Dopaminergic Function in Panic Disorder: Comparison with Major and Minor Depression

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Several lines of evidence suggest that dopamine might be involved in anxiety states. In this study, we assessed the growth hormone (GH) response to apomorphine (a dopaminergic agonist) 0.5 mg SC in nine drug-free inpatients meeting Research Diagnostic Criteria (RDC) for panic disorder who were age-matched and gender-matched with nine major depressive, and nine minor depressive inpatients. The three groups differed significantly in their mean GH peak response: 5.29 ± 2.75 ng/ml in major depressives, 26.27 ± 12.71 ng/ml in minor depressives, and 37.28 ± 10.58 ng/ml in panics, with a significantly higher response in panic than in either minor or major depressive patients. These results support dopaminergic overactivity in panic disorder as compared with major and minor depression.

Introduction

The currently most significant neurochemical theories about the pathophysiology of panic disorder (PD) involve serotonergic, noradrenergic, and benzodiazepine systems (Pecknold 1990; Charney et al 1990; Nutt et al 1990). However, an abnormal dopaminergic function has also been hypothesized to be implicated as an etiological factor in PD (Roy-Byrne et al 1985a,b,c, 1986). Indeed, several lines of evidence suggest that dopamine might be involved in anxiety states. Fadda et al (1978) showed the reduction of stress-induced increases in forebrain dopamine systems by benzodiazepines. In an animal study, Hjorth et al (1986) demonstrated that the anxiolytic-like action of low doses of apomorphine was related to the dopamine autoreceptor-mediated reduction of central dopaminergic activity. Recently, Stein et al (1990) showed a higher incidence of anxiety disorders, including panic attacks, in patients with Parkinson disease. Furthermore, Roy-Byrne et al (1986) found higher plasmatic concentration of homovanillic acid (HVA), a dopamine metabolite, in a subgroup of PD patients characterized by higher levels of anxiety and a greater number of panic attacks in the past year. However, they were unable to show a statistically significant difference between PD patients and controls in plasma HVA concentrations.

Several lines of evidence also suggest an implication of the dopaminergic system in the pathophysiology of depression (Willner 1985). Recently, our group showed a blunted

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growth hormone (GH) response to apomorphine, a selective dopaminergic agonist, in endogenous depression suggesting a hyposensitivity of dopaminergic hypothalamic receptors (Ansseau et al 1988). A common dopaminergic disturbance could be supported by a large body of data from clinical and neurobiological studies suggesting a common link between panic and affective disorders (Roy-Byrne and Uhde 1985a; Uhde et al 1985).

On these bases the purpose of the study was to investigate the dopaminergic functioning in PD patients compared to major depressive patients and controls by assessing the GH responses to a dopaminergic challenge (apomorphine). Indeed, GH secretion following injection of apomorphine, a selective dopaminergic agonist, provides an indirect method to assess central dopamine functioning in psychiatric patients.

Methods

Subjects

Nine inpatients meeting Research Diagnostic Criteria (RDC) (Spitzer et al 1978) for a panic disorder without major depression, were admitted in the Psychiatric Unit of the University Hospital of Liège, Belgium. The sample comprised 6 men and 3 women, with age ranging from 18 to 49 years (mean age (SD) = 32.9 years (9.8)).

The PD patients were matched for age (within 3 years) and gender, with 9 inpatients with RDC major depressive disorder without psychotic features and 9 inpatients with RDC minor depressive disorder and a score less than 15 on the 21-item Hamilton depression scale. There was no significant difference in mean weight between the three groups.

All patients were free of medical illness as evidenced by history, medical examination, electrocardiogram (EKG), chest X-ray, electroencephalogram (EEG) and routine laboratory tests. They had also been drug-free for at least 2 weeks prior to the study. Patients were only offered occasional low doses of benzodiazepines if necessary. Due to the influence of estrogen on GH release (Tulandi et al 1987), we included only premenopausal women and the neuroendocrine test was always performed between the third and the twelfth day of the menstrual cycle. 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 (t_0) GH level less than 5 ng/ml before the neuroendocrine test (Ansseau et al 1984). Finally, all patients were fully informed of the study and gave their consent.

