Suicidal Behavior and Growth Hormone Response to Apomorphine Test

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Several cerebrospinal fluid (CSF) studies have provided support for a possible role for the dopaminergic system as a biological correlate of suicidal behavior. Indeed, low CSF levels of the dopamine metabolite homovanillic acid (HVA) have been described in depressed patients with a history of suicide attempts.

In this study, we assessed the dopamine receptor sensitivity in relationship to suicidal behavior by measuring growth hormone (GH) response to apomorphine 0.5 mg subcutaneously (sc) in 15 DSM-III-R (APA 1987) major depressive inpatients with a history of suicide attempts, compared to age-matched and gender-matched major depressive inpatients without a history of suicide.

Patients with a history of suicidal behavior exhibited a significantly lower GH response to apomorphine than patients who never attempted suicide ($t = 3.60$, $df = 1.28$, $p = 0.0012$). *Therefore, these results suggest that a blunted GH response to apomorphine could represent a biological marker of suicidal behavior.*

Introduction

Over the last 15 years, cerebrospinal fluid (CSF) studies have provided interesting biological probes of suicidal behavior. In 1976 Asberg et al (1976a) found a bimodal distribution of CSF concentration of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in depression. They showed that patients who attempted suicide before admission to hospital exhibited low CSF 5-HIAA levels compared to those without history of suicide attempt (Asberg et al 1976b). The relationship between low CSF 5-HIAA levels and suicidal behavior has been confirmed in a large number of studies (Brown et al 1979, 1982; van Praag 1982; Agren 1980; Ninan et al 1984; van Praag 1983). The involvement of serotonin as a biological correlate of suicidality was also assessed in postmortem (Asberg et al 1987; Mann et al 1986) and platelet studies (Meltzer and Arora 1986) with controversial results.

The role of the dopaminergic system has been less evaluated. Some studies reported low CSF levels of the dopamine metabolite homovanillic acid (HVA) in depressed patients with a history of suicide attempts (Agren 1980; Träskman et al 1981; Agren 1983;

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Montgomery and Montgomery 1982; Roy et al 1986). According to Montgomery and Montgomery (1982) and Agren (1983), who studied both CSF HVA and 5-HIAA, low CSF HVA levels could be a more reliable index of suicidal behavior than low CSF 5-HIAA concentrations.

However, the measure of CSF HVA levels represents a presynaptic index of dopamine activity. In contrast neuroendocrine strategy may provide an indirect index of central neurotransmission at the postsynaptic receptor level. The purpose of the study was to assess the dopamine receptor sensitivity in relationship to suicidal behavior in major depressed patients. We therefore compared the growth hormone (GH) response to apomorphine, a selective dopaminergic agonist, in hospitalized depressed patients with and without history of suicide attempts.

Methods

The study was performed in 15 DSM-III-R major depressive inpatients with a history of suicide attempt, representing consecutive admissions to the Psychiatric Unit of the University Hospital of Liège, Belgium. Their individual characteristics are displayed in Table 1 (patients 1–15). The sample comprised nine men and six premenopausal women with a mean age (SD) of 37.1 (9.1). These patients were individually matched for gender, age (within three years), and, in the case of women, menopausal status with 15 major depressive inpatients without history of suicidal behavior (Table 1: patients 16–30). The two groups did not differ in mean age ($t = 0.021$, $p = 0.88$) or weight ($t = 0.02$, $p = 0.87$). All patients had a score of at least 18 on the 17-item Hamilton depression scale at the end of a drug-free period of at least 2 weeks during which patients were only offered occasional low doses of benzodiazepines if necessary.

