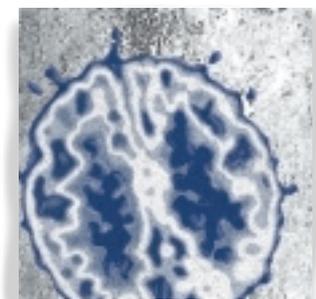


# Basic research

## *Interaction between the serotonergic system and HPA and HPT axes in patients with major depression: implications for pathogenesis of suicidal behavior*

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**R**etrospective studies, using prolactin (PRL) response to *d*-fenfluramine test (d-FEN; a presynaptic serotonin [5-hydroxytryptamine, 5-HT]–releasing and –uptake-inhibiting agent), have suggested that reduced serotonergic functioning may be a marker of increased suicide risk in patients with major depression<sup>1</sup> and schizophrenia.<sup>2</sup> The etiology of this abnormality remains unknown, but it has been suggested<sup>3</sup> that overactivation of the hypothalamic-pituitary-adrenal (HPA) axis by chronic stress, and the associated hypercortisolism, could directly induce changes in 5-HT pathways. Consequently, it has been hypothesized that 5-HT abnormality in patients with a history of suicidal behavior could be secondary to hyperactivity of the HPA axis.

*Disturbances in the serotonin (5-hydroxytryptamine, 5-HT) system constitute the neurobiological abnormality most consistently associated with suicide. This abnormality could be a marker of vulnerability predisposing individuals to auto-aggressive and impulsive behavior. However, other abnormalities, such as hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, have also been described in suicide victims. While inhibitory effects of adrenocorticosteroids on 5-HT<sub>1A</sub> receptor function have been shown in animals, HPA axis hyperactivity does not seem to be responsible for the reduced 5-HT activity found in depressed patients with a history of suicidal behavior. On the other hand, hypothalamic-pituitary-thyroid (HPT) axis dysfunction, frequently observed in depression, may represent a compensatory response to reduced central 5-HT neurotransmission. Moreover, in depressed patients with a history of suicidal behavior, the absence of a functional link between HPT and dopamine activity at the hypothalamic level may be implicated in the pathophysiology of suicidal behavior. Future research is needed to determine why compensatory mechanisms are not efficient in patients with suicidal behavior.*

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**Keywords:** *serotonin; dopamine; d-fenfluramine test; thyrotropin-releasing hormone test; dexamethasone suppression test; depression; suicide*

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## Selected abbreviations and acronyms

|              |                                       |
|--------------|---------------------------------------|
| <b>ACTH</b>  | adrenocorticotrophic hormone          |
| <b>APO</b>   | apomorphine                           |
| <b>CRH</b>   | corticotropin-releasing hormone       |
| <b>DA</b>    | dopamine                              |
| <b>d-FEN</b> | d-fenfluramine                        |
| <b>DST</b>   | dexamethasone suppression test        |
| <b>GH</b>    | growth hormone                        |
| <b>HPA</b>   | hypothalamic-pituitary-adrenal (axis) |
| <b>HPT</b>   | hypothalamic-pituitary-thyroid (axis) |
| <b>5-HT</b>  | 5-hydroxytryptamine (serotonin)       |
| <b>PRL</b>   | prolactin                             |
| <b>TRH</b>   | thyrotropin-releasing hormone         |
| <b>TSH</b>   | thyroid-stimulating hormone           |

The hypothesis of hyperactivity of the HPA is supported by the postmortem findings of increased cerebrospinal fluid (CSF) corticotropin-releasing hormone (CRH) concentrations and reduced CRH receptor binding sites in the frontal cortex of suicide victims (interpreted as downregulation following CRH hypersecretion) and dexamethasone nonsuppression in some, but not all, suicide attempters.<sup>4</sup> While there is evidence for inhibitory effects of the HPA on 5-HT activity in animals, studies in healthy humans and depressed patients have produced disparate findings. It has been reported, in small samples, that acute treatment with hydrocortisone attenuates PRL response to d-FEN,<sup>5</sup> though subchronic administration of hydro-

cortisone induces no change in PRL response to d-FEN.<sup>6</sup> It has also been found that pretreatment with dexamethasone decreases cortisol—but not PRL—response to d-FEN.<sup>7</sup> In depression, some authors have hypothesized<sup>8,9</sup> that raised cortisol levels could lead to impaired neuroendocrine responses to the d-FEN challenge. This modification could be related more specifically to blunted 5-HT<sub>1A</sub> receptor function, rather than to reduced 5-HT presynaptic release or 5-HT<sub>2</sub> receptor function. Indeed, preclinical studies have shown that chronic hypercortisolemia inhibits 5-HT<sub>1A</sub> receptor function, while 5-HT turnover and 5-HT<sub>2</sub> receptor function are enhanced.<sup>10</sup>

