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Blunted Response of Growth Hormone to Clonidine and Apomorphine in Endogenous Depression

M. ANSSEAU, R. VON FRENCKELL, J. L. CERFONTAINE, P. PAPART, G. FRANCK, M. TIMSIT-BERTHIER, V. GEENEN and J. J. LEGROS

We measured the growth hormone (GH) response to clonidine (an alpha-2-adrenergic agonist) and to apomorphine (a dopaminergic agonist) in 15 major endogenous and 15 minor depressive in-patients matched for gender and age. Results showed a significantly smaller GH response in the major depressives to both clonidine ($P<0.01$) and apomorphine ($P<0.001$). No significant difference existed between the two groups with regard to changes in blood pressure and pulse rate during either test. While major depressives showed a trend toward smaller sedative side-effects than minor depressives after clonidine, they showed significantly smaller sedative and gastro-intestinal side-effects after apomorphine. No significant correlation was present either in the major depressive or in the minor depressive group between the GH responses following clonidine and apomorphine challenges. These results support the hypothesis of both noradrenergic and dopaminergic neurotransmitter disturbances in major depression, with individual variability with regard to those biochemical anomalies.

Neuroendocrine strategy may provide an indirect index of central neurotransmission which is particularly interesting in biological psychiatry. Indeed, the release of anterior pituitary hormones depends on hypothalamic releasing factors, the secretion of which is controlled by neurotransmitters also implicated in mental illnesses. The greatest amount of information on this can be obtained from the study of growth hormone (GH) response to specific pharmacological challenges: indeed, GH secretion is stimulated by dopamine, noradrenaline through alpha receptors, and possibly serotonin, while it is inhibited by noradrenaline through beta receptors and by gamma-aminobutyric acid (GABA) (Checkley, 1980).

The current main pathophysiological theory of endogenous depression hypothesises a decreased activity in central neurotransmitter systems: noradrenergic, serotonergic, and possibly dopaminergic (Willner, 1985). These disturbances could result from a diminished neurotransmitter release or, as suggested more recently, from disturbances in the 'sensitivity' of specific receptors. Possible central catecholaminergic disturbances in depressive disorders have been assessed by the study of the GH response to various pharmacological challenges such as amphetamine, clonidine, desipramine, L-dopa, apomorphine, and carbidopa (Checkley, 1980).

With regard to noradrenergic receptors, most studies, although using poorly specific pharmacological challenges (i.e. amphetamine or desipramine), converge to suggest a smaller GH response among major depressive patients (Siever & Uhde, 1984). In comparison with those pharmacological agents, clonidine exhibits a more specific alpha-2-adrenergic agonistic activity and stimulates GH secretion through postsynaptic alpha-2-adrenergic receptors in the hypothalamus (Lal & 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; Siever *et al*, 1982; Charney *et al*, 1982; Siever & Uhde, 1984; Boyer *et al*, 1986), supporting an alpha-2-adrenergic receptor disturbance in major depressive disorders.

Various lines of evidence also suggest a role for dopamine in the pathophysiology of depression (Willner, 1985); but the studies of GH response to dopaminergic agonists such as L-dopa or apomorphine have failed to show any differences for major depressive patients (Sachar *et al*, 1975; Casper & Davis, 1977; Maany *et al*, 1979; Linkowski *et al*, 1983; Corn *et al*, 1984*a*; Jimerson *et al*, 1984; Meltzer *et al*, 1984). However, it should be noted that most studies have used L-dopa, which has a low priority potency or specificity. Moreover, most results should be interpreted with caution because the samples of depressive patients and control subjects differed with regard to age, gender, and endocrine status in women, all factors which modify the reactivity to dopaminergic agonists (Ettigi *et al*, 1975). In comparison with L-dopa, apomorphine appears to

be a more specific and more potent dopaminergic agonist and induces GH release in a more reproducible way (Rotrosen *et al*, 1976, 1979; La Rossa *et al*, 1977; Lal & Martin, 1980; Costain *et al*, 1982).

