients.

In conclusion, this study suggests that a blunted GH response to clonidine could serve as a biological marker of suicidal behavior. This hypothesis requires confirmation and further development.

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