## Lack of effect of HPA hyperactivity on 5-HT responsiveness in depressed patients

In a recent study,<sup>11</sup> we have examined the relationship between HPA axis activity and 5-HT function in major depression, particularly in patients with a history of suicidal behavior. We measured (i) cortisol levels at baseline and following dexamethasone suppression test (DST; 1 mg orally administered at midnight on day 1); and (ii) PRL, adrenocorticotrophic hormone (ACTH), and cortisol responses to challenge with d-FEN (45 mg orally, at 9 AM on day 5) in 71 drug-free *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*<sup>12</sup> major depressed inpatients (40 with a history of suicide attempt, 31 without) and 34 hospitalized healthy control subjects.

|                              | Control subjects (n=34) | Depressed patients (n=71) | P     |
|------------------------------|-------------------------|---------------------------|-------|
|                              | Mean (SEM)              | Mean (SEM)                |       |
| Age (years)                  | 39.6 (1.6)              | 40.2 (1.1)                | 0.81  |
| Range (years)                | 20-63                   | 19-60                     |       |
| Gender (M/F)                 | 14/20                   | 28/43                     | 0.86  |
| Weight (kg)                  | 66.5 (1.5)              | 65.5 (1.4)                | 0.80  |
| Range (kg)                   | 47-90                   | 42-93                     |       |
| Post-DST cortisol (nmol/L)   | 38 (4)                  | 98 (12)                   | 0.003 |
| No. of abnormal DSTs         | 1                       | 19                        | 0.008 |
| <b>Fenfluramine test</b>     |                         |                           |       |
| • Baseline PRL (µg/L)        | 12.4 (0.9)              | 14.5 (1.1)                | 0.73  |
| • ΔPRL (µg/L)                | 5.5 (0.8)               | 4.3 (1.3)                 | 0.09  |
| • Baseline ACTH (ng/L)       | 25.5 (3.1)              | 24.7 (2.0)                | 0.98  |
| • ΔACTH (ng/L)               | 11.2 (4.6)              | 8.1 (1.2)                 | 0.57  |
| • Baseline cortisol (nmol/L) | 358 (20)                | 378 (21)                  | 0.90  |
| • ΔCortisol (nmol/L)         | 88 (27)                 | 83 (18)                   | 0.74  |

**Table 1.** Demographic characteristics and biological data for depressed patients and normal control subjects. DST, dexamethasone suppression test; No. of abnormal DSTs, number of subjects with highest post-DST cortisol level >130 nmol/L; Δ, peak concentration minus baseline value; PRL, prolactin; ACTH, adrenocorticotrophic hormone.

We hypothesized that, if HPA overactivity is at the origin of reduced 5-HT function, high cortisol levels (basal or post-DST) would be associated with low hormonal responses to d-FEN.

Depressed patients had higher post-DST cortisol levels (Table I), but similar responses to d-FEN compared with control subjects. Hormonal responses to d-FEN were not correlated with cortisol levels (basal or post-DST). Among depressed patients, DST suppressors and DST nonsuppressors exhibited no significant difference in endocrine response to d-FEN. Patients were subsequently classified according to their basal cortisol values (ie, >550 nmol/L). When patients with high basal cortisol values (n=10) were compared with patients with normal basal cortisol values (n=61), they showed no significant difference in post-d-FEN values. These results suggest that high cortisol levels (at baseline or post-DST) have no significant effect on PRL or ACTH/cortisol responses to d-FEN.

In our sample, DST nonsuppression was associated with psychotic depression ( $P<0.0008$ ), increased age ( $P<0.004$ ), and global severity of depression ( $P<0.04$ ). Although the exact pathophysiology underlying DST suppression remains unclear, it has been suggested that abnormal cortisol response reflects impaired negative feedback (at the level of the pituitary corticotroph) on endogenous HPA axis hyperactivity (ie, increase in hypothalamic corti-

cotropin-releasing factor and vasopressin drive that overrides the action of dexamethasone).<sup>13</sup>

When patients with a history of suicide attempt were compared with patients without such a history, they showed lower hormonal responses to d-FEN, but comparable basal and post-DST cortisol levels (Table II). Taken together these results suggest that (i) increased HPA axis activity does not impair the ability of the brain's 5-HT system to respond normally; and consequently (ii) increased HPA axis activity is not at the origin of reduced 5-HT activity observed in a subgroup of depressed patients with a history of suicide attempts.