Past history of suicide attempt was based on interviews of the patients and their family. Suicide attempts were classified as violent (hanging, drowning, deep cuts, and shooting) or nonviolent (drug overdoses and superficial wrist cuts). All patients were free of medical illness as evidenced by history, medical examination, electrocardiogram (EKG), chest x-ray, electroencephalogram (EEG), and routine laboratory tests. The apomorphine test was performed between the third and the twelfth day of the menstrual cycle in premenopausal women. Patients with a basal systolic blood pressure less than 100 mmHG were excluded from the study. Moreover, in order to be included, patients had to present basal (t0) GH level less than 5 ng/ml before the pharmacological challenge (Ansseau et al 1984). The exclusion of subjects with basal GH value greater than 5 ng/ml was recommended by Laakmann (1990) who demonstrated that "prestimulator" healthy volunteers responded significantly less to a noradrenergic challenge than healthy volunteers with low basal values. Finally, all patients were fully informed of the study and gave their consent.

The apomorphine test was performed in all subjects at bedrest after an overnight fast. At 7 AM, 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 AM of 0.5 mg apomorphine diluted in saline to obtain 0.5 ml subcutaneously.

GH was measured with a double antibody radioimmunoassay (Franchimont 1968), with intraassay 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.

Table 1. Individual Characteristics of the Sample and Neuroendocrine Results

Patient	Gender	Age	Weight (kg)	HAM-D	Tsa	Nsa	Diagnosis	History of suicide attempt	Apomorphine test (GH peak: ng/ml)
1	F	23	62	20	2	4	MDD, without melanch., UP	drug overdose	3.7
2	M	26	64	25	2.5	2	MDD, without melanch., UP	drug overdose	6.9
3	M	27	83	29	2	3	MDD, without melanch., UP	drug overdose	3.8
4	F	29	70	23	2	1	MDD, with melanch., UP	deep cuts	10.0
5	F	33	51	38	3	2	MDD, with melanch., UP	drug overdose	8.0
6	F	33	73	18	5	2	MDD, without melanch., UP	drug overdose	7.4
7	M	34	76	25	2	1	MDD, without melanch., UP	hanging	4.9
8	M	36	66	38	6	1	MDD, with melanch., UP	defenestration	9.0
9	M	38	60	24	3	2	MDD, with melanch., UP	hanging	21.6
10	M	41	70	35	150	1	MDD, with melanch., UP	hanging	1.8
11	M	42	79	18	4	1	MDD, without melanch., UP	drowning	3.0
12	F	44	69	25	2	3	MDD, with melanch., UP	drug overdose	5.5
13	F	46	63	35	24	1	MDD, with melanch., UP	drug overdose	5.5
14	M	49	83	33	100	1	MDD, without melanch., UP	shooting	0.2
15	M	55	87	20	48	1	MDD, without melanch., UP	hanging	5.8
Mean	9M, 6F	37.1	70.4	27.06	23.7				6.4
SD		9.1	9.9	7.10	43.9				4.9
16	F	26	90	23	—	—	MDD, without melanch., UP	—	4.0
17	M	29	70	26	—	—	MDD, with melanch., UP	—	2.7
18	M	29	70	26	—	—	MDD, with melanch., UP	—	21.6
19	F	27	50	27	—	—	MDD, without melanch., UP	—	21.5
20	F	36	49	35	—	—	MDD, without melanch., UP	—	8.0
21	F	32	55	25	—	—	MDD, without melanch., UP	—	8.7
22	M	37	87	29	—	—	MDD, with melanch., BP	—	28.4
23	M	34	84	28	—	—	MDD, without melanch., UP	—	32.0
24	M	36	74	30	—	—	MDD, without melanch., UP	—	6.4
25	M	41	88	23	—	—	MDD, without melanch., UP	—	14.0
26	M	45	103	18	—	—	MDD, without melanch., UP	—	20.8
27	F	42	52	21	—	—	MDD, without melanch., UP	—	36.9
28	F	44	52	25	—	—	MDD, with melanch., UP	—	17.4
29	M	48	72	24	—	—	MDD, without melanch., UP	—	12.6
30	M	57	72	27	—	—	MDD, without melanch., UP	—	21.5
Mean	9M, 6F	37.5	71.2	25.8					17.1
SD		8.7	16.9	4.0					10.3

MDD = major depressive disorder; melanch = melancholia; UP = unipolar; BP = bipolar; Tsa = time between the suicide attempt and the investigation; Nsa = number of suicide attempts.

