The Human Growth Hormone Response to Clonidine: Relationship to Clinical and Neuroendocrine Profile in Depression

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The authors found a significant negative correlation between human growth hormone (HGH) response to clonidine and urinary free cortisol level in 14 depressed patients. The HGH response did not distinguish endogenous depression from nonendogenous depression.

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Several studies (1–4) have shown that the human growth hormone (HGH) response to clonidine is impaired in depressed patients compared to control subjects. Furthermore, it has been reported that this blunted response occurs in patients with endogenous depression but not in those with neurotic or reactive depression (1).

The relationship of this finding to abnormal neuroendocrine function such as disinhibition of the hypothalamic-pituitary-adrenal (HPA) axis or abnormalities of the hypothalamic-pituitary-thyroid axis has largely been unexplored. Siever and Uhde (5) found that decreased receptor-mediated responses to clonidine were associated with high plasma cortisol levels. They suggested that the blunted HGH response could reflect subsensitivity of hypothalamic adrenoceptors, which in turn could be the cause of decreased inhibition of cortisol secretion. However, Matussek et al. (1)

found no relationship between serum cortisol levels and the HGH response.

The aim of this pilot study was to examine the relationship between HGH response and neuroendocrine function. Second, we hoped to replicate the reported differences in HGH response between endogenous and neurotic depression.

METHOD

Fourteen depressed patients (seven men and seven women) who met the Research Diagnostic Criteria (RDC) (6) for primary depression were included in the study. These subjects were the first 14 patients recruited as part of a large-scale investigation of neuroendocrine function in depression (7, 8). All 14 subjects gave written informed consent. The depressed subjects had all been drug free for a minimum of 2 weeks before the study. All of the female patients were premenopausal, and neuroendocrine assessment was carried out in the first 14 days of their cycles. The mean±SD age of the subjects was 39.7±9.6 years. All of the patients had a basal HGH level of less than 3 ng/ml. The patients were assessed using the RDC, the Hamilton Rating Scale for Depression (9), the Newcastle Diagnostic Index (10), and the Present State Examination (PSE) (11). A further classification into endogenous and neurotic categories was made using the CATEGO program of the PSE, a computerized diagnostic method. Patients with affective disorder are allocated by the CATEGO program to three diagnostic classes—D, R, and N. While D and N fall, respectively, within the conventional *ICD* classifications of "psychotic depression" and "depressive neurosis," R does not readily conform to a particular *ICD* classification.

However, given that it is characterized by such symptoms as retardation and pathological guilt, it was taken to be a close enough approximation of the symptom pattern of endogenous depression to be used as synonymous with this classification. Therefore, patients classified as R and D on this program were taken to be endogenous, while patients classified as N were taken to be neurotic. The presence or absence of precipitating events was assessed using the Life Event and Difficulties Schedule (12).

A 24-hour urine collection was taken from 11:00 p.m. on day 1 to 11:00 p.m. on day 2 (mean±SD volume=1104±402 cc/24 hours; mean±SD creatinine concentration=1.1±0.4 g/24 hours). A second 24-hour urine collection was started on day 2 after oral administration of 1 mg of dexamethasone at 11:00 p.m. (mean±SD volume=1176±385 cc/24 hours; mean±SD creatinine concentration=1.0±0.38 g/24 hours). At 4:00 p.m. on day 3, a blood sample was taken for the measurement of plasma cortisol. The two 24-hour urine collections were assessed for pre- and postdexamethasone urinary free cortisol, respectively. Cortisol in plasma and urine was measured in duplicate using a double antibody radioimmunoassay method. The coefficient of variation for repeated assay was 4.4%. A cutoff of 5 μg/dl was used to define nonsuppression on the 4:00 p.m. plasma cortisol levels.

