Paradoxical GH response to TRH during status epilepticus in man

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Abstract

Information on GH in relation to epilepsy is sparse, and to our knowledge there is no information on GH levels during status epilepticus in man. We studied GH in serum in six patients during status epilepticus, and in a control group of six seizure-free patients with epilepsy, before and after injection of TRH. The baseline GH values before TRH administration were within the normal range in all patients. After injection of TRH all patients with status epilepticus showed a paradoxical peak-shaped increase of GH to at least twice their baseline levels within 45 min after the injection (median basal GH value 1.5 mU/l and median peak GH value 6.5 mU/l, mean increase 330%). No uniform reaction to TRH was observed in the control group (median basal GH value 2.7 mU/l and median of the highest value within 45 min 5.2 mU/l). A paradoxical peak reaction of GH to TRH was significantly more frequent in the status epilepticus group compared with the control group ($P = 0.008$, Fisher exact probability test). TRH is not considered a GH-releasing hormone in humans during normal conditions, but a paradoxical response of GH to TRH, similar to that observed during status epilepticus, has been reported in various other pathological conditions, such as acromegaly, liver cirrhosis, mental depression and hypothyroidism. Our results of GH release after TRH administration in patients with status epilepticus suggest an altered regulation of GH as a result of the long-standing epileptic activity.

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Introduction

Neuroendocrinological changes in relation to epilepsy and antiepileptic medication have gained a great deal of interest in recent decades. Prolactin (PRL) has been the focus of attention since epileptic seizures were shown to be associated with a transient increase in serum PRL (1, 2). This observation is used clinically to differentiate between true epileptic and psychogenic seizures (2, 3). However, the localisations of the epileptic discharges in the brain, as well as their duration, influence their effect on serum PRL. Involvement of the temporal lobes and limbic structures seems to be crucial in producing significant PRL increase after epileptic seizures (4–6).

Hypothetically, effects on the regulation of hormone secretion of epileptic discharges in temporal and limbic structures may be mediated by, for example, the medial corticohypothalamic tract, which projects on the arcuate nucleus of the hypothalamus (7). This area contains tuberoinfundibular dopaminergic neurons, which are believed to be the source of PRL-regulating dopamine. In addition, galanin, growth hormone-releasing factor-like immunoreactivity, gamma-aminobutyric acid and somatostatin – hormones and peptides involved in the regulation of the anterior pituitary – are all present in the arcuate nucleus (8, 9).

Very short, as well as prolonged, seizure activity, such as in status epilepticus, seems to fail to produce significant PRL alterations (10–12). The mechanisms behind the divergent effects of status epilepticus and single seizures are unclear. More insight might be gained by analysing other pituitary-related hormones during epileptic seizure activity. We therefore extended our previous investigation and set out to study growth hormone (GH) and cortisol in patients with status epilepticus.

Patients and methods

Patients

We studied GH and cortisol responses to thyrotrophin-releasing hormone (TRH) in six patients with status epilepticus and in six seizure-free epileptic control patients, matched for age and sex. Patients with status epilepticus were consecutive cases available for investigation. All were female, and they represented three different types of status epilepticus. Status epilepticus was defined as a continuous seizure activity lasting 30 min or more, or at least two recurrent seizures without full recovery of consciousness in between. Clinical data are presented in Table 1. The diagnosis and

Table 1 Clinical data on six patients with status epilepticus.

