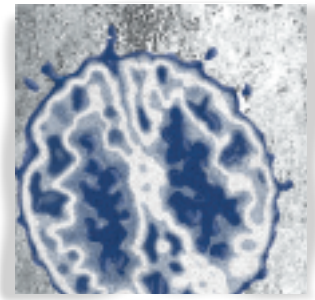
Serotonergic and noradrenergic function in depression: clinical correlates

Fabrice Duval, MD; Marie-Claude Mokrani, PhD; Paul Bailey, MD; Humberto Corrêa, MD; Marc-Antoine Crocq, MD; Thanh Son Diep, MD; Jean-Paul Macher, MD



Several lines of evidence suggest that both central serotonin (5-HT) and noradrenaline (NA) dysfunction may play a role in the pathogenesis or pathophysiology of major depression.[1-5] The serotonergic hypothesis of depression[6] is based on several findings: the ability of tryptophan depletion to induce depressive symptoms, higher postmortem 5-$HT_{2A/C}$ receptor binding and lower postmortem 5-HT_{1A} receptor binding in the brains of depressed patients, and reduced responsiveness of the serotonergic system to neuroendocrine challenge studies. Various serotonin probes have been proposed as an index of the overall functional status of the central serotonergic system, but fenfluramine (a 5-HT releaser/uptake inhibitor) is the most widely used. Both *d*-fenfluramine (*d*-FEN) and the racemate have been used, but the former is a more specific serotonergic probe, since it lacks the dopaminergic and noradrenergic action of *dl*-fenfluramine. There have been some studies of the hormonal response to *d*-FEN in depressed

The present study was conducted in order to investigate the relationships between central noradrenergic (NA) and serotonergic (5-HT) function and clinical characteristics of a major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. *We measured growth hormone response (ΔGH) to clonidine (CLO) (an α_2 NA agonist), as an index of central NA function, and prolactin response (ΔPRL) to* d*-fenfluramine (*d*-FEN) (a specific 5-HT releaser/uptake inhibitor), as an index of central 5-HT function, in 53 medication-free depressed inpatients. On the basis of their CLO and* d*-FEN test responses, patients were classified into 4 groups. Group 1 (blunted $\Delta PRL_{d\text{-}FEN}$ alone [11%]) was characterized by a recent violent suicide attempt, a high degree of medical damage, and mild anxiety. Group 2 (blunted ΔGH_{CLO} alone [32%]) was characterized by an absence of a history of suicide attempt and by severe anxiety. Group 3 (combination of blunted ΔGH_{CLO} and $\Delta PRL_{d\text{-}FEN}$ [18%]) was characterized by a history of suicide attempts, total duration of the illness of over 10 years, age over 40 years, and more than 3 previous hospitalizations. Group 4 (no abnormality [39%]) had no specific clinical profile. These results suggest that, in depression, specific psychopathological features may be linked to 5-HT and/or NA dysfunction. However, our results also suggest that NA and/or 5-HT dysfunction are less likely to be the primary cause of mood disorders but are more indicative of failure of compensatory mechanisms involved in affective homeostatic processes.*

Keywords: *serotonin; norepinephrine; clonidine test;* d*-fenfluramine test; depression; suicide; anxiety*

Author affiliations: FORENAP - Institute for Research in Neuroscience and Neuropsychiatry, Rouffach, France

Address for correspondence: Dr Fabrice Duval, FORENAP, BP 29, 68250 Rouffach, France
(e-mail: fduval@forenap.asso.fr)

Selected abbreviations and acronyms

CLO	*clonidine*
FCA	*factorial correspondence analysis*
d-*FEN*	d-*fenfluramine*
GH	*growth hormone*
5-HT	*serotonin*
NA	*noradrenaline*
PRL	*prolactin*

patients but the results are inconsistent. Some authors[7] found a decreased prolactin (PRL) response in patients with major depression compared with normal control subjects, but others[8] could not replicate this finding. However, these studies did not address whether a blunted PRL response correlates with suicidal behavior. A recent study[9] analyzed a sample of outpatients without a history of a suicide attempt and did not find a difference between normal volunteers and depressed patients in the PRL response to *d*-FEN.

