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ORIGINAL PAPER

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The influence of 4-week treatment with sertraline on the combined T3/TRH test in depressed patients

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Abstract In the present study, the influence of a 4-week treatment with sertraline on the regulation of hypothalamic-pituitary-thyroid (HPT) axis activity in depression was investigated, in particular the impact of sertraline on the thyroid receptor (TR)-mediated negative feedback control as measured by the combined T3/TRH test. In 20 drug-free patients (8 men, 12 women) suffering from a major depressive episode according to DSM-IV criteria the single TRH-stimulation test (administration of 200 µg TRH at 09:00h) was carried out followed by a combined T3/TRH test (pre-treatment with 40 µg 3,5,3'-triiodothyronine [T3] the night before; administration of 200 µg TRH at 09:00h the next day). After 4 weeks of treatment with sertraline at a standard dosage of 50 mg/day, both the single TRH test and the combined T3/TRH test were repeated in the depressed patients. Using repeated-measures ANOVA for statistical analysis, antidepressant therapy with sertraline did not have any significant impact on the TRH-induced TSH and prolactin stimulation (ΔTSH, ΔPRL) during the single TRH test nor during the combined T3/TRH test, neither in responders (n = 10) nor in non-responders (n = 10). Moreover, the percentage suppression of TRH-induced TSH stimulation (ΔTSH) after pre-treatment with 40 µg T3 was comparable before (–61.07 %) and after the 4-week treatment with sertraline (–58.92 %). Apparently, the therapeutic efficacy of antidepressants such as sertraline is not related to the regulation of HPT axis activity in depressed patients.

Key words depressive disorder · sertraline · TRH test · T3/TRH test · triiodothyronine

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Introduction

Preclinical and clinical studies suggest that hypothalamic-pituitary-adrenal (HPA) system dysregulation is related to the occurrence of depression and that normalization of HPA axis hyperactivity precedes successful treatment with antidepressants (for review see Holsboer 2001). Using the combined dexamethasone/CRH test (DEX/CRH test) for measuring HPA axis activity, tricyclic antidepressants such as amitriptyline (Heuser et al. 1996) or selective serotonin reuptake inhibitors such as paroxetine (Nickel et al. 2003) have been demonstrated to gradually reduce HPA axis hyperactivity in depression within several weeks suggesting that the restoration of the disturbed HPA system feedback control is related to antidepressant efficacy.

Besides HPA axis hyperactivity, a reduced ("blunted") thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH) in about 30 % of depressed patients is one of the best documented endocrinological findings in depression which was first reported by Prange et al. (1972) and Kastin et al. (1972) and has been extensively replicated (e. g. Loosen 1985). In addition, some investigators have reported an increase in TRH-induced TSH response during antidepressant treatment in some but not all depressed patients irrespective of the kind of antidepressant drug used in the studies (e. g. Kirkegaard 1981; Linkowski et al. 1981; Extein et al. 1982; Langer et al. 1984; Targum 1983; Krog-Meyer et al. 1985). Whereas earlier studies surmised that a blunted TSH response to TRH in depressive patients before treatment might predict a good response to antidepressant therapy (e. g. Langer et al. 1986; Itoh et al. 1987; Joyce and Paykel 1989), a more recent study could not confirm this as-

sumption suggesting a limited prognostic utility for the TRH test in depression (Amsterdam et al. 1996).

In addition to the single TRH test, the combined T3/TRH test (pre-treatment with triiodothyronine [T3], followed by a TRH test) which has been introduced in a recent investigation of our research group (Schüle et al. in press) may be a useful tool to assess the regulation and the feedback control of the hypothalamic-pituitary-thyroid (HPT) system in depression. In this recent study, both the single TRH test and the combined T3/TRH test were significantly blunted in depressed patients as compared to age- and sex-matched healthy controls; however the percentage suppression of TRH-induced TSH stimulation after pre-treatment with T3 was comparable in the depressive patients (61.07 %) and the healthy volunteers (64.20 %) (Schüle et al. in press). However, no data are available so far whether treatment with antidepressants may have an impact on the blunted TSH response both in the single TRH test and the combined T3/TRH test and may influence in particular the thyroid receptor (TR)-mediated negative feedback regulation of the HPT system in depressed patients, as measured by the T3/TRH test. Moreover, it is not known whether putative changes in the results of the TRH test and the combined T3/TRH test during antidepressant therapy may differ between responders and non-responders and may be related to antidepressant efficacy.