Patient no.	Age/duration of epilepsy (years)/sex	Type of status/duration of status (h)	Antiepileptic drug therapy (mg/day)	Diazepam i.v. in relation to TRH injection	Concomitant disease	Additional regular medication (mg/day)	Time of day for baseline value before TRH
1	41/28/F	Typical absence/2	Phenytoin (400) Carbamazepine (500)	5 mg at the same time as TRH	None	None	0950
2	72/6/F	Complex partial/140	None	5 mg 20 min after	Status – post tick-borne encephalitis* Hypertension	Atenolol (50); oxazepam (10)	1450
3	68/–/F	Complex partial/24	None	5 mg 20 min after	Heart failure Depression	Furosemide (80); amloride (5); amitryptiline (100)	1345
4	62/14/F	Complex partial/70	Phenytoin (200)	5 mg 30 min after	Status – post ischaemic stroke† Asthma Uterine cervix carcinoma	None	1545
5	64/–/F	GTC/14	None	5 mg × 3 more than 1 h before	Alcoholism	None	1000
6	80/2/F	GTC/8	None	5 mg × 3 more than 1 h before	Dementia Diabetes Asthma Heart failure Angina pectoris	Glyceryl nitrate (2.6); flunitrazepam (0.5)	1745

* Tick-borne encephalitis 6 years before the study.

† Ischaemic stroke 14 years and cervix carcinoma 6 years before the study.

classification were based on typical clinical expression in the patients with generalised tonic-clonic (GTC) status and on EEG recordings during status in the remaining four patients (13, 14). Status was the first manifestation of epilepsy in two patients. Although four had a previous history of epilepsy, only two were on antiepileptic drugs prior to the status episode. All patients received acute treatment with diazepam for their status epilepticus (for details see Table 1). In two, diazepam was administered more than 1 h before the TRH injection. In one, diazepam was given at the same time as TRH, and in three at least 20 min after TRH administration. The patients with GTC status received in addition i.v. injection of phenytoin (PHT) at the time of TRH injection (patient no. 5) and 20 min after (no. 6). Although the duration of status epilepticus was excessively long in some cases, none of the patients was clinically in a state of semistarvation (Table 1).

Six female patients with epilepsy, seizure free for at least 1 month, served as controls (for clinical data, see Table 2). All control patients were on chronic antiepileptic drug therapy with PHT.

To our knowledge none of the patients suffered from thyroid dysfunction or any other disorder previously known to affect the GH response to TRH.

The study was approved by the local Ethics Committee (VSO-SSO No. 90–17).

Methods

TRH, 100 µg (Thyrefact, Hoechst Marion Roussel, Frankfurt am Main, Germany) was injected into an antecubital vein. The patients with status epilepticus received the TRH injection during status. The patients in the control group were studied in the morning, non-fasting, in a recumbent position after a short rest. Blood samples were drawn between –30 and 0 min before and 15, 30, 60, 90 and 120 min after TRH administration. Samples from the status group were analysed by GH RIA (Kabi-Pharmacia, Uppsala, Sweden). With this kit it

is expected that 95% of the values will be below 13.5 mU/l. Cross reactivity with PRL is less than 1%. The detection limit is 0.4 mU/l. Samples from the control group were analysed using an AutoDELFIA hGH kit (Wallac, Turku, Finland). Expected values for the kit are 95% below 11.5 mU/l for healthy adult females. Cross reactivity with PRL is less than 0.001% and the detection limit is 0.03 mU/l.

A significant GH response to TRH is defined as >100% increase from baseline values (15).

The serum concentrations of cortisol were measured by ELISA (ES 300, Boehringer Mannheim, Basel, Switzerland). Normal values from 0700 to 1000 h are 160–690 nmol/l, from 1000 to 1500 h 100–550 nmol/l and from 1500 to 1900 h 70–450 nmol/l. The intra-assay coefficient of variation is 7%.

Statistical analysis

The Fisher exact probability test for 2×2 tables was used for analysing differences in the occurrence of GH responses.

Results

Serum GH levels before and after injection of TRH during status epilepticus are shown in Fig. 1. GH levels before TRH injection ranged between 0.4 and 8.8 mU/l, with a median of 1.5 mU/l and a mean of 2.7 mU/l. In all six status patients, GH levels increased at least two-fold within 15–30 min after the TRH injection. In one patient (no. 4) the value at 45 min was the highest for that patient, but it was also the last, due to missing blood samples. GH levels had fallen in the other five patients by 60 min after the TRH injection. The peak concentrations of GH after injection ranged from 1.9 to 19.4 mU/l; median levels were 6.5 mU/l and the mean was 8.4 mU/l. For the status epilepticus group as a whole, the mean increase of median GH values from baseline to peak within 45 min was 330%.

