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Dexamethasone Suppression and Multiple Hormonal Responses (TSH, Prolactin and Growth Hormone) to TRH in some Psychiatric Disorders

Csaba M. Banki[1], Maria Vojnik[1], Mihaly Arato[2], Zsuzsa Papp[3], and Zsuzsa Kovacs[4]

[1] The Regional Neuropsychiatric Institute, P.O. Box 37, H-4321 Nagykallo, Hungary
[2] Hamilton Psychiatric Hospital, Hamilton, Ontario L8N 3K7, Canada
[3] National Institute for Nervous and Mental Diseases, Budapest
[4] Postgraduate Medical School, Endocrinological Laboratory, Budapest, Hungary

Summary. Baseline and TRH-induced changes of thyroid stimulating hormone (TSH), prolactin (PRL), and growth hormone (GH) were measured in 15 healthy control subjects and 63 psychiatric inpatients with DSM-III diagnoses of major depression ($n = 19$), schizophrenic disorder ($n = 20$), alcohol dependence ($n = 10$), and adjustment disorder ($n = 14$); baseline and postdexamethasone cortisol (CS) were also determined 3–6 days after the TRH-challenge. All patients and controls were women of similar mean age, weight, height, and they were free from interfering illness or drugs.

Baseline TSH and PRL were lower in depression, TRH-induced TSH and PRL responses were lower in the whole patient group, but most markedly in depression and alcohol dependence. Postdexamethasone CS was significantly higher in depression, schizophrenia and alcohol dependence. Basal GH did not differentiate the subgroups; TRH-induced pathological GH responses were sometimes found in the patient groups. The differences were most marked quantitatively in major depression: a multivariate analysis of variance showed that ΔTSH, postdexamethasone CS and ΔPRL were the most important variables in separating patients from controls. A discriminant function derived from these variables classified all controls and 18 of 19 depressed patients correctly; however, 25 of the 44 other patients were also classified with depression.

It was confirmed that psychiatric patients show significantly more endocrine disturbances than controls, and this was seen not only in major depression but also in at least three other conditions. Further work is needed to identify other neuroendocrine patterns more specific to depressive disorder.

Key words: Depression – Schizophrenia – Alcohol dependence – DST – TRH – TSH – Prolactin – Growth hormone

Introduction

Both the dexamethasone suppression test (DST) and the thyroid stimulation test (TST) thyroid stimulating hormone (TSH) thyroid releasing hormone response to intravenously administered (TRH) have been proposed for the diagnosis of "endogenous" depression or "melancholia" (Carroll 1982). There have, however, been many conflicting reports regarding the claimed specificity of the DST: patients with schizophrenia (Dewan et al. 1982), senile dementia (Raskind et al. 1982), alcohol abuse (Abou-Saleh et al. 1984) or other psychiatric disorders (Coppen et al. 1983) and even healthy controls (Hällström et al. 1983) were sometimes found to have abnormal DST results. The DST has also failed to differentiate subtypes of depression in some studies: endogenous from nonendogenous (Berger et al. 1982), unipolar from bipolar (Stokes et al. 1984) or familial subtypes from each other (Fleming et al. 1983).

The TST has also proved to be controversial in differentiating subtypes of depression defined by polarity (Bjørum et al. 1979; Mendlewicz et al. 1979) or family history (Fleming et al. 1983; Targum et al. 1982). On the other hand, the TST has seemed to be fairly sensitive in identifying patients with major depression, a broader concept of a severe affective disorder as defined in the Research Diagnostic Criteria (Spitzer et al. 1978) or in the DSM-III (APA 1980): most studies reported significantly blunted TSH responses in depressed patients (Loosen and Prange 1982). There have been only sporadic reports on TST administered to nonaffective patients: Extein et al. (1980) found that manic patients could be differentiated from schizophrenic subjects by their smaller TSH responses, while Ferrier et al. (1983) reported blunted hormonal responses in schizophrenic patients as compared with healthy controls.