The efficacy and safety of sertraline in the treatment of depression has been established in large placebo-controlled and active comparator trials using tricyclic antidepressants or other SSRI (Anderson 2000). In several fixed-dose studies in depressed patients, 50 mg/day sertraline has been demonstrated to be an effective dose relative to placebo, and higher doses (up to 200 mg/day) have been found not to result in increased antidepressant efficacy (Schatzberg 1991; Preskorn and Lane 1995; Fabre et al. 1995; Möller et al. 2000; Schweizer et al. 2001). N-demethylation of sertraline to desmethyl-sertraline (DM-sertraline) yields a compound with 10- to 20-fold less potency blocking serotonin reuptake as measured in vitro (Bolden-Watson and Richelson 1993) and in vivo (Sprouse et al. 1996) suggesting that DM-sertraline does not contribute significantly to the antidepressant efficacy of sertraline.

To answer the question whether antidepressant therapy may have an impact on a possibly disturbed feedback control mechanism of the HPT system in depression, we performed the combined T3/TRH test before and after 4 weeks of sertraline treatment (50 mg/day). In order to assess to which extent the TRH-induced TSH stimulation is suppressed by pre-treatment with triiodothyronine (T3) before and after 4-week antidepressant therapy with sertraline, a single TRH test preceded the combined T3/TRH test the previous day, respectively.

Methods

Study population and study design

A total of 20 drug-free depressed inpatients (8 men, 12 women) aged between 28 and 74 years (mean age 46.30 ± 11.61 years) entered the study after the procedures had been fully explained and written informed consent had been obtained before study participation. Inclusion criteria for the depressed patients were a) a major depressive episode according to DSM-IV criteria (bipolar disorder not included), b) a sum score of at least 18 on the 21-item version of the Hamilton Depression Rating Scale (21-HAMD) (Hamilton 1960), c) exclusion of major medical disorders, in particular any disease of the thyroid gland; availability of normal laboratory parameters including normal values of TSH, free triiodothyronine (FT3), and thyroxine (FT4); exclusion of thyroid autoimmunity by measurement of anti-thyroid peroxidase (anti-TPO), anti-thyrotropin receptor (anti-TSHR), and anti-thyroglobulin (anti-Tg) auto-antibodies; normal palpation finding of the thyroid gland; normal thyroid echography; normal blood pressure; normal electrocardiogram; and normal encephalogram, d) exclusion of addiction or other comorbid psychiatric diagnoses, e) no psychotropic drugs for at least 5 days before and throughout the study with the exception of chloralhydrate in case of sleep difficulties, f) exclusion of pregnancy or use of oral contraceptives. None of the patients had been pre-treated with fluoxetine. Out of the 20 patients included in the study, 10 patients did not receive any pre-treatment (being drug-free for at least 35 days) when entering the study. None of the patients had been pre-treated with fluoxetine, mood stabilizers or neuroleptics. Two patients had been pre-treated with tricyclic antidepressants, 2 patients with selective serotonin reuptake inhibitors, 2 patients with venlafaxine, 2 patients with mirtazapine, 1 patient with the MAO-inhibitor tranylcypromine (wash-out period 14 days), 1 patient with St. John's wort. The patients investigated in the present study were the same as in a recent study of our research group comparing HPT regulation in depressed patients and healthy subjects (Schüle et al. in press). Clinical characteristics are given in Table 1.

