

## Neuroendocrine Evaluation of Catecholaminergic Neurotransmission in Mania

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**Abstract.** Several lines of evidence suggest catecholamine overactivity (noradrenergic and/or dopaminergic) in mania. We studied the growth hormone (GH) response to clonidine (an  $\alpha$ -adrenergic agonist) and apomorphine (a dopaminergic agonist) in seven inpatients meeting Research Diagnostic Criteria for mania. They had been completely drug free for at least 3 months before the neuroendocrine procedures and were age- and sex-matched to seven major depressive and seven minor depressive inpatients, drug free for at least 2 weeks. GH was assayed every 20 min for 40 min before and 120 min after either clonidine (0.15 mg i.v.) or apomorphine (0.5 mg s.c.), with an interval of at least 2 days between the tests. The three groups differed significantly in the GH peak response: after clonidine (mean  $\pm$  SD),  $3.2 \pm 2.4$  ng/ml in manics,  $3.2 \pm 2.4$  ng/ml in major depressives, and  $13.2 \pm 8.7$  ng/ml in minor depressives; after apomorphine,  $10.5 \pm 7.4$ ,  $3.2 \pm 1.9$ , and  $26.9 \pm 15.8$ , respectively. While there were significant differences between manics and minor depressives and between major and minor depressives after both clonidine and apomorphine, manics did not significantly differ from major depressives on either test. These results do not provide neuroendocrine support to the catecholaminergic hypothesis of manic disorders.

**Key Words.** Clonidine test, apomorphine test, mania, growth hormone.

Several lines of evidence suggest disturbances in catecholaminergic neurotransmission in mania (Post, 1980; Silverstone, 1985). In contrast to depression, mania may be characterized by increased noradrenergic and/or dopaminergic neurotransmission. Elevation in noradrenergic metabolism is supported by the higher excretion of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) in manic as compared to depressive episodes and the notable increase in cerebrospinal fluid (CSF) noradrenalin (NA) itself. Moreover, indirect pharmacological data suggest that agents which decrease noradrenergic function, such as reserpine, might be associated with an increased incidence of depression and therapeutic effects in

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mania. Conversely, most tricyclic and monoamine oxidase inhibitor antidepressants potentiate the noradrenergic system and may potentiate manic shifts. Moreover, the  $\alpha$ -adrenergic agonist clonidine, which decreases firing of the noradrenergic cells of the locus ceruleus by acting preferentially at presynaptic autoreceptors (Svensson et al., 1975), has antimanic properties (Jouvent et al., 1980).

Other arguments favor dopaminergic overactivity. Drugs that reduce dopaminergic neurotransmission by inhibiting dopamine (DA) synthesis ( $\alpha$ -methyl-paratyrosine) or by blocking DA receptors (pimozide) are effective in reducing manic symptoms (Brodie et al., 1971; Cookson et al., 1981). Moreover, cis-clophenthixol, the isomer of clophenthixol which possesses DA receptor blocking properties, is an effective antimanic agent, whereas trans-clophenthixol, which is devoid of DA receptor blocking activity, is clinically ineffective in mania (Nolen, 1983). Conversely, drugs that enhance dopaminergic neurotransmission by increasing DA synthesis (levodopa), by stimulating DA release (amphetamine), or by activating DA receptors directly (bromocriptine, piribedil) all precipitate mania, particularly in bipolar depressive patients (Murphy, 1972; Gerner et al., 1976; Silverstone, 1984).

