Erciyes Tıp Dergisi 14: 187-192, 1992.

GH RESPONSE TO L-DOPA STIMULATION IN DEPRESSION AND ANXIETY DISORDERS (*)

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Depresyon ve anksiyete bozukluklarında l-dopa'ya büyüme hormonu cevabı

Özet: Stimülasyona körleşmiş büyüme hormonu (GH) cevabının, depresyon ve anksiyete bozuklukları için bir "biyolojik işaretleyici" olup olmadığını incelemek maksadıyla bu çalışmayı gerçekleştirdik. DSM-III R kriterlerine göre teşhis edilmiş major depresyon (N = 17), distimik bozukluk (N = 19), anksiyete bozukluğu (N = 18) vakası ile 20 sağlıklı kontrol şahısda bazal GH seviyeleri RIA tekniği ile ölçüldü. L-Dopa verildikten sonra 30, 60, 90 ve 120. dakikalarda kan örneği alma işlemi tekrarlandı. Gruplar maksimum cevap ile bazal hormon konsantrasyonu farkı olan "Δ peak GH" değerleri bakımından karşılaştırıldığında, sadece major depresyon grubunda önemli derecede körleşmiş GH cevapları elde edildi (KW= 10.1 $p < 0.05$) Bu sonuç, körleşmiş GH cevaplarının major depresyonda bozuk "alfa-adrenerjik" aktiviteyi yansıttığı şeklinde yorumlanabilir.

Anahtar Kelimeler: Büyüme hormonu, major depresyon, biyolojik işaretleyici

Summary: We replicated the challenge studies investigating blunting growth hormone (GH) response to stimulation whether it was a "biological marker" for depressive and anxiety disorders. The baseline GH levels were determined by radioimmunoassay technique in DSM-III R-defined major depresed (N=17), dysthymic (N=19), anxiety disorder patients (N=18) and healthy control subjects (N=20). Assay procedure repeated on 30th, 60th, 90th and 120th minutes after administration of L-Dopa. When we compared the values of " Δ peak GH (the difference between maximum response and baseline hormone concentration)" of the groups investigated by analysis of variance, we found a significant blunting GH response to L-Dopa stimulation in only major depressed group (KW = 10.1 $p < 0.05$). This result may be interpreted that blunting GH response might indicate a deficient alfa-adrenergic function in major depression.

Key words: Growth hormone, major depression, biological marker

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(*) This study has been sponsored by "Erciyes University Research Foundation"
This report has been presented at:
. 27th National Congress of Psychiatric Sciences 6-9 Nov, 1991 Antalya-TURKİYE
. 18th Collegium Internationale Psycho-Neuropharmacologicum Congress 28 June-2 July, 1992 Nice-FRANCE
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Many neuroendocrine abnormalities, including GH (growth hormone) secretory patterns, have been reported in psychiatric disorders. Since brain biogenic amines have been considered to be closely related to the secretion of GH, certain changes of them may be involved in the abnormal secreting mechanism of GH in depression (12). In connection with this idea, hormonal responses to pharmacological challenges have been used to examine central neurotransmitter function indirectly, in depression (13). But considerable contraversy about the specifity of these challenges for neurotransmitter systems is still present.

Accumulating evidence suggests extensive overlap between anxious and depressive disorders, both in symptoms and neurological characteristics (3). Neurobiologically, panic and major depressive disorders appear to share abnormalities both in the "hypothalamic-pituitary-adrenal" axis and the central noradrenergic systems (6).

We replicated the challenge studies of GH in order to investigate whether abnormal GH responses reflect a common or separate underlying pathophysiological mechanism in depressive and anxiety disorders.

METHODS

Subjects

Three groups of hospitalized patients with major depression (N=17, 9 females, 8 males. Mean (±SD) age:38.94±12.74), dysthymic disorder (N=19, 10 females, 9 males. Mean (±SD) age:29.10±6.17), and anxiety disorder (N=18, 10 females, 8 males. Mean (±SD) age:27.66±5.95) were included in the study. All patients were diagnosed by DSM-III R criteria with the SCID-I (21), and free of ECT or psychotropic medication for at least 2 weeks before the start of the study.

Age and sex-mached normal controls (N=20, 10 females, 10 males. Mean (±SD) age: 34.66-5.95) gave no history of psychiatric disorders or none had an axis 1 diagnosis.

Subjects with significant medical illnesses, regular alcohol intake or exceeding ideal weight by more than 20 % were excluded.

Severity of clinical symptomatology was assessed using MADRS (14) and the Clinical Anxiety Scale (19).

Test protocol

GH stimulation test was conducted on all subjects at rest in bed at 8.30 a.m. after an overnight fast. A catheter (No:19) was inserted into an antecubital vein, and infusing saline, half-an-hour was allowed for adjustment. Then, a blood sample was obtained for baseline values (0 min.). Other samples were collected at 30, 60, 90, 120 min. into heparinized tubes after administration of L-Dopa (500 mg orally). Samples were immidiately placed on ice, centrifuged at 4 oC and 1000 g for 15 min. within 2 hours of collection, and stored at -70 ^{o}C until analysis.

Biochemical analysis

GH plasma concentrations were measured using standart RIA technique (Diagnostic Product Corporation-USA kit). The detection limit for GH assay was 0.2 ng/ml. Intra- assay and interassay coefficients of variation were 5.0 % and 6.0 % respectively, at a concentration of 3 ng/ml. All measurements were done in duplicate, and clinical and laboratory staff were blind to each other's data.

Data analysis

Comparisons of baseline GH values were made by using the mean of two basal values for each subject. Hormonal responses were expressed as the absolute increase to peak above baseline (Dpeak GH: Maximum level of GH after stimulation minus baseline GH level).

