

Sumatriptan-Induced Growth Hormone Release in Patients with Major Depression, Mania, and Normal Controls

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The purpose of this study was to assess serotonergic function in patients with major depression or mania using sumatriptan, a novel 5-HT_{1D} receptor agonist, as a pharmacological probe in a neuroendocrine challenge paradigm. We studied 18 drug free patients (10 with acute unipolar major depression and 8 with acute mania) who met DSM-IV criteria, and healthy controls. Subjects presented for testing after an overnight fast. After obtaining a blood sample for baseline growth hormone (GH) levels, sumatriptan (6 mg) was given subcutaneously, and further blood samples were collected at half hour intervals for 2

hours. The results showed that GH responses to sumatriptan were blunted in depressed patients but not in manics, compared to healthy controls. There were no differences in basal GH levels between the 3 groups. The results of this study provide further support for the role of serotonergic system in pathophysiology of major depression, but not in mania. [Neuropsychopharmacology 17:258-263, 1997] © 1997 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

KEY WORDS: Sumatriptan; Major depression; Mania; 5-HT_{1D} receptors; Growth hormone

Hormonal responses to challenges with various pharmacological probes provide a simple, dynamic, *in vivo* means of assessing central neurotransmitter function in humans (Yatham and Steiner 1993). This paradigm has been widely used to assess central serotonin (5-hydroxytryptamine, 5-HT) function in major depression, and the studies have in general provided evidence for 5-HT dysfunction in this condition. For instance, several investigations have shown blunted prolactin and/or corti-

sol responses to challenges with L-tryptophan (Cowen and Charig 1987), clomipramine (Golden et al. 1992), fenfluramine (O'Keane and Dinan 1992), and ipsapirone (Lesch et al. 1990) in patients with major depression compared to healthy controls. In contrast, only three studies, to date, used this approach to assess 5-HT function in acute mania (Meltzer et al. 1984; Yatham 1994; Yatham 1996). In part, this may reflect the difficulty of recruiting drug free manics during acute phase. One of the 3 studies reported an enhanced cortisol response to 5-hydroxytryptophan (5-HTP) challenge (Meltzer et al. 1984), whereas the other 2 found no differences in prolactin and/or cortisol release to fenfluramine (Yatham 1996) or buspirone (Yatham 1994) challenges between manic patients and healthy controls.

Sumatriptan is a novel 5-HT_{1D} receptor agonist used in treating acute migraine (Fowler et al. 1991). When given subcutaneously in normal volunteers, it increases growth hormone (GH) release significantly without al-

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tering the release of other hormones such as prolactin, cortisol, or adrenocorticotrophin (ACTH) (Franceschini et al. 1994). GH levels peak at 30 to 60 minutes after sumatriptan injection, and return to baseline after 120 minutes (Franceschini et al. 1994). The purpose of this study was to compare sumatriptan induced GH release in patients with major depression or acute mania, and healthy controls.

METHODS

A total of 21 patients (13 with acute unipolar major depression and 8 with acute mania) and twelve normal controls were recruited. Of these, 3 healthy controls and 3 depressed patients had baseline GH levels above 5 µg/L, and were excluded from the analysis because, after a GH secretory episode, the pituitary is relatively refractory (Vance et al. 1985). The subjects were physically healthy and gave written informed consent for participation in the study. The DSM-IV diagnosis of major depressive disorder or bipolar disorder—current episode mania, was made by the consensus of the research team using the information generated from a clinical interview by a psychiatrist, and a structured clinical interview for DSM-111-R diagnosis (SCID) performed by a research assistant. Those that met criteria for other Axis 1 diagnoses, substance or alcohol abuse were excluded. The healthy controls had no lifetime history of psychiatric illness as determined by SCID-non-patient version. The severity of depressive symptoms was assessed by the Hamilton rating scale for depression (HAM-D 21 item) (Hamilton 1960), and manic symptoms were assessed by the Young mania rating scale (Young et al. 1978). Patients with depression had a mean 21 item HAM-D score of 25.6 ± 5.56 , whereas manic patients had a mean score of 32.75 ± 5.23 on Young mania rating scale. All study subjects except one manic patient were drug free for at least 10 days, with the exception of lorazepam prn, (mean dose received was less than 0.5 mg per day). None of the subjects had received fluoxetine in the preceding 6 months. The testing was conducted at the Mood disorders clinical research unit. Subjects having fasted since midnight presented for testing between 7.30 and 8.00 AM. An indwelling intravenous catheter was inserted in a forearm vein at 8 AM and subjects were allowed to rest but not sleep, smoke, or eat. The blood for baseline GH was obtained at 9.00 AM (time 0) and 6 mg of sumatriptan were given subcutaneously at this time. Further bloods were obtained at 30 minute intervals during the next 2 hours. The blood samples were placed on ice until all the samples were obtained for each subject. The samples were centrifuged, serum separated, and stored at -70 C for assay at a later time. Subjects rated at baseline, 30,

60, 90, and 120 minutes on 10 cm visual analogue scales (VAS) on the following items: least/most nauseated, best/worst concentration, and least/most drowsiness.