The growth hormone (GH) response to specific pharmacological challenges could provide an indirect index of catecholaminergic neurotransmission. Indeed, GH release is stimulated by NA as well as DA. This approach has already been applied successfully in psychiatric disorders such as depression (Checkley, 1980), but has been little studied in mania, perhaps because of the difficulties in maintaining manic patients drug free long enough to interpret hormonal results. Frazer (1975) described a decreased GH response to levodopa in three hypomanic patients who all responded normally to apomorphine. Gold et al. (1976) found a lower GH response to levodopa in five bipolar patients in the manic phase as compared to seven bipolar patients in the depressed phase. Casper et al. (1977) found a trend toward lower GH response after apomorphine in four manic patients as compared to eight control subjects. Moreover, this response was significantly lower than in nine acute schizophrenics but not different from eight major depressive patients. Garver et al. (1981) confirmed a possible hyposensitivity of DA receptors in four manics who had lower GH response to apomorphine than eight unipolar depressives and seven normal controls. In the largest study to date, however, Meltzer et al. (1984) did not find significant difference in the GH response to apomorphine between 18 manic patients and other diagnostic groups or normal controls, despite a twofold difference between the relatively high mean in manic patients and the relatively low mean in patients with major depression. More recently, Hirschowitz et al. (1986) found lower GH response to apomorphine in 8 manics as compared to 18 schizoaffective and 45 schizophrenic subjects.

Those neuroendocrine studies did not all control for age, gender, and menopausal status of women, factors known to influence endocrine responses to dopaminergic agonists (Ettigi et al., 1975). Moreover, the drug-free period was not always sufficient and, in some cases, not even mentioned. The period of the menstrual cycle in women who underwent neuroendocrine challenges was not specified in any study. Finally, there is no published report concerning the GH response to a selective  $\alpha_2$ -adrenergic agonist, such as clonidine, in manic patients, although various groups

have found a blunted response among endogenous depressive patients (Matussek et al., 1980).

Therefore, the purpose of our study was to test the GH response to a dopaminergic challenge (apomorphine) and to a noradrenergic challenge (clonidine) in carefully selected drug-free manic patients, with controls for age, gender, menopausal status, and period of menstrual cycle.

## Methods

**Subjects.** Seven inpatients (three males, four females; mean age 44.9, SD 8.5, range 32-55) meeting Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) for a definite manic disorder were studied (Table 1). The subjects were hospitalized at the beginning of a manic episode and tested before any drug treatment. All subjects had been drug free for > 3 months. Diagnostic assessments were performed by two independent psychiatrists. All patients selected exhibited euphoria as predominant mood, and depressive features were never associated. The patients were in their first (patients 2, 4, 5, and 7) or second (patients 1, 3, and 6) manic episodes and had never received lithium.

The manic patients were matched for age (within 3 years), sex, and, in women, menopausal status with seven inpatients with RDC major depressive disorder, endogenous subtype, and seven inpatients with RDC minor depressive disorder. All depressives were tested after a drug-free period  $\geq 2$  weeks. Minor depressives were chosen as a control group instead of normal volunteers due to the practical impossibility of testing normal subjects in the same conditions.

All patients were free of medical illness, as evidenced by history, medical examination, electrocardiogram, chest X-ray, electroencephalogram, and routine laboratory tests. The neuroendocrine tests were performed between day 3 and day 12 of the menstrual cycle in premenopausal women (two in each group). Patients with a basal blood pressure < 100/70 mmHg were excluded from the study. Moreover, to be included, patients had to have basal (time 0) GH level < 5 ng/ml before both pharmacological challenges (Ansseau et al., 1984).

**Neuroendocrine Test Procedures.** Clonidine and apomorphine challenge tests were performed as follows, with at least a 2-day interval between tests: At 7 a.m., after an overnight fast, an indwelling catheter was inserted in a forearm vein. Blood samples (10 cc) were collected every 20 min for 40 min before and 120 min after injection at 8 a.m. of either of the following: clonidine, 0.15 mg, diluted in saline to obtain 20 cc, i.v., in 10 min; or apomorphine, 0.5 mg, diluted in saline to obtain 0.5 cc, s.c.

