CLINICAL STUDY

Thyrotropin, but not a polymorphism in type II deiodinase, predicts response to paroxetine in major depression

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Abstract

Objective: The determinants of response to antidepressant treatment in major depression are unknown at present. The aim of the present study was to establish whether response is predicted by Hypothalamus–Pituitary–Thyroid (HPT) axis parameters or by a recently discovered polymorphism in the enzyme type II deiodinase (DII), which catalyzes the production of T₃ in the brain.

Design: We analyzed prediction of response to paroxetine treatment by calculating response rates per tertile of HPT-axis parameters and per DII genotype.

Methods: Ninety-eight outpatients with major depression (DSM-IV) were included. Serum concentrations of TSH, FT₄ and delta TSH in a DEX/CRH-TRH test were measured. In addition, the presence of a polymorphism in the DII sequence (Thr92Ala) was determined.

Results: The overall treatment response was 48 of 98 patients (49%). After exclusion of patients with subclinical hypothyroidism and/or TPO antibodies (n = 16), higher serum TSH significantly predicted response (response rate per tertile from low to high TSH: 36%, 42%, and 67%). Heterozygous patients for the DII polymorphism (44%) had slightly lower serum TSH (P = 0.03) as compared to patients with the wild-type DII (47%). The polymorphism was unrelated to treatment response.

Conclusion: Higher serum TSH was associated with response to paroxetine in patients with major depression.

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Introduction

Treatment of major depressive disorder with a first trial of antidepressant therapy is only effective in 60–70% of patients (1). The determinants of treatment response are not well known. In depression, changes have been described in the Hypothalamic–Pituitary–Thyroid (HPT) axis, such as a lower serum thyrotropin (TSH) and a higher serum-free thyroxine (FT₄), but no change in serum tri-iodothyronine (T₃) concentrations. Furthermore, the presence of thyroid peroxidase (TPO) auto-antibodies and subclinical hypothyroidism have been reported to be associated with major depression (2, 3). In dynamic tests, the delta TSH to thyrotropin-releasing hormone (TRH) is blunted in some 25% of depressed patients (4, 5).

These changes may be of clinical significance, since they have been related to response by some (6, 7) but not all authors (8). So far, the nature of a relation

between thyroid function and response seems unclear; Duval *et al.* (6) described higher evening TSH concentrations in treatment responders, while Sullivan *et al.* (7) found that non-response was predicted by a high delta TSH in the TRH test. However, most studies were retrospective and included only small groups of patients (6, 9–12). Furthermore, no studies so far included TPO antibodies in their analysis, although thyroid auto-immunity is an important determinant of TSH levels (13) or may be a predictor of response itself. These factors may explain the different outcomes of these studies.

Given these HPT-axis aberrations the response to antidepressant treatment may also be associated with polymorphisms in genes involved in this axis. The local production of T₃ from T₄ in the brain is determined to a large extent by the enzyme type II deiodinase (DII) (14). The activity of DII in rat brain is increased by antidepressants of various classes, including selective

serotonin reuptake inhibitors (SSRIs) (15–17). Since T_3 increases the availability of serotonin in the frontal cortex (18), DII may modulate the antidepressant effect of SSRIs. The DII enzyme plays a role in the anterior pituitary as well, where it mediates the negative feedback of T_4 on TSH secretion (19). Recently, an A/G polymorphism was identified at position 674 of the DII sequence, leading to a change in amino acids (Thr92Ala). This polymorphism was found to be associated with serum TSH concentration and insulin resistance (20, 21).

We hypothesized that baseline thyroid function (TSH, delta TSH and FT_4) and/or the DII polymorphism predict response to an SSRI. We tested this hypothesis in patients with major depression, who participated in a randomized clinical trial addressing the efficacy of T_3 addition to paroxetine. As the response rate in the trial was exactly similar in T_3 addition as in placebo addition groups (22), we regarded this as a paroxetine alone treated group. Nevertheless, to be sure that T_3 addition was not a determinant of treatment response, results were corrected for T_3 treatment.