GH was assayed by Quantitope HGH Radioimmunoassay (Kallestad diagnostics). The samples were assayed blind to the diagnostic status of subjects. In addition, all samples from each subject were assayed in the same batch. The sensitivity of GH assay was 0.2 µg/L. The intra-assay coefficients for GH were 6.8%, 5%, and 9.1% for GH pools of 2.5 µg/L, 5.4 µg/L, 35.2 µg/L respectively. The interassay coefficients of variation were 10.8 % for GH pool of 2.6 µg/L, 6.6% for GH pool of 5.8 µg/L, and 5.7% for GH pool of 11.3 µg/L.

An analysis of variance (ANOVA) with repeated measures was used to compare differences in sumatriptan-induced GH release among patients with depression or mania, and healthy controls. The Δ GH (peak minus baseline GH value) levels among the three groups were compared using Kruskal-Wallis test, and post-hoc analysis was carried out using Mann-Whitney test. Chi-square and Kruskal-Wallis tests were used, to compute the differences in sex and Δ VAS (peak minus baseline values) scores among the three groups. The correlations between Δ GH and HAM-D21, Δ GH and the Young mania scale scores, and Δ GH levels and Δ VAS scores were computed with Pearson's and Spearman's correlation tests.

RESULTS

The age, sex, and baseline and peak GH levels, for the 27 study subjects, are presented in Table 1. There was no difference in age (depressed patients = 45.7 ± 9.53 , manic patients = 42.62 ± 13.39 , healthy controls = 39.33 ± 11.9 ; one way ANOVA: $F = 0.74$, $df = 2,24$, $p = 0.48$), or sex (Chi-Square test, $\chi^2 = 2.90$, $df = 2$, $p = 0.23$) among the three diagnostic groups.

The GH levels during baseline and at various time points, following sumatriptan administration, are plotted in Figure 1. A one way ANOVA comparing baseline GH levels in patients with major depression or mania, and healthy controls showed no differences among the three groups ($F = 0.37$, $df = 2,24$, $p = .68$). The GH levels in the three groups, following sumatriptan administration, were compared using ANOVA with repeated measures which showed a main effect for time ($F = 12.7$, $df = 4,96$, $p < .001$) and for group by time interaction ($F = 2.01$, $df = 8,96$, $p = .05$), but no main effect for group ($F = 2.01$, $df = 2,24$, $p = 0.15$). When GH levels in patients with major depression, were compared with GH levels in healthy controls, ANOVA showed a group by time interaction effect ($F = 4.10$, $df = 4,68$, $p < .005$), as well as a trend for a group effect ($F = 3.80$, $df = 1,17$, $p < .06$), but no group by time interaction ($F = 0.47$, $df = 4,60$, $p = .76$) or group effect was noted when manic pa-

Table 1. Demographic and Hormonal Data for Patients with Depression or Mania, and Healthy Controls

	Age (years)	Sex	Baseline GH (uG/L)	Peak GH (uG/L)
Depression				
1	59	Female	1.2	1.4
2	60	Male	2.6	1.6
3	51	Male	1.4	2.6
4	41	Female	1.4	3.1
5	44	Female	1.7	2.5
6	39	Female	1.4	1.7
7	49	Female	2.7	3.6
8	48	Female	3.6	3.3
9	34	Male	0.6	0.8
10	33	Male	3.7	3.1
Mean ± SD	45.8 ± 9.3	-	2.03 ± 1.05	2.37 ± 0.94
Mania				
1	32	Female	1.0	6.2
2	44	Female	0.7	8.1
3	49	Female	0.6	0.9
4	24	Female	1.1	1.7
5	66	Female	1.4	1.7
6	33	Male	1.0	1.0
7	40	Female	4.1	3.7
8	53	Female	3.4	6.6
Mean ± SD	42.6 ± 13.3	-	1.66 ± 1.32	3.66 ± 2.92
Healthy controls				
1	47	Female	1.9	4.7
2	52	Female	1.2	3.1
3	39	Female	1.3	7.3
4	23	Female	1.3	3.0
5	49	Female	1.7	1.7
6	44	Female	2.0	3.1
7	23	Female	2.2	10.2
8	27	Female	2.3	10.6
9	50	Male	1.5	2.0
Mean ± SD	39.3 ± 11.9	-	1.71 ± 0.41	5.07 ± 3.44

tients were compared with healthy controls ($F = 1.30$, $df = 1,15$, $p = .27$).

