Suicide is a major public health issue in the West, where it is among the top 10 causes of death. Throughout the world, suicide accounts for about 1 million deaths per year, i.e., 1 death every 40 seconds, according to the World Health Organization, and constitutes a heavy familial, social, and economic burden.

Some data concerning suicide are of major interest. First, despite effort in prevention, suicide rates do not appear to be decreasing (Figure 1) and, in many industrialized countries, the number of people dying through suicide is significantly higher than the number of people dying in automobile accidents. Second, suicide rates in adolescents and young adults increased in the last two or three decades, and in many countries suicide mortality rates are the third, or even the second, cause of death among young people.

In view of these data, much effort has been made to study the biology of suicide, and a central serotonergic dysfunction is possibly the most studied biological parameter. Initial in vivo evidence comes from a study showing a lower concentration of acid 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) of depressed suicidal patients compared with depressed nonsuicidal patients. Many have further confirmed this result, not only in depression but also in schizophrenia and personality disorder, showing that lower 5-HIAA CSF concentration is associated with suicidal behavior regardless of psychiatric diagnosis.

We carried out two studies to test the hypothesis that altered central serotonergic function, as assessed by lower prolactin (PRL) response to d-fenfluramine (D-FEN), is more closely associated with suicidal behavior than a particular psychiatric diagnosis. A D-FEN test was performed in 85 major depressed inpatients, 33 schizophrenic inpatients, and 18 healthy controls. We showed that PRL response to D-FEN is a marker of suicidality, regardless of psychiatric disorder. We then examined the association between the serotonin (5-hydroxytryptamine) receptor 5-HT2A gene polymorphism (T102C) and suicide in a sample of Brazilian psychiatric inpatients (95 with schizophrenia, 78 with major depression) and 52 healthy controls. No differences were found in genotypic frequencies across patients and controls. Overall, no differences were found between patients with (n=66) and without (n=107) a history of suicide attempts. We also compared patients with a history of severe suicide attempts (lethality>3; n=32) and patients without such a history (n=107), but they did not exhibit different genotypic frequencies either. These results show that the 5-HT2A gene polymorphism (T102C) may not be involved in the genetic susceptibility to suicidal behavior.

Keywords: serotonin; suicidal behavior; genetic susceptibility; depression; schizophrenia
Neuroendocrine studies

A limitation of CSF studies is that they do not address the question of whether overall serotonergic transmission in the brain is decreased, since it is primarily a metabolic measure; furthermore, these studies are rather invasive. In this context, neuroendocrine tests offer a good alternative method of assessing central serotonergic function. Various serotonin probes have been proposed in order to obtain an index of the overall functional status of the central serotonergic system, but fenfluramine is the most widely used. Both d-fenfluramine (D-FEN) and the racemate have been used, but the former is a more specific serotonin probe, lacking the dopaminergic and noradrenergic action of dl-fenfluramine.

D-FEN promotes release and inhibits uptake of serotonin, increasing intrasynaptic levels of the neurotransmitter. This action results in a dose-dependent response of prolactin (PRL) release, which is thought to be mediated by the serotonin (5-hydroxytryptamine, 5-HT) receptors 5-HT2A/5-HT2C or by the 5-HT1A receptors, or an interaction between the two. Furthermore, D-FEN was demonstrated to elicit an increase in PRL secretion compared with control (saline) test in patients with depression, schizophrenia, or personality disorder. Thus, a blunted PRL response to D-FEN seems to reflect a deficit in central serotonergic function.

There have been many studies of the hormonal response to D-FEN in depressed patients but results are inconsistent. Some authors found a decreased PRL response in patients with major depression compared with normal control subjects, but others could not replicate this finding. However, these studies did not address whether blunted PRL response correlates with suicidal behavior. Kavoussi et al analyzed a sample of outpatients without a history of suicide attempt and did not find a difference between normal volunteers and depressed patients in PRL response to D-FEN. On the other hand, our previous study showed a difference between depressed inpatients and controls, but no clinical difference was observed between depressed patients with reduced and normal PRL response to D-FEN, except that the former had a history of repeated suicide attempts.