After each blood sampling, blood pressure, pulse rate, and sedative and digestive side effects were recorded. Moreover, at the end of the procedure, sedative and digestive side effects were globally rated on a 6-point scale by a research nurse. Modifications in vigilance were scored as follows: 0 = no change; 1 = very slight drowsiness; 2 = slight drowsiness; 3 = drowsiness; 4 = important drowsiness; 5 = sleep. Digestive reactions were scored as follows: 0 = no reaction; 1 = slight and transitory nausea; 2 = nausea; 3 = strong nausea without emesis; 4 = emesis; 5 = severe emesis.

GH was measured with a double antibody radioimmunoassay (Franchimont and Salmon, 1962). Intra-assay and interassay coefficients of variation were  $13.3 \pm 4.7\%$  and  $14.8 \pm 9.6\%$ , respectively.

**Data Analysis.** GH responses after clonidine and apomorphine were assessed by two methods: by GH peak values following injection and by the areas under the curve situated between injection (time 0) and the last blood sampling (time 120 min). Both analyses were performed using absolute GH values as well as differences related to basal levels (relative values). Since the correlations between absolute and relative results (assessed by Pearson's correlation coefficient) were very high ( $r > 0.98$ ), only the absolute values are reported.

Table 1. Sample characteristics and responses to clonidine and apomorphine challenges

Patient #	Sex	Age	Clonidine test			Apomorphine test			
			GH peak (ng/ml)	GH AUC (ng min/ml)	Sedation	GH peak (ng/ml)	GH AUC (ng min/ml)	Digestive effects	Sedation
<b>Mania</b>									
1	F	32	1.8	132	3	4.8	246	0	0
2	M	38	0.8	57	3	18.2	910	0	3
3	F	40	1.4	78	2	4.8	335	0	0
4	F	46	6.2	393	1	23.1	1596	0	3
5	F	51	5.0	252	5	8.6	333	0	3
6	M	52	1.4	103	2	9.2	518	3	3
7	M	55	4.5	254	1	4.5	241	0	1
<b>Major depression, endogenous unipolar</b>									
8	F	30	6.8	446	2	5.2	381	4	3
9	M	38	1.7	111	0	2.2	165	1	1
10	F	41	4.6	362	2	5.0	265	1	0
11	F	47	5.5	408	2	5.5	245	1	0
12	F	53	1.4	111	1	1.6	147	0	0
13	M	51	1.6	123	1	1.4	111	1	0
14	M	55	0.6	55	4	0.6	84	0	0
<b>Minor depression</b>									
15	F	35	12.8	735	2	18.5	877	3	2
16	M	41	14.9	709	3	14.5	694	2	3
17	F	41	11.4	592	0	25.0	1391	4	1
18	F	43	29.6	1992	3	48.5	2433	4	1
19	F	50	4.7	352	5	11.1	464	2	1
20	M	51	15.4	820	0	49.5	2180	3	0
21	M	54	3.2	106	4	20.9	1113	3	0

AUC = area under the 0-120 min curve. GH = growth hormone.

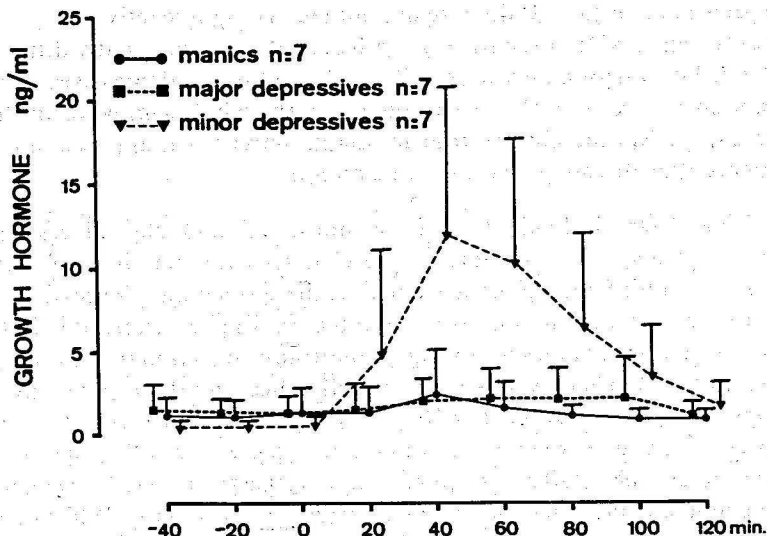
Then, GH responses, as well as global sedative and digestive side effects in the three groups, were compared using an analysis of variance (ANOVA) and the conservative Bonferroni test for pairwise contrasts, while changes over time in blood pressure and pulse rate were assessed by ANOVA with repeated measures. Finally, the relationships between GH response and sedative and digestive side effects, as well as between the endocrine responses to both challenges, were assessed by Pearson's correlation coefficient. GH data were transformed in logarithms to normalize their distribution.

