BLUNTED GROWTH HORMONE RESPONSES TO CLONIDINE AND APOMORPHINE CHALLENGES IN ENDOGENOUS DEPRESSION

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ABSTRACT

The growth hormone (GH) responses to clonidine (an alpha-adrenergic agonist) and to apomorphine (a dopaminergic agonist) were significantly reduced in 15 major endogenous depressive inpatients as compared to 15 minor depressive inpatients matched for gender and age. These results support noradrenergic as well as dopaminergic neurotransmitter disturbances in major depression.

INTRODUCTION

Neuroendocrine strategy may provide an indirect index of central neurotransmission which is particularly interesting in the biological assessment of depressive disorders. The study of growth hormone (GH) response to specific pharmacologic challenges can bring the largest amount of information : indeed, its secretion is stimulated by dopamine (DA), noradrenaline (NA) through alpha receptors and possibly serotonin, while it is inhibited by NA through beta receptors and by GABA [1].

In this context, the purpose of our study was to compare the GH responses following clonidine (an alpha-adrenergic agonist) and apomorphine (a dopaminergic agonist) challenges between major and minor depressive patients. We wanted to verify if major depression is associated with disturbances in alpha-adrenergic or dopaminergic receptors and to which extent these two biochemical abnormalities are correlated.

METHODS

1. Subjects

Fifteen inpatients (7 males and 8 females, aged 26-61, mean age = 45.0 ± 11.3) who met Research Diagnostic Criteria for major depressive disorder, endogenous subtype were included in the study. They also had a score of at least 6 on the Newcastle endogenicity scale and of at least 20 on the Hamilton depression scale at the end of a drug-free period of at least two weeks.

These patients were matched for gender, age (within 3 years) and menopausal status for women with 15 inpatients meeting Research Diagnostic Criteria for minor depression, having a score less than 6 on the Newcastle endogenicity scale and less than 20 on the Hamilton depression scale.

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2. Neuroendocrine test procedures

Clonidine and apomorphine challenge tests were performed in this order according to the same procedure with at least a 2-day interval.

At 7 AM, after an overnight fast, an indwelling catether was inserted in a forearm vein. Blood samples of 10 ml were collected every 20 minutes for 40 minutes before and 120 minutes after injection at 8 AM of : either clonidine 0.15 mg diluted in saline to obtain 20 ml intravenously in 10 minutes; or apomorphine 0.5 mg diluted in saline to obtain 0.5 ml subcutaneously.

GH was measured by radioimmunoassay, with intra- and inter-assay coefficients of variation of respectively 13.3 ± 4.7 and 14.8 ± 9.6 %.

3. Data analysis

GH responses following clonidine and apomorphine were assessed by GH peak values following injection and by the areas under the curve between 0 and 120 min and compared between the two groups by the Willcoxon nonparametric test while the relationship between the individual responses to the two challenges was assessed by the Pearson's correlation coefficient.

RESULTS

1. Clonidine test

Following clonidine challenge, major depressives exhibited a significantly lower GH response as compared to minor depressives : for peak values, 4.0 ± 6.8 ng/ml vs 11.7 ± 7.5 ng/ml, $z = -3.3$, $p < .01$ and for the area under the response curve, 300.6 ± 538.3 ng/120 min vs 652.5 ± 423.7 ng/120 min, $z = 2.9$, $p < .01$ (Fig. 1).

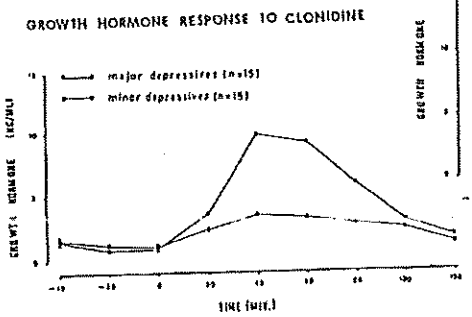

FIG. 1. Changes over time in mean GH level following clonidine.

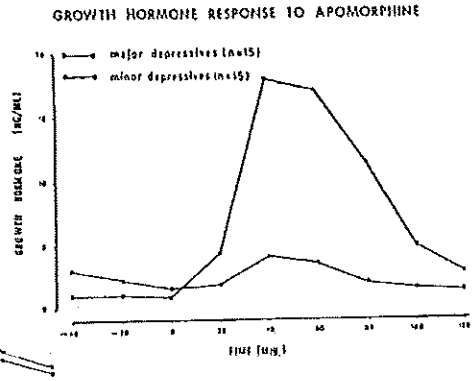

FIG. 2. Changes over time in mean GH level following apomorphine

2. Apomorphine test

Following apomorphine challenge, 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 281.3 ± 159.1 ng/120 min vs 1134.4 ± 744.6 ng/120 min, $z = 3.7$, $p < 0.001$ for the area under the response curve (Fig. 2).

3. Relationship between GH responses following clonidine and apomorphine

No significant correlation was present between individual GH peaks following clonidine and apomorphine among major depressives (r = 0.11) as well as minor depressives (r = 0.06).

DISCUSSION

The decreased GH response following clonidine in major as compared to minor depressive patients, in agreement with previous studies [2,3], suggests a hyposensitivity of postsynaptic alpha-adrenergic hypothalamic receptors in major depression.

The diminished GH response to apomorphine in major as compared to minor depressives, which suggests an associated dopaminergic hyposensitivity in major depression, contradicts previous reports using L-DOPA [4,5]. However, compared to L-DOPA, apomorphine seems to induce GH release by more specifically dopaminergic mechanisms and is far more potent and reproducible. Few studies have used apomorphine-induced GH stimulation in depressive patients and none has shown differences with normal subjects [6-9]. Whereas the three first reports included probably a too limited sample to show statistically significant differences, the study of Jimerson et al. [8] compared 14 male major depressive patients with 16 male normal controls. A possible explanation to these negative results is the use in this study (as well as in the three previous ones) of an apomorphine dose of 0.75 mg instead of 0.50 mg 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.

The lack of correlation found in each of the two groups between the GH responses to the two pharmacologic challenges suggests that clonidine and apomorphine actually assess the fonctional state of different receptors (most probably of alpha-noradrenergic type following clonidine and of dopaminergic type following apomorphine) and that depressives are characterized by individual biochemical patterns. Those results could lead to define homogeneous biochemical subtypes of depression and to select more specific pharmacologic treatment.

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