The original catecholamine depletion hypothesis of depression has been reformulated as the "noradrenergic dysregulation hypothesis,"[10] which emphasizes a primary subsensitivity or downregulation in nerve terminal α_2-adrenoreceptors, leading to impaired negative feedback on the presynaptic neuron, which, in turn, may induce a disinhibition of NA output and exaggerated NA release in response to any activation of the catecholaminergic system. One of the most consistently reported abnormal findings in depression is a blunted growth hormone (GH) response to the acute administration of clonidine, a partial α_2-adrenoreceptor agonist, suggesting subsensitive postsynaptic α_2-adrenoreceptors at the hypothalamic level. Some studies have suggested that a dysregulation of the noradrenergic system may lead to increased anxiety in depressive patients.[11,12] It has also been found that a blunted GH response to clonidine may be a biological correlate of suicidal behavior.[13]

The objective of this study was to examine the relationships between central NA and 5-HT function and the clinical characteristics of a major depressive episode.

Subjects and methods

Subjects

Fifty-three inpatients meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*[14] criteria for a current major depressive episode (26 males/27 females; age, mean ± SEM, 40.9±1.3 years) formed the patient group. All patients had been drug-free for a minimum of 15 days, and washout was supervised in hospital. The severity of depression was measured with the 17-item Hamilton rating scale for depression[15] (HAM-D); inclusion in the study required a baseline HAM-D of 18 or greater (mean ± SEM: 25.0±0.7). Six patients had a single major depressive episode, 37 had a recurrent episode with full interepisode recovery, and 10 had a recurrent episode without full interepisode recovery. Thirty-seven patients had concomitant symptoms of anxiety, with a score greater than 15 on the Hamilton rating scale for anxiety (HAM-A).[16]

Subjects with clinical evidence of thyroid or other endocrine diseases, concomitant physical illness, a history of alcoholism or other drug abuse, previous treatment with fluoxetine, lithium salts, carbamazepine, monoamine oxidase inhibitors (MAOIs), or electroconvulsive therapy, and women taking oral contraceptives were excluded. All subjects were within 15% of their ideal body weight. Since there is a transient increase in PRL at ovulation, all females, except for 6 postmenopausal women, were tested outside the periovulatory phase of the menstrual cycle in order to minimize the influence of the menstrual phase on PRL secretion. All subjects were on a caffeine-restricted diet for at least 3 days before testing, and their environments were synchronized, with diurnal activity from 8 AM to 11 PM and nocturnal rest (sleep). This research was approved by the local ethics committee.

Thirty-two patients had a history of a suicide attempt (mean ± SD, 2.0±1.1 lifetime suicide attempts) and 21 did not. Patients with a positive suicide history were then classified as: past suicide attempters (n=13), if the most recent suicide attempt had not occurred during the current depressive episode (*d*-FEN test performed 5 to 86 months after most recent suicide attempt); or recent suicide attempters (violent: n=7; nonviolent: n=12), if the suicidal act had occurred during the current depressive episode, and had triggered their psychiatric hospitalization (*d*-FEN test performed 11 to 37 days after most recent suicide attempt). The Lethality Rating Scale[17] was used to measure the degree of medical damage of the most lethal lifetime suicide attempt. Medical damage is defined as the danger to life from a suicide attempt. Following Malone et al,[18] we scored no medical damage = 0 and death = 8 (mean ± SD, 2.8±1.3). The suicide attempt

methods were classified as nonviolent (drug overdose) or violent (cutting beyond a superficial scratch, jumping from a height, shooting, hanging).[19]

Neuroendocrine investigations

On day 1, a clonidine (CLO) test was carried out at 9 AM, after an overnight fast. A GH assay was performed at -30, -15, 0, 15, 30, 60, 90, 120, and 150 minutes. The change in GH after CLO (5 µg/kg orally) was expressed as the maximum increment above the baseline level (mean of -30, -15, 0 minutes) (ΔGH). Subjects who had baseline GH levels >2 ng/mL were excluded. We defined a blunted ΔGH as a level ≤5 ng/mL.[11]

A *d*-FEN test (45 mg orally) was carried out at 9 AM, on day 5, after an overnight fast. An assay of PRL was performed at -30, -15, 0, 60, 120, 180, 240, and 300 minutes. The change in PRL after *d*-FEN was expressed as the maximum increment above the level at t0 (ΔPRL), since, in the morning, PRL concentrations decrease (due to the normal circadian rhythm). We excluded from the study all patients with a baseline PRL greater than 20 ng/mL. We defined a blunted ΔPRL as a level ≤0 ng/mL.[20]

