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Effect of Previous Antidepressant Therapy on the Growth Hormone Response to Apomorphine

Abstract

Several lines of evidence suggest a role for dopamine in the pathophysiology of depression. In 1988, we reported a blunted response of growth hormone (GH) to apomorphine, a dopaminergic agonist, in endogenous depression. However, an antidepressant washout period is a major confounding factor in studies assessing the GH response to apomorphine. Indeed, whereas the influence of tricyclic antidepressants on the GH response to apomorphine is presently unknown, several reports have suggested that tricyclics may impair the GH response to clonidine for periods longer than 3 weeks following their discontinuation. In the present study, we hypothesized that a blunted GH response to apomorphine in depressed patients could be related to the recent administration of antidepressants. Therefore, the GH response to apomorphine (0.5 mg) was studied in 11 male DSM-III-R major depressive inpatients who had never received antidepressant therapy (group 1) compared to 11 normal controls and 11 major depressive inpatients drug free for at least 2 weeks (group 2). The three groups differed significantly in the GH peak response to apomorphine: mean (SD) 5.4 (4.0) ng/ml in group 1, 25.5 (10.7) in normal controls, and 5.5 (5.1) in group 2 (F = 15.5, df = 3, 30, p = 0.00001). While group 1 and normal controls (F = 21.8, p = 0.0002) as well as group 2 and controls (F = 5.6, p = 0.03) differed significantly, group 1 and group 2 did not (F = 0.18, p = 0.68). These results suggest that a washout period of 2 weeks could be sufficient in studies assessing the GH response to apomorphine.

Introduction

The current main pathophysiological theory of endogenous depression hypothesizes a decreased activity in central neurotransmitters activity, and principally serotonin and noradrenaline. However, various lines of evidence also suggest a role for dopamine in the pathophysiology of depression [1, 2]. Indeed, low cerebrospinal fluid levels of homovanillic acid, a dopaminergic metabolite, in depression [3], an increased incidence of depression in Parkinson's disease [4] and the depressogenic effect of dopaminergic antagonists [5] support the hypothesis of dopaminergic disturbances in affective disorders.

These disturbances could result from a diminished neurotransmitter release, or from a dysfunction in the sensitivity of specific receptors. In that sense, a neuroen-

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Table 1. GH peak values after injection of apomorphine and characteristics of previous antidepressant therapy in patients drug free for at least 15 days

Patients	GH	Duration of antidepressant washout (days)	Type of antidepressant	Doses mg
1	16.6	15	fluvoxamine	100
2	4.8	15	mianserin	120
3	5.8	15	amitriptyline	75
4	0.3	15	desipramine	100
5	2.2	15	clomipramine	75
6	0.2	30	clomipramine	75
7	10.3	15	clomipramine	75
8	2.4	15	nortriptyline	100
9	1.6	21	maprotiline	200
10	5.8	15	maprotiline	150
11	10.7	15	fluoxetine	20

docrine strategy may provide an indirect index of central neurotransmission at the postsynaptic receptor level and test the functional state of neurotransmission systems. Indeed, the release of anterior pituitary hormones depends on hypothalamic releasing factors, the secretion of which is controlled by neurotransmitters implicated in depression. In the study of the dopaminergic function, the greatest amount of information can be obtained from the analysis of growth hormone (GH), the secretion of which is stimulated by dopamine [6]. In 1988, Ansseau et al. [7] confirmed the role of dopamine in the pathophysiology of depression by demonstrating a blunted GH response to apomorphine, a dopaminergic agonist, in endogenous depressive patients. This finding suggested a hyposensitivity of the dopaminergic hypothalamic receptors controlling GH release in major depression. Recently, we reported a lower GH response to apomorphine in depressed patients with a history of suicide attempts compared to patients without history of suicidal behavior suggesting that a blunted GH response to apomorphine could represent a biological marker of suicidal behavior [8]. Moreover, we have also shown that depressed patients with psychomotor retardation had a decreased GH response to apomorphine compared to agitated depressed patients linking dopaminergic hypoactivity in depression to motor retardation [2].

A major methodological problem in these studies assessing the GH response to apomorphine is the length of the drug-free washout period. Indeed, whereas the influence of tricyclic antidepressants on the GH responses

to apomorphine is presently unknown, several reports have suggested that tricyclics may impair the GH response to clonidine for periods longer than 3 weeks following their discontinuation [9, 10]. Therefore, the blunted GH response to apomorphine in depressed patients could be related to the recent administration of antidepressants.

In this study, we hypothesized that a washout period of 2 weeks of antidepressants might be insufficient in studies assessing GH response to apomorphine. In order to test this hypothesis, we compared a group of depressed patients who had never received antidepressant treatment with depressed patients drug free for at least 15 days and normal controls.

Patients and Methods

Subjects

The study was performed in a group of 11 male DSM-III-R major depressed inpatients, mean age (SD) = 35.2 (11.8), who had never received antidepressants. The sample included 3 melancholic patients. They were compared with 11 male DSM-III-R major depressive inpatients, mean age (SD) = 39.2 (6.2), including 6 melancholics and 5 nonmelancholics, who were drug free for at least 15 days before the neuroendocrine investigation [mean drug-free period: 16.9 (4.7) days; table 1]. All the patients had a score of at least 18 on the 17-item Hamilton Depression Scale (HAMD). In both groups, patients were only offered occasional low doses of benzodiazepines if necessary. Both groups were compared with 11 male normal controls, mean age (SD) = 25.9 (3.2). Moreover, none of the patients had taken antipsychotic drugs during the 3 months before the neuroendocrine investigation. The two groups of depressive patients did not differ in mean age (F = 0.98, p = 0.34) or HAMD scores (F = 0.96, p = 0.34). Patients with a history of psychosis, alcoholism or bipolar disorder were excluded from the study.