Subjects and methods

Subjects

The depressed patients took part in a randomized clinical trial evaluating the efficacy of thyroid hormone (T_3) addition to treatment with an SSRI, as described elsewhere (22). To be eligible for the study patients had to be between 18 and 65 years of age, to be free of antidepressant medication for at least 3 months and to fulfil the diagnostic criteria for major depressive disorder according to the fourth edition of diagnostic and statistical manual of mental disorders (DSM-IV) (23). Patients were required to have a score of at least 16 on the 17-item Hamilton Rating Scale for Depression (HRSD), a commonly used questionnaire to rate depression severity.

Exclusion criteria were bipolar disorder, substance abuse or dependence disorder for alcohol or drugs, clinically manifest thyroid or adrenocortical disease. Patients were not allowed to have taken corticosteroids or drugs interfering with thyroid hormone metabolism (e.g. amiodarone), thyroid hormone, or any psychotropic drug during the last 3 months before inclusion, with the exception of a low dose benzodiazepine (equivalent to 30 mg oxazepam daily). To obtain accurate measurement of treatment response, patients were only included when they had taken study medication for at least 6 weeks. All randomized patients provided written informed consent and the study was approved by the medical ethical committee of the Academic Medical Center and the Free University Medical Center.

Medication schedule and psychiatric outcome measures

After the measurements of endocrine parameters, patients were randomly assigned to study treatment comprising three groups: placebo, 25 μg T_3 or 50 μg T_3 in a ratio of 2: 1: 1 respectively. This double-blinded study medication was given in addition to open label antidepressant treatment with 30 mg paroxetine. In total patients were treated for 8 weeks. Ratings of HRSD were obtained every 2 weeks and a physician (B.C.A and J.P.B) monitored compliance. Primary outcome was the score on the 17-item HRSD at 8 weeks or the last HRSD-score obtained. Response was defined as $\geq 50\%$ reduction in HRSD score from baseline to week 8.

Procedures, hormone measurements and DII polymorphism analyses

Subjects had an intravenous puncture for blood withdrawal in the morning (before 1000 h) to determine baseline levels of serum TSH, FT_4 , TPO antibodies and isolation of DNA. A DEX/CRH test was performed as described by Heuser *et al.* (24) with the addition of a TRH stimulation test (DEX/CRH-TRH test). Because dexamethasone suppresses TSH, a dose of 400 μg TRH (as was used by others (7;11;25;26)) was chosen. At the day prior to the test, subjects took a tablet of 1.5 mg dexamethasone at 2300 h. On the day of the test, an intravenous catheter was inserted at 1400 h. From 1445 h until 1630 h blood samples were taken every 15 min for the assessment of serum TSH. At 1500 h, 100 μg CRH (Ferring Hoofddorp, Holland) was injected, followed directly by 400 μg TRH (Protirelin, Hoechst AG, Frankfurt am Main, Germany). Delta TSH was calculated by subtracting the value before injection from the maximal value after injection of TRH.

Sera were kept at -20°C . Hormone assays were conducted in the Endocrinology Laboratory of the Academic Medical Center in Amsterdam. Free T_4 and TSH were measured by time-resolved fluoroimmunoassay (Delfia FT_4 and hTSH Ultra respectively Wallac Oy, Turku, Finland), with a detection limit of 2 pmol/l and 0.01 mU/l respectively. The intra-assay coefficient of variation was 4–6% and 1–2%; the inter-assay coefficient of variation was 5–8% and 3–4% respectively. The reference value for serum TSH was 0.40–4.00 mU/l (27) and for FT_4 10–23 pmol/l. Subclinical hypothyroidism was defined as an increased serum TSH and a normal serum FT_4 . Anti-TPO was measured by chemiluminescence immunoassay (LUMI-test anti-TPO, BRAHMS, Berlin, Germany) with a detection limit of 30 kU/l. The intra-assay coefficient of variation was 3–7%; the inter-assay coefficient of variation was 8–12%. The cut-off value for a positive anti-TPO titer was 60 kU/l. DNA was extracted from 7 ml of blood using a phenol/chloroform extraction method. After isolation of all DNA samples, a restriction

fragment length polymorphism (RFLP) analysis was performed twice for every patient as described earlier (21).