## Results

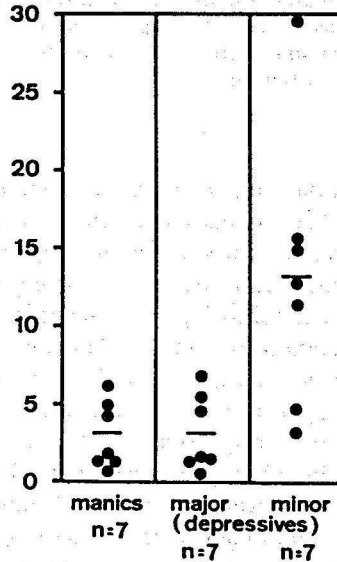
**Clonidine Test.** Individual data for hormonal and clinical responses to clonidine are displayed in Table 1. The changes over time in mean GH level following clonidine among the seven manics, the seven major depressives, and the seven minor depressives matched for gender and age are presented in Fig. 1, while individual distribution of GH peak values following clonidine injection in the three groups is presented in Fig. 2. A significant difference in GH response existed among the three groups: GH peak (SD) reached 3.2 (2.4) ng/ml in manics, 3.2 (2.4) ng/ml in major depressives, and 13.2 (8.7) ng/ml in minor depressives ( $F = 8.0$ ,  $p < 0.01$ ) and the areas under the response curve, respectively, 181 (122) ng min/ml, 231 (166) ng min/ml, and 758 (598) ng min/ml ( $F = 5.4$ ,  $p < 0.05$ ). However, while manics and minor depressives ( $p < 0.05$ ), as well as major and minor depressives ( $p < 0.01$ ), differed significantly, manics and major depressives did not.

Blood pressure decreased significantly after clonidine ( $p < 0.00001$  for systolic blood pressure;  $p < 0.001$  for diastolic blood pressure). There was a trend toward a significant difference among the three groups in basal systolic but not diastolic blood

**Fig. 1. Changes over time in mean growth hormone level after clonidine (0.15 mg i.v.) in 7 manics, 7 major depressives, and 7 minor depressives matched for age and sex**



**Fig. 2. Distribution of growth hormone peak values after clonidine (0.15 mg i.v.) in 7 manics, 7 major depressives, and 7 minor depressives matched for age and sex**



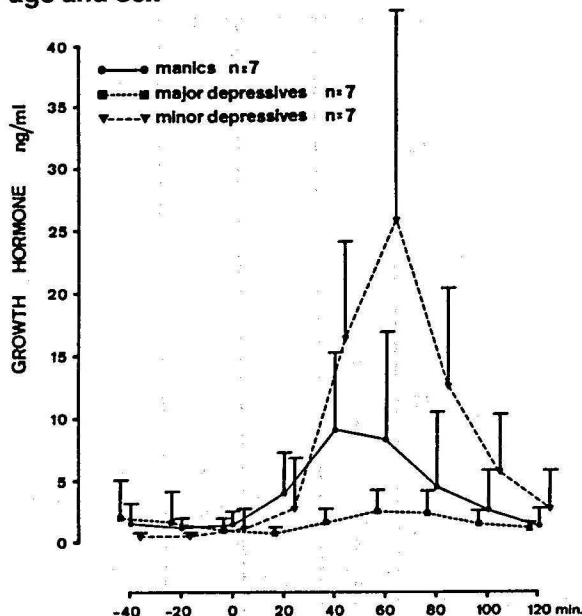
Mean values are represented by a horizontal line.