Before treatment with sertraline, in each patient a single TRH test (TRH $test_{week0}$) was performed followed by a combined T3/TRH test (T3/TRH $test_{week0}$) the next day. On day –1 (TRH $test_{week0}$) the patients had to rest supine on a bed at 08:00h. An intravenous catheter was inserted into the antecubital vein before 08:15h and kept open with physiological saline solution. Blood samples were collected at 08:00h (t = –60 min), 09:00h (t = 0 min), 09:30h (t = 30 min), 10:00h (t = 60 min), 10:30h (t = 90 min), and 11:00h (t = 120 min). Each sample was immediately centrifuged and stored at –80 °C for hormone measurement (thyrotropin [TSH], free triiodothyronine [FT3], free thyroxine [FT4], prolactin [PRL], cortisol [COR], corticotropin [ACTH], growth hormone [GH]). At 09:02h, 1 ml Relefact® (corresponding to 200 µg TRH) was injected within 30 s. To prepare for day 0 (T3/TRH $test_{week0}$), the patients received an oral dose of 40 µg 3,5,3'-triidothyronine (T3; German commercial drug name: Thybon®) at 23:00h on day –1. After sleeping for one night, the participants had to rest supine again on the following day (day 0) on a bed at 08:00h. Thereafter, the TRH test was repeated in the same manner as described above with the only exception of having taken pre-treatment with 40 µg T3 the night before. On day –1 and day 0, the participants fasted from completion of the evening meal the day before until 11:00h the following day (end of drawing blood).

After baseline endocrinological testing (day –1, 0) all patients were treated with sertraline at a standard dosage of 50 mg per day for 4 weeks (day 1 up to day 29) given as a single morning dose. In case of sleep difficulties, chloralhydrate (up to 1000 mg per day) was allowed as concomitant medication. Severity of depression was estimated weekly (days 0, 7, 14, 21, 28) using the 21-HAMD (Hamilton 1960). All raters were experienced psychiatrists and blind to hormonal measurements. Clinical response was defined by a reduction of at least 50 % in the 21-HAMD sum score after four weeks of treatment with sertraline. On day 28 and day 29, the single TRH test (TRH $test_{week4}$) and the combined T3/TRH test (T3/TRH $test_{week4}$) were carried out again according to the same protocol used before sertraline treatment (week 0).

Table 1 Clinical and demographic data in responders and non-responders to 4-week antidepressant treatment with sertraline (50 mg per day). Data represent mean ± SD. $C_{(sertraline)}$, $C_{(DM\text{-}sertraline)}$, $C_{(sertraline + DM\text{-}sertraline)}$ serum concentrations of sertraline, desmethyl-sertraline (DM-sertraline) and the sum of both at week 4

	All patients (n = 20)	Non-responders (n = 10)	Responders (n = 10)
Age (years)	46.30 ± 11.61	48.50 ± 11.78	44.10 ± 11.63
Height (cm)	170.00 ± 6.14	170.50 ± 5.38	169.50 ± 7.08
Weight (kg)	74.20 ± 21.80	73.00 ± 21.75	75.40 ± 22.96
Duration of illness (years)	7.73 ± 8.31	8.15 ± 10.69	7.32 ± 5.57
Age of onset (years)	39.25 ± 10.78	42.50 ± 6.85	36.00 ± 13.22
Number of episodes	3.35 ± 4.89	3.70 ± 6.48	3.00 ± 2.87
$C_{(sertraline)}$ (ng/ml)	20.88 ± 10.29	22.16 ± 11.04	19.61 ± 9.91
$C_{(DM\text{-}sertraline)}$ (ng/ml)	36.39 ± 20.94	39.05 ± 24.21	33.74 ± 18.01
$C_{(sertraline + DM\text{-}sertraline)}$ (ng/ml)	57.28 ± 30.81	61.21 ± 35.03	53.35 ± 27.26
21-HAMD sum score week 0	27.00 ± 4.98	28.20 ± 5.31	25.80 ± 4.59
21-HAMD sum score week 1	21.70 ± 6.40	23.50 ± 6.74	19.90 ± 5.82
21-HAMD sum score week 2	19.95 ± 7.82	23.60 ± 6.96	16.30 ± 7.13
21-HAMD sum score week 3	18.10 ± 7.25	22.30 ± 5.40	13.90 ± 6.54
21-HAMD sum score week 4	15.10 ± 7.50	20.90 ± 5.13	9.30 ± 4.22

The study was carried out according to the fifth revision of the Declaration of Helsinki (World Medical Association 2000) and had been approved by a local ethics committee.