To the best of our knowledge, there are only two studies comparing the PRL response to D-FEN in patients with schizophrenia and healthy subjects, which showed an increased PRL response to D-FEN in the former. Two other studies compared patients with schizophrenia and patients with depression showing conflicting results. Whereas Duval et al found no significant difference in the hormonal response to D-FEN between the two groups, Abel et al found that PRL, but not cortisol, response to D-FEN was significantly greater in schizophrenia than in depression. To our knowledge, there have not been any D-FEN studies that specifically address the question of suicidal behavior in schizophrenia.

In view of these data, we carried out two studies to test the hypothesis that altered central serotonergic function, as assessed by lower PRL response to D-FEN, is more closely associated with suicidal behavior than to a particular psychiatric diagnosis.

Neuroendocrine study in patients with major depression

A D-FEN test was performed, as previously described, in 85 inpatients with major depression and 18 healthy controls. Diagnosis was made by an experienced research psychiatrist, who conducted a structured interview. The minimum severity criterion was defined as Hamilton Rating Scale for Depression (HAM-D–17) score of greater than 18 on the first 17 items. To be included patients could not have other current comorbid Axis I psychiatric disorders, such as anxiety disorders, substance abuse or dependence, or a previous manic or hypomanic episode. They had to be free of medication known to affect the serotonergic system for at least 15 days, depending on the half-life of the drug used, before the endocrine investigation and drug washout was supervised in hospital.

Suicide history was assessed by an experienced psychiatrist, blind to endocrine results, by means of a semistructured interview, and a review of medical records. Forty-nine patients had a history of suicide attempt (mean±SD,
2±1.1 lifetime suicide attempts) and 36 did not. Patients with a positive suicide history were then classified as recent suicide attempters (n=26) 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); or past suicide attempters (n=23) 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).

The Lethality Rating Scale 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., we scored no medical damage as zero and death as 8 (mean±SD, 2.8±1.3 scored on the Lethality Rating Scale in our sample).

Following other investigators, we expressed the changes in PRL after D-FEN (ΔPRL) as PRL peak concentration value after D-FEN administration minus PRL baseline concentration value. In the morning, PRL concentrations decrease owing to the normal circadian rhythm. Therefore, we used the values at t=0 min as baseline levels.

Despite logarithmic or other transformations, the distribution of some data remained nonnormal (Kolmogorov-Smirnov one-sample test for goodness of fit), thus non-parametric statistical methods were used. Differences between groups were tested by analysis of variance (Kruskal-Wallis, H test) and, when the overall effect was significant, the Mann-Whitney (U test) was used with Bonferroni’s adjustment for three pairwise comparisons when applicable. Correlations between quantitative variables were estimated using the Spearman rank coefficient (ρ). Categorical data were analyzed using Fisher’s exact test. All tests were two-tailed. Results were considered significant when P≤0.05.

The three groups were comparable for age and sex distribution, as well as for baseline hormone values (Table I). The levels of PRL before and after D-FEN were not significantly influenced by age, sex, or weight in the three groups studied. There was no significant influence of the baseline PRL or cortisol levels on ΔPRL values. Basal cortisol levels were not different in the three groups and these values did not differ with suicidal status. Moreover, ΔPRL values were comparable between premenopausal women tested in the luteal phase and those tested in the follicular phase, both in the controls and in the patients. Therefore, the difference in ΔPRL values between depressed patients with a suicide history and the two other subgroups could not be explained by menstrual status.