pressure:  $125.7 \pm 14.3/76.4 \pm 12.5$  mmHg in manics,  $120.7 \pm 12.7/76.4 \pm 10.7$  mmHg in major depressives, and  $110.0 \pm 7.6/68.6 \pm 8.5$  mmHg in minor depressives ( $F = 3.2$ ,  $p = 0.07$  for systolic blood pressure;  $F = 1.3$ , NS for diastolic blood pressure). There was also a trend toward a difference among the three groups in the fall of systolic blood pressure ( $p = 0.07$ ), with manics showing a greater decrease 20 to 40 min after the injection. Pulse rate did not change significantly.

The level (mean  $\pm$  SD) of sedative side effects did not significantly differ among manics ( $2.4 \pm 1.4$ ), major depressives ( $1.7 \pm 1.3$ ), and minor depressives ( $2.4 \pm 1.9$ ) and was not correlated with the GH responses in the whole sample or in the three diagnostic groups. Specifically, no true antimanic activity was apparent among the manic patients after this single injection of clonidine.

**Apomorphine Test.** Individual data for hormonal and clinical responses to apomorphine are displayed in Table 1. The changes over time in mean GH level following apomorphine among the seven manic, the seven major depressive, and the seven minor depressive patients are presented in Fig. 3, while the individual distribution of GH peak values following apomorphine injection in the three groups is presented in Fig. 4. There were significant differences in GH response among the three groups: GH peak (SD) reaches 10.5 (7.3) ng/ml in manics, 3.2 (1.9) ng/ml in major depressives, and 26.9 (15.8) ng/ml in minor depressives ( $F = 10.0$ ,  $p < 0.01$ ) and the areas under the 0-120 min response curve, respectively, 597 (498) ng min/ml, 200 (104) ng min/ml, and 1307 (747) ng min/ml ( $F = 8.1$ ,  $p < 0.01$ ). While there were

**Fig. 3.** Changes over time in mean growth hormone level after apomorphine (0.5 mg s.c.) in 7 manics, 7 major depressives, and 7 minor depressives matched for age and sex

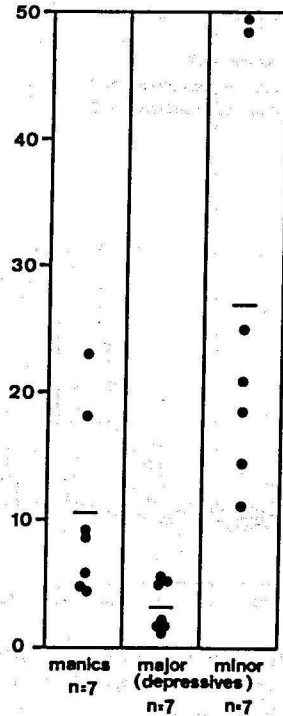


significant differences between manics and minor depressives ( $p < 0.05$ ) and between major and minor depressives ( $p < 0.01$ ), the difference between manics and major depressives did not reach significance.