Procedures

The apomorphine challenge test was performed in all subjects at bedrest after an overnight fast. At 7 AM, an indwelling catheter was inserted in 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 apomorphine (0.5 mg) diluted in saline to obtain 0.5 ml subcutaneously. A large number of studies have demonstrated that subcutaneous apomorphine administration induced a reliable GH release in humans (Lal et al 1972; La Rossa et al 1977; Maany et al 1975).

After each blood sampling, blood pressure, pulse rate, sedative, and gastrointestinal side effects were recorded. In addition, at the end of the procedure, sedative and gastrointestinal side effects were globally rated according to a six-point scale by a research nurse blind to diagnosis. The level of alertness was rated according to the following scores: 0 = no change; 1 = very slight drowsiness; 2 = slight drowsiness; 3 = drowsiness; 4 = important drowsiness; 5 = sleep. Gastrointestinal reactions were rated

Table 1. Individual Characteristics of the Sample

Patients	Gender	Age	Apomorphine test GH peak ng/ml	GI effects	Sedation
Panic disorder					
1	M	18	37.1	4	5
2	F	19	33.0	2	2
3	M	28	45.2	2	5
4	M	35	37.6	1	1
5	M	35	37.0	0	0
6	M	36	32.0	3	0
7	F	36	37.2	0	1
8	F	40	58	0	1
9	M	49	18.4	3	3
Mean	6M, 3F	32.9	37.3	1.7	2.0
SD		9.8	10.6	1.5	1.9
Major depression, endogenous					
10	M	21	6.9	0	3
11	F	22	3.7	0	1
12	M	30	2.7	0	0
13	M	34	11.3	0	0
14	M	36	6.4	0	0
15	M	39	2.6	0	1
16	F	39	3.3	0	2
17	F	41	5.0	1	0
18	M	47	5.7	4	0
Mean	6M, 3F	34.3	5.3	0.6	0.8
SD		8.7	2.8	1.3	1.1
Minor depression					
19	M	21	55.0	2	2
20	F	21	30.0	0	2
21	M	28	23.9	1	1
22	M	34	32.2	0	0
23	M	36	21.4	4	3
24	M	37	14.0	0	1
25	F	38	23.8	0	2
26	F	41	25.0	4	1
27	M	47	11.1	3	0
Mean	6M, 3F	33.7	26.3	1.6	1.3
SD		8.8	12.7	1.7	1.0

GI = gastrointestinal.

according to the following scores: 0 = no reaction, 1 = slight and transitory nausea, 2 = nausea, 3 = strong nausea without vomiting, 4 = vomiting, and 5 = severe vomiting.

GH Assay

GH was measured with a double antibody radioimmunoassay (Franchimont 1968), with intraassay and interassay coefficients of variation of respectively 13.3 ± 4.7% and 14.8 ± 9.6% and a detection limit of 0.2 ng/ml.