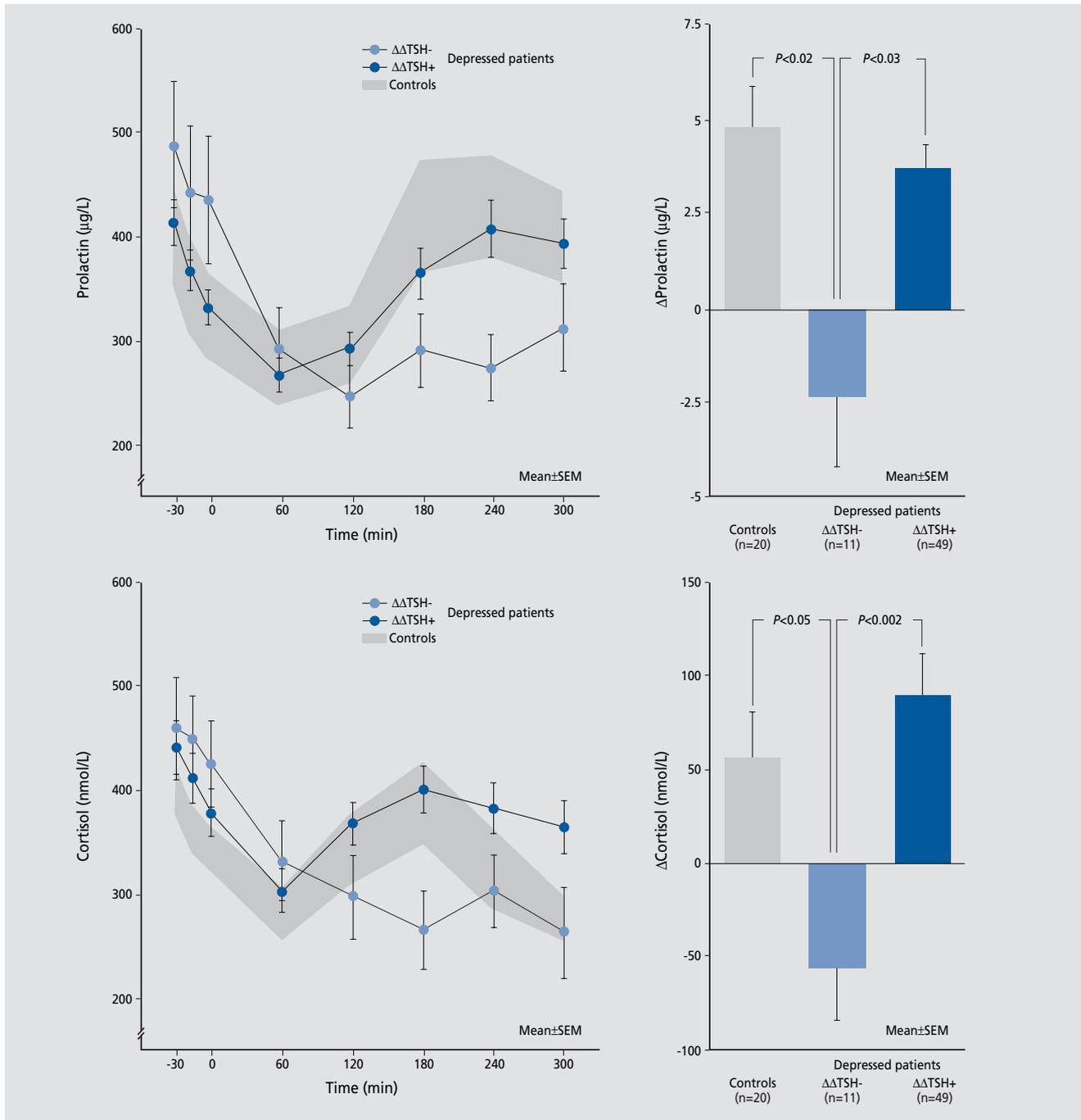
However, given the pharmacological properties of d-FEN, the extent of response to this compound, which is dose-dependent, depends on a combined effect on the synthesis and release of 5-HT and the stimulation of postsynaptic 5-HT receptors (ie, 5-HT<sub>1A</sub> or 5-HT<sub>2A/2C</sub> receptors, or both), without defining which 5-HT receptor subtypes might be dysregulated. In this context, it is conceivable that altered 5-HT<sub>1A</sub> receptor function by glucocorticoids—although not unanimously found in depression<sup>14</sup>—may be compensated by increased 5-HT turnover and 5-HT<sub>2</sub> receptor activity, therefore leading to normal responses to d-FEN test.