Systolic blood pressure showed a trend toward a significant decrease in the whole sample ( $p = 0.07$ ), but diastolic blood pressure did not change significantly. Basal systolic blood pressure (mean  $\pm$  SD) showed a trend toward a significant difference among the three groups ( $130.0 \pm 27.8$  in manics,  $119.6 \pm 19.8$  in major depressives, and  $105.6 \pm 8.0$  mmHg in minor depressives ( $F = 3.0$ ,  $p = 0.07$ ) while diastolic blood pressure differed significantly ( $80.7 \pm 14.8$ ;  $77.9 \pm 8.1$ ; and  $62.1 \pm 8.1$  mmHg, respectively;  $F = 6.0$ ,  $p < 0.05$ ). Manics and major depressives both had higher diastolic blood pressure than minor depressives ( $p < 0.05$ ). However, the changes over time in blood pressure did not differ among the three groups. Pulse rate did not show any significant changes after apomorphine.

With regard to side effects, only one manic patient showed digestive effects, as compared to five major depressives and all minor depressives. Mean ( $\pm$  SD) level was significantly different among the three groups ( $0.4 \pm 1.1$  in manics,  $1.1 \pm 1.3$  in major depressives, and  $3.0 \pm 0.8$  in minor depressives;  $F = 9.8$ ,  $p < 0.01$ ). Manics and major depressives both had significantly fewer side effects than minor depressives ( $p < 0.01$  and  $p < 0.05$ , respectively), but did not differ significantly from each other. Sedative side effects did not differentiate among the three groups ( $1.9 \pm 1.5$  in manics,  $0.6 \pm 1.1$  in major depressives, and  $1.1 \pm 1.1$  in minor depressives;  $F = 1.9$ , NS). Finally, no correlation was noted between GH responses and levels of side effects in the whole sample or in the various diagnostic groups.

Fig. 4. Distribution of growth hormone peak values after apomorphine (0.5 mg s.c.) in 7 manics, 7 major depressives, and 7 minor depressives matched for age and sex



Mean values are represented by a horizontal line.

**Relationship Between Clonidine and Apomorphine Tests.** A significant correlation was present between the GH responses to clonidine and apomorphine in the whole sample for the GH peak values ( $r = 0.73$ ,  $p < 0.001$ ) and for the areas under the response curve ( $r = 0.61$ ,  $p < 0.003$ ). This relationship was also significant among major depressive patients ( $r = 0.98$ ,  $p < 0.001$ ;  $r = 0.94$ ,  $p < 0.001$ , respectively) but not among manics ( $r = 0.13$  and  $r = 0.09$ ) or minor depressives ( $r = 0.61$  and  $r = 0.46$ ).

## Discussion

The present results, which show a similar blunted GH response to clonidine in mania and in major depression, do not support opposite noradrenergic function in the two affective illnesses. This hypothesis was based on higher urinary levels of MHPG, a metabolite of NA, in the manic phase as compared to the depressive phase of bipolar depression and on indirect pharmacological data suggesting that drugs which decrease noradrenergic function exacerbate depression but improve mania while drugs which potentiate the noradrenergic system aggravate manic symptoms and improve depression (Post, 1980).

In suggesting similar noradrenergic disturbances in mania and in major



depression, our results confirm unpublished data presented by Watanabe et al. (1985) showing similarly blunted GH response to clonidine in four manics, seven major depressives, and seven remitted depressives. They are also in agreement with previous data of Casper et al. (1977), who found similar blunted GH responses to insulin-induced hypoglycemia in manic and depressive patients as compared to control subjects. Indeed, various arguments suggest that the GH response to insulin hypoglycemia may be modulated in humans by the activity of noradrenergic systems (Garver et al., 1975). The blunted GH response following clonidine in major depression has been confirmed by various groups (Matussek et al., 1980; Checkley et al., 1981, 1984b; Charney et al., 1982; Siever et al., 1982; Ansseau et al., 1984) and has been interpreted as a decreased sensitivity of postsynaptic  $\alpha_2$ -adrenergic receptors. Indeed, the GH response to clonidine is mediated by postsynaptic  $\alpha_2$ -adrenergic receptors in the hypothalamus (Siever et al., 1982).