Patients were then classified into 4 groups *(Table I)*: group 1 (n=6; 11%) was defined by blunted $\Delta PRL_{d\text{-}FEN}$ alone; group 2 (n=17; 32%) was defined by blunted ΔGH_{CLO} alone; group 3 (n=9; 18%) had a combination of blunted $\Delta PRL_{d\text{-}FEN}$ and ΔGH_{CLO}; group 4 (n=21; 39%) had no abnormality in the *d*-FEN and CLO tests.

Assays

Blood samples were immediately centrifuged at 1500 *g* and 4°C; plasma samples were then stored at -20°C until assay. Hormonal concentrations were determined by radioimmunoassay techniques (GH; sensitivity: 0.2 ng/mL; intra-assay and interassay coefficients of variation: 3.7% and 4.5% [Pharmacia hGH RIA 100, Uppsala, Sweden]), or immunometric techniques based on enhanced luminescence (PRL; sensitivity: 1.3 ng/mL; intra-assay and interassay coefficients of variation: 5.5% and 6.0% [Amerlite Prolactin Assay, Amersham SA, UK]).

Data analysis

Between-group differences were tested for significance by analysis of variance (Kruskal-Wallis *H* test), and, where the overall effect was significant, by means of the Mann-Whitney two-tailed test (*U* test), using Bonferroni's correction. Correlations between quantitative variables were estimated using the Spearman rank coefficient (ρ). Categorical data were analyzed by either the χ^2 test or Fisher's exact test. The level of statistical significance was set at P=0.05.

	Group 1 (n=6;11%) Bl.ΔPRL_{FEN}	Group 2 (n=17;32%) Bl.ΔGH_{CLO}	Group 3 (n=9;18%) Bl.$\Delta PRL_{FEN}\Delta GH_{CLO}$	Group 4 (n=21;39%) No abnormality	ANOVA (H test) *P* values
Age (years)	35.8±2.3	42.8 ± 2.2	46.2±1.9	38.5±2.3	0.07
Sex (M/F)	4/2	9/8	2/7	11/10	NS*
Weight (kg)	75.3±6.0	68.1±2.8	67.7±1.8	65.1±2.9	NS
$\Delta PRL_{d\text{-}FEN}$ (ng/mL)	0.0±0.0	8.4±2.5	0.0±0.0	9.6±3.1	0.00001
ΔGH_{CLO} (ng/mL)	7.3±1.3	0.9±0.4	0.9±0.3	10.5±1.6	0.00001
$HAM\text{-}D_{17}$	25.3±1.9	26.3±1.6	25.3±1.5	23.6±1.0	NS
HAM-A	15.2±3.0	23.1±1.8	21.3±2.6	17.7±1.5	0.06
Number of episodes	5.8±2.7	3.7±0.6	9.3±2.8	2.7±0.3	0.01
Total duration (years)	5.2±3.5	10.0±2.8	16.8±2.2	9.5±2.0	0.04
No. of suicide attempts	2.0±0.6	0.5±0.2	2.1±0.4	1.1±0.2	0.004
Lethality	3.3±0.7	0.6±0.3	3.1±0.4	1.8±0.4	0.001

Table I. Clinical characteristics of the 4 groups defined by their responses to *d*-fenfluramine and clonidine tests (mean ± SEM). Bl.ΔPRL_{FEN}, indicates blunted peak concentration minus basal prolactin concentration (*d*-fenfluramine [*d*-FEN] test); Bl.ΔGH_{CLO}, blunted peak concentration minus basal growth hormone concentration (clonidine [CLO] test); $HAM\text{-}D_{17}$, Hamilton Rating Scale for Depression, 17-item version; HAM-A, Hamilton Rating Scale for Anxiety; lethality: medical damage caused by the most severe lifetime suicide attempt; *with χ^2 test; NS, not significant.