In fact, even if the hypothesis of hypercortisolism leading to reduced 5-HT function had been confirmed, this

|                              | History of suicide attempt (n=40) | No history of suicide attempt (n=31) | P      |
|------------------------------|-----------------------------------|--------------------------------------|--------|
|                              | Mean (SEM)                        | Mean (SEM)                           |        |
| Age (years)                  | 40.7 (1.4)                        | 39.5 (1.8)                           | 0.50   |
| Range (years)                | 19-58                             | 19-60                                |        |
| Gender (M/F)                 | 17/23                             | 11/20                                | 0.36   |
| Weight (kg)                  | 66.3 (1.9)                        | 62.8 (1.4)                           | 0.24   |
| Range (kg)                   | 42-93                             | 43-85                                |        |
| HDRS                         | 27.7 (0.8)                        | 26.7 (1.6)                           | 0.17   |
| Range                        | 18-38                             | 18-36                                |        |
| Post-DST cortisol (nmol/L)   | 108 (19)                          | 84 (12)                              | 0.93   |
| No. of abnormal DSTs         | 12                                | 7                                    | 0.33   |
| <i>Fenfluramine test</i>     |                                   |                                      |        |
| • Baseline PRL (µg/L)        | 13.4 (1.4)                        | 16.1 (1.7)                           | 0.30   |
| • ΔPRL (µg/L)                | 0.7 (0.9)                         | 8.9 (2.6)                            | 0.0001 |
| • Baseline ACTH (ng/L)       | 27.9 (3.1)                        | 20.8 (2.3)                           | 0.07   |
| • ΔACTH (ng/L)               | 6.4 (1.7)                         | 10.4 (2.0)                           | 0.05   |
| • Baseline cortisol (nmol/L) | 383 (31)                          | 372 (25)                             | 0.85   |
| • ΔCortisol (nmol/L)         | 48 (21)                           | 128 (28)                             | 0.02   |

**Table II.** Demographic characteristics and biological data for depressed patients according to their history suicide attempt. HDRS, Hamilton Depression Rating Scale score (17-item); DST, dexamethasone suppression test; No. of abnormal DSTs, number of subjects with highest post-DST cortisol level >130 nmol/L; Δ, peak concentration minus baseline value; PRL, prolactin; ACTH, adrenocorticotrophic hormone.

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**Figure 1.** Serum prolactin levels before and after administration of 45 mg *d*-fenfluramine hydrochloride in 20 control subjects and 60 depressed patients classified according to the presence ( $\Delta\Delta$ TSH+,  $n=49$ ) or absence ( $\Delta\Delta$ TSH-,  $n=11$ ) of hyperthalamic-pituitary-thyroid axis dysregulation.<sup>17</sup> The histograms ( $\pm$ SEM) represent the mean maximum increment in serum prolactin level above baseline ( $\Delta$ Prolactin). *P* values are obtained by Mann-Whitney two-tailed *U* test corrected by Bonferroni's method for three pairwise comparisons.  $\Delta\Delta$ TSH, difference in thyroid-stimulating hormone response between 11 PM and 8 AM thyrotropin-releasing hormone tests.

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hypothesis would not have clarified why about two thirds of patients with a history of suicidal behavior had not exhibited hypercortisolism. One may argue that hypercortisolism could be associated with a specific form of suicidal behavior (ie, violent, although studies on this topic are conflicting); but considering hypercortisolism as etiological may be restrictive since HPA axis hyperactivity is not specific to a particular psychiatric diagnosis.

### Increased HPT axis activity as a compensatory mechanism for diminished 5-HT function in depressed patients

Hypothalamic-pituitary-thyroid (HPT) axis activity is altered in a substantial proportion of depressed patients. It is generally accepted that approximately one quarter of euthyroid depressed patients have a blunted thyrotropin (thyroid-stimulating hormone, TSH) response to morning administration of protirelin (thyrotropin-releasing hormone, TRH).<sup>15</sup> We have reported that the 11 PM TRH test (200 µg, intravenous [IV]) is more sensitive than the 8 AM TRH test, and that the difference in TSH response between 11 PM and 8 AM TRH tests ( $\Delta\Delta$ TSH) is an even more sensitive measure: this chronobiological index is reduced in about 70% of inpatients with major depression.<sup>16</sup> It has been suggested that blunted TRH-induced TSH stimulation might reflect a downregulation of the

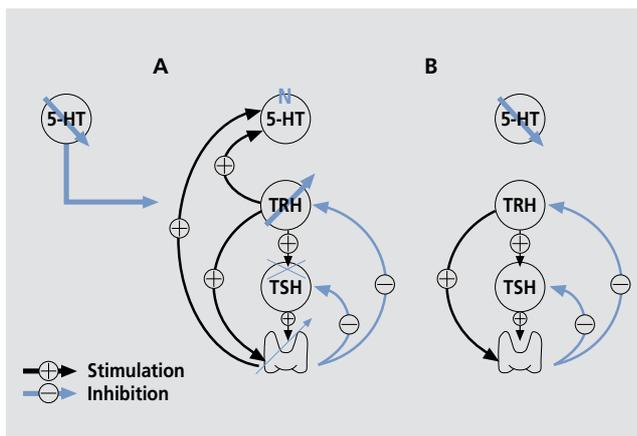
TRH receptors in the pituitary gland secondary to a prolonged increase in hypothalamic TRH stimulation.<sup>15</sup> On the basis of recent animal studies, the effects of 5-HT on the central regulation of TRH secretion are believed to be predominantly inhibitory. According to this assumption, a reduced 5-HT function could lead to hypersecretion of TRH, and therefore to blunted TSH response to TRH in depression.