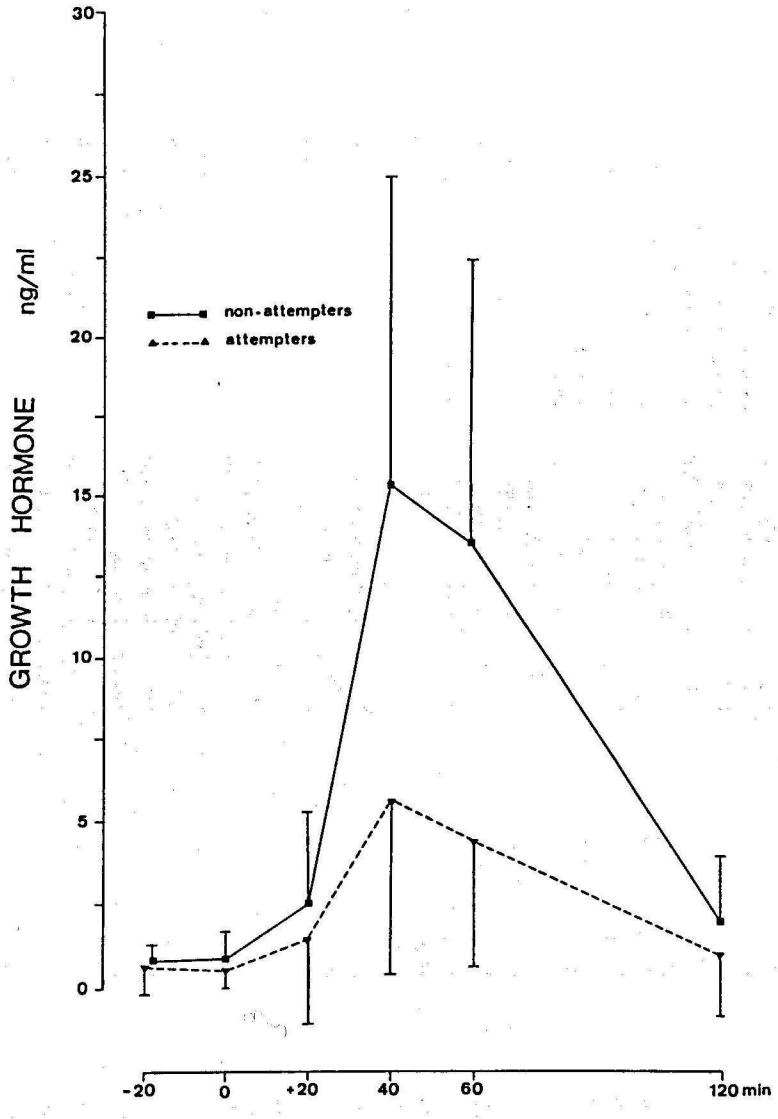

Figure 1

Data Analysis

GH responses to apomorphine were assessed by two different methods: by GH peak values following injection and by the areas under the curve (AUC) situated between injection (t0) and the last blood sampling (t120 min). Both analyses were 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 responses of patients with and without history of suicide attempt were compared using analysis of variance (ANOVA), whereas

the comparison of violent and nonviolent suicide attempters by covarying for age. We also used Pearson's correlation coefficient.

