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18. Supported by PHS grant OH-00352-02.

26 January 1972; revised 2 October 1972

Growth Hormone Responses to L-Dopa in Depressed Patients

Abstract. *Plasma human growth hormone responses to oral administration of 500 milligrams of* L-*dopa were analyzed in three groups of subjects: normals, age 20 to 32; normals, age 48 to 68; and unipolar depressed patients, age 45 to 68. While only 7 percent of the young normals had deficient human growth hormone responses to this stimulus, 36 percent of the older normals and 77 percent of the depressed patients failed to have adequate responses, suggesting an effect of age and a further effect of depressive illness. Because the release of human growth hormone appears to be closely related to brain catecholamine metabolism, the deficient responses in the depressed patients may provide further support to the concept of a neurochemical defect in depressive illness.*

The hypothalamic regulation of growth hormone (GH) release from the anterior pituitary appears to be closely related to brain catecholamine metabolism (*1*). Intraventricular infusions of norepinephrine provoke GH release in animals (*2*). Norepinephrine depletors, such as reserpine and α-methyl-*p*-tyrosine inhibit the normal GH response to insulin-induced hypoglycemia, whereas prior treatment with a monoamine oxidase inhibitor reverses the reserpine blockade (*3*). Intravenous infusion of phentolamine, an alpha adrenergic blocking agent, inhibits the GH response to hypoglycemia (*4*). Single oral doses of 500 mg of L-dihydroxyphenylalanine (L-dopa), a precursor of dopamine and norepinephrine, stimulate human growth hormone (HGH) release in patients with Parkinson's disease (*5*) and in normal young adults (*6*). Intravenous infusion of phentolamine inhibits the HGH response to L-dopa (*6*).

Since there is increasing evidence for a functional depletion of brain norepinephrine in at least certain depressive illnesses (*7*), we may hypothesize that such patients would manifest an impairment of HGH release to the usual stimuli. Sachar *et al.* have indicated that a substantial subgroup of depressed patients failed to release HGH in adequate amounts in response to insulin-induced hypoglycemia (*8*). Powell *et al.* have also reported that children with the syndrome of maternal deprivation and failure to grow also failed to release HGH in response to insulin-induced hypoglycemia; after a period of emotionally supportive hospital care, the HGH response returned and growth was resumed (*9*). We have now measured the plasma HGH response to a single oral dose of 500 mg of L-dopa in 16 normal subjects, age 20 to 32; 14 normal subjects, age 48 to 68; and 13 unipolar depressed patients, age 45 to 68.

All subjects were medically healthy and were receiving no medication. None of the subjects had received regimens of drugs that affect HGH secretion within 2 months of the test. None of the normal subjects had a history of significant psychiatric disturbance. All 43 subjects but one were within 25 percent of ideal body weight, and none were cachectic. All the depressed patients were unipolar by history (that is, no history of manic episodes), and none had a history of schizophrenic episodes. The depressive syndromes were all characterized by marked depressive mood, fatigue, sleep disturbance, pessimism, loss of interest, decreased responsiveness to the environment, and anhedonia; most also manifested agitation or retardation, loss of appetite, and guilty and worthless feelings.

On the experimental day, a sterile cannula was inserted in a forearm vein of the subject, who had fasted for at least 6 hours. While the subject reclined in bed, blood samples were drawn (and heparinized) every 15 minutes for 1 hour before and 2¼ hours after administration of 500 mg of L-dopa orally. The plasma was separated by centrifugation; samples were frozen and subsequently analyzed in duplicate for HGH by radioimmunoassay, with the use of dextran-coated charcoal to separate bound from free hormone (*10*), so that we were able to make accurate measurements at concentrations as low as 0.5 ng/ml. Subjects whose HGH concentration exceeded 4 ng/ml just prior to L-dopa administration were eliminated from the study. This premature HGH release, presumably due to anxiety induced by the procedure (*11*) required elimination of eight young normals, but none of the older normals or depressives. The minimum plasma HGH response to L-dopa considered adequate was above 5 ng/ml, a conservative figure accepted as the clinical standard (*12*).

The maximum HGH responses occurred 60 to 120 minutes after L-dopa ingestion, consistent with reports by

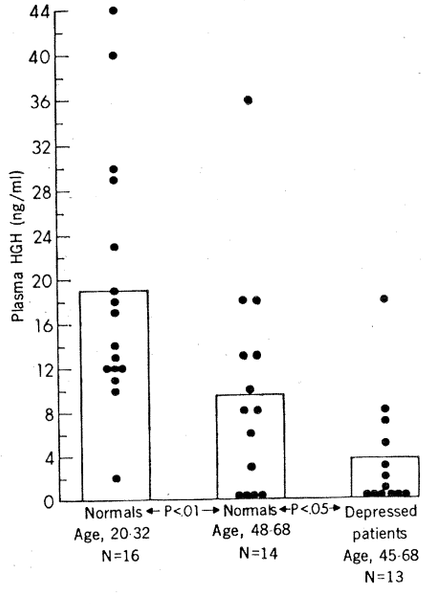
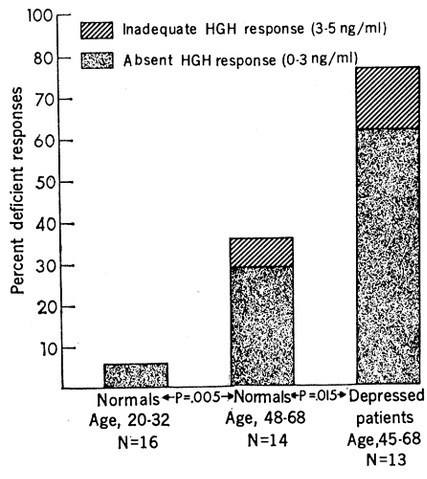