In this context, the purpose of our study was to compare the GH response after clonidine and apomorphine challenges in two samples of major depressive and minor depressive patients matched for gender and age. We wanted to verify if major depression was associated with disturbances in alpha-2-adrenergic or dopaminergic receptors and to what extent these two different abnormalities were correlated.

Method

Subjects

Fifteen in-patients consecutively admitted to the Biological Psychiatry and Psychopharmacology Unit of the University Hospital of Liège, Belgium, were included in the study. They met Research Diagnostic Criteria for major depressive disorder, endogenous subtype. Moreover, they had a score of at least 6 on the Newcastle index for endogenous depression and of at least 20 on the Hamilton depression scale at the end of a drug-free period of at least two weeks. All patients were unipolar and none of them exhibited psychotic features. This sample comprised seven male and eight female patients, aged 26-61 years (mean age = 45.2 ± 11.3). Their individual characteristics are presented in Table I.

These patients were matched for gender, age (within three years) and, in the case of women, menopausal status with 15 in-patients meeting Research Diagnostic Criteria for minor depression, having a score less than 6 on the Newcastle index and less than 20 on the Hamilton depression scale (Table I). Weight ranges were 62–81 kg for major depressives (mean weight = 69.5 kg ± 7.0) and 61–76 kg for minor depressives (mean weight = 69.8 kg ± 7.4), without significant differences between the two groups ($t = 0.1$, d.f. = 28, NS).

Diagnostic procedures were performed independently by two research psychiatrists blind to neuroendocrine test results. All patients were free of medical illness as evidenced by history, medical examination, ECG, chest X-ray, EEG, and routine laboratory tests. They had also been free of drugs, including benzodiazepines, for at least two weeks at the time of the study. The neuroendocrine tests were performed between the third and the twelfth day of the menstrual cycle in pre-menopausal women (four in each group: patients 1, 3, 5, 7 and 16, 18, 20, 22). Patients with a basal systolic blood pressure less than 100 mmHg were excluded from the study. Moreover, in order to be included, patients had to present basal ($t0$) GH level less than 5 ng/ml before both pharmacological challenges (Ansseau *et al*, 1984). All patients were fully informed of the purpose of the study and gave written consent.

Neuroendocrine test procedures

Clonidine and apomorphine challenge tests were performed in this order according to the same procedure with an interval of at least two days between the tests.

At 07:00, after an overnight fast, an indwelling catheter was inserted in a forearm vein. Blood samples of 10 ml were collected every 20 minutes from 40 minutes before to 120 minutes after injection, at 08:00, of either clonidine (0.15 mg diluted in saline to obtain 20 ml intravenously in ten minutes), or apomorphine (0.5 mg diluted in saline to obtain 0.5 ml subcutaneously).

After each blood sampling, blood pressure, pulse rate and sedative and gastro-intestinal side-effects were recorded. In addition, at the end of the procedure, sedative and gastro-intestinal side-effects were globally rated according to a six-point scale by a research nurse blind to diagnosis. The level of alertness was rated according to the following scores: 0 = no change; 1 = very slight drowsiness; 2 = slight drowsiness; 3 = drowsiness; 4 = important drowsiness; 5 = sleep. Gastro-intestinal reactions were rated according to the following scores: 0 = no reaction; 1 = slight and transitory nausea; 2 = nausea; 3 = strong nausea without vomiting; 4 = vomiting; 5 = severe vomiting.

GH assay

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

Data analysis

GH responses following clonidine and apomorphine were assessed by two different methods: by GH peak values following injection and by the areas under the curve situated between injection ($t0$) and the last blood sampling ($t120$ min). Both analyses were performed using absolute GH values as well as differences related to basal ($t0$) levels (relative values). Since the correlations between absolute and relative values (assessed by Pearson's correlation coefficient) were very high ($r > 0.98$), only the absolute values are reported here.