Intravenous TRH stimulates not only TSH but also prolactin (PRL), and in some cases growth hormone (GH) secretion. These latter measurements have also been investigated in depressed patients, and again yielded contradictory data: PRL responses were found to be blunted (Linnoila et al. 1979) or normal (Loosen et al. 1983) in the patients who had blunted TSH responses. PRL responses tended to be smaller in depression (Targum et al. 1982b) and in schizophrenia (Ferrier et al. 1983) as compared to healthy controls. The GH response to TRH is considered abnormal (Collu 1979): it is seen in several medical and endocrinological illness and, in addition, in depression (Maeda et al. 1975) and in schizophrenia (Ferrier et al. 1983).

Some investigators have tested depressed patients and controls with more than one endocrine challenge and measured

Offprint requests to: C. M. Banki at the above address

several hormonal responses to such stimuli in the same patients (Amsterdam et al. 1983; Winokur et al. 1983). Although this procedure improved the predicting power of the neuroendocrine strategy in some studies (Winokur et al. 1982; Targum et al. 1982a), this was not seen consistently, and patients often differed only by their greater variability in the endocrine responses.

In the present study we investigated TSH, PRL and GH responses to TRH in healthy subjects and four groups of patients with clearcut DSM-III diagnoses. All were subsequently given a 1.mg DST; all four baseline and drug-induced hormonal measurements were then analyzed both qualitatively and quantitatively for uni- and multivariate differences among the clinical categories.

Patients and Methods

Healthy controls were recruited from staff members ($n = 15$), after a careful medical and laboratory examination to rule out any physical, endocrine or metabolic illness. Only women who had never taken major psychotropic drugs (neuroleptics, antidepressants, lithium, antiepileptics, etc.), and who had been free from any regularly taken drug (including contraceptives) for at least 6 months were asked to participate. None were heavy smokers or regular drinkers. Personal for family history of any psychiatric disorder or treatment and (possible) pregnancy also constituted exclusion criteria. The age in the final group was 22–53 (mean 42 ± 11) years, the body weight within 49–78 (mean 60 ± 10) kg and stable for at least 3–4 months.

The patients were 63 recently hospitalized women between 19–69 (mean 41 ± 13) years; they had been free from regular major psychotropic medication for at least 2 weeks, although we could not check this by plasma drug measurement but relied on personal information from the patients, her relatives and her physician. None of the patients had received lithium, steroid hormones or iodide for at least 6 months, and all were free from any significant medical or neurological illness at the time of the study. Their body weight ranged from 40–88 (mean: 62 ± 17) kg and had not changed dramatically (i.e. by more than 10 kg) before admission. Standardized interviews were conducted on subsequent days by two psychiatrists (blindly and in random order) and only concordant diagnoses, using DSM-III terms, were accepted. In this way more than 90 patients were screened, and 63 were selected for the study, after giving written informed consent. The diagnoses were: major depression in 19 cases (12 with melancholia and 7 with psychotic features), schizophrenic disorder in 20 cases (4 disorganized, 7 catatonic, 9 paranoid subtype), alcohol dependence in 10 cases (without any other diagnosable DSM-III disorder, and on the 7th-22nd postwithdrawal day), and adjustment disorder in 14 cases (7 with depressed and 5 with anxious mood, 2 with mixed emotional features). This last category corresponded to the more European term "reactive" depressive or anxiety states (ICD-9: 309).

After 3–7 days on a regular hospital diet and placebo only the patients received 0.2 mg synthetic (Jenapharm, GDR) TRH IV between 0900 and 1000 hours, after overnight fasting and bedrest. Blood samples (5 ml) were taken before and 30 and 60 min after the TRH injection; the samples were then centrifuged and frozen to −60°C until assayed. Then 3–6 days later—still drug free other than single doses of chlormethiazole or diazepam if required for excessive anxiety or agitation—1 mg dexamethasone was given orally at 2200 hours (ingestion checked by the personnel) followed by blood sampling at 0800 and 1500 hours the next day.

Serum triiodothyronine (T_3), thyroxine (T_4) and T_3-uptake were all measured in the pre-TRH sample: they were all within normal limits (using RIA methods, isotope and antisera from the Isotope Institute, Hungarian Academy of Sciences). Baseline and TRH-induced TSH, PRL and GH were also determined by RIA methods, using commercial kits (Byk-Mallinckrodt RIA-mat TSH, CIS CEA-Sorin PROLK, Serono hGH). Baseline cortisol (CS) was measured in the pre-TRH sample and in both postdexamethasone samples by competitive protein binding. TRH-induced responses were calculated as the peak-minus-baseline change in each hormone (these were observed without exception at 30 min for both TSH and PRL, and at 60 min in 6 subjects for GH).