The data were analysed by analysis of variance (Kruskall-Wallis). Mann-Whitney U test was used for group comparisons and Spearman's rank-order correlation test was used to investigate the possible correlations.

RESULTS

There were no significant differences in baseline values of GH among the patients and control groups. Maximum GH levels were observed at 90 min. in 48 % of the subjects.

Analysis of variance revealed a significant difference in the values of "Δpeak GH" among the groups investigated. Cross comparisons of the groups showed a significant blunting in the major depressed group only, when compared to the other groups (Comparisons of the group of control, anxiety disorder and dysthymic disorder respectively were: $u=260.5$ $p<0.05$, $u=227.0$ $p<0.05$, $u=229.5$ $p<0.05$).

No group had any difference between the females and males in the values of "Δpeak GH".

No correlation was found between the values of "Δpeak GH" and MADRS-CAS scores or age in any group.

DISCUSSION

Our findings do not confirm the reports indicating blunted GH responses to stimulation in panic disorder (2, 17), generalized anxiety disorder (1) and dysthymic disorder (4, 20) as compared to controls. But they are consistent with the studies reporting no difference in GH responses between the patients with panic disorder (18) or dysthymic disorder (5, 15) and controls.

In the current study, we found no significantly different baseline GH levels among the patients and control groups, but also found significantly blunted GH responses to L-Dopa stimulation in the major depressed group only, as compared to the others. Baseline plasma GH has been reported to be within normal limits in depression (16) as we found. But previous studies of GH responsiveness in depression are contraversial. One group has consistently reported a lower GH response to stimulation (9, 10, 11). Another group reported that they had found a higher GH response in depression (7). A third group reported normal GH response in depression (15, 22). Our finding is consistent with that of the first group.

It is difficult to explain these differences among the clinical studies, but lack of placebo-controlled strategy, having small sample sizes and not strictly considering some other variables known to affect the GH response, such as menstrual cycle phase (10), history of exposure to tricyclic antidepressants (18), or smoking habits (8) may be responsible for these discrepancies.

The stimulation mechanism for L-Dopa is not clear enough, but it may stimulate GH by an α-adrenergic pathway (8). Reduced responsiveness of GH has been postulated to reflect a subsensitivity in central α adrenoreceptor functioning (10). Blunted GH response we found supports the "noradrenergic functional deficiency" hypothesis for a subgroup of depressive disorder. In addition, it has been previously

Table I. GH baseline values and responses to L-Dopa stimulation in the patients and control groups

	GROUPS									
	Major depression (N=17)		Dysthymic disorder (N=19)		Anxiety disorder (N=18)		Control (N=20)		Comparison	
TIME(min)	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	KW	p
0	3.45	3.32	2.89	4.24	2.92	4.05	2.55	2.00	3.28	NS
30	3.26	2.94	4.42	5.91	3.61	3.79	3.40	2.85	-	-
60	3.55	2.74	5.88	6.37	5.23	7.81	5.45	5.31	-	-
90	4.25	3.35	7.26	5.96	8.90	7.64	10.73	9.71	-	-
120	4.25	3.62	5.75	4.36	7.18	6.45	7.95	7.42	-	-
Peak	6.79	3.51	9.27	6.64	10.36	8.02	12.56	9.48	5.09	NS
Δpeak GH	3.34	2.93	6.38	5.21	7.44	6.23	10.02	6.59	10.1	0.05*

*Statistically significant

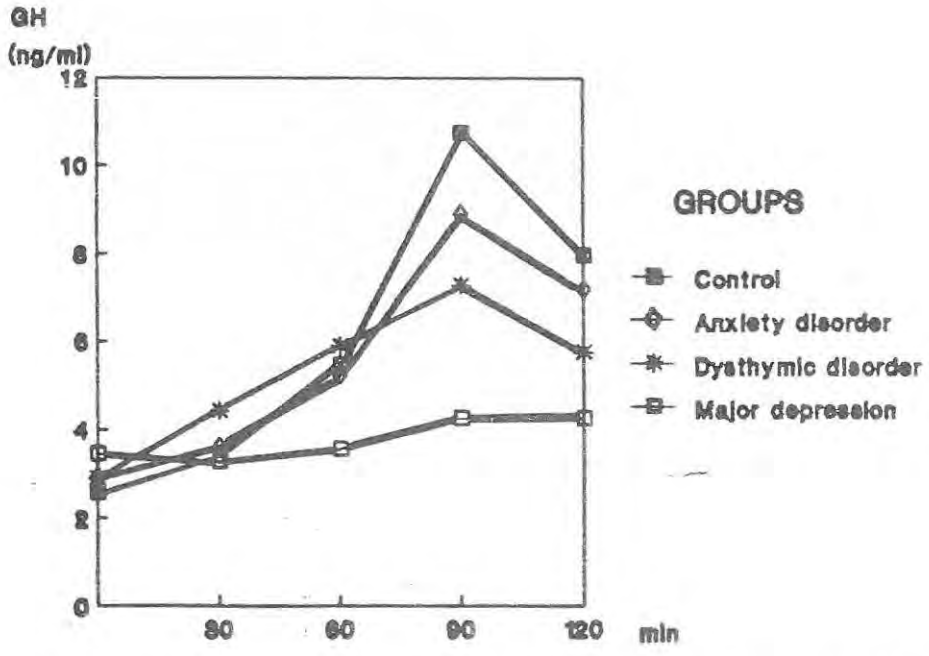

Figure 1. GH responsiveness to L-Dopa of the patients and control groups.

reported that the depressives retested in their symptom-free intervals had shown deficient GH responses (8). Based on these evidences, does the deficient GH responsiveness indicate a "vulnerability" for depression or is it a "trait marker" for depression? The answer awaits further investigations.

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