Changes over time in blood pressure and pulse rate were assessed by variance analysis (ANOVA) with repeated measures. GH responses and sedative and gastro-intestinal side-effects in major and minor depressives were compared using paired t-tests. Since some variances were high compared with mean values, the comparison was also performed by means of the Wilcoxon non-parametric test. The relationship between individual GH responses after clonidine and apomorphine as well as the relationships between GH response and sedative and gastro-intestinal side-effects were assessed by Pearson's correlation coefficient.

Results

Clonidine test

The changes over time in mean GH level following clonidine among the 15 major and the 15 minor depressive patients

TABLE I

Characteristics of the sample and individual responses to clonidine and apomorphine challenges

Patient	*Sex*	*Age*	*Diagnosis*[1]	*Clonidine test*		*Apomorphine test*		
				GH peak: ng/ml	*Sedation rating*	*GH peak: ng/ml*	*Gastro-intestinal effects rating*	*Sedation rating*
1	F	26	Major, end., UP	1.2	1	2.9	0	2
2	M	30	Major, end., UP	27.7	2	5.7	0	0
3	F	30	Major, end., UP	6.8	2	5.2	4	3
4	M	38	Major, end., UP	1.7	0	2.2	1	0
5	F	38	Major, end., UP	1.8	3	12.9	0	3
6	M	39	Major, end., UP	5.5	5	12.5	0	0
7	F	41	Major, end., UP	4.6	1	5.0	1	0
8	M	50	Major, end., UP	1.0	0	5.7	4	0
9	F	51	Major, end., UP	1.4	2	7.4	0	0
10	M	51	Major, end., UP	1.6	1	1.8	1	0
11	F	53	Major, end., UP	1.1	1	1.6	0	0
12	M	55	Major, end., UP	1.0	2	9.7	0	0
13	F	56	Major, end., UP	0.5	4	1.3	0	0
14	M	59	Major, end., UP	2.3	0	3.6	2	0
15	F	61	Major, end., UP	1.6	0	2.7	2	0
16	F	26	Minor	7.6	5	32.4	3	4
17	M	28	Minor	3.8	2	23.9	3	5
18	F	28	Minor	14.1	5	27.9	4	2
19	M	36	Minor	13.4	3	21.4	4	3
20	F	36	Minor	12.8	4	5.9	2	2
21	M	42	Minor	14.9	3	14.5	2	3
22	F	41	Minor	11.4	0	25.0	3	2
23	M	47	Minor	4.7	5	11.1	3	0
24	F	51	Minor	1.2	2	18.1	0	0
25	M	52	Minor	24.0	3	7.3	5	2
26	F	52	Minor	17.7	2	0.8	1	0
27	M	54	Minor	3.2	4	20.9	3	1
28	F	54	Minor	15.4	0	49.5	3	0
29	M	60	Minor	26.4	0	35.1	3	3
30	F	63	Minor	5.6	3	12.5	0	4

1. Major = major depression; Minor = minor depression; end. = endogenous; UP = unipolar.

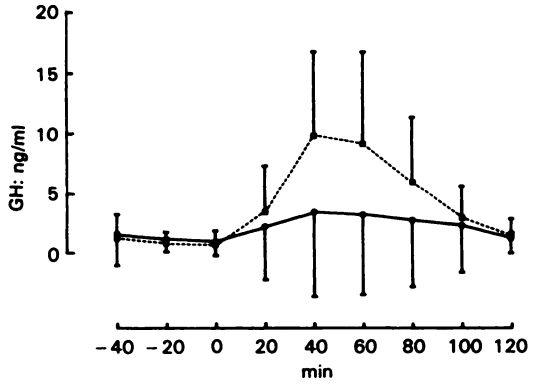

FIG. 1 Changes over time in mean GH level (± s.d.) following clonidine (0.15 mg i.v.) in 15 major (●——●) and 15 minor (■----■) depressive patients.

matched for gender and age are presented in Fig. 1. Individual endocrine and clinical data are shown in Table I. Major depressives exhibited a significantly lower GH response than minor depressives: for peak values, 4.0 ± 6.8 ng/ml *vs* 11.7 ± 7.5 ng/ml, $z = -3.3$, $P < 0.01$, and for the areas under the response curve, 301 ± 538 ng min/ml *vs* 653 ± 424 ng min/ml, $z = 2.9$, $P < 0.01$.