Data analysis

To compare response rates between the three treatment arms, we performed a Pearson Chi-square test. For the prediction of response, we used the following endocrine parameters: baseline serum concentrations of TSH, FT₄, delta TSH (maximal minus baseline TSH) and the fold increase of TSH (maximal divided by baseline TSH) in the DEX/CRH-TRH test. We divided the patients over three equal groups (tertiles) of these parameters. For each parameter the mean decrease in HRSD score and response rates per tertile were calculated. To determine if response rates were significantly different, the chance on response (named relative response rate) with 95% confidence intervals were calculated for the two higher tertiles relative to the low tertile. We investigated whether the relation between baseline TSH and the response rate was due to T₃ treatment or influenced by TPO antibodies, by a logistic regression (method: enter) with response as the dependent variable. For the analysis of response prediction by the DII polymorphism, we calculated response rates and relative response rates with 95% confidence intervals (CI) per genotype. For the comparison of HPT-axis parameters in the DII genotypes, ANOVA tests with *post hoc* analyses were performed. Serum TSH and delta TSH were first log-transformed to normalize the distribution. For all tests a *P* value of ≤ 0.05 was considered statistically significant and all tests were two-tailed.

The statistical analysis was conceived and supervised by co-author J.G.P. Tijssen, Professor of Clinical Epidemiology and Biostatistics at the Academic Medical Center in Amsterdam.

Results

Clinical characteristics

A total of 113 patients with depression met the criteria for eligibility and 98 patients completed 8 weeks of study medication, except for one, who completed 6 weeks. The overall response rate, defined as a 50% reduction in HRSD score, was 48 of 98 patients (49%). Response rates in the three treatment arms (placebo, 25 µg T₃, 50 µg T₃) were similar (50%, 46%, 50% respectively; χ^2 : 0.11, df = 2, *P* = 0.95). Characteristics of responders and non-responders were not statistically different between responders and non-responders (Table 1). The 17-item HRSD scores indicate that the majority of patients had a moderately severe depression and that quite a large proportion of subjects with recurrent (43%), chronic (52%) and therapy resistant (38%) depression were included.

Table 1 Clinical characteristics.

	Non-responders <i>n</i> = 50	Responders <i>n</i> = 48
Age (mean $\pm$ s.d.)	46 $\pm$ 11	47 $\pm$ 12
Woman (<i>n</i> , %)	31 (62%)	32 (67%)
17-HRSD (mean $\pm$ s.d.)	20 $\pm$ 3	21 $\pm$ 3
Chronic depression (<i>n</i> , %)	20 (40%)	22 (46%)
Recurrent depression (<i>n</i> , %)	26 (52%)	25 (52%)
Therapy resistant* (<i>n</i> , %)	19 (38%)	17 (35%)

*Therapy resistance was defined as having a score of 1 or more in the Thase and Rush classification for therapy resistance (39).

Prediction of treatment response by HPT-axis parameters

The response rates per tertile of each endocrine parameter are presented in Table 2. There was a trend towards increased treatment response in tertiles with higher serum TSH-values (response per tertile from low to high TSH: 37%, 51%, 58%). The relative response rate (RR) as compared to the low tertile was 1.4 (CI 0.79–2.48) in the middle tertile and 1.57 (CI: 0.88–2.74) in the high tertile. There was no difference in response rates between the tertiles of serum FT₄, delta TSH, nor in the fold increase of TSH. The prevalence of patients with positive TPO-antibodies (*n* = 9) and subclinical hypothyroidism (*n* = 10) was too low to be analyzed as separate determinants of response.

The slightly positive relation between tertiles of TSH and treatment response was corrected for T₃ treatment in a logistic regression model. T₃ treatment appeared not to affect the trend between TSH and response (before correction: OR = 1.53, CI: 0.92–2.53 and after correction: OR = 1.52, CI: 0.92–2.53). However, after additional correction for TPO antibodies, the association between TSH and response rather strengthened (before correction: OR = 1.53, CI: 0.92–2.53 and after correction: OR = 1.63, CI: 0.96–2.74). To further exclude the possibility that T₃ addition was beneficial in patients with subclinical thyroid disease and thereby caused the association between TSH and response rate, we reanalyzed the data after exclusion of patients with subclinical hypothyroidism and/or positive TPO antibodies. The association in the remaining 82 patients was now statistically significant in the high TSH-tertile (1.87; CI 1.07–3.26; Table 3). This appeared to be mainly due to the exclusion of patients with TPO antibodies, since the mere exclusion of patients with TPO antibodies resulted in a significant association (RR in the high TSH-tertile: 1.81, CI 1.03–3.17), while exclusion of patients with subclinical hypothyroidism did not (RR = 1.62, CI 0.93–2.81). Free T₄ nor delta TSH or the fold increase in TSH (response rate from low to high tertile: 59%, 36% and 52%) revealed any trend towards the prediction of response after exclusion of patients with positive TPO antibodies and/or subclinical hypothyroidism.