Table 2 Summary of clinical data on the control group, six female patients with epilepsy, free of seizures.

Patient no.	Age/duration of epilepsy (years)	Type of epilepsy	Seizure-free period before study	Antiepileptic drug therapy (mg/day)	Additional disease	Additional regular medication
1	69/20	Unspecified	6 years	Phenytoin (200)	Allergy	None
2	57/38	Unspecified	7 years	Phenytoin (300)	Migraine	None
3	58/38	Localisation-related	10 years	Phenytoin (200) Phenobarbital (30)	None	None
4	63/5	Localisation-related	2 years	Phenytoin (350)	Status post operated intra-cerebral aneurysm; hypertension	Atenolol (50 mg/day)
5	74/44	Localisation-related	10 years	Phenytoin (100)	None	None
6	59/13	Localisation-related	2 months	Phenytoin (350) Lamotrigine (200) Vigabatrin (1500)	Dermoid cyst, intracerebral	None

Figure 1 GH response to TRH in six patients with status epilepticus. Blood samples at time zero were drawn before the status was terminated and before TRH injection.

Serum GH levels in the control group, before and after TRH injection, are presented in Fig. 2. GH levels before TRH injection ranged between 0.9 and 8.3 mU/l, the median being 2.7 mU/l and the mean 4.0 mU/l. GH levels before TRH injection were not increased in any patient and no uniform reaction to TRH was seen for the group. The median of the highest value within 45 min

was 5.2 mU/l, mean 5.9 mU/l. A GH response to TRH (according to our criterion) was observed in only one control patient; two other patients had non-significant increases in GH after TRH. For the group, the mean of the median change in GH values from basal levels to the highest value within 45 min was less than 100%. Three of the six patients showed a decline in GH levels after

Figure 2 GH response to TRH in six seizure-free control patients with epilepsy. Blood samples at time zero were drawn before TRH injection.

TRH injection. Significantly more patients with status epilepticus had a significant GH response to TRH compared with control patients ($P = 0.008$).

Serum glucose levels before and during the TRH test are depicted in Fig. 3 for patients with status epilepticus, and in Fig. 4 for control patients. Serum glucose levels ranged between 3 and 7 mmol/l in patients with status as well as in controls.

Serum cortisol concentrations in connection with status epilepticus are presented in Fig. 5. Cortisol levels before TRH ranged between 529 to 1463 nmol/l (median 632 nmol/l and mean 779 nmol/l), and remained relatively stable after TRH in all but one patient (no. 1). The cortisol levels are considered to be elevated since they represent afternoon samples (normal range 70–550 nmol/l) in the majority of cases (Table 1). The one patient with decreasing cortisol levels was the only patient with a prompt and lasting effect of treatment of the status epilepticus.

Discussion

Epileptic seizures have been demonstrated to influence pituitary hormonal release (1, 2, 4–6, 10–11). Presumably, the excessive synchronised epileptic neuronal discharges affect areas within the brain involved in the regulation of pituitary hormones. Depending on the localisation, the seizure activity may stimulate or inhibit hormonal systems. Single epileptic seizures that involve

Figure 4 Glucose levels in six control patients with epilepsy, seizure free. Blood samples at time zero were drawn before TRH injection.

certain areas of the brain such as the temporal lobes are frequently followed by a transient increase of serum PRL (3), whereas seizures in other areas of the brain do not result in any changes of PRL (4). The PRL response

Figure 3 Glucose levels in six patients with status epilepticus. Blood samples at time zero were drawn before status was terminated and before TRH injection.

