Eur Arch Psychiatr Neurol Sci (1985) 235:140–142

European Archives of Psychiatry and Neurological Sciences

Growth Hormone Release After Desipramine in Depressive Illness

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Summary. The effect of i.m. administration of 75 mg of desipramine on growth hormone (GH) secretion was investigated in a sample of 87 patients with major depressive disorders and in 31 normal controls. The GH response was lower in depressed females compared to depressed males, but no such difference was present in controls. In the premenopausal female group, GH response was significantly lower in depressed patients than in controls. No significant difference was found between normal males and male depressed patients. In the premenopausal group, no difference emerged between endogenous and nonendogenous depressed women.

Key words: Desipramine – Growth hormone – Depression

Introduction

In recent years, neuroendocrine tests have been explored in psychiatry, because these tests could potentially reflect aminergic central disturbances in mental disorders. Human growth hormone (GH) response to different pharmacological stimulating agents has been particularly investigated in affectively ill patients. Sachar et al. (1971) observed that a subgroup of depressed patients failed to release GH in response to insulin-induced hypoglycemia. They further reported a blunted GH response to a single oral dose of 500 mg of L-dopa in unipolar depressed patients (Sachar et al. 1972) but this neuroendocrine abnormality was mainly due to the lack of estrogens in postmenopausal unipolar depressive woman (Sachar et al. 1975). The influence of ovarian status on the GH response to L-dopa in depressed woman has also been emphasized by our group (Mendlewicz and Linkowski 1977). Langer et al. (1976) found a significant reduction in GH response after i.v. administration of D-amphetamine in endogenous depressive patients as compared to normal subjects, although the specificity of this finding could not be confirmed in a subsequent study (Halbreich et al. 1982). Matussek et al. (1980) demonstrated a diminished GH response to clonidine (α_2 agonist) in endogenous depression but not in neurotic reactive depression, schizophrenia and normal controls, suggesting the presence of a postsynaptic noradrenergic deficiency in some depressed patients. Checkley et al. (1981) also reported reduced GH responses to clonidine in depressed patients as compared with control subjects. Laakman and colleagues (1977, 1980) have recently tested GH stimulation and desipramine (DMI) (a presynaptic noradrenaline uptake blocker) in healthy subjects and depressive patients. A lower GH peak after DMI administration was reported for male and female endogenous depressed patients. This blunted GH response after DMI was also found in endogenous premenopausal depressive woman compared to healthy woman with the same ovarian status, but no differences were found between postmenopausal depressive and healthy woman (Matussek and Laakman 1981). A smaller GH response after DMI was also found in endogenous depressive men when compared to healthy male subjects. In the present study, GH response to i.m. injection of 75 mg of DMI was investigated in 87 depressed patients and compared to 31 age and sex matched control subjects.

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Methods

Sample. A total of 87 patients (47 females, 40 males) consecutively admitted to the department of psychiatry between 1980 and 1983 for a major primary depressive episode according to the Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) were included in the study. All patients were subdiagnosed into certain endogenous and nonendogenous depression according to the RDC. All patients included in this study scored 16 or above on the Hamilton Rating Scale (NIMH 24 items form; Hamilton 1960). Patients presenting somatic problems, pregnant women, and obese subjects, were excluded from the study, together with alcoholics and drug addicts. All patients were free of neuroleptics and monoamine oxidase inhibitors for at least 3 weeks before the investigation, and free of tricyclic antidepressants for at least 2 weeks before the study. The control group consisted of 31 healthy subjects (12 females, 19 males), free of personal and familial history of psychiatric disorders. The control subjects were paid for their participation to the study, and informed consent was obtained for all patients.

Endodrine Test. The test procedure started at 7:30 a.m. after an overnight fast. A cannula was inserted in a forearm vein and the first blood sample (GH baseline level), was taken after 1 h in a resting position, followed by i.m. administration of 75 mg of DMI. Five blood samples were taken at 30, 60, 90, 120, and 180 min after DMI administration. Blood pressure was measured before and during the test.

