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A Comparison of the Growth Hormone Responses to Clonidine and Apomorphine in the Same Patients with Endogenous Depression

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Summary: The growth hormone responses to clonidine (1.3 μg/kgm) and apomorphine (0.005 mg/kgm) have been measured in 8 drug free patients with endogenous depression. In these patients the growth hormone responses to clonidine were significantly smaller than to apomorphine. As these doses of clonidine and apomorphine have previously been reported to cause similar growth hormone responses in normal subjects, these findings support the hypothesis of a defect in the adrenergic but not the dopaminergic regulation of growth hormone in patients with endogenous depression.

One of the few available ways of examining central neuroreceptor function in patients with mental illness is to measure the responses of pituitary hormones to the stimulation of neuroreceptors with appropriate drugs. In man the main neural regulation of growth hormone (GH) release is mediated through alpha adrenoceptors and dopamine receptors. Drugs which stimulate these receptors stimulate the release of GH and drugs which block these receptors block the release of GH (Checkley, 1980).

For example, clonidine releases GH through the direct stimulation of fore-brain alpha$_2$ adrenoceptors (Lovinger *et al*, 1976; Rudolph *et al*, 1980; Eriksson *et al*, 1982; Krulich *et al*, 1982; Cella *et al*, 1983; McWilliam and Meldrum, 1983). Desipramine releases GH, probably through the indirect stimulation of alpha$_2$ adrenoceptors (Laakmann, 1980). Patients with endogenous depression have been reported to have impaired GH responses both to clonidine (Matussek *et al*, 1980; Checkley *et al*, 1981; Charney *et al*, 1982; Siever *et al*, 1982) and to desipramine (Laakman, 1980).

In contrast, apomorphine stimulates the release of GH through the stimulation of dopamine receptors (Lal *et al*, 1973; Lal *et al*, 1977; Nair *et al*, 1979; Rotrosen *et al*, 1979). Although this response has received less systematic study it has been reported to be normal in patients with endogenous depression (Frazer, 1975; Caspar *et al*, 1977). Such findings of impaired GH responses to an alpha$_2$ agonist but of normal responses to a dopamine agonist clearly imply a defect at alpha$_2$ adrenoceptors in a neuroendocrine system in endogenous depression.

The most stringent test of this hypothesis would be to determine whether the same patients who have impaired growth hormone responses to clonidine also have normal growth hormone responses to apomorphine. The present study is a preliminary attempt to test this hypothesis.

Methods

Selection of patients

The patients studied had all been referred to the Geoffrey Knight Psychosurgical Unit for assessment for a stereotactic subcaudate tractotomy (Göktepe *et al*, 1975). Their clinical evaluation was supplemented by use of the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978), the Newcastle Questionnaire (Carney *et al*, 1965), and the Hamilton Depression Rating Scale (Hamilton, 1967). All had clinical diagnoses of depression, met the research diagnostic criteria for endogenous depression (Spitzer *et al*, 1977), and had diagnostic scores on the Newcastle Scale of greater than 6. Patients were free of psychotropic medication other than night sedation with benzodiazepines, for three weeks prior to testing. No patient had other psychiatric or medical diagnoses, and none drank alcohol other than occasionally (Matussek *et al*, 1980).

Neuroendocrine testing

Patients were fasted overnight and at 9.30 a.m. a

catheter was inserted into a forearm vein. For at least 60 minutes no observations were made. Baseline observations were then collected for 30 minutes after which time clonidine (1.3 μg/kgm body weight) was injected over 10 minutes. Observations were continued for 90 minutes after starting the infusion. Throughout the procedure pulse and blood pressure were recorded every 5 minutes and blood samples were taken every 15 minutes for estimation of GH, and care was taken to ensure that drowsy patients did not progress into sleep.

Five days after the clonidine test all patients received an apomorphine test. This followed an identical protocol except that instead of the clonidine patients received apomorphine (0.005 mg/kgm body weight) subcutaneously.

Growth hormone was estimated using a double antibody radioimmunoassay which has a sensitivity of 0.2 ng/ml, a within batch coefficient of variation of 5.2 per cent and a between batch coefficient of variation of 8.1 per cent for a mean plasma growth hormone of 11.0 ng/ml. For each test plasma growth hormone was plotted against time and the growth hormone response was measured as the area under the curve following the injection of the drug. As the data were paired and non-parametric the growth hormone responses to the two drugs were compared using Wilcoxon's signed rank test. As GH inhibits its own release (Sakuma and Knobil, 1970) we routinely exclude data from patients in whom the baseline GH value exceeds 3.0 ng/ml: in this sample no patients had raised baseline GH values.

Results

The 8 patients studied included 6 females of whom 4 were post menopausal. The mean age of the patients was 52.2 years (SEM 2.6 years) and the mean Hamilton Depression Score was 31.7 (SEM 2.9). Clinical characteristics of this group are shown in Table I.