Kruskal-Wallis test was used to compare the differences in Δ GH levels among the three groups ($\chi^2 = 6.22$, $df = 2$, $p < .04$). Post-hoc comparisons were made with Mann-Whitney test which showed a significant difference between patients with major depression and healthy controls (Mann-Whitney $U = 13.5$, $Z = -2.57$, $p < .008$), but not between manic patients and healthy controls (Mann-Whitney $U = 22.5$, $Z = -1.30$, $p = .20$). There were, however, no significant correlations between Δ GH levels and HAM-D 21 item scores, or between Δ GH levels and scores on the Young mania rating scale.

For behavioural measure, Δ VAS scores for nausea, concentration and drowsiness were calculated by subtracting baseline values from peak values, and analyzed by Kruskal - Wallis test. There were no differences in Δ VAS scores of nausea ($\chi^2 = 0.97$, $df = 2$, $p = .61$), concentration ($\chi^2 = 0.27$, $df = 2$, $p = .87$), or drowsiness

($\chi^2 = 4.73$, $df = 2$, $p = .09$) among the three diagnostic groups. sumatriptan was in general well tolerated by all three groups. There was no correlation between Δ GH levels and Δ VAS scores of nausea, concentration, or drowsiness in any of the three diagnostic groups (data not shown).

DISCUSSION

To our knowledge, this is the first study that measured sumatriptan induced GH release in patients with major depression or mania. The results indicated that patients with major depression had blunted GH release compared to healthy controls, whereas GH release in manic patients was not different from healthy controls.

GH responses to other 5-HT challenges such as L-tryptophan (Cowen and Charig 1987) and m-chlorophenylpiperazine (Anand et al. 1995) have been reported to be blunted in major depression. The finding of a