The form of multivariate analysis chosen was a factorial correspondence analysis (FCA).[21-23] This analysis is based on categorical data recorded in a contingency table, ie, clinical variables (column) in each group defined by neuroendocrine tests (row). FCA may be regarded informally as a form of principal component analysis in which the contribution of each element in a row (or column) of the contingency table is weighted according to the contribution of the row (or column) to the total variance of the table. This form of analysis is thus particularly suited to summarizing the clinical characteristics of predefined biological groups, since variables contributing relatively little to the total variance will receive relatively low weighting. The following principles[24] were applied for the interpretation of the FCA results: (1) determination of the number of necessary axes—the contribution to the total inertia made by these axes must be at least 80%; (2) selection of the most important factors on each axis, ie, having a high relative contribution to the total inertia explained by the axis—the sum of these contributions must reach at least 80% of the inertia explained by the axis and/or the square of the cosine of the factor loading on the axis must exceed 0.80; and (3) the coordinates of these factors on the axes determine their association or their opposition, ie, whether they are on the same or on opposing sides of the axis.

Results

As summarized in *Table I*, gender distribution, weight, and severity of depression were comparable among the 4 groups defined by their responses to *d*-FEN and CLO tests. There was a trend towards higher age and anxiety scores in group 2 and 3. On the other hand, groups 1 and 3 had higher numbers of suicide attempts than groups 2 and 4.

Relationships between *d*-FEN and CLO test responses and clinical characteristics among the depressed patients

The *d*-FEN and CLO test responses were not correlated (ρ=0.15; ns), and neither of these tests was correlated with the severity of depression as evaluated with total HAM-D scores *(Table II)*. However, $\Delta PRL_{d\text{-FEN}}$ values were negatively correlated with the number of suicide attempts, medical damage caused by the most severe lifetime suicide attempt, and number of previous depressive episodes. It may be noted that the number of suicide attempts was positively correlated with medical damage caused by the most severe lifetime suicide attempt (ρ=0.91, $P<0.00001$) but not with the number of previous depressive episodes (ρ=0.10).

	PRL response to *d*-FEN ($\Delta PRL_{d\text{-FEN}}$)	GH response to CLO (ΔGH_{CLO})
Age	ρ=0.03 (NS)	ρ=-0.39 (P=0.005)
HAM-A scores	ρ=0.08 (NS)	ρ=-0.39 (P=0.005)
HAM-D_{17} scores	ρ=-0.06 (NS)	ρ=-0.19 (NS)
Number of suicide attempts	ρ=-0.50 (P=0.0003)	ρ=0.13 (NS)
Lethality	ρ=-0.57 (P<0.00001)	ρ=0.07 (NS)
Number of previous episodes	ρ=-0.33 (P=0.02)	ρ=-0.35 (P=0.01)

Table II. Relationships between *d*-fenfluramine and clonidine test responses and clinical characteristics among 53 *DSM-IV* drug-free major depressed inpatients. Expressed as: Spearman rank coefficient (significance level). $\Delta PRL_{d\text{-FEN}}$ indicates peak concentration minus basal prolactin concentration (*d*-fenfluramine [*d*-FEN] test); ΔGH_{CLO}, peak concentration minus basal growth hormone concentration (clonidine [CLO] test); HAM-D_{17}, Hamilton Rating Scale for Depression, 17-item version; HAM-A, Hamilton Rating Scale for Anxiety; lethality, medical damage caused by the most severe lifetime suicide attempt; NS, not significant.

With regard to the clonidine test, ΔGH_{CLO} values were negatively correlated with HAM-A, number of previous depressive episodes, and age. The number of previous depressive episodes was positively correlated with age (ρ=0.49; P=0.0006) and total duration of illness (ρ=0.75; P<0.00001); age was correlated with total duration of illness (ρ=0.59; P<0.00001).

Factorial correspondence analysis (FCA)

This analysis, performed on clinical data, provides a graphical representation, shown in *Figure 1*. The representation of the analysis as a scatterplot of each feature allows the interpretation of relative positions in terms of similarity or association between the categories. In the present study, such an analysis was used to describe the characteristics of the four groups defined by the responses to the *d*-FEN and CLO tests *(Table III)*. The distribution of certain clinical characteristics was significantly different across the groups when each characteristic was considered separately: age and total duration of the illness were higher in group 3 (χ^2=7.68, df=3, P=0.05; χ^2=15.50, df=3, P=0.016, respectively); patients in groups 1 and 3 more often had a history of suicide attempt (χ^2=14.06, df=3, P<0.003); the medical damage caused by the most severe lifetime suicide attempt was higher in group 1 (χ^2=14.50, df=3, P=0.02); patients in group 2 had more often severe anxiety (χ^2=19.08, df=6, P=0.004).