Measurements of hormones and sertraline serum concentrations

Serum and plasma samples were separated by centrifugation as soon as possible, frozen at – 80 °C, and stored for the assay of hormone concentrations. Serum concentrations of TSH, FT3, FT4, PRL, COR, and GH, and plasma concentrations of ACTH were determined in each blood sample. TSH, FT3, and FT4 concentrations were measured using an electro-chemiluminescent immunoassay (ECLIA). Normal ranges were 0.230–3.800 mU/l for TSH, 2.92–7.53 pmol/l for FT3, and 11.58–24.45 pmol/l for FT4. The minimum detectable concentrations of ECLIA were 0.005 mU/l for TSH, 0.40 pmol/l for FT3, and 0.30 pmol/l for FT4. Functional sensitivity for TSH was 0.014 mU/l. Within-assay imprecision (intraassay CVs) was below 3.3 % for TSH, 2.7 % for FT3, and 3.3 % for FT4. Interassay CVs were below 3.2 % for TSH, 2.5 % for FT3, and 2.6 % for FT4. COR, GH, and PRL levels were determined by double-antibody radioimmunoassay (RIA) and fluoroimmunoassay methods. The sensitivity ("minimal detectable dose") of the commercially available immunoassay kits was approximately 6.1 nmol/l for the COR RIA (Diagnostic Products Corporation®); 4.5 pmol/l for the GH fluoroimmunoassay (DELFIA® hGH); and 1.74 pmol/l for the PRL fluoroimmunoassay (DELFIA® Prolactin). The specificity (percental crossreactivity) was up to 6.8 % for the COR RIA (although some steroids exhibit slight crossreactivity, their normal physiological concentrations are low compared to COR so as not to significantly cause interference in the Double Antibody Cortisol procedure); 0.1 % for the GH fluoroimmunoassay; and < 0.01 % for the PRL fluoroimmunoassay. The total variation (% CV) was 6.6 % for the COR RIA; 3.9 % for the GH fluoroimmunoassay; and 2.7 % for the PRL fluoroimmunoassay. ACTH was measured using a chemiluminescence immunometric assay (Nichols, San Juan Capistrano, California, USA); the lower detection limit of this assay is 0.11 pmol/l, intra- and inter-assay CVs are below 4 % and 7 %, respectively.

The detection of sertraline and desmethyl-sertraline (DM-sertraline) in the serum after 4 weeks of treatment was accomplished via an isocratic reversed-phase high-performance liquid chromatography (HPLC) separation and ultraviolet detection at 214 nm. The HPLC system was composed of Waters 515 pump, Waters 717 auto sampler and Waters 2487 dual wavelength UV detector (Waters, Milford, MA). The chromatographic separation was achieved by using an end-capped C18 reversed-phase HPLC column (Merck, Germany) connected with a guard column (Merck, Germany). Stock solutions of the analytes (1 mg/ml) were prepared in methanol and added to human drug-free serum obtained from healthy donors to establish five different calibration concentrations. The standard curves for sertraline and its metabolite DM-sertraline ranged from 20 to 150 ng/ml. The five-point calibration curves were plotted by the peak-high (peak area for sertraline and DM-sertraline) ratios of each analyte/internal standard versus concentrations of the respective analyte in serum. The mean inter-day precision of 5.2 % was determined by analyzing 10 control samples at a concentration of 50 ng/ml. The limit of detection was defined as the lowest concentration of the drug resulting in a signal-to-noise ratio of 3:1. It was 2.5 ng/ml for sertraline and 1.25 ng/ml for DM-sertraline.

Data analysis

Homogeneity between sertraline responders and non-responders in some clinical and demographic variables at baseline was analyzed by Fisher's exact test with respect to qualitative variables (gender distribution) or by two-tailed t-tests for independent samples with regard to quantitative variables (21-HAMD sum score, age of onset and duration of depressive illness, number of depressive episodes, age, height, and weight).