However, when depressed patients are classified on the basis of their  $\Delta\Delta$ TSH test status, patients with reduced  $\Delta\Delta$ TSH values ( $\leq 2.5$  µU/mL) have hormonal d-FEN responses comparable to those of controls. Conversely, patients with normal  $\Delta\Delta$ TSH values (ie, without HPT axis abnormality) show lower PRL and cortisol responses to d-FEN than controls and patients with abnormal  $\Delta\Delta$ TSH values (*Figure 1*).<sup>17</sup> ACTH response to d-FEN—which correlated with cortisol ( $r=0.66$ ;  $n=80$ ;  $P<0.00001$ ) and PRL ( $r=0.41$ ;  $n=80$ ;  $P<0.0003$ ) response—is also lower in patients without HPT axis abnormality when compared with controls ( $P<0.009$ ) and patients with HPT dysfunction (ie, reduced  $\Delta\Delta$ TSH values;  $P<0.0002$ ).

Thus, patients with normal HPT axis activity exhibit reduced PRL and ACTH/cortisol responses compatible with a 5-HT deficit. On the other hand, patients with abnormal HPT axis activity show a level of 5-HT function comparable to that found in healthy subjects. Therefore, according to the TRH hypothesis,<sup>15</sup> one may hypothesize that TRH overactivity, which produces both pituitary TRH receptor downregulation and direct activation of the thyroid gland,<sup>18,19</sup> could also stimulate 5-HT activity. Indeed, it has been found in animal studies that (i) TRH stimulates 5-HT neurotransmission via 5-HT<sub>1</sub> receptors; and (ii) thyroid hormones enhance 5-HT activity in certain brain areas (such as the cerebral cortex). Furthermore, the reduced central 5-HT activity found in patients with hypothyroidism is reversed by thyroxine replacement therapy.<sup>20</sup> In the context of major depression, the effects of increased HPT axis hormones (ie, increased secretion of TRH and elevated circulating concentrations of thyroid hormones well within the physiological range<sup>19</sup>) may be regarded as a compensatory mechanism in order to correct reduced central 5-HT activity.

Schematically, one may define two situations (*Figure 2*):

- The compensatory mechanisms are effective; in this case a signal (such as a decrease in 5-HT function) leads to a series of biological modifications (such as an increase in thyroid axis activity). These modifications may be



**Figure 2.** A. When the compensatory mechanisms are effective, a decrease in the serotonin (5-hydroxytryptamine, 5-HT) function leads to an increase in thyroid axis activity. B. When the compensatory mechanisms are not effective, the 5-HT dysfunction remains. In depressed patients with a history of suicidal behavior, 5-HT alteration may be understood as a failure of the compensatory mechanism. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; N, normal.

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understood as a repairing process aiming to restore an efficient 5-HT functioning.

- The compensatory mechanisms are not effective; in this case the 5-HT dysfunction remains. In depressed patients with a history of suicidal behavior, 5-HT alteration may be understood as a failure of the compensatory mechanisms.

## Interactions between the dopaminergic system and the HTP axis in depression

Given the interactions between dopamine (DA) and HPT and 5-HT, one may hypothesize that DA may also be involved in the compensatory mechanisms. It is known that the mesolimbic DA system plays a key role in goal-directed and motivational behavior. In depression, it has been suggested that hypofunction in mesolimbic DA system may be involved in anhedonia and amotivational apathy.<sup>21</sup> DA agonists can facilitate the action of antidepressant drugs in certain animal models of depression and in some depressed patients.

While at the hypothalamic level the interregulations of DA and 5-HT systems are complex and not fully understood, preclinical studies have shown that dopamine D<sub>2</sub> receptors stimulate the release of hypothalamic TRH

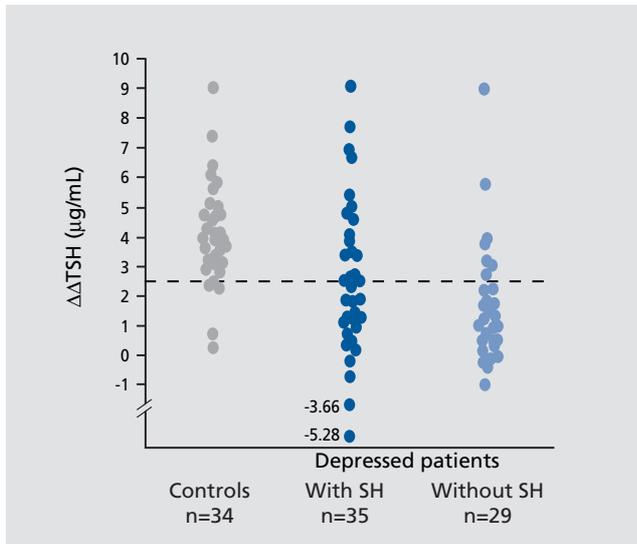
and inhibit TSH production at the pituitary level. In turn, TRH and thyroid hormones stimulate the DA system, and induce a downregulation of D<sub>2</sub> receptors.