Results

Mean peak GH response to apomorphine test was significantly lower in the group of depressed patients with a history of suicide attempts than in the group without history of suicidal behavior: for peak values 6.4 ± 4.9 ng/ml versus 17.10 ± 10.3 ng/ml, $t = 3.60$, df = 1.28, $p = 0.0012$, and for the areas under the response curve, 354 ± 284 ng min/ml versus 971 ± 539 ng min/ml, $F = 15.36$, df = 1.28, $p = 0.0005$. Adding melancholia, gender, age, and weight in an ANCOVA set-up only decreased the F-value for suicide from 12.92 to 12.22 ($p = 0.0019$). Moreover, no significant correlation existed between GH responses and scores on the Hamilton rating scale for depression ($r = -0.13$).

There was no significant difference in mean GH response between nonviolent (x = 5.8 ng/ml ± 1.7 SD) and violent (x = 7.0 ng/ml ± 6.7 SD) attempters ($t = 0.21$, df = 1.13, $p = 0.654$). Moreover, time between the suicide attempt (Tsa) and the investigation was not correlated with GH responses ($r = -0.41$, $p = 0.12$).

Discussion

The results of this study support an involvement of the dopaminergic system in the control of suicidal behavior. Indeed, patients with a history of suicidal behavior exhibited a significantly lower GH response to apomorphine challenge than patients who had never attempted suicide. This finding suggests that a hyposensitivity of dopaminergic receptors could be a factor in suicidal behavior. The lack of correlation between GH responses and the time between suicide attempts and neuroendocrine investigations suggests that apomorphine test could be considered as a "trait marker" of suicidal behavior. However, this hypothesis should be confirmed by comparing two groups of suicide attempters with or without recent attempts.

No statistically significant difference in GH response to apomorphine was present between violent and nonviolent suicide attempters. However, our sample is too small to definitively exclude a particular role for the dopaminergic system in the type of suicide attempt.

Our results are in agreement with previous studies assessing dopaminergic activity by measuring CSF dopamine metabolites, and particularly HVA levels. Indeed, Träskman et al (1981) found lower levels of CSF HVA in patients with a history of either violent or nonviolent suicide attempts than in normal controls. Montgomery and Montgomery (1982) and Agren (1983) also showed a highly significant relationship between low CSF HVA levels and suicidal behavior, and a weaker correlation with low CSF 5-HIAA levels. Moreover, recently Roy et al (1986) lend support to the hypothesis that low CSF HVA levels could be a more potent predictive index of suicide than low CSF 5-HIAA concentrations. However, these three latter studies did not include nondepressed control patients. In their study, Träskman et al (1981) observed a lower CSF HVA level in the depressed group than in the nondepressed group, and suggested that a low level of HVA could be more a diagnostic marker of depressive illness rather than a biological predictor of suicidal behavior. Indeed, several lines of evidence suggest a role for dopamine in the pathophysiology of depression (Willner 1985). Van Praag and Korf (1971) found a

correlation between low CSF HVA levels and retarded depression by comparing two groups of depressed patients with and without motor retardation and lack of initiative. Our group previously confirmed the implication of dopamine in depression by demonstrating a blunted GH response to apomorphine in endogenous depressive patients (Ansseau et al 1988). However, in the present study, we did not measure motor activity and our sample comprised both endogenous and nonendogenous depressed patients. Therefore, it would be interesting to investigate GH response to apomorphine in nondepressed suicidal patients. Moreover, a drug-free wash-out period of 2 weeks could be insufficient. 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 (Corn et al 1984; Schittecatte et al 1989). Another pitfall in this study is the lack of availability of apomorphine plasma levels, to exclude the possibility that pharmacokinetic factors explain the differences between the groups. None of the previous studies indicated individual differences in apomorphine plasma levels following sc injection.

In conclusion, this study suggests that a blunted GH response to apomorphine could be considered as a biological marker of suicidal behavior. Nevertheless, this measure of impaired dopamine activity in depressed patients could also be related to the diagnosis of depression or to certain aspects of symptomatology, particularly motor retardation. Thus, our study requires confirmation and further development to assess the importance of the dopaminergic system as a correlate of suicidal behavior.

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