The graphical presentation of the FCA was made using two axes: the first axis accounted for 51% and the second for 30% of the total variance. The first axis contrasted group 2 (contributing 44%) with group 3 (contributing 42%), and the second axis contrasted group 1 (contributing 74%) with group 3 (contributing 24%). Therefore, these three groups were well separated on the FCA representation and their clinical characteristics could be defined.

The patients in group 1 (ie, with serotonin dysfunction—as measured by the *d*-FEN test—and without noradrenergic dysfunction) were characterized by violent suicidal behavior, a high degree of medical damage, and mild anxiety. The patients in group 2 (ie, with noradrenergic dysfunction—as measured by the CLO test—and without serotonergic dysfunction) were characterized by an absence of a history of a suicide attempt and severe anxiety.

The patients in group 3 (ie, with combined serotonin and noradrenergic dysfunction) were characterized by a history of suicide attempts, total duration of the illness over 10 years, age over 40 years, and more than 3 previous hospitalizations. The patients in group 4 (ie, without

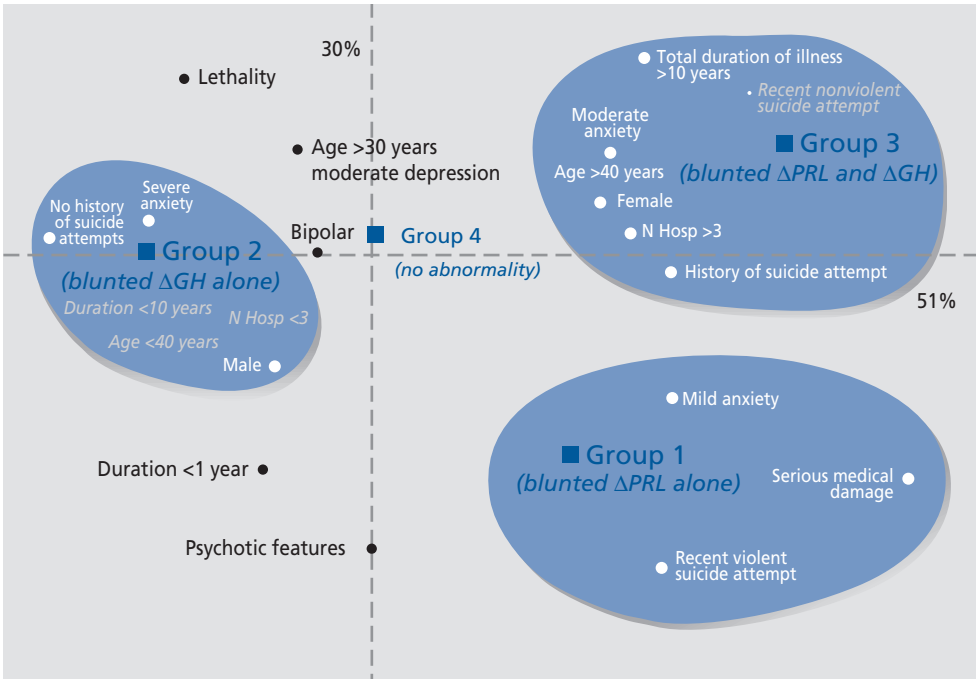


Figure 1. Representation of the four biological groups, defined by *d*-fenfluramine and clonidine test status, by means of a factorial correspondence analysis (see text for details). GH, growth hormone; N Hosp, number of hospitalizations; PRL, prolactin.