Biochemical Analysis. The plasma samples were analyzed using a radioimmunoassay (Phadebas Hgh Prist). Paper discs were used as the solid phase, and GH antibodies were covalently coupled to the paper disc and reacted during a first incu-

Table 1. Clinical and demographic characteristics of depressed patients and controls

Patients (n = 87)	*Males* (n = 40)	*Females* (n = 47)
Age range	24–70	24–73
Age mean (± SD)	47 ± 12	50 ± 12
Endogenous	n = 30	n = 25 (premenopausal n = 10) (postmenopausal n = 15)
Nonendogenous	n = 10	n = 20 (premenopausal n = 8) (postmenopausal n = 12)
Bipolar	n = 21	n = 11
Unipolar	n = 19	n = 36
Controls (n = 31)	*Males* (n = 19)	*Females* (n = 12)
Age range	15–78	22–70
Age mean (± SD)	39 ± 17	45 ± 16 (premenopausal n = 6) (postmenopausal n = 6)

bation with the sample. After washing, a fixed amount of ^{125}I-labeled immunosorbent purified GH antibodies were added, forming a specific complex with the GH molecules in the sample which were bound to the antibodies on the paper discs during the previous incubation. The radioactivity of this duplex was measured in a gamma counter (Wide 1971; Ceska and Lundkvist 1972). The coefficients of variation within the assay were 4.5% and 5.2% for sample values in the region of 2.5 ng/ml and 10.5 ng/ml respectively. The coefficients of variation between assays were 5.8% and 8.3% for sample values in the region of 2.5 ng/ml and 10.5 ng/ml respectively.

Endocrine Evaluation. The GH response to DMI was determined by the area under the curve (ng/ml per 180 min) and by the max (ng/ml). Similar results were obtained in the different comparison for these two evaluations of GH response. The area under the curve was selected because of its ability to reflect the underlying physiological phenomena.

Statistical Methods. The means of two groups were compared by Student's t-test. One-way analysis of variance and orthogonal contrasts were used to assess differences between groups. The relationship between variables were described using Pearson's correlation (Snedecor and Cochran 1967). The results are expressed in ng/ml per 180 min (mean ± SD).

Results

The demographic and clinical characteristics of our patients and controls are included in Table 1. The mean age ± SD of the male depressed patients was 47 ± 12 years and the mean age of the female depressed patients was 50 ± 12 years. As shown in the Table, the mean age of the male control group was 39 ± 17 years and 45 ± 16 years for the female control group. In the male depressed group, there were 21 bipolar and 19 unipolar patients for 11 bipolar and 36 unipolar patients in the female depressed group. In the male group, 30 of the 40 suffered from certain endogenous depression. In the female group, 25 patients were classified certain endogenous and 20 were classified nonendogenous, 2 female patients could not be classified as endogenous or nonendogenous because of lack of information. The distribution of unipolar and bipolar depression was similar in endogenous and nonendogenous depressed patients. The age and the sex distribution were comparable in patients and controls. For the normal controls, GH response to DMI was similar in males (24.4 ± 17.3 ng/ml per 180 min) and in females (20.0 ± 3.4 ng/ml per 180 min) (t = 1.01; P = NS). In depressed patients however, significantly higher