After the patients fasted overnight on day 4, an intravenous catheter was inserted at 8:15 a.m. in order to perform a short thyrotropin-releasing hormone (TRH) test. A blunted thyrotropin (TSH) response to TRH was defined as a response less than 7 μU/ml. The intravenous line was kept open by flushing with a heparin solution. A baseline sample was obtained at 11:00 a.m., after which an oral solution of clonidine, 5 μg/kg of body weight, was administered, diluted in water. Blood samples for determination of plasma HGH were obtained at 20, 60, 90, and 120 minutes after ingestion of HGH, and were assayed in plasma using a double antibody radioimmunoassay technique. The coefficient of variation for repeated assays was 5.0%.

The HGH response was measured as area under the response time curves. Statistical analysis was carried out after log transformation of HGH and cortisol values. The statistics used were two-tailed t tests for unrelated samples and Pearson product-moment correlations.

RESULTS

The patients' mean±SD Hamilton scale score was 21.2±6.4. There were no significant differences in mean±SD HGH responses to clonidine in patients classified as endogenous (N=7) or nonendogenous (N=7) according to the RDC (4.63±3.60 ng/ml versus 8.60±6.52 ng/ml) or as endogenous (N=6) or neurotic (N=8) on the Newcastle index (7.6±4.3 versus 5.0±6.2 ng/ml). There was a slight trend for patients classified as endogenous on the CATEGO program (R or D) of the PSE to have a more blunted HGH response than did patients given a CATEGO diagnosis of neurotic depression (mean±SD=3.80±3.88 ng/ml versus 10.04±9.24 ng/ml; t=1.48, df=12, p=.13).

There was no significant relationship between the clonidine-HGH response and any of the indices of thyroid function (FT_1, basal TSH, TSH response to TRH). None of the patients exhibited an HGH response to TRH. There were no differences in the mean HGH response to clonidine of patients classified as having blunted (N=6) or nonblunted (N=8) responses on the TRH test.

A significant negative relationship emerged between predexamethasone urinary free cortisol levels and HGH response (r=−.52, df=13, p<.05), indicating that patients with higher cortisol levels had a more blunted response. A trend in the same direction was also evident for postdexamethasone urinary free cortisol levels (r=−.39, df=13, p<.08). There were no differences in the mean HGH responses of patients classified as suppressors or nonsuppressors on the DST.

DISCUSSION

The findings reported here do not uphold previous reports of a different HGH response to clonidine in endogenous depressed patients than in neurotic depressed ones (1). Possible explanations include our small sample size, which would require a large difference between the groups in order for a statistically significant result to be found, and the fact that an oral rather than an intravenous method of clonidine administration was used. A further source of difference may be the methods we used to assign patients to endogenous and neurotic categories. There are no universally agreed-upon definitions of these categories and, indeed, the distinction itself is open to dispute. In particular, the different methods for assessing the presence or absence of precipitants, especially with the Newcastle index, may lead to discrepant results. We used a standardized and reliable instrument, the Life Event and Difficulties Schedule, to assess the presence of precipitants. Finally, it is possible that the prior performance of a TRH test may have interfered with the HGH response to clonidine: none of our patients exhibited an HGH response to TRH. Furthermore, Kierkegaard et al. (13) reported that in depressed patients and normal control subjects, the HGH response to TRH, if present, is of modest proportions and maximal at 20 minutes, with a return to baseline at 60 minutes.

The association between HGH response and 24-hour urinary free cortisol excretion levels is of considerable interest. Siever and Uhde (5) reported decreased receptor-mediated responses to clonidine, as measured by a decrease in plasma 3-methoxy-4-hydroxyphenyl-

glycol level, following clonidine infusion and elevation of baseline plasma cortisol level. The association we found between an impaired HGH response to clonidine and high levels of cortisol may reflect on postsynaptic α_2-adrenergic sensitivity. This phenomenon, however, may not be specific to depression. Blunted HGH response to clonidine has also been reported in alcoholic patients (1), in patients with schizoaffective disorder (1), in normal control subjects, and, in particular, in women who are postmenopausal (1, 5).

Thus, the meaning of the blunted HGH response to clonidine is not clear, but it may be related to features of all these conditions. It is of interest that high cortisol levels have been reported in all these conditions. Further research, therefore, should be directed toward establishing the nature of the relationship between a blunted response to HGH and HPA axis disinhibition across diagnostic categories.

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