Comparison of ΔPRL between depressed patients without a suicidal history and control subjects showed no difference, but depressed patients with a suicidal history exhibited a significantly lower ΔPRL when compared with controls or depressed patients without a suicidal history (Figure 2). No differences were found between the two groups of depressed patients in clinical or anamnesis.

| Table I. Demographic characteristics and biological data for normal controls and depressed patients according to their suicide history. Values are means±SD. BPRL, basal prolactin concentration; ΔPRL, peak concentration minus basal prolactin concentration; HAM-D–17, Hamilton Rating Scale for Depression, 17-item version; NSHDP, depressive patients with no suicidal history; SHDP, depressive patients with a suicidal history. Mann-Whitney 2-tailed U test, adjusted with Bonferroni’s method for multiple comparisons, for the difference between: *P<0.02 SHDP vs controls; or **P<0.001 SHDP vs NSHDP. |

| Controls (n=18) | NSHDP (n=36) | SHDP (n=49) |
|----------------|-------------|-------------|
| Age (years)    | 36.8±11.4   | 40.8±10.1   | 40±10.9     |
| Sex (M/F)      | 7/11        | 12/24       | 21/28       |
| BPRL (µg/L)    | 15.6±7      | 15.8±9.4    | 12.5±8.5    |
| ΔPRL (µg/L)    | 6.6±5.3*    | 8.5±13.5**  | 2.5±5.5     |
| HAM-D–17       | -           | 23.5±5.3    | 25±4.8      |

Figure 2. The histograms (±SEM) represent ΔPRL (peak concentration value of prolactin [PRL] after administration of d-fenfluramine [D-FEN] minus PRL baseline concentration value) in 18 control subjects and 33 patients with schizophrenia, classified according to previous suicide attempt (SHSP, n=12) or no previous suicide attempt (n=21). *P<0.0003 by Mann-Whitney two-tailed U test, adjusted with Bonferroni’s method for multiple comparisons, for the difference between SHSP and controls.

**P<0.004 by Mann-Whitney two-tailed U test, adjusted with Bonferroni’s method for multiple comparisons, for the difference between SHSP and NSHSP.
tic data: age at illness onset in years (mean±SD, 31.2±9.5 versus 31.6±10.9; *P<0.9 by U test), length of the current depressive episode in weeks (mean±SD; 21.3±21.5 versus 19.7±14.9; *P<0.9 by U test); number of previous episodes (mean±SD, 4.2±4.9 versus 3.3±2.1; *P<0.9 by U test); Hamilton Anxiety (HAMA) scale scores (mean±SD, 19.7±7.1 versus 18.8±8; *P<0.9 by U test); and distribution of psychotic features (7 versus 5 patients with psychotic features; *P<0.9 by Fisher’s exact test).

Patients with a recent or past suicide attempt showed no differences in baseline PRL or PRL response to D-FEN. These values were not significantly influenced by age, weight, or sex. Recent and past suicide attempter subgroups exhibited no statistical differences in number of suicide attempts (mean±SD, 1.9±1.2 versus 2.1±1; *P>0.4 by U test) or lethality of the most lethal lifetime suicide attempt (mean±SD, 2.9±1.2 versus 2.7±1.4 score on Lethality Rating Scale; *P>0.3 by U test). The other clinical and anamnestic characteristics were also not statistically different between these two subgroups, except that recent suicide attempters presented a lower HAM-D score than past suicide attempters (Table II).

In the whole sample of suicide attempt patients, we found negative correlations between ∆PRL and (i) lethality of the most lethal lifetime suicide attempt (ρ=-0.4; *P<0.006; n=49), and (ii) number of suicide attempts (ρ=-0.3; *P<0.04; n=49). Following Malone et al.,23 we subdivided suicidal patients into those with high-lethality suicide attempt (score ≥3) and those with low-lethality suicide attempt (score <3), as measured by the Lethality Rating Scale, considering the lethality of the most lethal lifetime suicide attempt. The high-lethality subgroup (n=25) showed significantly lower ∆PRL levels than the low-lethality subgroup (mean±SD, 0.35±3.6 µg/L versus 4.7±6.4 µg/L; *P<0.002 by U test). There was no statistical difference in baseline PRL values between these groups (mean±SD, 12.9±9 µg/L versus 12.1±8 µg/L; *P>0.7 by U test). These values were not significantly influenced by sex, age, or weight. The clinical and anamnestic characteristics studied were not statistically different between these two subgroups.

These results gave us some important information:

- We found that serotonergic dysfunction was associated with suicidal behavior in depressed patients, but not with depression itself. This could explain the divergent results observed with this neuroendocrine test in previous studies, which did not specifically address the question of suicidal behavior in the samples of depressed patients.