	Group 1 (n=6; 11%) Bl.ΔPRL$_{d\text{-FEN}}$	Group 2 (n=17; 32%) Bl.ΔGH$_{CLO}$	Group 3 (n=9; 18%) Bl.ΔPRL and ΔGH	Group 4 (n=21; 39%) No abnormality
Gender				
Men	4 (67%)	9 (53%)	2 (22%)	11 (52%)
Women	2 (33%)	8 (47%)	7 (78%)	10 (48%)
Age				
≤40 years	4 (67%)	10 (59%)	1 (11%)	13 (62%)
>40 years	2 (33%)	7 (41%)	8 (89%)	8 (38%)
Severity of depression				
Moderate	2 (33%)	7 (41%)	4 (44%)	10 (48%)
Severe	2 (33%)	7 (41%)	4 (44%)	10 (48%)
With psychotic features	2 (33%)	3 (18%)	1 (11%)	1 (4%)
No. of hospitalizations				
<3	3 (50%)	10 (59%)	2 (22%)	12 (57%)
≥3	3 (50%)	7 (41%)	7 (78%)	7 (33%)
Total duration of disorder				
≤1 year	3 (50%)	3 (18%)	0 (0%)	4 (19%)
Between 1 and 10 years	2 (33%)	10 (59%)	1 (11%)	8 (38%)
>10 years	1 (17%)	4 (23%)	8 (89%)	7 (33%)
History of suicide attempt				
Yes	5 (83%)	5 (29%)	9 (100%)	13 (62%)
No	1 (17%)	12 (71%)	0 (0%)	8 (38%)
Recent suicide attempt*				
No	2 (33%)	16 (94%)	4 (44%)	12 (57%)
Violent	3 (50%)	1 (6%)	1 (11%)	2 (10%)
Nonviolent	1 (17%)	0 (0%)	4 (44%)	7 (33%)
Lethality†				
<3	0 (0%)	4 (80%)	5 (56%)	12 (92%)
≥3	5 (100%)	1 (20%)	4 (44%)	1 (8%)
Course				
Single episode	0 (0%)	2 (12%)	0 (0%)	4 (19%)
Recurrent	5 (83%)	10 (59%)	7 (78%)	15 (71%)
Bipolar	1 (17%)	5 (29%)	2 (22%)	2 (10%)
Anxiety				
Mild	3 (50%)	0 (0%)	1 (11%)	6 (29%)
Moderate	1 (17%)	2 (12%)	5 (56%)	8 (38%)
Severe	2 (33%)	15 (88%)	3 (33%)	7 (33%)

Table III. Clinical characteristics of groups defined by *d*-fenfluramine and clonidine test status.
* The suicidal act had occurred during the current depressive episode and had triggered the psychiatric hospitalization.
† Medical damage caused by the most severe lifetime suicide attempt.

abnormality of the *d*-FEN and CLO tests) had no specific clinical profile.
However, neither serotonin dysfunction nor noradrenergic dysfunction was associated, in our sample, with core depressive symptoms, such as depressed mood, feelings of guilt, loss of interest, psychomotor retardation, or with severity of depressive symptoms.

Discussion

Our study clearly shows that serotonergic dysfunction, as measured by the *d*-FEN test, is associated with suicidal behavior, and that noradrenergic dysfunction, as measured by the CLO test, is mainly associated with severe anxiety in depressed patients. These results are in accordance with previous studies.[9,11,12,18,19]

Prolactin response to *d*-fenfluramine and suicidal behavior

It is known that *d*-FEN activates 5-HT transmission in the brain by stimulating the release of 5-HT and by inhibiting the uptake of this amine at the presynaptic level, leading to an increase in the concentration of 5-HT in the synaptic cleft.[25] However, at the postsynaptic level, the exact process by which *d*-FEN stimulates PRL release remains to be clarified. It has been suggested that 5-HT_{1A} receptors are involved in PRL secretion,[26] whilst some authors have shown a role for the 5-HT_{2A} and/or 5-HT_{2C} receptors,[27,28] and little or no role for the 5-HT_{1A}[29] and 5-HT_3 receptors.[30] Finally, others suggest that both 5-HT_{1A} receptors and 5-$HT_{2A/2C}$ must be occupied by endogenous 5-HT in order to stimulate PRL release.[31] Given this pharmacological background, a blunted PRL response to *d*-FEN may be indicative of a dysfunction of the hypothalamic-pituitary serotonergic system, ie, a reduced serotonergic tone perhaps secondary to reduced 5-HT presynaptic release, but does not define which serotonin receptor subtypes, at the postsynaptic level, are dysregulated.
In our study, we found that patients with a recent violent suicide attempt—and high degree of medical damage—have a blunted PRL response to *d*-FEN, suggesting that 5-HT dysfunction is associated with such suicidal behavior. Moreover, serotonin dysfunction was correlated with the number of suicide attempts, suggesting that reduced serotonergic function may be indicative of susceptibility to suicidal behavior. In addition, there was a negative correlation between PRL response to *d*-FEN and lethality, suggesting that the lower the level of 5-HT function, the more the depressed patients make suicide attempts over time and the more lethal they are. On the other hand, 5-HT dysfunction was not associated with the core symptoms of depression, which may indicate that decreased 5-HT function is more closely associated with suicide than with depression itself. This hypothesis is supported by a double-blind randomized study[32] that has shown that paroxetine, a serotonergic antidepressant, reduced suicidal behavior in patients with repeated suicide attempts but not suffering from major depression. In addition, our group[33] recently found lower *d*-FEN–induced PRL stimulation in nondepressed schizophrenic patients with a history of suicide attempts compared with controls and schizophrenic patients without a history of suicide attempts. Taken together, these data suggest that serotonergic dysfunction is associated with suicidal behavior independently of nosological status.