Blood pressure exhibited a significant decrease following clonidine for the whole sample ($F(6, 168) = 16.4$, $P < 0.00001$ for systolic blood pressure, and $F(6, 168) = 5.5$, $P < 0.0005$ for diastolic blood pressure), but without significant difference between major and minor depressives ($F(1, 28) = 0.5$, NS for systolic blood pressure, and $F(1, 28) = 0.1$, NS for diastolic blood pressure). Pulse rate did not show any significant change.

Ratings of sedative effects exhibited a trend toward lesser severity among major depressive than among minor depressive patients (1.6 *vs* 2.7, $U = -1.8$, $P = 0.07$). No significant relationship was present between individual

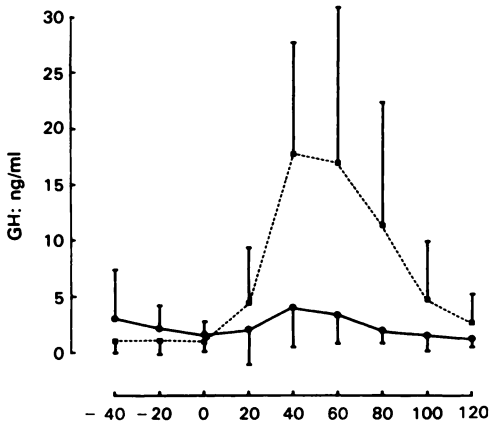

FIG. 2 Changes over time in mean GH level (±s.d.) following apomorphine (0.5 mg s.c.) in 15 major (●——●) and 15 minor (■---■) depressive patients.

GH responses and ratings of sedative reactions ($r = -0.17$, d.f. = 28, NS).

Apomorphine test

The changes over time in mean GH level following apomorphine among the 15 major and the 15 minor depressive patients are presented in Fig. 2. Individual endocrine and clinical data are shown in Table I. Major depressive patients exhibited a significantly lower GH response than minor depressives: 5.3 ± 3.8 ng/ml *vs* 20.4 ± 12.7 ng/ml, $z = 3.5$, $P < 0.001$ for peak values, and 281 ± 159 ng min/ml *vs* 1134 ± 745 ng min/ml, $z = 3.7$, $P < 0.001$ for the areas under the response curve.

Blood pressure exhibited a significant decrease for the whole sample ($F(6, 168) = 3.2$, $P < 0.05$ for systolic blood pressure, and $F(6, 168) = 2.8$, $P < 0.05$ for diastolic blood pressure), without significant difference between the two groups ($F(1, 28) = 0.5$, NS for systolic blood pressure, and $F(1, 28) = 3.0$, NS for diastolic blood pressure). Pulse rate did not exhibit any significant changes over time.

Ratings of both gastro-intestinal and sedative side-effects were significantly lower among major as compared with minor depressives (respectively 1.0 *vs* 2.6, $U = 2.7$, $P < 0.01$, and 0.5 *vs* 2.1, $U = 2.7$, $P < 0.01$). While the relationships between gastro-intestinal side-effects and GH response and between sedative side-effects and GH response were not significant in either of the two isolated groups (for gastro-intestinal reactions, $r = -0.20$ among major depressives and $r = 0.29$ among minor depressives; for sedative reactions, $r = 0.29$ among major depressives and $r = 0.11$ among minor depressives), these relationships became significant when the whole sample was included in the analysis ($r = 0.42$, d.f. = 28, $P < 0.05$ for gastro-intestinal reactions, and $r = 0.40$, d.f. = 28, $P < 0.05$ for sedative reactions).