Analyzing the effects of TRH on hormone concentrations, the areas under the curve (AUCs, 0–120 minutes) were calculated according to the trapezoid rule (Simpson 1956), representing the total FT3, FT4, COR, ACTH, and GH secretions during the single TRH test and the combined T3/TRH test. With respect to TSH and PRL secretion, the Δvalues were preferred ($\Delta TSH = TSH_{t=30min} - TSH_{t=0min}$; $\Delta PRL = PRL_{t=30min} - PRL_{t=0min}$) for the following reasons: The peak TSH response occurs about 30–35 minutes after TRH injection and ΔTSH yields as much information as TSH AUC up to 3 hours after the challenge (Wilkin et al. 1979; Loosen et al. 1982) or, as kinetic modeling indicated, ΔTSH may even be the most consistent reflection of TSH elevation rather than TSH AUC (Swartz et al. 1986). Similarly, the TRH-induced PRL peak usually occurs after about 10 minutes declining thereafter (L'Hermite et al. 1972; Jacobs et al. 1973). Therefore, most studies use ΔPRL instead of PRL AUC since ΔPRL may be more sensitive in indicating stimulatory effects of TRH on PRL release (for review see Baumgartner et al. 1988).

Hormonal parameters (ΔTSH, FT3 AUC, FT4 AUC, ΔPRL, COR AUC, ACTH AUC, GH AUC) during the single TRH test and combined T3/TRH test before and after 4 weeks of sertraline treatment were analyzed by a three-way MANCOVA with a repeated-measures design considering "treatment" (i. e. hormone concentrations before and after 4-week treatment with sertraline) and "time" (i. e. hormonal parameters before and after pre-treatment with 40 µg T3) as the two within-subjects factors: "group" (i. e. response versus non-response to sertraline) as the between-subjects factor, and "concentration" (i. e. serum levels of sertraline plus serum levels of DM-sertraline at week 4) as the covariate. To approach normality and homogeneity in the hormonal values, they were subjected to the log-transformation

(x* = ln [x]) before entering the ANOVA analysis. When a significant factor effect was found in the MANCOVAs, univariate F-tests followed to identify those hormonal parameters that contributed significantly to these effects. Moreover, to analyze a possible impact of pre-treatment on the results in endocrine testing at the beginning of the study (week 0), a repeated-measures ANOVA was carried out using "time" (single TRH test, followed by combined T3/TRH test) and "group" (10 pre-treated patients versus 10 non-pretreated patients) as within-subjects and between-subjects factors. As a nominal level of significance, alpha = 0.05 was accepted. To keep the type I error equal to 0.05, post hoc univariate F-tests were performed at a reduced level of significance (alpha adjusted according to Bonferroni procedure).

The software program SPSS version 12.0 was used for data analysis.

Results

A total of 10 patients (5 men, 5 women) responded to the 4-week treatment with sertraline (50 mg/day), whereas the other 10 patients (3 men, 7 women) were non-responders (21-HAMD sum score reduction < 50 %). At baseline, responders and non-responders did not differ significantly in gender distribution (Fisher's exact test: p = 0.650), age, weight, height, 21-HAMD sum score, age of onset of depression, duration of depressive illness, or number of depressive episodes (two-sided t-test for independent samples: p > 0.05, respectively; Table 1).

Using repeated-measures ANOVA, pre-treatment did not have any significant impact on the hormone concentrations during the TRH test and the T3/TRH test at week 0 (no significant "group" effect: F(9,10) = 0.339, sign. of F = 0.941). When analyzing the hormonal parameters during the 4-week study (Δvalues, AUC values), the three-way MANCOVA with a repeated-measures design (Wilks multivariate tests of significance) revealed a significant "time" effect (F = 10.111; d. f. = 7, 11; p = 0.001). Using univariate F-tests, this "time" effect could be attributed to the ΔTSH- (F = 72.394; d. f. = 1, 17; p < 0.001) and FT3 AUC values (F = 75.927; d. f. = 1, 17; p < 0.001), i. e. pre-treatment with 40 µg T3 significantly increased FT3 AUC values and decreased ΔTSH values during the T3/TRH test, compared to the single TRH test (Table 2; Fig. 1). However, according to the repeated-measures MANCOVA, there was no significant "treatment" effect (F = 0.455; d. f. = 7, 11; p = 0.847) nor was there a significant "group" effect (F = 0.234; d. f. = 7, 11;