To examine the functional relationships between HPT axis activity and DA function in depressed patients, especially in those with a history of suicidal behavior, we measured hormonal responses to 8 AM and 11 PM TRH tests and to apomorphine (APO) test in 64 drug-free inpatients with *DSM-IV*<sup>12</sup> major depression (35 with a history of suicide attempt, 29 without) and 34 hospitalized healthy controls. APO, a direct-acting DA agonist with high affinities for D<sub>2</sub> and D<sub>3</sub> receptors and a partial agonist at the D<sub>1</sub> receptor, decreases PRL and stimulates growth hormone (GH), ACTH, and cortisol secretion.<sup>22</sup>

Compared with controls, patients demonstrate lower TRH and TSH responses and lower APO-induced PRL suppression (*Table III*). PRL response to APO provides an indirect index of central neurotransmission by assessing postsynaptic D<sub>2</sub> receptor sensitivity at the pituitary level. A lower PRL response to APO may reflect a decreased D<sub>2</sub> receptor function. This abnormality may represent (i) a primary deficit in D<sub>2</sub> receptor sensitivity in the pituitary in depressed patients; or (ii) a downregulation of D<sub>2</sub> receptors secondary to increased presynaptic DA activity. Cooccurrence of HPT axis and tuberoinfundibular DA

|                              | Control (n=34)<br>Mean (SEM) | Depressed patients (n=64)<br>Mean (SEM) | P                    |
|------------------------------|------------------------------|---|----------------------|
| Age (years)                  | 37.7 (1.6)                   | 40.4 (1.4)                              | 0.24                 |
| Gender (M/F)                 | 14/20                        | 32/32                                   | 0.52                 |
| <i>TRH tests</i>             |                              |   |                      |
| • 8 AM baseline TSH (μU/mL)  | 1.20 (0.09)                  | 0.94 (0.06)                             | 0.007                |
| • 8 AM ΔTSH (μU/mL)          | 8.43 (0.57)                  | 6.21 (0.41)                             | 2.3 10 <sup>-4</sup> |
| • 11 PM baseline TSH (μU/mL) | 1.19 (0.11)                  | 0.80 (0.05)                             | 0.002                |
| • 11 PM ΔTSH (μU/mL)         | 12.34 (0.65)                 | 8.06 (0.50)                             | 4.7 10 <sup>-7</sup> |
| • ΔΔTSH (μU/mL)              | 3.9 (0.25)                   | 1.83 (0.27)                             | 1.1 10 <sup>-7</sup> |
| <i>Apomorphine test</i>      |                              |   |                      |
| • Baseline PRL (μg/L)        | 10.6 (0.9)                   | 13.3 (1.0)                              | 0.18                 |
| • PRL suppression (%)        | 39.5 (1.5)                   | 28.5 (2.0)                              | 1.2 10 <sup>-4</sup> |
| • Baseline GH (ng/mL)        | 0.4 (0.3)                    | 0.3 (0.2)                               | 0.88                 |
| • ΔGH (ng/mL)                | 12.3 (1.6)                   | 12.5 (1.2)                              | 0.89                 |
| • Baseline ACTH (ng/L)       | 26.5 (3.1)                   | 28.1 (2.3)                              | 0.55                 |
| • ΔACTH (ng/L)               | 61.5 (19.0)                  | 50.1 (11.6)                             | 0.94                 |
| • Baseline cortisol (nmol/L) | 305 (17)                     | 283 (15)                                | 0.33                 |
| • ΔCortisol (nmol/L)         | 175 (31)                     | 117 (17)                                | 0.15                 |

**Table III.** Demographic characteristics and biological data for depressed patients and normal control subjects. Δ, peak concentration minus baseline value; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; PRL, prolactin; PRL suppression = (PRL<sub>AUC</sub>/baseline PRL<sub>AUC</sub>)×100; GH, growth hormone; ACTH, adrenocorticotrophic hormone.