- Patients with a history of recent suicide attempt did not have a different PRL response to D-FEN from that of patients having made a suicide attempt in the distant past. This indicates that the medical damage itself did not account for the reduced serotonergic function observed in the suicide attempt group, and suggests that this reduced serotonergic function may be a trait marker of vulnerability to suicide.

### The D-FEN test in schizophrenia

A D-FEN test, as previously described,29 was performed in 33 drug-free Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) inpatients with schizophrenia (12 with a suicide attempt, 21 without) and 18 hospitalized healthy controls. Since comorbidity of depressive symptoms is frequent in schizophrenic patients,31,32 we did not include in our study patients presenting a significant depressive symptomatology, excluding any patients with a HAM-D–17 greater than 15, to reduce this eventual confounding factor.

Diagnosis was made by two experienced psychiatrists; one conducted an unstructured interview and the other used a structured instrument (Schedule for Affective Disorders and Schizophrenia-Lifetime version).20 The final diagnoses were made by consensus of the two psy-

|         | RSHA (n=26) | PSHA (n= 23) |
|---------|------------|--------------|
| Age (years) | 37.2±11.4  | 43.2±9.7     |
| Sex (M/F) | 12/14      | 9/14         |
| BPRL (µg/L) | 14±8.7    | 10.8±8.1     |
| ∆PRL (µg/L) | 2.9±5     | 2±6.1        |
| HAM-D–17   | 23.5±3.7   | 26.8±5.4*    |

Table II. Demographic characteristics and biological data for depressed patients with recent and past suicide history. Values are mean±SD. BPRL, basal prolactin concentration; ∆PRL, peak concentration minus basal prolactin concentration; HAM-D–17, Hamilton Rating Scale for Depression, 17-item version; RSHA, history of recent suicide attempt; PSHA, history of past suicide attempt. *P<0.05 analysis by Mann-Whitney test.
Healthy controls and patients with schizophrenia, subgrouped by suicide history, presented no difference in demographic characteristics or baseline hormonal values as shown in Table III. The patients with schizophrenia and a suicide attempt history showed no demographic, clinical, or anamnestic differences compared with patients without such a history. Age in years (30.4±11.1 versus 32±11.7; \( P>0.9 \) by U test), weight (61.3±8.8 kg versus 62.2±9.2 kg; \( P>0.75 \) by U test), age of illness onset in years (21.3±4.9 versus 24.9±8.7; \( P>0.3 \) by U test), number of previous hospitalizations (3.0±1.7 versus 2.8±1.9; \( P>0.5 \) by U test), and distribution of schizophrenia subtypes (paranoid 5 versus 11; undifferentiated 3 versus 2; and disorganized 4 versus 8) were not statistically different between patients with schizophrenia with or without a suicidal history. Psychopathological data (HAM-D–17 and Brief Psychiatric Rating Scale [BPRS]) was also evaluated. No differences in HAM-D–17 scores or in the BPRS total or factor scores were found between patients with or without a history of suicide attempt (Table IV).

Patients with a recent suicide attempt (\( n=5 \)) exhibited comparable basal and post-fenfluramine hormonal levels when compared with patients with a past suicide attempt (\( n=7 \)). Demographic and clinical characteristics were similar between these two subgroups (Table V). These results show us that:

- A serotonergic dysfunction was associated with suicidal behavior in patients with schizophrenia, but not with schizophrenia itself.
- Patients with a history of a recent suicide attempt did not have a different PRL response to D-FEN to patients with a suicide attempt in the distant past. This indicates that the injury itself did not account for the reduced serotonergic function observed in the suicide attempt group.

**Basic research**

controls, blinded to the endocrine data. Suicide history attempt assessment and statistical analysis were conducted following the same procedures described above for depressed patients.