Recently, several groups suggested that blunted GH response to clonidine might be a "trait marker" for depressive illness (Siever and Uhde, 1984; Checkley et al., 1984a; Hoehe et al., 1986; Siever et al., 1986). Indeed, depressive patients in complete remission still exhibited blunted GH response to clonidine. Our results may support this hypothesis: bipolar depressive patients might exhibit the same noradrenergic defect no matter if they are tested in the depressive or in the manic phase. However, our findings that certain  $\alpha_2$ -receptors controlling GH release are equally insensitive during major depression and mania does not rule out the possibility that noradrenergic neurons are more active during mania than during depression. Indeed, this study does not evaluate the responsiveness of other adrenergic receptor subtypes (e.g.,  $\alpha_1$ -adrenergic or  $\beta$ -adrenergic). As  $\alpha_2$ -adrenergic and  $\beta$ -adrenergic receptors are reciprocally regulated (Maggi et al., 1980), it cannot be excluded that transmission may be decreased at  $\alpha_2$ -adrenergic receptors but increased at  $\beta$ -adrenergic receptors. Thus, the results of this study should be interpreted cautiously; they suggest reduced (not increased)  $\alpha_2$ -adrenergic receptor responsiveness in mania. Moreover, the GH response to clonidine is mediated by hypothalamic receptors. Therefore, our findings cannot be extended to conclusions about the role of NA receptors in other areas of the brain and the limbic system.

The findings with regard to GH response following apomorphine are more difficult to interpret. Indeed, manic patients had a somewhat greater GH response than major depressive patients but, possibly due to the low number of subjects included in the study, the difference did not reach statistical significance. There was considerably greater variance in the GH response to apomorphine in manics: three patients exhibit completely blunted GH response (GH peak  $< 5$  ng/ml), two patients exhibit intermediate response (GH peak  $\sim 10$  ng/ml), and two patients exhibit rather high GH response (peak  $\sim 20$  ng/ml). Such increased variance, already noted by Meltzer et al. (1984), suggests clinical heterogeneity among manic patients, with some of them showing a trend toward greater receptor sensitivity. Higher GH responses to apomorphine were recently described by Hirschowitz et al. (1986) in schizoaffective patients with mood-incongruent delusions or hallucinations. However, no schizoaffective subject was included in our study, and all delusional or hallucinatory symptoms were characteristically of the affective type. Moreover, as

compared to minor depressives, manic subjects were not characterized by higher GH response but rather by significantly lower response. These results are in agreement with a recent study of Meltzer et al. (1984), who found nonsignificantly higher apomorphine-induced GH release in 18 manics compared to 11 major depressives and with an older study of Casper et al. (1977), which found a trend toward lower GH response in four manics as compared to eight normal controls. These latter results were recently confirmed in a comparison of 8 manics and 15 normal controls (Hirschowitz et al., 1986). However, a previous study using levodopa found significantly lower GH response in five bipolar manics compared to seven bipolar depressives (Gold et al., 1976). The results of the last study have never been confirmed (Sachar et al., 1975; Mendlewicz, 1977) and may depend on differences in the low monoamine diet (Langer and Sachar, 1977).