Table 2 Hormone concentrations after TRH challenge (Δvalues and AUC values) during the single TRH test and the combined T3/TRH test before and after a 4-week treatment with sertraline (TRH $test_{week0}$, T3/TRH $test_{week0}$, TRH $test_{week4}$, T3/TRH $test_{week4}$). Data represent mean ± SD.
Percentage change between single TRH test and combined T3/TRH test before and after the 4-week treatment with sertraline (a positive value represents an increase, a negative value represents a decrease)

Week 0	ΔTSH [mU/l]	FT3 AUC [pmol/l x min]	FT4 AUC [pmol/l x min]	ΔPRL [pmol/l]	COR AUC [nmol/l x min]	ACTH AUC [pmol/l x min]	GH AUC [pmol/l x min]
TRH $test_{week0}$							
All (n = 20)	6.77 ± 3.22	606.9 ± 109.2	2013.3 ± 397.1	1120.8 ± 1012.5	50815.2 ± 28572.5	723.2 ± 395.4	2829.5 ± 4147.7
Non-responders (n = 10)	7.27 ± 3.77	623.4 ± 128.9	1975.8 ± 421.2	1190.9 ± 673.0	52735.3 ± 29012.9	633.9 ± 402.6	3214.4 ± 4998.8
Responders (n = 10)	6.27 ± 2.67	590.5 ± 89.2	2050.7 ± 390.4	1050.7 ± 1304.0	48895.3 ± 29555.8	812.5 ± 387.6	2444.6 ± 3316.7
T3/TRH $test_{week0}$							
All (n = 20)	2.64 ± 1.18	1002.1 ± 151.8	2014.6 ± 364.6	1137.0 ± 1229.8	45423.8 ± 22506.2	713.7 ± 443.8	5074.4 ± 13211.9
Non-responders (n = 10)	2.71 ± 1.19	1059.2 ± 186.5	1979.7 ± 329.6	1075.8 ± 594.3	44984.7 ± 22088.1	599.2 ± 369.9	1317.3 ± 851.5
Responders (n = 10)	2.56 ± 1.23	945.0 ± 81.2	2049.5 ± 411.5	1198.2 ± 1682.7	45862.8 ± 24104.4	828.3 ± 499.8	8831.6 ± 18341.4
Week 4	**ΔTSH [mU/l]**	**FT3 AUC [pmol/l x min]**	**FT4 AUC [pmol/l x min]**	**ΔPRL [pmol/l]**	**COR AUC [nmol/l x min]**	**ACTH AUC [pmol/l x min]**	**GH AUC [pmol/l x min]**
TRH $test_{week4}$							
All (n = 20)	7.42 ± 3.26	545.9 ± 78.9	1752.1 ± 266.1	1156.3 ± 656.7	44995.9 ± 22266.7	732.9 ± 345.7	1578.7 ± 1538.4
Non-responders (n = 10)	8.03 ± 4.19	529.8 ± 82.5	1737.0 ± 309.7	1244.4 ± 675.2	46213.0 ± 22868.5	696.3 ± 414.8	1780.0 ± 2079.3
Responders (n = 10)	6.81 ± 2.02	562.0 ± 76.0	1767.1 ± 230.2	1068.1 ± 661.2	43778.8 ± 22813.3	769.5 ± 277.9	1377.3 ± 763.2
T3/TRH $test_{week4}$							
All (n = 20)	3.05 ± 1.01	979.5 ± 115.9	1784.5 ± 252.3	1077.6 ± 642.9	43178.7 ± 20682.9	729.0 ± 350.6	2577.2 ± 4010.3
Non-responders (n = 10)	3.14 ± 1.14	973.9 ± 126.2	1720.4 ± 264.4	1208.8 ± 656.5	44938.0 ± 22399.0	730.8 ± 433.2	1936.7 ± 1878.4
Responders (n = 10)	2.96 ± 0.92	985.1 ± 111.2	1848.6 ± 235.2	946.5 ± 635.1	41419.5 ± 19862.2	727.1 ± 267.8	3217.7 ± 5432.5
Percentage change after pre-treatment with 40 µg T3	**ΔTSH [%]**	**FT3 AUC [%]**	**FT4 AUC [%]**	**ΔPRL [%]**	**COR AUC [%]**	**ACTH AUC [%]**	**GH AUC [%]**
Week 0							
All (n = 20)	−61.07	65.11	0.06	1.44	−10.61	−1.31	79.34
Non-responders (n = 10)	−62.74	69.91	0.20	−9.66	−14.70	−5.48	−59.02
Responders (n = 10)	−59.15	60.04	−0.06	14.03	−6.20	1.95	261.27
Week 4							
All (n = 20)	−58.92	79.43	1.85	−6.80	−4.04	−0.54	63.25
Non-responders (n = 10)	−60.90	83.83	−0.95	−2.86	−2.76	4.96	8.80
Responders (n = 10)	−56.59	75.28	4.61	−11.39	−5.39	−5.52	133.62