The schizophrenic patients as a whole showed no significantly different baseline PRL values (13.9±7 µg/L versus 15.6±7 µg/L; \( P>0.8 \) by the U test) when compared with healthy controls. However, DPRL was significantly lower in this group when compared with normal volunteers (2±6.1 µg/L versus 6.6±5.3 µg/L; \( P<0.01 \) by the U test). This difference was mainly accounted for by the significantly lower PRL levels in suicidal patients, since a subgroup analysis showed that patients with schizophrenia and a suicide history exhibit lower levels of PRL in response to D-FEN compared with patients with schizophrenia without such a history, and also compared with healthy controls. No difference in ΔPRL levels was found between patients with schizophrenia without a suicide history and controls.

### Table III

Demographic characteristics and biological data for normal controls and patients with schizophrenia according to their suicide history. Values are expressed as means±SD. BPRL, basal prolactin concentration; ΔPRL indicates peak concentration minus basal prolactin concentration; SHSP, schizophrenic patients with a suicide attempt history; NSHSP, schizophrenic patients without a suicide attempt history. Mann-Whitney 2-tailed U test, adjusted for multiple comparisons, for the difference between: *P<0.04 SHSP vs NSHSP; or **P<0.0003 SHSP vs controls.

|         | Controls (n=18) | SHSP (n=12) | NSHSP (n=21) |
|---------|----------------|------------|-------------|
| Age (years) | 36.8±11.4 | 30.4±11.1 | 32±11.7 |
| Sex (M/F) | 7/11 | 5/7 | 12/9 |
| BPRL | 15.6±7 | 16.9±8.6 | 12.2±5.5 |
| ΔPRL | 6.6±5.3* | -1.8±4.4 | 4.2±5.8** |

### Table IV

Psychopathological data for patients with schizophrenia according to their suicide history. Values are expressed as means±SD. HAM-D–17, Hamilton Rating Scale for Depression, 17-item version; BPRS, Brief Psychiatric Rating Scale; SHSP, patients with schizophrenia and a suicide attempt history; NSHSP, patients with schizophrenia but no suicide attempt history.

|         | SHSP (n=5) | NSHSP (n=7) |
|---------|------------|-------------|
| Age (years) | 31.3±12.5 | 29.2±10.2 |
| Sex (M/F) | 3/4 | 2/3 |
| BPRL (µg/L) | 15.5±8.6 | 18.7±9.1 |
| ΔPRL (µg/L) | -1.3±4.1 | -2.5±5.2 |
| BPRS | 52.8±9.7 | 49.8±10.5 |
| HAM-D–17 | 11.7±1.9 | 12.4±3.1 |
suggesting that a lower serotonergic function may be a trait marker for suicidality in schizophrenia too.

• We failed to replicate previous studies showing that a serotonergic dysfunction may be associated with more lethal suicide attempts. A type β error is probably the reason for this discrepancy, in view of our small sample (n=12) of suicide attempt patients.

Molecular approach

As described above, serotonergic dysfunction in the brain has been reported to be involved in suicidal behavior independently of the presence of a specific psychiatric disorder. There is much evidence suggesting that suicidal behavior is, at least partially, genetically determined, as shown by many familial, twin, and adoption studies. A search for the gene, or more probably the genes, involved in suicidal behavior could involve a investigation of the entire genome. Current debate concerns whether there is a relationship between genetic polymorphisms with intermediate phenotypes, such as impulsivity, psychomotor abnormalities, and aggression, and other biological abnormalities including specific gene products.

Serotonergic function is a complex equation depending on the functional state of enzymes, reuptake protein, and about 15 different receptors. However, since D-FEN–induced increase in PRL plasma levels is mediated by 5-HT3A, 5-HT3C, or 5-HT1A receptors, the genes for these receptors, as well as others related to important steps in serotonergic function, like the serotonin transporter and tryptophan hydroxylase, are also candidates associated with suicidal behavior.