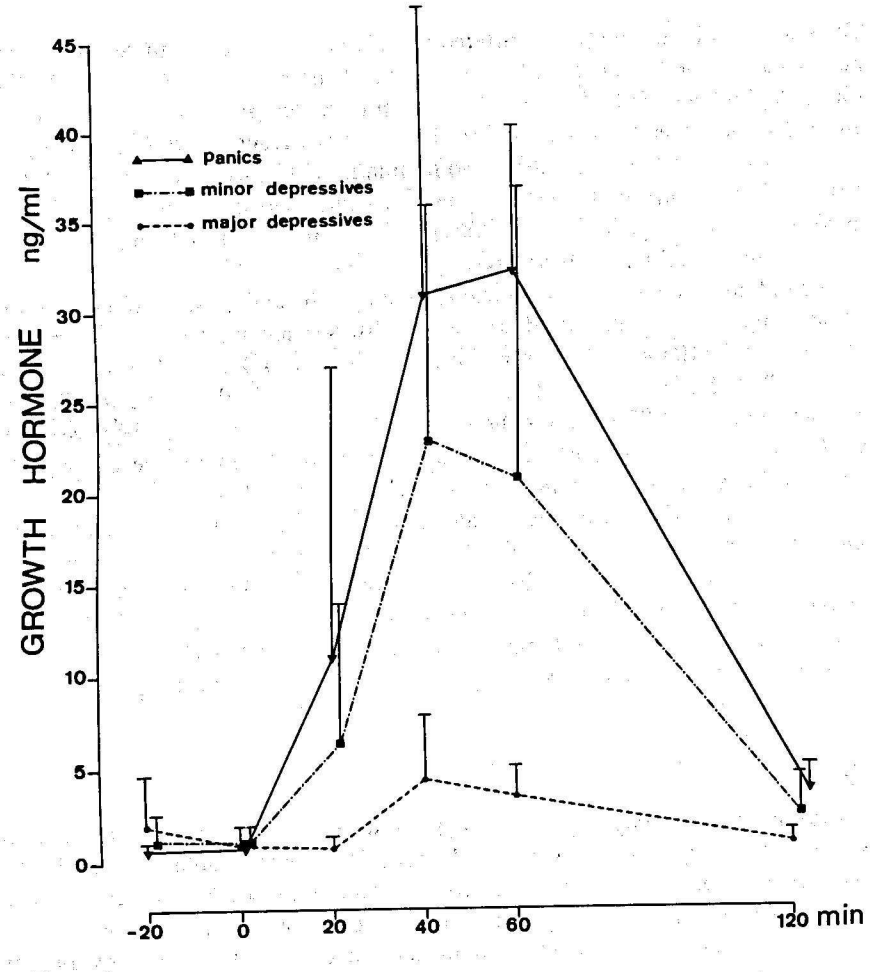

Figure 1

Data Analysis

GH responses following apomorphine were assessed by two different methods: by GH peak values following injection and by the areas under the curve situated between injection (t_0) and the last blood sampling (t_{120}). Both analyses were performed using absolute GH values as well as differences related to basal (t_0) levels (relative values). Because the correlations between absolute and relative values (assessed by Pearson's correlation coefficient) were very high ($r > 0.98$), only the absolute values are reported here.

GH responses, as well as global sedative and digestive side effects in the three groups, were compared using an analysis of variance (ANOVA), whereas changes over time in blood pressure and pulse rate were assessed by ANOVA with repeated measure. Because some variances were high compared with mean values, the comparison was also performed by means of the Wilcoxon nonparametric test. The relationship between GH responses and sedative and gastrointestinal side effects were assessed by Pearson's correlation coefficient.

Results

GH responses to apomorphine differed significantly among the three groups: mean GH peak (SD) reached 5.29 ± 2.75 ng/ml in major depressives, 26.27 ± 12.71 ng/ml in minor depressives, and 37.28 ± 10.58 ng/ml in panics [$F(2,24) = 25.38, p = 0.0001$] and the areas under the 0–120 min response curve, respectively 285 (114) ng min/ml, 1513 (894) ng min/ml, and 2261 (749) ng min/ml [$F(2,24) = 19.54, p = 0.0001$]. We found a significantly higher GH response in panic than in either minor ($p = 0.03$) or major depressive patients ($p = 0.0001$). A very significant difference was also present between minor and major depressives ($p = 0.0008$).

We did not find any significant decrease of systolic and diastolic blood pressure in the whole sample. No significant difference was observed among the three groups for systolic (mean ± (SD) 104.4 ± 17.0 in major depressives, 120.0 ± 19.8 in minor depressives and 106.7 ± 6.6 mmHG in panics; $F(2,22) = 2.35, p = 0.12$) and for diastolic blood pressure (66.1 ± 8.9 in major depressives, 68.6 ± 20.3 in minor depressives and 66.1 ± 8.6 mmHg in panics; $F(2,22) = 0.09, p = 0.92$). Pulse rate did not show any significant changes after apomorphine [$F(2,22) = 0.06$, NS).

Mean (± SD) level of digestive side effects was not significantly different among the three groups (0.56 ± 1.33 in major depressives, 1.56 ± 1.74 in minor depressives and 1.67 ± 1.50 in panics; $p = 0.20$). Sedative side effects did not differentiate among the three groups (0.78 ± 1.09 in major depressives, 1.33 ± 1.0 in minor depressives and 2.0 ± 1.94 in panics; $p = 0.55$). Finally, no correlation was noted between GH responses and levels of side effects in the whole sample or in the various diagnostic groups.