Table 2 Treatment response per tertile of HPT-axis parameters.

		N	Value of parameter median (range)	HRSD at baseline (mean $\pm$ S.D.)	Decrease in HRSD (mean $\pm$ S.D.)	Response rate n (%)	Relative response rate	95% CI
Serum TSH ^a mU/l	low	30	1.20 (0.49–1.50)	20 $\pm$ 3	7 $\pm$ 6	11 (37%)	1.00	
	middle	35	1.90 (1.60–2.30)	22 $\pm$ 4	10 $\pm$ 6	18 (51%)	1.40	0.79–2.48
	high	33	2.80 (2.40–9.50)	21 $\pm$ 3	11 $\pm$ 6	19 (58%)	1.57	0.88–2.74
Serum FT ₄ ^a pmol/l	low	34	11.7 (9.2–12.5)	21 $\pm$ 3	10 $\pm$ 6	17 (50%)	1.00	
	middle	31	13.6 (12.6–14.6)	21 $\pm$ 3	11 $\pm$ 6	20 (65%)	1.24	0.84–2.30
	high	33	15.9 (15.0–18.7)	21 $\pm$ 4	7 $\pm$ 6	11 (33%)	0.67	0.37–1.20
Delta TSH ^b mU/l	low	32	7.12 (1.52–9.27)	20 $\pm$ 3	9 $\pm$ 7	17 (53%)	1.00	
	middle	33	11.52 (9.33–14.23)	21 $\pm$ 3	9 $\pm$ 6	14 (42%)	0.80	0.48–1.37
	high	33	18.70 (14.73–108.50)	21 $\pm$ 3	10 $\pm$ 7	17 (52%)	0.97	0.61–1.54

Per HPT-axis parameter, patients ($n=98$) are divided in three equal groups (tertiles). Response rates are shown per tertile.

^aMorning hormone values measured before dexamethasone ingestion.

^bThe absolute increase in TSH concentration after i.v. injection of 400 μ g TRH and 100 μ g CRH. Patients had ingested 1.5 mg dexamethasone the evening before testing (modified DEX/CRH test, Heuser *et al.* (24)).

Characteristics and treatment response according to DII polymorphism

The presence of the DII polymorphism was determined in 93 patients. In these patients, 44 (47%) had the AA genotype, 41 (44%) were heterozygous and 8 (9%) were homozygous for the G allele. The clinical and endocrine characteristics of the patients with these genotypes are presented in Table 4. Age, gender, HRSD score at baseline, the course of the depression and the presence of previous therapy resistance were similar in the three groups. Interestingly, there were differences between the groups in serum TSH and delta TSH ($F=4.00$, $df=2$, 90 , $P=0.02$ and $F=3.08$, $df=2$, 90 , $P=0.05$ respectively), but not in the fold increase of TSH ($F=1.23$, $df=2$, 90 , $P=0.30$). Post-hoc analysis revealed that both serum TSH and delta TSH were significantly lower in the heterozygous group as compared to the AA-genotype. After exclusion of patients with subclinical hypothyroidism and/or positive TPO-antibodies,

differences in serum TSH were similar, but not statistically significant anymore. Serum FT₄ values were similar in the various genotypes.

No association was found between the DII polymorphism and response rate (RR of subjects with the DII polymorphism compared to wild type: 0.84, CI 0.54–1.31 in heterozygous patients and RR=0.96, CI 0.45–2.02 in homozygous patients) (Table 5).

Discussion

Our finding that higher TSH, but not FT₄, is related to response, is in agreement with studies measuring evening TSH concentrations (6, 28). Other studies measuring TSH in the morning did not find such a relation (8–12). We only found a significant association after exclusion of patients with positive TPO titers. Since other studies analyzing morning TSH in relation to

Table 3 Treatment response per tertile of HPT-axis parameter, biochemical thyroid abnormalities excluded.