Several postmortem studies have reported an increased 5-HT2A binding in prefrontal cortex in suicide victims, when compared with controls, which makes 5-HT2A an interesting candidate gene in suicidal behavior. However, investigations in unselected suicide completers did not suggest any evidence of association between genetic variation at this gene when tested for the T102C and A1438G polymorphisms, as well as the Thr25Asp, His542Tyr, and C516T polymorphisms and completed suicide, even though evidence was found for a relationship between genetic variation at the T102C and A1438G loci and 5-HT2A binding in the prefrontal cortex. Negative association results were also found in other studies that investigated suicide completers with major depression and suicide attempters. However, two other studies reported positive results. Zhang et al investigated the T102C polymorphism and found a slight difference in genotype distribution in 15 subjects with a history of suicide attempt and 87 subjects without suicidal behavior. The same polymorphism was investigated in suicidal ideation in patients with major depression and an increase in the C (T102C) allele in suicidal ideation was found. Thus, studies on Caucasian populations have not been conclusive. Bjork et al investigated whether this polymorphism could be specifically related to impaired impulse control in adults recruited from the community. They reported that the 102C/102C genotype was jointly associated with a greater incidence of past mood disorder or substance use disorder, as well as significantly more commission errors on CPT (continuous performance test) compared with the 102T/102C and 102C/102C genotypes, suggesting that the T102C 5-HT2A receptor polymorphism might be a marker for impaired behavior in the context of psychiatric disorder history. Taking all that into account, we examined the role of T102C polymorphism of the 5-HT2A gene in a selected Brazilian population.

A total of 225 unrelated subjects were enrolled after a full explanation of this study and signing an informed consent. This study was approved by University’s Ethics Committee. Patient eligibility was ascertained after consecutive admissions at two Belo Horizonte hospitals (Hospital Santa Maria and Clínica Pinel) meeting the DSM-IV diagnostic criteria based on a structured interview (MINI-PLUS). Only patients with a diagnosis of recurrent major depression (n=78) or schizophrenia (n=95) without any other current comorbid Axis I disorder were selected. Healthy controls were students, nurses, and staff members (n=52), all free of psychiatric and medical illness, with no family history of Axis I psychiatric disorder in first-degree relatives.

A review of medical records was performed and suicide history was independently assessed, using a semistructured interview. Sixty-six patients had a history of suicide attempts (2.5±1.2, mean±SD). The Lethality Rating Scale, adapted as previously described, was used to measure the degree of medical damage of the most lethal lifetime suicide attempt. DNA was isolated from lymphocytes using routine procedures. Polymerase chain reaction (PCR) amplification of the HT2A/T102C region containing the polymorphic site produced a 372-bp fragment. This was digested with the restriction enzyme HpaII. The uncut product corresponded to the nucleotide sequence TCT. Digested products with 216 and 126 bp corresponded to TCC.
alleles as described elsewhere. Chi-square tests were used to compare frequencies. Patients and controls were not different in terms of demographic characteristics like age and sex. Moreover, no differences were observed in genotypic frequencies across these groups (Table VI).

No allele differences (TT, TC, or CC) were found between patients with a suicide attempt history (n=66) and without (n=107): TT (18 [27.3%], 30 [28%]); TC (35 [53%], 55 [51.4%]); CC (13 [19.7%], 22 [20.5%]). Patients with a history of severe suicide attempts (lethality>3; n=32) and patients without such a history (n=107) also did not exhibit a statistically significant difference in genotypic frequencies: TT (12 [37.5%], 30 [28%]); TC (17 [53%], 55 [51.4%]); CC (3 [9.4%], 22 [20.5%]).

Our study comprised a rather homogeneous sample of inpatients with major depression or schizophrenia, as assessed with structured instruments to evaluate diagnosis and suicide attempt history. This is important since suicide history can be underevaluated with simple clinical interviews. Overall, we did not find differences between patients with and without a suicide attempt history, regardless of its severity.

More work in this area is of great value. We cannot reliably exclude a type II error accounting for the negative association. It may be possible that 5-HT2A has a role in suicide susceptibility, but the number of subjects in this study did not afford enough power to detect this effect. There seem to be more 5-HT2A receptors in suicide victims and a functional polymorphism involving the promoter region that affect the gene expression may explain this fact. Interestingly, Ohara et al found that the -1438G/A promoter polymorphism was in linkage disequilibrium with T102C.

We are currently investigating genetic polymorphisms in other candidate genes of the serotonergic function, like the receptors 5-HT1A and 5-HT2C, the enzyme tryptophan hydroxylase and the membrane serotonin transporter.