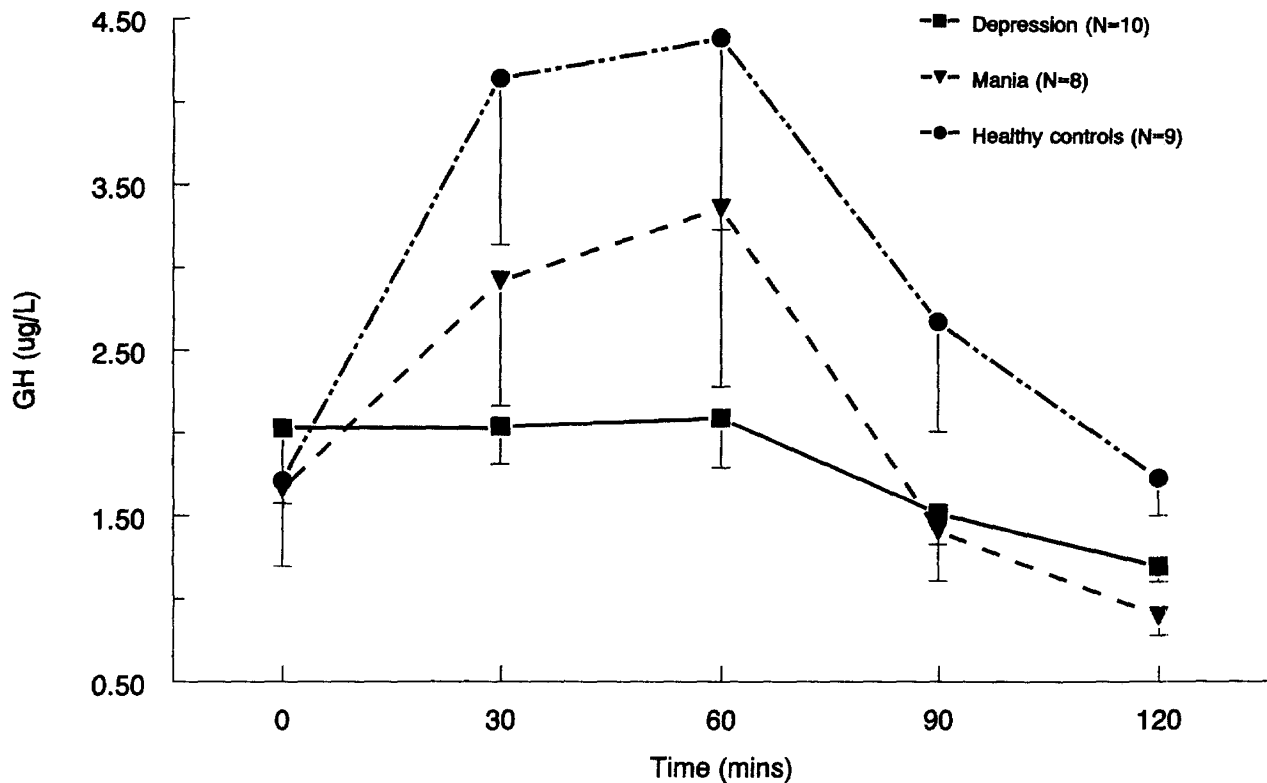


Figure 1. Growth hormone (mean \pm SEM) responses to sumatriptan in patients with major depression ($N = 10$) or mania ($N = 8$), and healthy controls ($N = 9$).

blunted GH release to sumatriptan in depressed patients in this study, thus is in agreement with previous studies, providing further support for 5-HT dysfunction in major depression. Sumatriptan is a selective 5-HT₁ agonist with no affinity for other 5-HTergic, dopaminergic, adrenergic, or muscarinic receptors (Schoeffter et al. 1989; Humphrey et al. 1991). Within the 5-HT₁ receptor family, it binds with 4 to 20 fold higher affinity to 5-HT_{1D} receptors over 5-HT_{1A} receptors (Schoeffter et al. 1989; Humphrey et al. 1991). This would suggest that sumatriptan induces GH release by stimulating 5-HT_{1D} receptors, although the role of 5-HT_{1A} receptors cannot be excluded. Other studies assessing 5-HT_{1A} responsiveness in depressed patients have yielded conflicting results. For instance, buspirone induced GH release, which is considered to be mediated by 5-HT_{1A} receptors (Anderson and Cowen 1992), was unaltered in depressed patients compared to normal controls (Cowen et al. 1994), whereas cortisol and ACTH release evoked by ipsapirone (also mediated by 5-HT_{1A} receptors) was blunted (Lesch et al. 1990). A further study in healthy volunteers assessing the effects of pindolol, a β -blocker with 5-HT_{1A} antagonistic properties (Hamon et al. 1987), on sumatriptan induced GH release might help to resolve this issue.

The release of GH from the pituitary is regulated by the stimulating effects of GH releasing hormone (GHRH)

(Sawchenko et al. 1985) and the inhibiting effects of somatostatin (Urman et al. 1995). 5-HT does not stimulate GH from the pituitary in vitro (Kato et al. 1980). There is evidence that 5-HT increases release of GHRH (Murakami et al. 1986) but it has no effect on somatostatin (Chihara et al. 1979). Therefore, it is likely that 5-HT agonists evoke GH release from the pituitary by increasing the release of GHRH. A blunted GH release has been reported not only with 5-HT challenges but also with adrenergic drugs such as clonidine and desipramine (Checkley et al. 1981; Dinan and Barry 1990) and dopaminergic drugs, such as apomorphine (Ansseau et al. 1988) in depressed patients. This raises the question whether there is a defect in GH secretion at the pituitary level in patients with major depression, perhaps due to an alteration in sensitivity of pituitary somatotrophs. Studies that assessed pituitary somatotroph responsivity by measuring GH release to GHRH challenge in depressed patients have yielded conflicting results, with some showing a normal release and others a decreased release, in comparison to controls (Krishnan et al. 1988; Thomas et al. 1989; Leach et al. 1987). Further studies are clearly needed to resolve this issue.

In regards to manic patients, the GH responses were not different than the ones obtained from healthy controls. Since we studied only 8 manic patients we cannot exclude the possibility of a type 2 error. GH responses

to 5-HT challenges have not been assessed in manic patients, in any of the previous investigations. However, of the 3 previous neuroendocrine studies that measured prolactin and/or cortisol to fenfluramine (Yatham 1996), buspirone (Yatham 1994), and 5-hydroxytryptophan (Meltzer et al 1984) challenges, 2 reported no differences in hormone release (Yatham 1994; Yatham 1996), whereas the third found enhanced responses (Meltzer et al. 1984) in manics compared to controls. The GH responses in manics, in the present study, were somewhat lower, but not significantly different, from GH responses in healthy controls. The results of this investigation, therefore, are in agreement with 2 previous studies, providing little support for 5-HT dysfunction in this condition.

In summary, the results of this study showed blunted GH release to sumatriptan challenge in depression, but not in mania. These findings, therefore, provide support for 5HT dysfunction in depression, but not in mania.

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