Relationship between GH responses following clonidine and apomorphine

No significant correlation was present between individual GH peaks following clonidine and apomorphine among major depressive or minor depressive patients ($r = 0.11$ for major depressives and $r = 0.06$ for minor depressives). However, if both subgroups were pooled together, a slightly significant relationship existed ($r = 0.36$, d.f. = 28, $P < 0.05$).

Discussion

Concerning the clonidine test, the results of our study show a smaller GH response in major depressive as compared with minor depressive patients. These results are in agreement with previous studies comparing the GH response to clonidine in major depressive patients and normal controls (Matussek *et al*, 1980; Checkley *et al*, 1981; Charney *et al*, 1982; Siever *et al*, 1982; Siever & Uhde, 1984; Boyer *et al*, 1986) or reactive depressives (Checkley *et al*, 1984). The only negative report used oral clonidine in a small sample of seven endogenous and seven non-endogenous depressive patients (Dolan & Calloway, 1986); it is unclear if 0.15 mg of oral clonidine is able to consistently stimulate GH release over a two-hour period. These findings suggest a hyposensitivity of postsynaptic alpha-2-adrenergic hypothalamic receptors in major depression, since GH response to clonidine seems to depend on the stimulation of those receptors (review in Siever *et al*, 1982).

The lack of difference between major and minor depressives with regard to hypotensive response following clonidine is in agreement with three previous studies showing similar changes in blood pressure among major depressives and normal controls (Checkley *et al*, 1981; Siever & Uhde, 1984; Siever *et al*, 1984). The lack of global modification of pulse rate following clonidine also confirms the study of Checkley *et al* (1981). However, Siever & Uhde (1984) and Siever *et al* (1984) found a smaller decrease in pulse rate in major depressives than in normal subjects. It should be noted, however, that besides the classical mechanism explaining clonidine-induced hypotension by a stimulation of alpha-2-adrenergic receptors in the brain areas responsible for cardiovascular control, various lines of evidence suggest a role for H_2 histaminic receptors (review in Pettinger, 1980).

The trend toward smaller sedative side-effects in the major depressive group is in agreement with the hypothesis of a central noradrenergic hyposensitivity. However, Checkley *et al* (1981) did not find any significant difference between major depressives and normal subjects in the changes over time of sedative effect assessed by visual analogue scales completed

by the subject every 15 minutes. It should be noted that the mechanism of the sedative effect induced by clonidine is most probably of noradrenergic origin; a possible interpretation of these sedative effects in muscarinic receptor or H_2 histaminic receptor stimulation did not find experimental support (Spyraki & Fibiger, 1982).

Following apomorphine, major depressive patients also exhibit a smaller GH response as compared with minor depressive patients. These results, which suggest a hyposensitivity of dopaminergic hypothalamic receptors controlling GH release in major depression, disagree with previous reports. Most studies have used L-dopa without finding disturbances in GH response in unipolar depressive patients (Sachar *et al*, 1975; Maany *et al*, 1979; Linkowski *et al*, 1983). It should be noted, however, that L-dopa has a low dose of specificity for the dopamine receptors and that it is not demonstrated that L-dopa-induced GH response depends on dopaminergic receptor stimulation. Indeed, this release is inhibited not only by chlorpromazine, a dopaminergic receptor antagonist, but also by phentolamine, an alpha-adrenergic antagonist, and by cyproheptadine, a serotonergic antagonist; moreover, L-dopa-induced GH response is increased by propanolol, a beta-blocker (review in Lal & Martin, 1980). Compared to L-dopa, apomorphine seems to induce GH secretion by more specifically dopaminergic mechanisms. Indeed, apomorphine-induced GH release is only inhibited by pharmacological agents exhibiting dopaminergic antagonist properties (neuroleptics), such as chlorpromazine, haloperidol, pimozide, sulpiride, or clozapine (review in Lal & Martin, 1980). Moreover, apomorphine appears a much more potent and reproducible stimulus of GH secretion than L-dopa. In three studies where GH responses to apomorphine (0.75 mg subcutaneously) and L-dopa (500 mg orally) were compared in the same normal subjects, apomorphine induced a GH response in all 26 subjects, while L-dopa was only effective in 16 subjects (62%) (Lal *et al*, 1975; Rotrosen *et al*, 1976; La Rossa *et al*, 1977). Moreover, the GH response is highly reproducible in the same subjects if the test is repeated (Rotrosen *et al*, 1979; Costain *et al*, 1982).