The molecular study has the financial support of CNPq-550395016.

### Table VI. Demographic and genotypic differences among groups.

|               | Schizophrenia | Depression | Controls |
|---------------|---------------|------------|----------|
| n             | 95            | 78         | 52       |
| Sex (M/F)     | 50/45         | 38/40      | 25/27    |
| TT            | 28 (29.5%)    | 20 (25.7%) | 15 (28.8%)|
| TC            | 47 (49.5%)    | 43 (55.1%) | 27 (52%) |
| CC            | 20 (21%)      | 15 (19.2%) | 10 (19.2%)|

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Investigación sobre la serotonina y la conducta suicida: aproximaciones neuroendocrina y molecular

Nosotros realizamos dos estudios para probar la hipótesis de la alteración de la función serotonérgica central –la cual se evalúa mediante la menor respuesta de prolactina (PRL) a la d-fenfluramina (D-FEN)– que está más estrechamente asociada con la conducta suicida que con cualquier otro diagnóstico psiquiátrico. Se realizó una prueba de D-FEN en 85 pacientes hospitalizados con depresión mayor, 33 pacientes hospitalizados esquizofrénicos y 18 controles normales. Nosotros mostramos que la respuesta de PRL a D-FEN es un marcador de suicidialidad, independiente del diagnóstico psiquiátrico. Luego examinamos la asociación entre el polimorfismo del gen del receptor de serotonina (5-hidroxitriptamina) 5-HT<sub>2A</sub> (T102C) y el suicidio en una muestra de pacientes psiquiátricos brasileños hospitalizados (95 con esquizofrenia, 78 con depresión mayor) y 52 controles sanos. No se encontraron diferencias en las frecuencias de los genotipos entre los pacientes y controles. En conjunto, no se encontraron diferencias entre pacientes con (n=66) y sin (n=107) historia de intentos suicidas. Nosotros también comparamos pacientes con historia de intentos suicidas severos (letalidad >3, n=32) y pacientes sin tal historia (n=107) y no se encontraron frecuencias genotípicas diferentes entre ellos. Estos resultados demuestran que el polimorfismo del gen de 5-HT<sub>2A</sub> (T102C) no puede estar involucrado en la susceptibilidad genética a la conducta suicida.

Recherches sur la sérotonine et le comportement suicidaire : approches neuroendocrinienne et moléculaire

Nous avons mené deux études pour vérifier l’hypothèse selon laquelle l’altération de la fonction sérotoninergique centrale, dont le stigmate est une réponse plus basse de la prolactine (PRL) à la d-fenfluramine (D-FEN), serait plus étroitement associée à un comportement suicidaire qu’à un diagnostic psy- chiatrique particulier. Un test D-FEN a été réalisé chez des patients hospitalisés, dont 85 étaient atteints de dépression majeure et 33 de schizophrénie, et 18 témoins en bonne santé. Nous avons montré que la réponse de la PRL à la D-FEN est un marqueur de risque suicidaire, indépendamment de toute pathologie psychiatrique. Nous avons alors examiné l’association entre le polymorphisme génétique (T102C) du récepteur 5-HT<sub>2A</sub> à la sérotonine (5-hydroxytryptamine) et le suicide dans un échantillon de patients brésiliens hospitalisés atteints de pathologie psychiatrique (95 schizophrènes, 78 atteints de dépression majeure) et 52 témoins en bonne santé. Aucune différence de fréquences génotypiques n’a été observée entre les patients et les témoins. Au total, aucune différence n’a été retrouvée entre les patients avec (n = 66) ou sans (n = 107) antécédent de tentative de suicide. Nous avons aussi comparé les patients ayant un antécédent grave de tentative de suicide (mortalité > 3 ; n = 32) et les patients sans antécédent de ce type (n = 107), mais eux non plus ne présentaient pas de fréquences génotypiques différentes. Ces résultats montrent que le polymorphisme génétique du 5-HT<sub>2A</sub> (T102C) peut ne pas être impliqué dans la sensibilité génétique au comportement suicidaire.
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