All patients were free of medical illness as evidenced by history, medical examination, electrocardiogram, chest X-ray, electroencephalogram and routine laboratory tests. None was overweight. Patients with a basal systolic blood pressure <100 mm Hg were excluded from the study. Moreover, in order to be included, patients had to present basal GH levels <5 ng/ml before the pharmacological challenge. The exclusion of subjects with basal GH value >5 ng/ml was recommmended by Laakmann [11] who demonstrated that 'prestimulator' healthy volunteers responded significantly less to noradrenergic challenge than healthy volunteers with low basal values. Finally, all patients were fully informed of the study and gave their consent.

Procedure

The apomorphine test was performed in all subjects at bedrest after an overnight fast. At 7 a.m., an indwelling catheter was inserted into a forearm vein. Blood samples of 10 ml were collected at –20, 0, 20, 40, 60 and 120 min after injection (at 8 a.m.) of 0.5 mg apomorphine diluted in saline to obtain 0.5 ml subcutaneously.

GH was measured with a double antibody radioimmunoassay [12], with intra- and interassay coefficients of variation of 13.3 ± 4.7 and 14.8 ± 9.6%, respectively, and a detection limit of 0.2 ng/ml.

GH response to apomorphine was assessed by GH peak values following injection. The analysis was performed using absolute GH values as well as differences related to basal (t0) levels (relative values). Because the correlations between absolute and relative values were very high (r > 0.98), only the absolute values are reported here. The GH responses of the three groups were compared using analysis of covariance with age as a covariate whereas the comparison of the two groups of depressed patients used age, melancholia and HAMD scores as covariates.

Results

A significant difference in GH response existed among the three groups: GH peak (SD) reached 5.4 (4.0) ng/ml in depressed patients who never received antidepressants (group 1), 5.5 (5.1) ng/ml in depressed patients drug-free for at least 15 days (group 2) and 25.5 (10.7) ng/ml in normal controls (F = 15.5, df = 3, 30, p = 0.00001). However, while group 1 and normal controls (F = 21.8, df = 3, 19, p = 0.0002) as well as group 2 and controls (F = 5.6, df = 3, 19, p = 0.03) differed significantly, group 1 and group 2 did not (F = 0.0, p = 0.96). Adding age, melancholia and HAMD in an ANCOVA setup for the comparison between group 1 and group 2 only increased the F value from 0.0 to 0.18 (p = 0.68).

All 11 controls (100%) tested with apomorphine 0.5 mg presented GH responses higher than 7 ng/ml. On this basis, we defined the cutoff GH peak following apomorphine as 7 ng/ml. Therefore, 7 patients (63%) in the first group and 8 (72%) in the second group presented a blunted GH response (Fischer's exact test, p = 0.5).

Discussion

The results of the present study showed that a washout period of 2 weeks of antidepressant therapy could be sufficient in studies assessing the GH response to apomorphine. Indeed, GH peak responses after apomorphine did not differ between patients who had never received antidepressants and patients drug free for at least 15 days. Moreover, untreated depressed patients exhibited a significantly lower GH response to apomorphine challenge than normal controls. Therefore, the blunted GH response to apomorphine in depression does not seem to be significantly influenced by the recent use of antidepressants.

The apparently weak effect of antidepressant therapy on the GH response to apomorphine could be explained by the fact that antidepressants do not alter the sensitivity of dopaminergic receptors mediating the GH release. In fact, the dopaminergic receptors associated with GH release are of the D2 rather than D1 subtype. Indeed, apomorphine-induced GH release is only inhibited by pharmacological agents exhibiting dopaminergic antagonist properties particularly at the level of D2 receptors such as chlorpromazine, haloperidol, pimozide or sulpiride [13]. Animal data have shown that antidepressants influence the dopaminergic system by acting on the D1 but not the D2 receptor subtypes. Indeed, some animal studies have reported increased sensitivity of mesolimbic dopaminergic mechanisms after chronic administration of paroxetine, fluoxetine and citalopram. Fluoxetine has also been shown to reduce the turnover of dopamine in several areas of the rat brain. However, repeated administration of either fluoxetine [14] or citalopram [15] had no effect on the binding of ^{3}H-spiperone to dopamine D2-receptor binding sites in the rat brain. Moreover, antidepressant agents such as imipramine or amitriptyline reduced the binding of ^{3}H-SCH-23390 to dopamine D1 receptors in the rat brain after repeated administration, but without changing ^{3}H-spiperone binding sites [16].

In 1989, Schittecatte et al. [10] suggested that the blunted GH response to clonidine in depressed patients could be due in part to the recent use of antidepressants. In 1992, they [17] showed that the downregulation of α_2-adrenoreceptors after desipramine treatment could last as long as 1 year. The long-lasting effects of tricyclic pretreatment on GH response to clonidine could result from an induced intrinsic abnormality in the hypothalamic-GH-somatomedin axis. The findings of the current study suggest that the axis is intact and that antidepressants specifically act on α_2-adrenoreceptors rather than on the integrity of the hypothalamic-GH-somatomedin axis.

In conclusion, the blunted GH response to apomorphine in some depressed patients is not due to the recent use of antidepressants. In addition, the statistically significant difference in GH response to apomorphine between untreated depressives and healthy controls supports the role of the dopaminergic system in the pathophysiology of major depression. In view of our recent findings on the relationship between suicide and dopaminergic activity, this conclusion suggests that GH response to apomorphine could have interesting implications in clinical practice.

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