		N	Value of parameter median (range)	HRSD at baseline (mean $\pm$ S.D.)	Decrease in HRSD (mean $\pm$ S.D.)	Response rate n (%)	Relative response rate	95% CI
Serum TSH ^a mU/l	low	28	1.20 (0.49–1.50)	20 $\pm$ 3	7 $\pm$ 6	10 (36%)	1.00	
	middle	24	1.75 (1.60–2.10)	21 $\pm$ 4	10 $\pm$ 6	10 (42%)	1.17	0.59–2.30
	high	30	2.50 (2.20–3.70)	22 $\pm$ 4	12 $\pm$ 6	20 (67%)	1.87	1.07–3.26
Serum FT ₄ ^a pmol/l	low	28	11.7 (9.2–12.5)	21 $\pm$ 3	10 $\pm$ 6	14 (50%)	1.00	
	middle	26	13.8 (12.7–15.1)	21 $\pm$ 4	11 $\pm$ 6	17 (65%)	1.31	0.82–2.08
	high	28	16.3 (15.2–18.7)	21 $\pm$ 4	7 $\pm$ 7	9 (32%)	0.73	0.38–1.43
Delta TSH ^b mU/l	low	27	6.70 (1.52–8.55)	20 $\pm$ 3	9 $\pm$ 7	14 (52%)	1.00	
	middle	28	10.93 (8.85–12.80)	21 $\pm$ 3	10 $\pm$ 6	13 (46%)	0.90	0.52–1.53
	high	27	16.03 (13.00–24.98)	21 $\pm$ 4	9 $\pm$ 7	13 (48%)	0.93	0.54–1.58

Per HPT-axis parameter, patients ($n=82$) are divided in three equal groups (tertiles) after exclusion of patients with subclinical hypothyroidism (TSH > 4.00 mU/l, $n=10$) and/or positive TPO antibodies ($n=9$). Response rates are shown per tertile.

^aMorning hormone values measured before dexamethasone ingestion.

^bThe absolute increase in TSH concentration after i.v. injection of 400 μ g TRH and 100 μ g CRH. Patients had ingested 1.5 mg dexamethasone the evening before testing (modified DEX/CRH test, Heuser *et al.* (24)).

Table 4 Clinical characteristics according to DII genotype.

	AA (wild type) <i>n</i> =44	AG (heterozygous) <i>n</i> =41	GG (homozygous) <i>n</i> =8
Age (mean $\pm$ s.d.)	46 $\pm$ 11	48 $\pm$ 11	46 $\pm$ 11
Woman (<i>n</i> , %)	28 (64%)	25 (61%)	5 (63%)
Chronic depression (<i>n</i> , %)	20 (46%)	18 (44%)	3 (38%)
Therapy resistant* (<i>n</i> , %)	19 (43%)	13 (32%)	3 (38%)
TSH mU/l ^{a†} (median, P^{10} – P^{90})	2.30 (1.10–4.35)	1.70 (0.90–2.78)	1.95 (1.40–7.00)
FT ₄ pmol/l ^a (mean $\pm$ s.d.)	13.5 $\pm$ 2.1	14.2 $\pm$ 2.1	12.9 $\pm$ 1.3
Delta TSH mU/l ^{b†} (median, P^{10} – P^{90})	12.55 (6.13–25.54)	10.00 (4.88–17.16)	13.25 (6.09–35.80)

*Therapy resistance was defined as having a score of 1 or more in the Thase and Rush classification for therapy resistance (39).

^aMorning hormone values measured before dexamethasone ingestion.

^bThe absolute increase of TSH after i.v. injection of 400 μ g TRH and 100 μ g CRH. Patients had ingested 1.5 mg dexamethasone the evening before testing (modified DEX/CRH test, Heuser *et al.* (24)).

[†]Serum TSH values were significantly different between the three genotypes ($F=4.00$, $df=2$, 90, $P=0.02$). Post-hoc tests revealed that the serum TSH difference between the AA genotype and heterozygous patients was significant ($P=0.01$, 95% CI: 0.03–0.22).