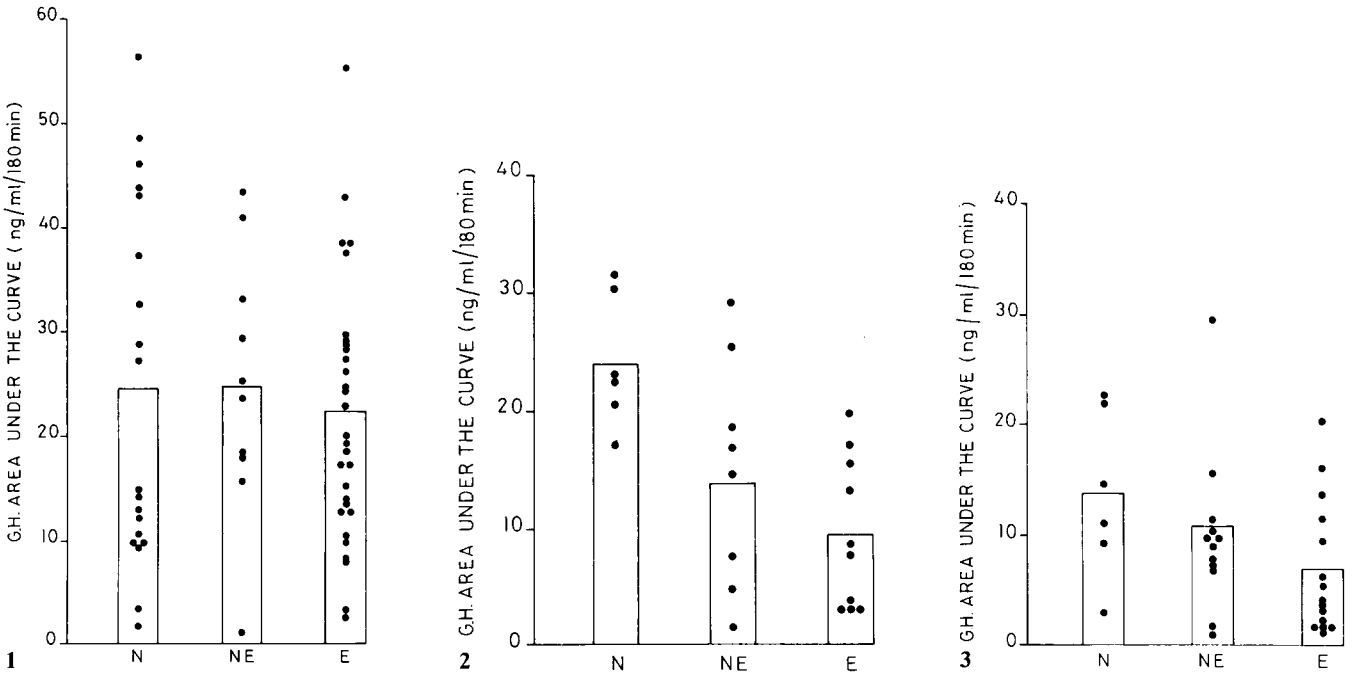

Fig. 1. GH in response to DMI in male subjects. N = normals; NE = nonendogenous, E = endogenous

Fig. 2. GH response to DMI in premenopausal females

Fig. 3. GH response to DMI in postmenopausal females

GH responses were observed in males (22.6 ± 12.3 ng/ml per 180 min) than in females (9.7 ± 7.3 ng/ml per 180 min) (t = 5.9; $P < 0.001$). The GH responses in depressed males and females were thus compared separately to proper controls. The GH responses in male subjects are illustrated in Fig. 1. No significant differences were observed between male controls (N) (24.4 ± 17.2 ng/ml per 180 min), male endogenous (E) depressed patients (21.8 ± 12.3 ng/ml per 180 min) and male nonendogenous (NE) depressed patients (24.8 ± 12.7 ng/ml per 180 mi). Considering the potential influence of the ovarian status in normal females, we found that the mean GH response to DMI was lower in the postmenopausal normal females (13.7 ± 7.6 ng/ml per 180 min) than in premenopausal normal females (24.2 ± 5.6 ng/ml per 180 min) (t = 2.2; $P <$ 0.025). In depressed women, a lower GH response was also observed in postmenopausal women (8.5 ± 6.5 ng/ml per 180 min) than in premenopausal women (11.5 ± 8.2 ng/ml per 180 min) but this difference was not significant (t = 1.4). Figure 2 illustrates the GH response in premenopausal women. The one-way analysis of variance showed a significant difference between the groups (F: 7.14; $P < 0.01$). Furthermore the analysis of contrasts revealed that the endogenous (E) and nonendogenous (NE) premenopausal depressed females (9.4 ± 6.5 ng/ml per 180 min) (14.9 ± 9.8 ng/ml per 180 min) showed a lower GH response compared to normal premenopausal females (24.2 ± 5.6 ng/ml per 180 min) ($P < 0.001$; $P < 0.05$). There was however no significant difference between premenopausal depressed women whether endogenous or nonendogenous according to the RDC. Although postmenopausal endogenous depressed women tended to have a lower GH response after DMI (6.9 ± ng/ml per 180 min), no significant differences could be observed among all subgroups (controls: 13.8 ± 7.7 ng/ml per 180 min; nonendogenous: 9.9 ± 7.2 ng/ml per 180 min). We did not find any significant correlation between the severity of depression and the GH response (max) in our male depressed patients ($r = -0.092$, P = NS) nor in the female subgroups (premenopausal r = 0.013; P = NS) (postmenopausal $r = -0.206$; P = NS).

Discussion

The reduced GH response to DMI in premenopausal depressed females in comparison to premenopausal normal females suggests the presence of a noradrenergic deficiency in this subgroup of depressed patients. This difference cannot be due to an effect of severity of depression since we did not find any correlation between severity of depression and GH response in various subgroups. We were not able to confirm the previously reported difference in GH response to DMI between endogenous and nonendogenous depressed patients (Laackman et al. 1977). In our hands, this test does not appear to be a good diagnostic tool to differentiate between endogenous and nonendogenous depression, but rather may be helpful in identifying a subgroup of depression in premenopausal females. However the potential influence of the ovarian activity on the GH response to DMI must be taken into account in the interpretation of the data. Postmenopausal control females also had a lower GH reponse to DMI than premenopausal controls, as was the case for depressed postmenopausal females when compared to depressed premenopausal females. These observations indicate that sex and ovarian status are important factors to be considered in neuroendocrine studies evaluating GH release after stimuli in psychiatric illnesses.

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Received January 16, 1985