Figure 5 Cortisol levels in six patients with status epilepticus. Blood samples at time zero were drawn before the status was terminated and before TRH injection.

seems to decrease with each seizure, if seizures occur in a series (16, 17); continuous prolonged seizure activity such as during status epilepticus appears to have a different effect on PRL release than single seizures (18). PRL levels are consistently low during status epilepticus in epilepsy patients (12, 19, 20); but a prompt response with PRL release to metoclopramide (19) or TRH (20) has excluded cellular depletion as an explanation for the low PRL levels during status.

Although prolonged seizure activity affects hormonal release in a different way than single isolated seizures, the mechanisms behind these different effects are unclear. In order to broaden our understanding of how status epilepticus affects hormonal release we have extended our analysis to include GH and cortisol, two other hormones related to the pituitary. The literature on GH levels in connection with epilepsy and single epileptic seizures is sparse, and partly conflicting results have been reported (1, 6, 21–23). To our knowledge, there is no previous information on GH levels in humans with status epilepticus.

Our findings were remarkably consistent, considering that the patients represent three different forms of status epilepticus with a considerable range in seizure duration. GH levels before TRH injections were within the normal range in all six patients. However, all patients responded to TRH with a significant peak-shaped increase in GH concentrations, despite a comparably low TRH dose. A similar effect is generally referred to as a paradoxical GH response, since TRH is considered to have no effect on GH levels in healthy humans, including the elderly (24, 25). TRH is invariably a GH-releasing factor in lower vertebrates. The pattern is different in mammals, where inhibitory interactions of TRH at central and pituitary sites may result in no GH change from baseline values (26).

Whereas all our patients with status epilepticus had a significant GH response to TRH, a similar response was seen in only one of the seizure-free control patients. This suggests that the response is linked to status epilepticus, rather than to the epilepsy diagnosis.

However, there are a number of different circumstances and conditions that may cause or otherwise be associated with an altered GH release, such as metabolic and nutritional alterations, drug therapy, other hormones and peptides, and age (27). Hypoglycaemia is one powerful GH-stimulating factor. Blood glucose levels were, however, normal in all our patients. Metabolic and nutritional factors, other than hypoglycaemia, are also known to influence GH release. Although two of our patients had long-standing GTC status, which might be associated with severe metabolic disturbances, the majority of our cases had other forms of status that should not affect the metabolic state of the patient. Nevertheless, despite this heterogeneity, we found uniform GH responses to TRH. Furthermore, if the GH release were induced by a metabolic abnormality, one would expect an increased GH level already before TRH

injection and not only a paradoxical response. Since this was not the case in any of our patients, we find it unlikely that the paradoxical response to TRH had a metabolic cause.

The GH release may also be influenced by cortisol. Serum cortisol levels are known to rise after single epileptic seizures (22, 23) and seem to remain elevated for up to 12 h after cessation of clinical seizures in status epilepticus in man (28). There seems to be a time factor involved in the GH response to corticoids in man. An acute potentiating effect on growth hormone-releasing hormone (GHRH) and a delayed blocking action on GHRH-induced GH secretion (12 h) has been reported (29). All our patients with status epilepticus had low GH levels before, and a distinct peak-shaped GH increase after TRH, while the cortisol levels remained at a stable, high level in five of the six patients. A direct cortisol-mediated action behind the GH response is therefore also unlikely.

GH levels may possibly also be affected by antiepileptic drugs. Carbamazepine (CBZ) and PHT may inhibit somatostatin (30, 31), which is the main regulating inhibitory hormone of GH. However, only two of our patients were on long-term treatment with CBZ and PHT at the time of status, and available data suggest little, if any, effects on GH by these drugs (1, 2). Furthermore, these two patients had very low GH levels before the administration of TRH, which speaks strongly against an inhibition of somatostatin.