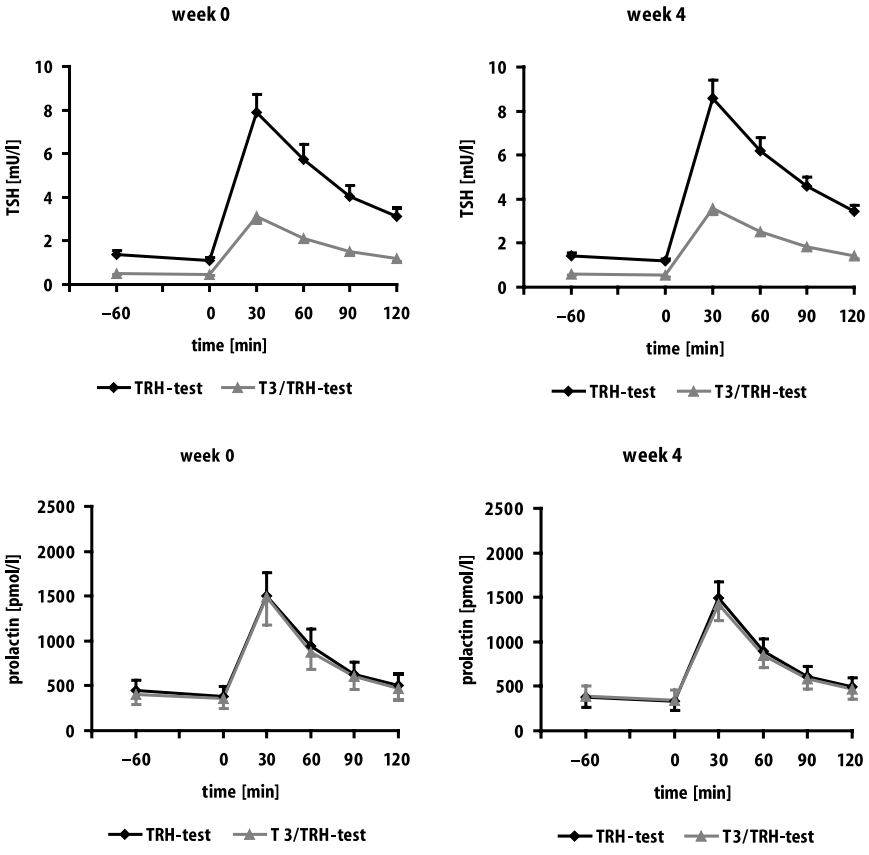

Fig. 1 Means ± S. E. M. of TSH and prolactin concentrations during the single TRH test and the combined T3/TRH test in 20 depressed patients before (week 0) and after the 4-week treatment with sertraline (week 4)

p = 0.968) and no significant interaction effect (p > 0.05, respectively), i. e. 4-week treatment with sertraline did not significantly influence hormonal secretion nor was there any significant difference between responders and non-responders to sertraline therapy. Moreover, when regarding "concentration" as a covariate, the serum levels of sertraline and its metabolite DM-sertraline at week 4 did not have a significant impact on the hormone levels after the TRH challenge (F = 0.582; d. f. = 7, 11; p = 0.758) (Table 1).