Qualitative statistical analysis was performed by comparing the number of subjects with values below (or above) an empirical cutoff level, determined by our laboratory from normal controls, between each patient group and the control group. Ouantitative analysis was made after log-transformation of the data because of the markedly skewed distribution of almost all hormonal values; this transformation did not normalize all variables but equalized the variances as checked by the Bartlett's test. Because of the non normality of some distributions nonparametric (Kruskal-Wallis) tests were also computed; otherwise analysis of variance (ANOVA) and finally multivariate analysis of variance (MANOVA) followed by discriminant function analysis were used.

Results

Baseline and TRH-induced TSH, PRL, and GH responses are shown in Figs. 1–3 separately for the control and the four patient groups; baseline and postdexamethasone CS values are presented in Fig. 4. In the latter, according to the convention of evaluating the DST, the *higher* of the two postdexame-

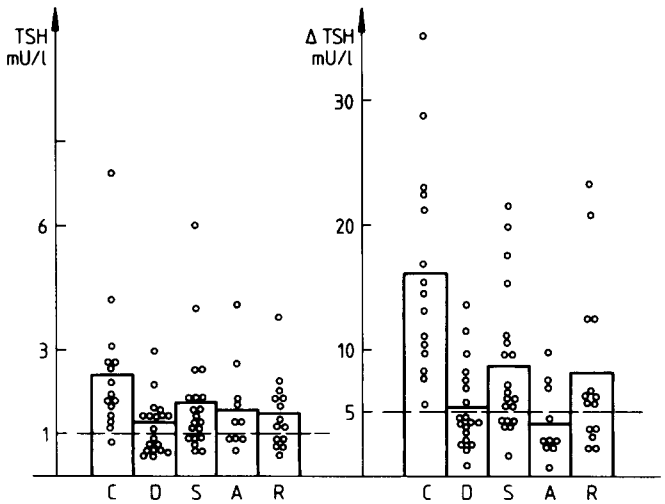

Fig. 1. Baseline TSH and maximal TSH response to TRH in healthy subjects and psychiatric patients. *C* = control ($n = 15$), *D* = depression ($n = 19$), *S* = schizophrenia ($n = 20$), *A* = alcohol dependence ($n = 10$), and *R* = adjustment disorder ($n = 14$). Columns represent group means, broken lines indicate empirical cutoff levels for "abnormal" values

thasone CS values is given. Table 1 contains the number of subjects from each group with "abnormal" values, i.e., with those below or above a fully empirical cutoff level (they are also given in the table).

Both baseline and TRH-induced TSH response data were normalized by log-transformation. The number of patients with basal TSH not exceeding 1 mU/l was significantly greater in the patient group as a whole, but separately this was significant only in major depression. ΔTSH values not exceeding 5 mU/l were much more common in all patient groups than in the control group (where actually no blunted response was found), and all the differences were statistically significant. An ANOVA with the log-data was significant for both variables (baseline: $F(4.73) = 2.98$, $P < 0.03$; ΔTSH: $F = 9.10$, $P < 0.001$); after omitting the control group (higher than the whole patient group for both baseline TSH ($P < 0.005$) and ΔTSH ($P < 0.001$)) the remaining patient groups were no more significantly different regarding their mean TSH level, butΔTSH still subdivided the patients into two subgroups: depressed and alcoholic vs. schizophrenic and adjustment disorder groups had ΔTSH levels with significantly different means.