Growth hormone response to clonidine and anxiety

The blunted GH response to CLO is well documented in depression.[2,10,34-36] Such a response may be due to hyporesponsivity of postsynaptic α_2-receptors, via hypothalamic growth hormone–releasing hormone (GHRH) release,[37] linked to an erratic release of norepinephrine.[38] However, a blunted GH response to CLO does not appear specific to depression, as it has also been observed in generalized anxiety disorder,[39] panic disorder,[40,41] and social phobia.[42] Our finding of a negative correlation between GH response to CLO and HAM-A scores suggests a link between anxiety and noradrenergic dysregulation even in depressed patients. This is further confirmed by the FCA results, since patients who had blunted CLO-induced GH stimulation alone (group 2) were those who exhibited the highest level of anxiety. On the other hand, the patients of this group 2 were also characterized by an absence of a history of a suicide attempt, suggesting that there is no link between noradrenergic dysregulation and suicidal behavior. This finding seems to contradict a previous report[43] which suggests that blunted GH response to CLO could be a biological correlate of suicidal behavior. It should be noted that these same authors were unable to confirm this preliminary finding in a subsequent report,[44] concluding that "noradrenergic disturbances, particularly at

the level of α_2-adrenergic receptors, seem to play a minor role in suicidal behavior." The results of our study are in agreement with such a conclusion.

Relationship between serotonergic and noradrenergic dysfunction

In our study, despite the known reciprocal relationship between the 5-HT and NA systems,[45] we found no correlation between the CLO and *d*-FEN test responses in depressed patients. In our sample, the combination of a blunted PRL response to *d*-FEN and a blunted GH response to CLO was observed in about 20% of patients. These patients were clinically characterized by a history of suicide attempts and long duration of mood disorder.

It has been found that abnormalities of adrenergic and serotonergic responsiveness persist in depressed patients in remission,[46] suggesting that these abnormalities could be a trait marker of depression. Our results agree with this hypothesis, since both PRL response to *d*-FEN and GH response to CLO are negatively correlated with the number of previous depressive episodes, suggesting therefore a vulnerability to depression. However, given the clinical characteristics of patients showing both noradrenergic and serotonergic abnormalities (ie, group 3), it seems that serotonergic dysfunction may be more specifically a trait marker of suicidality, while noradrenergic dysregulation may be a marker of recurrence of episodes of affective disorder.

However, there is an effect of age on the CLO-induced GH response, and this could be a confounding factor in the interpretation of the CLO test results. In our sample, the relationship between ΔGH and age was as strong as that between ΔGH and duration of mood disorder, and the effect of these two factors could not be separated. Moreover, the mean age of group 2 (ie, with blunted GH [CLO] alone) was comparable with that of group 4 (without *d*-FEN and CLO test abnormalities) and that of group 1 (with blunted PRL [*d*-FEN] alone), suggesting that the differences in endocrine responses to the tests could not be explained by differences in age.