None of the patients reported nausea in response to the apomorphine injection. In 7 of the 8 patients the GH response to apomorphine was greater than the GH response to clonidine, using the area under the GH response curve as the measure of response (Table I). This difference is statistically significant ($p < 0.05$, Wilcoxon signed rank test). Figure 1 shows the median GH responses to apomorphine and clonidine in the patients.

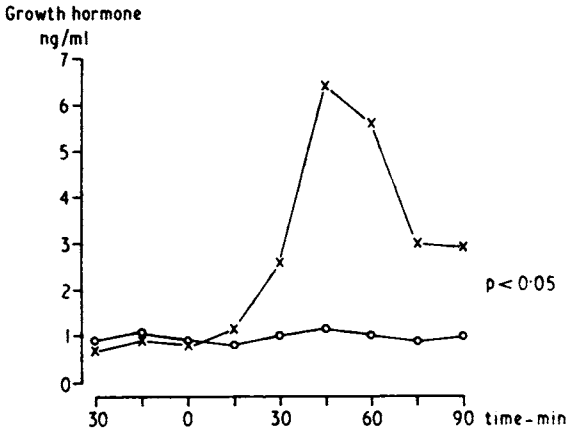

FIG 1.—Median growth hormone response to apomorphine (x – x) and to clonidine (o – o) in the same endogenously depressed patients (n = 8).

TABLE I

Clinical characteristics of patients, and results of neuroendocrine challenge tests

Patient	Age	Sex	Duration of illness (years)	Number of episodes	Family history	Bipolar/ unipolar	HRS	GH response (area under the curve) ng/ml	
								Clonidine	Apomorphine
1	51	F	3	2	+	uni	42	−0.18	+0.76
2	44	F	23	6	+	uni	27	+0.17	+4.32
3	58	F	29	31	−	bi	29	+1.09	+2.21
4	62	F	23	5	−	uni	32	−0.85	+3.41
5	40	F	20	4	+	bi	21	+0.11	+3.41
6	56	M	3	5	+	uni	46	+1.47	−0.09
7	53	F	7	2	−	uni	28	−0.46	+0.15
8	54	M	30	10	−	uni	29	−0.14	+22.50

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Discussion

Earlier studies have shown impaired GH responses to clonidine in patients with endogenous depression (Matussek *et al*, 1980; Slade and Checkley, 1980; Checkley *et al*, 1981; Charney *et al*, 1982; Glass *et al*, 1982; Siever *et al*, 1982; Checkley *et al*, 1984). Other studies have reported evidence of more normal GH responses to apomorphine (Frazer, 1975; Caspar *et al*, 1977). Inevitably, the two groups of studies were performed on different patients drawn from different treatment settings and studied under different drug free and other conditions. This is the first report in which GH responses to both clonidine and apomorphine have been studied in the same patients.

The doses of clonidine and apomorphine used in the present study were selected because they had given equivalent GH responses in normal subjects (Costain *et al*, 1982; Corn *et al*, 1984). In this sample of patients the responses to clonidine were significantly smaller than to apomorphine. The GH responses to apomorphine were virtually identical to those of normal subjects given the same dose of apomorphine (Costain *et al*, 1982), while the GH responses to clonidine were less than those reported in normal subjects (Corn *et al*, 1984). The GH response to clonidine involves the stimulation of alpha$_2$ adrenoceptors, while that to apomorphine involves dopamine receptors. Consequently the present findings indicate a defect in the vicinity of alpha$_2$ adrenoceptors in neuroendocrine systems in endogenous depression. Although these findings clearly support the hypothesis of a defect at alpha adrenoceptors in neuroendocrine systems the findings are preliminary.

Although the literature suggests that these doses of clonidine and apomorphine produce equivalent growth hormone responses in normal subjects, this must now be tested in normal subjects who are individually matched by age and sex with these and other patients. It is also possible that antidepressant drugs might differentially affect the growth hormone response to clonidine and apomorphine. Our recent findings from normal subjects suggest that at three weeks after discontinuing desipramine treatment the growth hormone response to clonidine may remain blunted (Corn *et al*, 1984). It is therefore necessary to examine the effects of desipramine upon the growth hormone response to apomorphine and to investigate in depressed patients, who have been free of psychotropic drugs for longer periods, the GH responses to both clonidine and apomorphine. One further reason for regarding these findings as preliminary is that they are made in a relatively small sample drawn from a population of patients with very severe and intractable depressive illness. The advantages of using such a group of patients with resistant depressive illness are that the illnesses are severe and the diagnoses unequivocal. Against this the main disadvantage is that other studies are needed to generalise the findings.

In more general terms, the present study demonstrates the value of using different pharmacoendocrine challenges within the same individuals. Such a strategy should control for non specific affects upon GH release such as weight loss and increased cortisol production (von Zerssen *et al*, 1984).

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