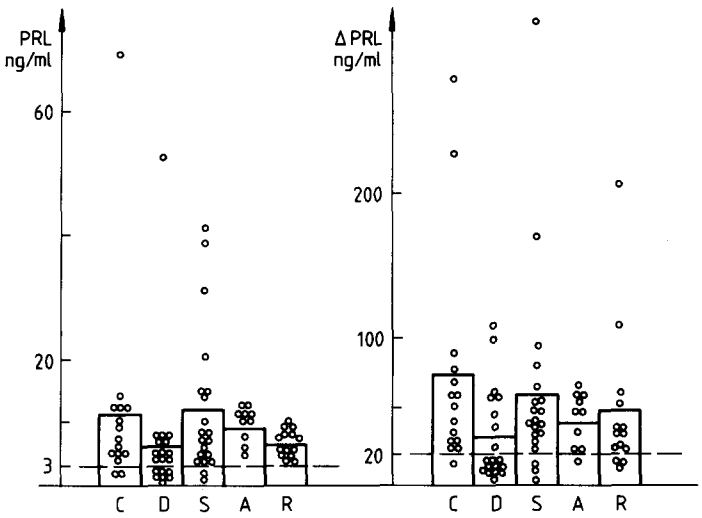

Fig. 3. Baseline PRL and maximal PRL response to TRH in healthy subjects and psychiatric patients. Abbreviations as in Fig. 1

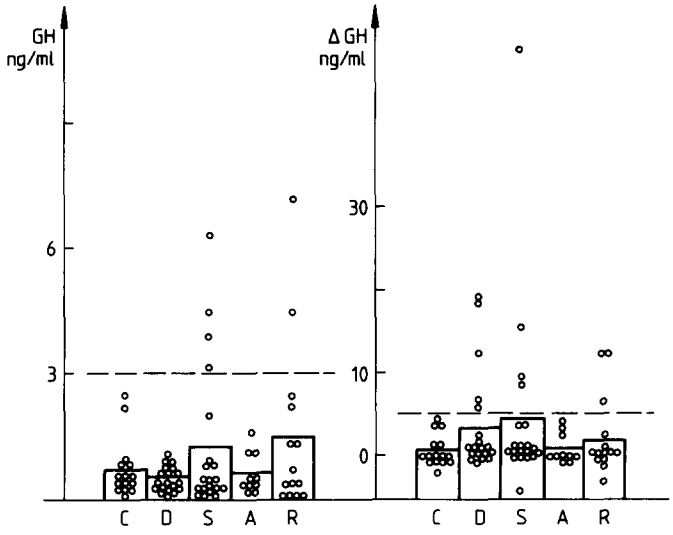

Fig. 2. Baseline GH and maximal GH response to TRH in healthy subjects and psychiatric patients. Abbreviations as in Fig. 1

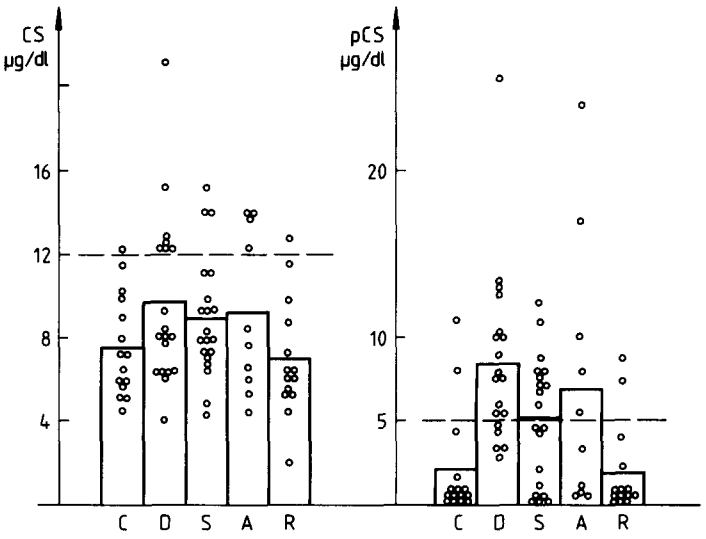

Fig. 4. Baseline CS and the higher of two postdexamethasone cortisol values (pCS) in healthy subjects and psychiatric patients. Abbreviations as in Fig. 1

Table 1. Subjects with deviant hormonal values in controls and 4 patient groups

	CON ($n = 15$)	DEP ($n = 19$)	SCH ($n = 20$)	ALC ($n = 10$)	ADJ ($n = 14$)	ALL ($n = 63$)
TSH ≤ 1 mU/l	1	9*	6	4	5	24*
ΔTSH ≤ 5 mU/l	0	12***	6*	7***	5*	30***
GH ≥ 3 ng/ml	0	0	4	0	2	6
ΔGH ≥ 5 ng/ml	0	5*	4	0	3	12
PRL ≤ 3 ng/ml	2	7	2	0	0	9
ΔPRL < 20 ng/ml	1	11**	3	1	3	18
CS > 12 μg/dl	1	7*	3	4	1	15
pCS > 5 μg/dl	2	14***	10**	5*	2	31**