Discussion

The results of this study support the hypothesis of an implication of the dopaminergic system in the etiopathogenesis of PD. Indeed, PD patients exhibit a significantly higher GH response to apomorphine test than major and minor depressive controls. These findings therefore suggest increased dopamine receptor sensitivity in PD.

Our results are in agreement with clinical and biological studies providing evidence of a dopamine dysfunction in anxiety states. Several studies reported that patients with Parkinson disease are more at risk to experience panic attacks than patients with chronic medical illnesses (Schiffer et al 1988; Stein et al 1990). These clinical data suggest that the high prevalence of PD in patients with Parkinson disease could be related to impaired dopamine activity. In 1985 Roy-Byrne et al reported indirect biological support for increased dopaminergic functioning in PD patients by demonstrating a blunted thyrotropin-stimulating hormone (TSH) and prolactin (PRL) response to thyrotropin-releasing hormone (TRH). Recently, plasma HVA studies confirmed the dopaminergic overactivity in some PD patients, and particularly those with a higher level of anxiety (Roy-Byrne et al 1986; Gurguis and Uhde 1988). In the present study, we did not specifically assess anxiety level. But recently we showed a positive correlation between GH response to apomorphine test and Minnesota Multiphasic Personality Inventory (MMPI) anxiety scale score relating dopamine receptor hypersensitivity to anxious psychopathology (Pitchot et al 1990–91). Therefore, dopaminergic disturbances could be related to some aspects of the symptomatology, in particular symptoms of generalized anxiety rather than to the diagnosis of PD. However, Eriksson et al (1991) did not find a statistically significant difference in cerebrospinal fluid (CSF) HVA levels between PD patients and normal controls matched

for age and gender. Moreover, in the same study CSF HVA concentrations were not correlated with neither the number of panic attacks nor the Hamilton Rating Scale for Anxiety.

The finding of a greater GH response to apomorphine in PD patients compared with major depressive patients do not support the hypothesis of an overlap between panic and affective disorders. This theory is based on epidemiological (Leckman et al 1990), clinical (Lesser 1990), and neurobiological (Stein and Uhde 1990) data. However, several biological parameters such as sleep architecture (Akiskal et al 1984), platelet imipramine binding (Pecknold and Luthe 1990), TSH responses to TRH (Stein and Uhde 1991) and dexamethasone suppression test (Roy-Byrne et al 1985c) were found to differentiate panic and depressed patients.

Although the GH response to apomorphine may well be dopamine-mediated, this is presumably occuring at the level of the hypothalamus. Regarding the dopaminergic hypothesis of anxiety disorders, we are particularly interested in dopaminergic function in mesocortical and mesolimbic systems and it is unclear to what extent a hypothalamically mediated endocrine response is informative about these systems. However, GH response to apomorphine is blunted in Parkinson disease (Agnoli et al 1980) and enhanced in Huntington chorea (Caraceni et al 1979), supporting the usefulness of the apomorphine test as a global assessment of central dopaminergic neurotransmission.

Minor depressives were chosen as a control group instead of normal volunteers due to the practical impossibility of testing normal subjects under the same conditions. Moreover, following apomorphine challenge (0.5 mg), we reported in a group of 20 young male normal volunteers a mean GH peak of 28.5 ng/ml (Timsit-Berthier et al 1986) very close to the response of our minor depressive group (26.3 ng/ml). Obviously, an important methodological problem is the fact that minor depressives do not represent a genuine control group. Therefore, the question of whether the dissimilarity between depressives and panics is due mainly to blunted responses in patients with depression or enhanced responses in patients with PD remains to be answered by a direct comparison of PD patients and normal controls.

Another pitfall in this study is the possible inadequacy of the drug-free wash-out period of 2 weeks. 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 confounding factor is that panic patients could be more prone to endocrine stress responses in conjunction with the apomorphine test procedure than depressed subjects (or normal controls). Therefore, the marked GH responses to apomorphine in the panic group could be partly a stress response. However, no endocrine stress effect has been observed in another study using a placebo challenge in PD patients compared with healthy volunteers (Charney and Heninger 1986).

In conclusion, this study provides additional support for dopaminergic hyperactivity in anxiety disorders, and PD in particular. However, these results are preliminary and should be confirmed in a larger sample.

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