All control patients were on long-term medication with PHT, and only one showed a paradoxical GH response to TRH. Thus PHT medication cannot explain the paradoxical GH release observed during status epilepticus. The use of diazepam for the acute treatment of status epilepticus could also have influenced the GH levels. Reports of diazepam effects on GH are somewhat conflicting, an increase or no effect has been observed (32, 33), although theoretically there are mechanisms by which benzodiazepines (BZD) may affect GH. As an example, micromolar but not nanomolar concentrations of midazolam have been shown to suppress basal somatostatin secretion from rat cell culture. The suppression of somatostatin is discussed as being the mechanism by which BZD can stimulate GH secretion (34). TRH and BZDs can also interact competitively on the binding site of TRH (35). Three of our patients did receive diazepam, either more than 1 h before (nos 5 and 6) or at the time of TRH injection (no. 1). The remaining three patients were given diazepam 20–30 min after TRH, which in general for them was after the onset of the GH peak. However, GH levels were not elevated before TRH administration in the two patients who were given diazepam before TRH. A hypothetical interaction between diazepam and TRH would presumably also have resulted in reduced GH peaks; in contrast these patients had significant peaks. The patient who was given diazepam at the same time as TRH had the lowest

GH levels in the group, but nevertheless a fourfold increase in GH after TRH. A competitive antagonising interaction between diazepam and TRH may explain the low values, but it obviously did not abolish a clear response to TRH. In conclusion it is most unlikely that the GH release in our status patients was induced by diazepam.

Finally, the GH peaks in our patients with status epilepticus may represent spontaneous secretory bursts, since GH is secreted episodically. However, this is also very unlikely, since five out of six of our patients were over 60, an age after which episodic secretion rarely occurs (27). The results from our age-matched control group, lacking a homogeneous GH response to TRH, also support the belief that the paradoxical GH secretion seen in the patients with status epilepticus is related to the long-standing epileptic discharges.

Having excluded these possible influences with reasonable certainty, we regard the GH response in our patients with status epilepticus as a true paradoxical one. Such responses have been obtained in connection with a variety of conditions: acromegaly, anorexia nervosa, chronic renal failure, diabetes mellitus, liver cirrhosis, mental depression, primary hypothyroidism, critical illness, and in constitutionally tall children (26). The mechanism behind paradoxical GH response is, however, unknown. Somatostatin and GHRH secretion occur, both in GH-secreting adenoma cells and in normal human pituitary cells. TRH stimulates somatostatin release from normal cells, while inhibition of somatostatin has been demonstrated after TRH in adenomatous tissue (36). These findings may be of interest in relation to paradoxical GH responses.

The concept for GH regulation is thus multifactorial, as is that for the regulation of PRL secretion. TRH is considered to be a PRL-releasing factor, while dopamine inhibits PRL. Dopamine also inhibits GH secretion from cultured pituitary cells, i.e. at the pituitary level (37, 38). In contrast, the systemic administration of dopamine results in GH increment (27), probably due to the activation of hypothalamic hormones stimulating GH release. However, in some conditions, such as acromegaly, systemic dopamine inhibits GH release, pointing at a dysregulation between the hypothalamus and the pituitary. A high proportion of patients with acromegaly have a paradoxical GH release after TRH administration, similar to our patients with status epilepticus. The possible dysregulation between the hypothalamus and the pituitary in patients with acromegaly also involves an abnormal reaction to dopamine (39). In contrast to the normal situation, dopamine often inhibits GH in patients with acromegaly. Critical illness is another condition where paradoxical GH release after TRH administration has been claimed. Infusion of dopamine in such patients further attenuates GH secretion through amplitude modulation. The peak GH response to TRH is, however, independent of dopamine (40, 41).

One may speculate that dopamine, in excess because of long-standing epileptic seizure activity, inhibits not only PRL but also GH, resulting in their low levels, which rise after TRH injection. The GH inhibition by dopamine as well as the GH increase after TRH in these patients is possibly due to hypothalamic dysfunction resulting in direct effects of dopamine and TRH at the pituitary level. Our observations of a paradoxical GH response to TRH are confined to patients during status epilepticus, while seizure-free patients with epilepsy do not show a uniform reaction. Further studies on epilepsy patients after single seizures are needed to clarify the role of the underlying seizure disorder, the seizure activity, and its duration.

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