Conclusion

The results of our study suggest that specific psychopathological features in depression may be linked to 5-HT and/or NA dysfunction. Future studies should evaluate whether these findings may be relevant for the selection of antidepressant strategies. However, the fact that 40% of major depressed inpatients do not show abnormalities of NA and/or 5-HT system responsiveness, and that NA and/or 5-HT dysfunction are not associated with the core of depressive symptoms, support the view that NA and/or 5-HT dysfunction is less likely to be the primary cause of mood disorders[47,48] but is more indicative of failure of compensatory mechanisms involved in affective homeostasic processes. ❑

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Funciones serotoninérgicas y noradrenérgicas en la depresión: correlaciones clínicas

El presente estudio se orientó hacia la investigación de las relaciones entre las funciones centrales noradrenérgicas (NA) y serotoninérgicas (5-HT) y las características clínicas del episodio depresivo mayor de acuerdo con el DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)*. Se midió la respuesta de la hormona del crecimiento (ΔGH) a la clonidina (CLO) – un agonista noradrenérgico α_2 – como un indicador de la función central de NA, y la respuesta de prolactina (ΔPRL) a* d-*fenfluramina (*d-*FEN) – un inhibidor específico de la liberación/recaptación de 5-HT – como un indicador de la función central de 5-HT en 53 pacientes depresivos, hospitalizados, sin medicación. De acuerdo con las respuestas a las pruebas de CLO y* d–*FEN, los pacientes se clasificaron en 4 grupos. El grupo 1 (sólo con disminución de* $\Delta PRL_{d\text{-}FEN}$ *[11%]) se caracterizó por un intento suicida violento reciente, un alto grado de alteraciones médicas y ansiedad leve. El grupo 2 (sólo con* ΔGH_{CLO} *disminuida [32%]) se caracterizó por la ausencia de una historia de intentos suicidas y por ansiedad severa. El grupo 3 (combinación de* ΔGH_{CLO} *y* $\Delta PRL_{d\text{-}FEN}$ *disminuidas [18%]) se caracterizó por una historia de intentos suicidas, una duración total de la enfermedad superior a 10 años, una edad mayor de 40 años y más de 3 hospitalizaciones previas. El grupo 4 (sin anormalidades en las pruebas [39%]) no tuvo ningún perfil clínico específico. Estos resultados sugieren que, en la depresión, las características psicopatológicas específicas pueden relacionarse con una disfunción 5-HT y/o NA. Sin embargo, nuestros resultados también sugieren que las disfunciones 5-HT y/o NA con menor probabilidad constituyen la causa primaria de los trastornos del ánimo, y ellas más bien son indicadoras de fallas en los mecanismos compensatorios que participan en los procesos de la homeostasis afectiva.*

Les fonctions serotoninergique et noradrenergique dans la depression : correlations cliniques

Cette étude a été conduite afin de rechercher les relations existantes entre les fonctions centrales noradrénergique (NA) et sérotoninergique (5-HT) et les caractéristiques cliniques d'un épisode dépressif qualifié de majeur d'après le DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). *Nous avons mesuré la réponse de l'hormone de croissance (ΔHG) à la clonidine (CLO, agoniste NA* α_2*) représentant la fonction NA centrale et la réponse de la prolactine (ΔPRL) à la* d-*fenfluramine (*d-*FEN, un inhibiteur spécifique de la recapture 5-HT et un libérateur de 5-HT) représentant la fonction 5-HT centrale, chez 53 patients hospitalisés pour dépression et non traités. Ces patients ont été classés en 4 groupes en fonction de leurs réponses aux tests CLO et* d-*FEN. Le groupe 1 (*$\Delta PRL_{d\text{-}FEN}$ *émoussée isolée [11%]) était caractérisé par une tentative de suicide violente récente, des lésions corporelles sévères et une anxiété légère. Le groupe 2 (*ΔHG_{CLO} *émoussée isolée [32%]) était caractérisé par l'absence de tentative de suicide dans les antécédents et une anxiété sévère. Le groupe 3 (association de* $\Delta PRL_{d\text{-}FEN}$ *et de* ΔHG_{CLO} *émoussées [18%]) était caractérisé par des antécédents plus nombreux de tentative de suicide, une durée totale de la maladie supérieure à 10 ans, un âge supérieur à 40 ans et plus de 3 hospitalisations antérieures. Le groupe 4 (pas d'anomalie [39%]) ne présentait pas de profil clinique particulier. Ces résultats suggèrent que, dans la dépression, des caractéristiques psychopathologiques spécifiques peuvent être liés à une dysfonction de 5-HT et/ou NA qui témoigne plus probablement d'un échec de la mise en œuvre des mécanismes compensatoires impliqués dans l'homéostasie des processus affectifs qu'elle n'est la cause primaire des troubles de l'humeur.*

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