Our findings do not support the hypothesis of dopaminergic overactivity in mania. This theory is mainly based on the antimanic activity of DA receptor blocking agents (e.g., pimozide) and on the induction of manic shifts in bipolar depressive patients by direct or indirect DA agonists such as levodopa, amphetamine, piribedil, or bromocriptine (Silverstone, 1985). While previous studies did not suggest diminished GH response to dopaminergic agonists in depression, we recently demonstrated significantly lower GH response following apomorphine injection in 15 major depressive inpatients as compared to 15 age- and sex-matched minor depressive inpatients (Anseau et al., 1986). The previous negative studies, however, generally used levodopa (Sachar et al., 1975; Gold et al., 1976; Casper et al., 1977; Mendlewicz et al., 1977; Maany et al., 1979; Linkowski et al., 1983; Corn et al., 1984). Compared to levodopa, apomorphine seems to induce GH release by more specifically dopaminergic mechanisms and is far more potent and reproducible. Few studies have used apomorphine-induced GH stimulation in depressive patients and none has shown differences with normal subjects (Casper and Davis, 1977; Maany et al., 1979; Jimerson et al., 1984; Meltzer et al., 1984). The two first reports probably included too limited a sample to show statistically significant differences, but the study of Jimerson et al. (1984) compared 14 male major depressive patients with 16 male normal controls, and that of Meltzer et al. (1984) included 11 major depressives and 16 normal controls. A possible explanation for these negative results is the use in these studies (as well as in the two previous ones) or an apomorphine dose of 0.75 mg instead of 0.50 mg in our study. A 0.75 mg dose could be potent enough to induce a complete GH response even in the case of relative hyposensitivity of hypothalamic receptors. The relative hyposensitivity of DA receptors in manics and major depressives as compared to minor depressives is confirmed by their lower rate of digestive side effects induced by apomorphine. Again, it should be noted that the GH response to apomorphine is mediated by hypothalamic receptors and that caution should be stressed in extending the conclusions to the role of DA receptors in other areas of the brain.

The GH responses to clonidine and apomorphine only show a significant correlation in the major depressive group. However, nearly all those subjects had blunted responses to both pharmacological challenges, and the correlation may simply depend on individual characteristics linked to age, weight, sex, and endocrine status. The significant relationship found for the whole sample probably stems from

the inclusion of different groups characterized by different levels of reactivity.

Another important consideration in interpreting these results is that the increased receptor sensitivity hypothesized to be related to mania (Bunney et al., 1977; Siever and Uhde, 1984) would be expected to peak in the later phases of bipolar depression before the "switch" to mania and to attenuate after the onset of the manic episode as receptors down-regulate in response to increased catecholaminergic availability. In fact, the only suggestions of augmented GH responses to catecholaminergic challenges have been found in bipolar depressed patients (Sachar et al., 1973; Gold et al., 1976); moreover, outliers with unusually high GH responses to clonidine are bipolar depressives rather than manics (Matussek et al., 1980; Siever et al., 1982). The results of this study do not suggest sustained increases in  $\alpha_2$ -adrenergic or dopaminergic receptor sensitivity in mania but cannot address the apparently more physiological hypothesis advanced by Bunney et al. (1977) that receptor increases precede the "switch" to mania, since our patients were evaluated at least several weeks after the onset of the manic episode. Obviously, the evaluation of the "switch" hypothesis needs longitudinal studies of bipolar patients.

The choice of a minor depressive group as a control may be disputed. In our study, their endocrine results following both clonidine and apomorphine are somewhat higher than those reported by some groups for normal controls (Siever and Uhde, 1984; Meltzer et al., 1984), raising the question of possible supersensitivity of GH systems (or of both dopaminergic and noradrenergic receptors) in minor depressive disorders. However, the GH peak following clonidine in our minor depressive group was rather similar to that of normal controls tested by Matussek et al. (1980) and by Checkley et al. (1981) and even lower than the GH response of reactive depressives (Checkley et al., 1984b). Following apomorphine challenge (0.5 mg), we recently reported in a group of 20 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 (26.9 ng/ml); moreover, similar results in normals (mean peak concentration of 28.1 ng/ml) were published previously (Lal et al., 1981). The heterogeneity of GH responses following pharmacological challenges among various control groups may depend on nonspecific factors such as age, sex, weight, and endocrine status, especially for women (Halbreich et al., 1986). At any rate, our failure to find differences in GH responses to clonidine and apomorphine between major depressives and manics remains valid without a control group.

In conclusion, our study does not support the hypothesis of increased noradrenergic and/or dopaminergic neurotransmission in mania, and suggests the need for other neuroendocrine assessment procedures to examine central neurotransmission abnormalities in manic disorders.

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