Fig. 1. Maximum HGH responses to L-dopa in normals and depressed patients. Circles represent individual HGH responses. Bars represent mean HGH response for each group.

Fig. 2. Percentage of deficient HGH responses (less than 5 ng/ml) to L-dopa among normals and depressed patients.



others (*5*, *6*). Figure 1 shows the maximum HGH concentrations achieved by the three groups of subjects. Of the 16 young normals, only one failed to have an adequate response; all the others achieved concentrations above 10 ng/ml. The mean maximum response of this group was 19 ng/ml, similar to the value reported by Kansal *et al.* (*6*).

Among the 14 older normals, however, five failed to have an adequate response, with a mean maximum response for the group of 9.5 ng/ml. The difference with the young normal group was significant at $P < .01$ (one-tailed *t*-test), suggesting that the HGH response to L-dopa diminishes with age.

The group of depressed patients responded quite differently. Ten of 13 patients failed to have an adequate HGH response, with the mean maximum response only 3.5 ng/ml. The difference with the normals of the same age (48 to 68) was significant to $P < .05$ (one-tailed *t*-test). When the data were analyzed in terms of percentage of deficient responses (Fig. 2) the differences between the young and older normals were significant at $P = .005$, between the older normals and the depressed patients at $P = .015$ (Fisher exact test). There was no apparent relation of magnitude of HGH response to sex or weight of the subjects, or to presence of the clinical side effect of nausea, which occurred in 50 percent of the subjects after L-dopa ingestion.

Five of the depressed nonresponders were tested again after psychiatric recovery induced by imipramine or electroconvulsive therapy. All five failed to release HGH to L-dopa afterward as well, suggesting an enduring characteristic of these patients that is possibly associated with their vulnerability to depressive illness. Studies of urinary and plasma cortisol production over a 24-hour period in these patients (*13*) ruled out the possibility of panhypopituitrism.

Several factors may account for the diminished HGH response in the depressed patients. For example, in the depressed patients, L-dopa may have been poorly absorbed from the gastrointestinal tract, or may have failed to reach the brain in adequate amounts. However, several of the depressed nonresponders also failed to release HGH in response to insulin-induced hypoglycemia, suggesting that a central nervous system mechanism was involved in at least some patients.

While the action of L-dopa in releasing HGH may be an amino acid effect similar to that of arginine, the most intriguing possibility is that the failure to release HGH after L-dopa is due to a central neurochemical disturbance in catecholamine metabolism or action, perhaps a failure to convert L-dopa to dopamine, or dopamine to norepinephrine. This latter transformation after L-dopa administration occurs transiently at about 30 to 60 minutes in animals (*14*), consistent with the time course of the HGH response to L-dopa. It is also possible that alpha adrenergic receptors in the depressed patients are less sensitive to catecholamines, and their deficient HGH responses are analogous to those of the young normal subjects treated with phentolamine (*6*). Another mechanism may be increased catabolism of catecholamines due, for example, to an excess of monoamine oxidase activity. Indeed, plasma and brain monoamine oxidase activity has been shown to increase with age, being particularly high in the age period (50 to 70) most at risk for depressive illness, and higher yet in depressed patients (*15*), paralleling the distribution of deficient HGH responses in our groups. While we have emphasized in our discussion the possible relation of brain catecholamines to GH release and depressive illness, the possible role of indoleamines should also be kept in mind, since the amino acid 5-hydroxytryptophan, a serotonin precursor, induces GH release in monkeys (*16*), and there is evidence that brain indoleamine metabolism may be affected in depressive illness (*7*).

Finally, it should be noted that our study was conducted on depressed patients with no history of mania; bipolar manic-depressive patients may respond differently, and several depressed patients with bipolar histories whom we have studied thus far have all secreted substantial amounts of HGH in response to both L-dopa and insulin-induced hypoglycemia. Such differences warrant further investigation, and emphasize the potential value of neuroendocrine techniques in studying the nature of hypothalamic dysfunctions in the affective disorders.

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17. Supported in part by PHS grants 5-K2 MH-22613, MH-13402, AM-14282, EC-00341, and RR-52. We thank J. Finney, B. Ward, and L. Liotta for technical assistance.

17 July 1972; revised 18 September 1972