Discussion

The main result of our study is the observation that 4-week antidepressant treatment with sertraline does not have any impact on the feedback regulation of the HPT system, irrespective of the clinical outcome. This is in contrast to studies investigating the relationship between restoration of the disturbed HPA axis regulation and clinical efficacy of antidepressant drugs (Heuser et al. 1996; Nickel et al. 2003). With regard to the HPA axis, depressed patients are characterized by non-suppression during the DEX/CRH test and a gradual down-regulation of HPA axis hyperactivity during antidepressant treatment within several weeks (Holsboer 2001). However, when studying the regulation of the HPT axis in depression, no escape-phenomenon or non-suppression in depressed patients can be observed during the combined T3/TRH test (Schüle et al. in press) nor does antidepressant treatment have any impact on the outcome of this test (present study). Pre-treatment with T3 suppresses the TRH-induced TSH stimulation to a similar extent before and after treatment with sertraline, both in responders and non-responders. Apparently, the therapeutic efficacy of antidepressants such as sertraline is not related to the regulation of HPT axis activity in depressed patients.

In contrast to the TSH release, in our study the PRL secretion after TRH challenge was not influenced by single pre-treatment with 40 µg T3 (Table 2, Fig. 1). This is in line with results of previous studies in healthy controls suggesting that a single oral T3 administration has less effect on the PRL response to TRH than on the TSH response (Wartofsky et al. 1976; Rapoport et al. 1973; Refetoff et al. 1974). Apparently, chronic treatment with T3 at higher dosages (e. g. in hypothyroid patients) is necessary to exert an inhibitory effect on the PRL response to TRH (Foley et al. 1972; Snyder et al. 1973; Yamaji 1974; Refetoff et al. 1974). Moreover, TRH hypersecretion can affect TSH- and PRL-secreting pituitary cells differently, since TRH stimulates TSH and prolactin secretion through distinct calcium-mediated mechanisms (Geras et al. 1982). Consistent with our data, the findings from most studies have failed to show a significant relationship between the TSH and PRL responses to TRH administration (Zis et al. 1986; Baumgartner et al. 1988; Maes et al. 1989; Rubin et al. 1989).

Several researchers have reported that some acutely depressed patients paradoxically have increased GH in response to intravenous TRH, other investigators have failed to replicate this finding (for review see: Hsiao et al. 1986; Rubin et al. 1990). In our study, an increase of GH release after TRH challenge was observed in some but not all responders to sertraline during the T3/TRH test after 4 weeks of treatment (Table 2). However, the results of a paradoxical GH response to TRH in depression should be interpreted with caution, since GH shows pulsatile secretion patterns with spontaneous elevations of GH concentrations up to 900 pmol/l and more that can lead to misinterpretation of the findings (Finkelstein et al. 1972).

In the present study, no down-tuning effect of the 4-week treatment with sertraline on COR and ACTH secretion during the endocrinological testing could be demonstrated (Table 2). Studies showing that antidepressants such as amitriptyline (Heuser et al. 1996), paroxetine and tianeptine (Nickel et al. 2003), or mirtazapine (Schüle et al. 2003) are able to reduce HPA axis hyperactivity in depressed patients used the DEX/CRH test which is a sophisticated tool for assessment of HPA function. Since the circadian rhythm of COR secretion is disturbed as well in depression and since the differences between patients and controls are most prominent in the afternoon, measurement of COR concentrations in the morning, as it was done in the present study, may be of limited value to detect possible effects of sertraline on HPA function.

In conclusion, our data suggest that antidepressants such as sertraline have a different effect on the feedback-loop of the HPA and the HPT system in depression.

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