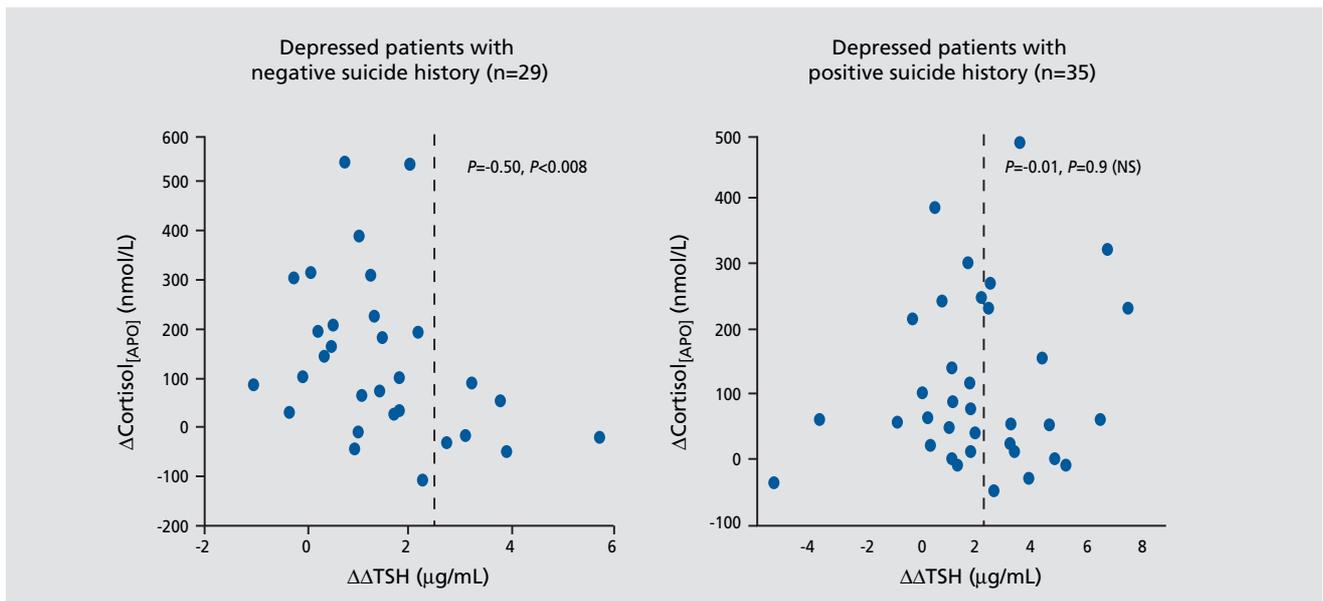


**Figure 3.** Differences between 11 PM and 8 AM maximum increments in thyroid-stimulating hormone ( $\Delta\Delta\text{TSH}$ ) in controls and in depressed patients with a suicidal history (SH) and without an SH. Blunted  $\Delta\Delta\text{TSH}$ , defined as a response below 2.5  $\mu\text{U}/\text{mL}$ , is more frequent in patients without SH ( $n=23$  [80%]) than in patients with ( $n=19$  [54%]) ( $P=0.03$  by Fisher's exact test).

dysregulation is compatible with a decreased TRH and  $\text{D}_2$  receptor function, possibly secondary to increased TRH tone, since TRH stimulates the DA system and induces a downregulation of  $\text{D}_2$  receptors.

When classifying patients according to their history of suicidal behavior, those with a negative history more frequently have reduced  $\Delta\Delta\text{TSH}$  values (Figure 3), but comparable hormonal APO responses (ie, PRL, ACTH, and cortisol), than those with a positive history. In patients without a history of suicide attempt, a negative correlation is found between  $\Delta\Delta\text{TSH}$  values and post-APO ACTH ( $\rho=-0.44$ ,  $P=0.02$ ) and cortisol ( $\rho=-0.50$ ,  $P<0.008$ ) levels. This correlation is found neither in patients with a history of suicide attempt (Figure 4) nor in control subjects.

The finding of a negative correlation between  $\Delta\Delta\text{TSH}$  and post-APO ACTH and cortisol values in patients without a history of suicidal behavior is rather paradoxical. Owing to the regulations between HPT and DA systems, one could have expected a positive correlation and not a negative one (ie, an increase in TRH secretion should have led to a decrease in  $\text{D}_2$  function). Whether hypofunctionality of  $\text{D}_2$  receptors exists on both hypothalamic and pituitary levels, the absence of GH, ACTH, and cortisol response to APO in depression would suggest an upregulation of other DA receptor subtypes



**Figure 4.** Scatterplots of  $\Delta\Delta\text{TSH}$  (difference in thyroid-stimulating hormone response between 11 PM and 8 AM thyrotropin-releasing hormone tests) and cortisol response to apomorphine ( $\Delta\text{Cortisol}_{[\text{APO}]}$ ) in depressed patients. Depressed patients with a history of suicidal behavior show a negative correlation between these parameters, while these parameters are not correlated in patients without such a history.