CON = controls, DEP = depression, SCH = schizophrenia, ALC = alcohol dependence, ADJ = adjustment disorder, ALL = patients together. TSH = thyroid stimulating hormone, GH = growth hormone, PRL = prolactin, CS = cortisol; Δ = peak-minus-baseline response to TRH, pCS = the higher of two postdexamethasone CS values.
Significance vs the control group (Fisher's exact probability test): * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Neither baseline nor ΔGH value distribution could be normalized by log-transformation. Although both variables showed some elevated values in the patients but not in the controls, this was only different between healthy subjects and major depression (for ΔGH). The GH and ΔGH means did not differ among the groups as shown by either an ANOVA from the log-data or by the nonparametric test (χ^2 for GH = 0.65, and for ΔGH = 4.3, $df = 4$).

Baseline PRL values only approached normality after log-transformation but ΔPRL distribution became convincingly normal. Qualitative differences were not found between controls and patients in the baseline PRL values, but ΔPRL was significantly more often blunted in major depression; other patient groups remained indistinguishable. Quantitatively, a Kruskal-Wallis test was able to detect significant differences among the groups ($\chi^2 = 13.49$, $P < 0.01$), and this remained significant among only the patients ($\chi^2 = 13.22$, $P < 0.005$) regarding basal PRL; the heterogeneity was caused by the low mean PRL in the major depression group. ΔPRL differences among the groups just failed to be significant by the Kruskal-Wallis test ($\chi^2 = 8.79$, $P < 0.07$) but reached significance by ANOVA ($P < 0.03$). Here again patients with major depression were the most different from either the controls or from the other patient groups ($F = 10.29$ and $F = 10.21$, respectively).

Lastly, both CS values were fully normalized by the log-transformation. Baseline CS means did not prove to be significantly different among the groups ($F = 1.85$), but postdexamethasone CS means were clearly heterogeneous: controls differed from the whole patient group ($F = 11.48$, $P < 0.002$), were similar to the adjustment group and contrasted the other three groups ($F = 29.24$, $P < 0.001$) which on the other hand, still remained heterogeneous. Depressed and alcohol dependent patients had the two highest, apparently identical mean postdexamethasone CS levels.

There were several weak and some moderately strong correlations among the eight endocrine variables (Table 2); therefore we computed a MANOVA to find the best possible separation of our patient groups. This calculation yielded a Hotelling's $T^2 = 1.32$ which is highly significant ($F(31.66) = 2.72$, $P < 0.001$). However, 82% of this T^2 was accounted for by only three variables: ΔTSH, postdexamethasone CS and ΔPRL, and therefore calculated discriminant functions between each pair of groups using only these three variables. By far the best discrimination was achieved between the controls and patients with major depression: this function classified all the controls and all but one of the depressed patients correctly (97%). However, the same equation classified 12 schizophrenic, 8 alcohol dependent and 5 "reactive" patients with the major depression group, which represents an average 57% "false positive" rate. Any other equation produced virtually identical, but less accurate classification.

There were no significant correlations between age, weight or height and any of the eight endocrine variables; mean age, height and weight did not differ among the groups.

Discussion

The main findings of the study are: (1) baseline hormonal levels have only limited value in separating patients from controls; (2) postdexamethasone CS and TRH-induced TSH response are both markedly deviant in patients with psychotic or "melancholic" (i.e., endogenous) depression as compared with healthy controls, but (3) they are also frequently abnormal in other psychiatric conditions such as schizophrenia, alcohol dependence and adjustment disorder with depressed or anxious mood; (4) TRH-induced PRL response has a similar, although weaker, pattern in these groups as the TSH response; (5) pathological GH responses to TRH occur in some patients but not in the controls, although this is not consistent enough to help differential diagnosis in most cases. Lastly, a discriminant function derived from ΔTSH, postdexamethasone CS and ΔPRL can accurately identify 97% of depressed patients and controls (but also classifies 25 of 44 patients with other diagnoses as similar to the depressed group).

