Decreased thyrotropin-releasing hormone gene expression in the hypothalamic paraventricular nucleus of patients with major depression

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SIR—Several studies have suggested that thyroid hormone comedication may increase response rates in subjects with major depression refractory to tricyclic antidepressants (TCA).[1] In addition, intrathecal administration of thyrotropin-releasing hormone (TRH) has shown beneficial effects in one study involving patients with treatment-resistant depression.[2] Furthermore, a number of subtle abnormalities in the hypothalamus–pituitary–thyroid (HPT)-axis occur in a large proportion of subjects with major depression. The thyroid-stimulating hormone (TSH) response to TRH is often blunted and the nocturnal TSH surge may be absent.[3] We hypothesized that alterations in hypothalamic TRH may be involved in the pathogenesis of these endocrine changes, and studied TRH gene expression in the hypothalamic paraventricular nucleus (PVN) of seven subjects with unipolar depression ($n=5$ major depression, $n=2$ depressive syndrome not otherwise specified) and seven control subjects matched for age, sex and for nonthyroidal illness.[4] In addition, we studied one subject with biochemically documented thyrotoxicosis 3 weeks before death (serum fT4 44.2 pmol/l (*n*: 10–23 pmol/l) and TSH <0.01 mU/l (*n*: 0.4–4.0 mU/l) as a reference point for possible changes in depression. Brain material was obtained from the Netherlands Brain Bank. The DSM-IV criteria were used for the psychiatric diagnosis. Both subjects with depressive syndrome not otherwise specified had suffered from severe chronic depression involving a long and consistent death-wish. Exclusion criteria were: drugs known to influence the HPT-axis and thyroidal or neurodegenerative disease. Methods for in situ *hybridization* and TRH mRNA quantification have been described previously.[4,5]

We used either the left ($n=13$) or right ($n=2$) hemihypothalamus dependent on availability. In three subjects, the posterior part of the PVN was incomplete, therefore complete TRH mRNA hybridization profiles over the entire PVN were obtained in only five of the seven matched couples. Total TRH mRNA hybridization signal was much lower in depressed subjects than in control subjects (median 24.5 and 56.8 arbitrary units (au), respectively, $P=0.047$, Mann–Whitney U-test (MW-U)) (Figure 1a–e). TRH mRNA hybridization density was calculated as mean value of the density of three sections within the PVN that showed highest density and showed a significant correlation with total TRH mRNA hybridization signal ($r=0.67$, $P=0.024$, Pearson's correlation analysis). Analysis of all seven couples showed that TRH hybridization density was lower in depressed sub-

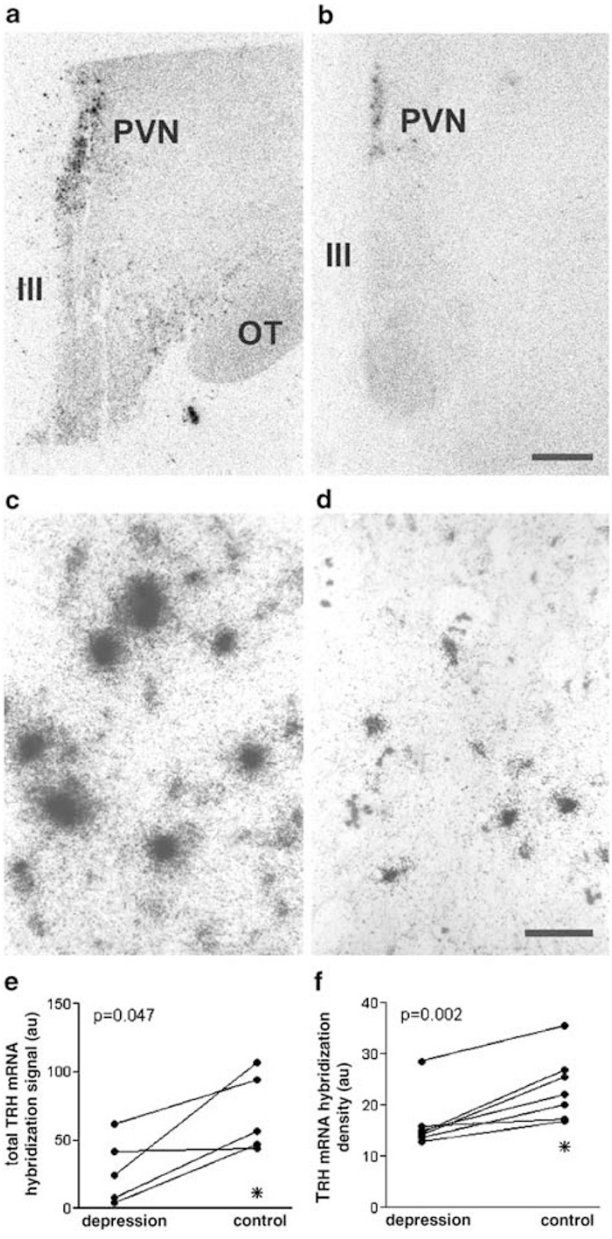

Figure 1 (a,b) Macroscopic photographs of film autoradiograms of representative sections of a control subject and weaker hybridization signal in a subject with major depression, respectively. (c,d) TRH mRNA containing cells in the PVN of the same subjects. Bars represent 2 mm (a,b) and 50 μm (c,d). OT = optic tract. (e,f) TRH mRNA hybridization signals in depressed subjects and controls. Matched pairs are interconnected with lines. Each dot represents one subject. Note strongly decreased TRH hybridization signal in subjects with depression. Asterisk represents the subject with primary hyperthyroidism.

jects than in control subjects as well (median 16.9 and 28.0 au, respectively, $P = 0.002$, (MW-U) (Figure 1f)). The hyperthyroid subject had a very low total TRH mRNA hybridization signal and hybridization density (11.5 and 12.9 au, respectively, Figure 1e–f). A multivariate regression analysis of the factors post-mortem delay, fixation duration and age did not yield significant differences.

An important issue is whether the decrease in TRH mRNA can be attributed to a pharmacological effect of antidepressants, that is, TCA, selective serotonin reuptake inhibitors (SSRI), non-selective MAO inhibitors and lithium. Studies in rat have shown that repeated treatment with TCA and SSRIs does not alter TRH content in the hypothalamus,[6] while in humans changes in serum TSH seem to result from the underlying psychiatric disease rather than from a direct effect of these antidepressants.[7] One depressed subject in our study used lithium, which is known to induce a rise in basal TSH reflecting primary hypothyroidism in susceptible patients.[7] Thus, the decrease in TRH mRNA that we found in this subject may even be underestimated. In sum, it is unlikely that the decreased TRH expression in our study results from pharmacological treatment.

Low TRH mRNA suggests that low TSH serum concentrations in unipolar depression result, at least in part, from a decreased hypothalamic TRH drive. The mild hypercortisolism, which is common in major depression[8] may contribute to this phenomenon. Rat studies have shown that glucocorticoids may induce a down-regulation of TRH mRNA in the PVN.[9] The association between TSH and ACTH responses in subjects with depression[10] also supports a role for hypercortisolism in the resetting of thyroid hormone regulation. Our future studies will aim at the relationship between TRH and CRH mRNA expression to further explore this.

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