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(such as D<sub>1</sub>) in the hypothalamus. Indeed, GH, ACTH, and cortisol response to APO reflects primarily stimulation of the hypothalamic releasing hormones (GH-releasing hormone and CRH, respectively) rather than a direct effect on the pituitary. Moreover, cortisol response to APO, which is correlated to ACTH ( $\rho=0.74$ ;  $n=98$ ;  $P<0.00001$ ), can be considered as an index of central DA function connected with the regulation of the HPA axis. Thus, the negative correlation between  $\Delta\Delta\text{TSH}$  and post-APO ACTH and cortisol values in patients without a history of suicidal behavior suggests that the efficacy of compensatory mechanisms requires a new functional balance between HPT and DA systems.

In the depressed group with a history of suicidal behavior, the absence of a functional link between HPT and DA activity in the hypothalamus may play a role in the pathophysiology of suicidal behavior. However, one may note that half of the patients of this group showed HPT and DA functional adjustment (Figure 4; ie, those exhibiting blunted  $\Delta\Delta\text{TSH}$  values), suggesting that this requirement is not sufficient in the efficacy of compensatory mechanisms. In other words, other processes—so far unknown—are also involved in the efficacy of compensatory mechanisms.

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## Conclusions

Taken together our findings in depressed inpatients suggest that:

- HPA axis hyperactivity is not responsible for the reduced 5-HT activity found in patients with a history of suicidal behavior.
- HPT dysregulation may be regarded as a compensatory mechanism for diminished central 5-HT activity.
- Cooccurrence of HPT axis and tuberoinfundibular DA dysregulation is compatible with a decreased TRH and D<sub>2</sub> receptor function (possibly secondary to increased TRH tone).
- The absence of a functional link between HPT and DA activity in the hypothalamus may be implicated in the pathogenesis of suicidal behavior.

A better knowledge of processes involved in the efficacy of compensatory mechanisms could lead to new therapeutic strategies in patients with recurrent major depressive disorder, especially those with a history of suicidal behavior. □

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**La interacción entre el sistema serotoninérgico y los ejes HHA e HHT en pacientes con depresión mayor: importancia para la patogénesis de la conducta suicida**

Las alteraciones en el sistema serotoninérgico (5-hidroxitriptamina, 5-HT) constituyen la anomalía neurobiológica más consistentemente asociada con el suicidio. Esta anomalía podría constituir un marcador de vulnerabilidad que predispusiera a los sujetos a conductas autoagresivas e impulsivas. Sin embargo, también han sido descritas otras anomalías en víctimas de suicidio como la hiperactividad del eje hipotálamo-hipófisis-adrenal (HHA). Mientras que en animales se han observado los efectos inhibitorios de los adrenocorticosteroides en la función del receptor 5-HT<sub>1A</sub>, en pacientes depresivos con una historia de conductas suicidas la hiperactividad del eje HHA no parece ser responsable de la reducción de la actividad serotoninérgica. Por otra parte, la disfunción del eje hipotálamo-hipófisis-tiroideos (HHT), que se observa con frecuencia en la depresión, puede representar una respuesta compensatoria a la reducción de la neurotransmisión central de serotonina. Sin embargo, en pacientes depresivos con una historia de conductas suicidas, la ausencia de una relación funcional entre la actividad HHT y la dopamina a nivel del hipotálamo puede estar involucrada en la fisiopatología de la conducta suicida. Se requiere de futuras investigaciones para determinar por qué los mecanismos compensatorios no son eficientes en pacientes con conductas suicidas.

**Interactions entre le système sérotoninergique et les axes HHS et HHT chez des patients atteints de dépression majeure : implications pour la pathogénèse du comportement suicidaire**

Les perturbations du système sérotoninergique (5-hydroxytryptamine, 5-HT) constituent l'anomalie neurobiologique la plus régulièrement associée au suicide. Cette anomalie pourrait être un marqueur de vulnérabilité prédisposant des individus à développer un comportement autoagressif et impulsif. Cependant, d'autres anomalies, comme l'hyperactivité de l'axe hypothalamo-hypophyso-surrénalien (HHS), ont aussi été décrites chez des victimes de suicide. Alors que les effets inhibiteurs des hormones corticosurrénales sur la fonction du récepteur 5-HT<sub>1A</sub> ont été montrés chez l'animal, l'hyperactivité de l'axe HHS ne semble pas responsable de l'activité 5-HT réduite retrouvée chez les patients déprimés et ayant des antécédents de comportement suicidaire. Par ailleurs, le dysfonctionnement de l'axe hypothalamo-hypophyso-thyroïdien (HHT), fréquemment observé dans la dépression, pourrait représenter une réponse compensatrice pour restaurer la neurotransmission centrale 5-HT. De plus, chez les patients déprimés ayant des antécédents de comportement suicidaire, l'absence de lien fonctionnel entre l'HHT et l'activité dopaminergique au niveau hypothalamique pourrait être impliquée dans la physiopathologie du comportement suicidaire. Des recherches sont nécessaires à l'avenir pour déterminer la raison pour laquelle les mécanismes compensateurs ne sont pas efficaces chez les patients suicidaires.