The high frequency of abnormal DST might be due to the fact that only psychotic or melancholic patients were included in the depression group; however, there were also many non-suppressions in schizophrenia and alcohol dependence, in agreement with others (Abou-Saleh et al. 1984; Dewan et al. 1982). Only 2 subjects from the control group had an abnormal DST, and only 2 in the adjustment disorder group; this might lend support to the claimed specificity of the DST in major depression (Carroll 1982). The DST alone correctly classified 13 controls and 11 depressed subjects (71% correct), whilst allocating 14 of 44 other cases (32%) to the depressed group; this is in accordance with most other observations (Hällström et al. 1983; Coppen et al. 1983).

Blunted TSH response to TRH was found in 12 of 19 depressed patients but in none of the controls; this again confirmed the validity of the TRH-test in identifying depression (Loosen and Prange 1982; Fleming et al. 1983). There were,

Table 2. Correlations between each pair of 8 neuroendocrine variables in the total group of 63 patients + 15 healthy controls. The values are Spearman's rank correlation coefficients with regard to the nonnormal distribution of the data

		ΔTSH	GH	ΔGH	PRL	ΔPRL	CS	pCS
TSH	1.00	0.51***	−0.10	−0.06	0.42***	0.16	−0.17	−0.35**
ΔTSH		1.00	0.15	0.04	0.26*	0.30**	−0.05	−0.31**
GH			1.00	0.19	0.11	0.19	0.11	0.00
ΔGH				1.00	−0.01	−0.08	0.18	0.17
PRL					1.00	0.42***	−0.08	−0.30**
ΔPRL						1.00	−0.05	−0.19
CS							1.00	0.49***
pCS								1.00

Abbreviations as in Table 1. * = ($P < 0.05$), ** = ($P < 0.01$), *** ($P < 0.001$)

however, 14 cases from other diagnostic groups with similarly blunted TSH-responses (39% "false positive" rate). There was some tendency for the TSH response to correlate with the DST (Spearman's R = −0.44, NS) in depression, and 11 patients had abnormal results in both tests.

TRH-induced PRL response was also found to be blunted in major depression, as reported by Linnoila et al. (1979); this measurement proved to be even somewhat more specific than the TSH response. There was, however, no correlation between the TSH and the PRL responses, as previously found by Loosen et al. (1983) in depression (R = 0.09); 8 patients had blunted responses of both hormones and 7 had divergent results. This lack of a strong correlation may explain why ΔPRL may be additionally useful in differentiating depressed patients from controls.

Pathological GH responses were seen in some patients, as indicated by other authors (Maeda et al. 1975; Gold et al. 1979), in schizophrenia (Ferrier et al. 1983) and in some adjustment disorder patients. This response was, however, altogether infrequent and did not prove to be particularly useful in identifying any subgroup of patients.

The observed hormonal changes might be subject to variability from many nonspecific sources; therefore we included only women to avoid sex variance (Amsterdam et al. 1983; Winokur et al. 1983), and excluded both extremely obese (Cavagnini et al. 1979) and anorectic patients (Maeda et al. 1976; Kline et al. 1983). Most baseline hormone values were within normal limits or at least they were not abnormal enough to indicate other endocrine illness. We could not find any correlation with height (Ågren and Wide 1982) for any endocrine variable, and similarly failed to find a relationship to age or body weight in this population. As a whole, there was no significant differences between pre- and postmenopausal patients or controls in any subgroup (Mendlewicz et al. 1979), but the menstrual cycle was not recorded and therefore there might be some differences due to this factor. It is, however, very unlikely that this uncontrolled variable would have contributed to the strong differences in TSH, GH and PRL responses to TRH in the patient groups.

In conclusion, we found that psychotic or melancholic major depression is characterized by strong blunting of TRH-induced TSH and PRL responses as compared to healthy controls, as well as by nonsuppression of dexamethasone. These three variables together can classify almost all patients and controls correctly; on the other hand, some other psychiatric disorders like schizophrenia, alcohol dependence (in the early withdrawal phase), and also adjustment disorder show similar hormonal patterns in a considerable proportion of the patients. Further investigation seems to be warranted to identify other endocrine parameters which could more sharply differentiate clinical categories from each other; or, conversely, more precise clinical work would be needed to correlate longitudinal variables (course, prognosis, treatment response, etc.) with the endocrine changes observed in the acute phase of the illness.

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