Few studies have used apomorphine-induced GH stimulation in depressive patients, and none has shown differences with normal subjects (Casper & Davis, 1977; Maany *et al*, 1979; Jimerson *et al*, 1984; Meltzer *et al*, 1984). A possible explanation for these negative results is the use in these studies of an apomorphine dose of 0.75 mg rather than 0.50 mg as in our study. A 0.75 mg dose could be potent enough to induce a complete GH response even in case of relative hyposensitivity of hypothalamic receptors.

Recently, Corn *et al* (1984*a*) performed clonidine and apomorphine challenges in the same eight patients with endogenous depression and found significantly lower GH response following clonidine than following apomorphine. However, no control group was included in this study and the selection of the doses of clonidine (1.3 μg/kg) and apomorphine (0.005 mg/kg) was based on small studies in different groups of normal subjects (Costain *et al*, 1982; Corn *et al*, 1984*b*) which showed striking interpatient variability in the GH response.

The relative hyposensitivity of dopamine receptors in major depressives as compared with minor depressives is confirmed by the major depressives' lower rate of sedative and gastro-intestinal side-effects induced by apomorphine. These effects have never before been specifically assessed in depressive patients.

We can interpret the blunted GH response to clonidine and apomorphine as indirect evidence for both noradrenergic and dopaminergic abnormalities in endogenous depression. However, an alternative and even more simple explanation could be that endogenous depressive patients exhibit disturbances in GH production or secretion itself (review in Matussek, 1988). Supporting this hypothesis, a recent study demonstrated lower spontaneous GH secretion over a four-hour period in endogenous depressive patients as compared with neurotic depressive patients and normal subjects (Boyer *et al*, 1986). However, a previous report of 24-hour profile of plasma GH concentrations showed diurnal hypersecretion of GH in major depressive patients as compared with normal subjects (Mendlewicz *et al*, 1985). In our study, no difference in GH secretion between major and minor depressive patients was present over the 40 minutes preceding clonidine or apomorphine injection.

Whether the blunted GH response to the various tests in endogenous depression is due to a GH releasing factor (GRF) deficit is uncertain. Cerebrospinal fluid GRF levels in bipolar patients were found to be the same as in controls (Berrettini *et al*, 1987), but several recent preliminary studies testing the GH response to GRF yielded controversial results. Eriksson (1985) and Krishnan *et al* (1986) found a significantly higher GH peak response to GRF in major depressive patients as compared with controls, while Risch *et al* (1986) reported a lower GH response 15 minutes after GRF injection in five major depressive patients as compared with eleven age- and gender-matched normal subjects.

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*M. Ansseau, MD, PhD, *Co-ordinator, Biological Psychiatry and Psychopharmacology Unit*; R. von Frenckell, PhD, *Chief Statistician*; J. L. Cerfontaine, MD; P. Papart, MD; *Biological Psychiatry and Psychopharmacology Unit*; G. Franck, MD, PhD, *Professor of Neuropsychiatry*; M. Timsit-Berthier, MD, PhD, *Department of Clinical Neurophysiology and Psychopathology*; V. Geenen, MD, PhD; J. J. Legros, MD, PhD; *Psychoneuroendocrinology Unit*

*Correspondence: *Centre Hospitalier Universitaire (B 35), B-4000 Liège Sart Tilman, Belgium*