[‡]Delta TSH was significantly different between the three genotypes ($F=3.08$, $df=2$, 90, $P=0.05$). Post-hoc tests revealed that the delta TSH difference between the AA genotype and heterozygous patients was significant ($P=0.03$, 95% CI: 0.02–0.23).

response did not assess TPO antibodies, this may explain some of the discrepancies in the literature.

The positive association between TSH and treatment response could not be attributed to T₃ treatment, since T₃-treatment was not a determinant of response in a logistic regression model. Furthermore, the exclusion of patients with subclinical hypothyroidism or positive TPO antibodies eliminates patients who might benefit from the T₃ treatment.

To explain the relation between TSH and treatment response is a matter of speculation. The often described hypercortisolism in depressed patients may induce lower serum TSH and indicate treatment resistant depression (29). However, as we described earlier, in this population low TSH was not related to high 24-hour urinary cortisol levels (30). Another explanation is that a relatively low TSH is due to relatively low TRH. Indeed, the expression of TRH in the hypothalamus of depressed patients as compared to control patients is decreased (31). Since TRH is influenced by serotonin in the rat brain (32), serum TSH concentrations may reflect a disturbed serotonin system.

The effect that TPO antibodies have on the relation between TSH and response can be explained by two factors. First, TPO antibodies are a first sign of thyroid autoimmune disease leading to increased TSH concentrations (13). TPO antibodies may, as a peripheral determinant of TSH concentration, obscure the proper relation between TSH and response. Second, TPO antibody positivity itself may be a (negative) determinant of response. Because of the low prevalence of

patients with a positive TPO antibody titer in our study, we could not address this hypothesis. Some indication of the importance of TPO antibodies was given by a study wherein the presence of TPO-antibodies in the first trimester of pregnancy, but not subclinical hypothyroidism *per se*, predicted postpartum depression (33). A recent study described that the presence of Thyroid Binding Inhibitory Immunoglobulins was related to treatment non-response in depressed patients (34). These findings support an association between the immune system and depression.

With respect to the TRH-test, one large study ($n=105$) found that high delta TSH predicted treatment non-response (7), while in a number of smaller studies this association was confirmed but also contradicted (6, 35, 36). In the present study, delta TSH did not predict response. An explanation for this discrepancy may be the dexamethasone pre-treatment in our study, since glucocorticoids suppress serum TSH (37).

The prevalence of the DII genotypes in the present study was comparable with that of a population of 156 healthy, Dutch blood donors (48% heterozygous and 15% homozygous subjects) (21). The age (46-years-old), but not the gender (35% females), of these subjects was similar to our patients. Despite the association between the DII polymorphism and serum TSH, this did not result in a prediction of response by the DII polymorphism. The present and the study by Peeters *et al.* (21) found that serum TSH in heterozygous subjects was lower than in the wild-type and homozygous subjects. This odd, but replicable observation

Table 5 Treatment response according to DII genotype.

	N total <i>n</i> =93	HRSD at baseline (mean $\pm$ s.d.)	Decrease in HRSD (mean $\pm$ s.d.)	Response rate <i>n</i> (%)	Relative response rate	95% CI
AA (wild type)	44	20 $\pm$ 3	10 $\pm$ 6	23 (52%)		
AG (heterozygous)	41	21 $\pm$ 4	10 $\pm$ 7	18 (44%)	0.84	0.54–1.31
GG (homozygous)	8	20 $\pm$ 3	9 $\pm$ 7	4 (50%)	0.96	0.45–2.02

Patients ($n=93$) are divided in groups according to DII genotype (AA = wild type, AG = heterozygous, GG = homozygous). Response rates are shown per genotype.

may be explained by a hypothesis that part of DII proteins form dimers (of both alleles) (38). Speculating on this, heterodimers of DII proteins, one with the polymorphism and one without, may have higher catalytic activity than homodimers that will result in higher T₃ concentrations in the anterior pituitary to suppress TSH.

Compared to other studies, we investigated a larger population of depressed patients and we investigated the predictive value of HPT-axis parameters prospectively after correction for TPO antibodies. These patients had been free of antidepressants for three months. Influence of previous treatments on baseline parameters was therefore unlikely. In this setting, higher serum TSH was significantly related to response rates after the exclusion of patients with positive TPO antibodies. Therefore, we recommend that in future studies, TPO antibodies should be included in studies on the prediction of antidepressant response.

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