

Characterization of growth hormone release in response to external heating Comparison to exercise induced release

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Abstract. The effects of increases in body temperature on growth hormone (GH)-release were studied in 10 young normal males in the fasting state as well as postprandially.

The temperature increase of one degree centigrade was attained by external heating using thermostatically controlled water blankets covered by heat-reflecting aluminium foil. The increase in plasma GH after heating was partially suppressed in the non-fasting state reaching a mean of 7.9 ± 3.5 (SEM), ng/ml, range 1.0–36 ng/ml. In contrast all subjects exhibited higher increases, mean 18.3 ± 4.0 ng/ml, range 7–44 ng/ml, in response to heating when fasting.

The results were compared in the same subjects to the plasma GH-responses obtained during exercise (450 kpm/min for 40 min) inducing a similar increase in body temperature of about one degree centigrade. Nevertheless the response in plasma GH (8.4 ± 3.3 ng/ml, range 0.4–34 ng/ml) was smaller than obtained by the heat test despite a rate of temperature increase on exercise which was about twice as high. Furthermore, the same exercise performed in a cold room under circumstances which precluded any major rises in core temperature resulted in complete inhibition of GH-release. The results indicate that exercise per se does not stimulate GH-secretion, indeed it may inhibit the response expected to be evoked by the exercise-induced rise in temperature.

Evidence is also presented that it is core and not cutaneous temperature which modulated GH release.

The procedure used for inducing the rise in temperature and plasma GH may be used as a simple, acceptable and safe clinical test for GH-insufficiency.

Assessment of growth hormone (GH)-release is central to the diagnosis of pituitary insufficiency especially in children as GH is often the most sensitive indicator of incipient hypopituitarism. Measurements of 'basal' plasma GH during daytime frequently fail to rule out the diagnosis, so application of one or more of the various GH-stimulation tests is almost always required. These may be inadequate, having a high incidence of falsely negative outcome, and the generally most dependable of them, insulin-induced hypoglycaemia, is because of its potential hazards used with increasing reluctance and has recently been banned in several centres (Greenwood et al. 1966; Lin & Tucci 1974).

The introduction of a safe, acceptable and reliable GH-stimulation test could be advantageous and we have explored the usefulness of inducing a rise in body temperature. Previous studies in this field have included pyrogen administration (Frohman et al. 1967), virus inoculation (Beisel et al. 1968), external heating in hot air (Brandenberger et al. 1979; Leppäluoto et al. 1975; Okada et al. 1972) and submersion into hot baths (Buckler 1973; Jurcovicová et al. 1980; Weeke & Gundersen

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1983; Weihl et al. 1981); all of them are rather onerous if they are to be used in clinical diagnosis and employ varying degrees of stress.

In the present study we describe a tolerable, easy and reproducible way of increasing body temperature and find evidence that it is elevation in core – not surface – temperature, which triggers GH-release. In addition we have in the same subjects attempted to quantify the participation of increasing temperature in the exercise-induced GH-response.

Subjects and Methods

The protocol was in accordance with the Helsinki declaration and approved by the regional ethic committee. Informed consent was obtained before the study.

Ten healthy non-obese male medical students were studied. None received any medications. Clinical data for the participants: mean age 24.6 ± 0.4 years, mean height 183.4 ± 1.8 cm and mean ideal body weight $101.0 \pm 1.7\%$. All subjects were examined in 4 different tests in random order: 1) heat-test, fasting, 2) heat-test, non-fasting, 3) exercise-test at 22°C and 4) exercise-test at 4°C . An interval of 2 to 5 days elapsed between each test.

Tests 1, 3 and 4 started before ambulation between 08.00 and 09.00 h after bedrest and overnight fasting at the hospital. Test 2 was preceded by a standard meal (11.3 g protein, 66.3 g carbohydrate and 14.0 g lipid: total 1878 kJ) served 30–60 min before the first blood sample. The subjects were ambulant previous to test 2 which was carried out between 08.00 and 12.00 h. The heat-test was also performed in 2 GH-deficient subjects.

Finally, two subjects were studied during local heating for 1 h by an electric heating pad covering the anterior truncus from the papillae to below the umbilicus, otherwise the protocol of test 1 was followed. No fluid or smoking was allowed during any of the test periods. Body mass was registered before and after all tests. Temperature of the tympanic membrane and pulse rate were recorded concomitantly with all samplings.

Thirty minutes before the first blood sample an indwelling catheter was placed in an antecubital vein and kept patent by 1.5 ml saline following each sample. All tests were preceded by 3 basal blood samples and followed by sampling every 10 min for 1 h. During heat-tests blood samples were obtained at 0, 5, 10, 15, and subsequently every 10 min. During exercise tests samples were collected at 0, 5, 10, 15, 20, 25, 30, 35 and 40 min. Samples were stored at -21°C . Samples from all 4 tests in each subject were run in one assay.

Plasma GH values were determined by radioimmunoassay (Ørskov et al. 1968) using wick chromatography; highly purified human GH (Nordic Insulin Laboratory, Copenhagen) was used as standard. Blood glucose was measured by a glucose oxidase method (Christensen 1967).

Tympanic membrane temperature

Measurement of tympanic membrane temperature (core temperature) was carried out using a thermocouple probe, type AI 15 (Ellab Instruments, Denmark). The probe was connected to an electronic direct reading thermometer with plotter, type du 81s (Ellab Instruments, Denmark). The accuracy of the thermometer recordings was checked to be within $\pm 0.1^\circ\text{C}$.

Heat-test

After the basal blood samples the subject was placed on another bed, where he was wrapped between cotton blankets, covered back and front by heating blankets size 140×104 cm (Heto Lab Equipment, Denmark), finally the bag was completed by silver-folio, 200×140 cm (Edelrid rescue blanket) and closed with tape. Outside the bag remained the head and one arm for blood sampling. A heat circulator, type 05 NF 623K (Heto) kept the circulating water in the heating blankets constant at 67°C with a checked stability of $\pm 0.5^\circ\text{C}$.

The application-time of the stimulus was defined as that covering an increase of 1°C from the pre-level temperature measured on the tympanic membrane.

Exercise-test

Exercise was performed on a bicycle ergometer (Monark 668, Sweden) 450 kmp/min for 40 min. The load was selected to give temperature elevations comparable to those obtained during the heat-test.

Exercise was carried out at ambient thermoneutral conditions of 22°C (test 3) in light hospital clothing. During tests in the cold-room at 4°C (test 4), probands were dressed in T-shirt and shorts. They were transported to the cold-room in bed immediately before start of test 4. Their clothing were moistened by cold water and cold wet towels were replaced at 10 min intervals around the neck and truncus. An air-fan directed at the truncus was mounted onto the handle bars of the bicycle ergometer. After the exercise, subjects were dressed in dry clothing and put to bed in a room at 22°C , where the last six samples were collected.

Presentation of data

Results are expressed as mean \pm SEM. To obtain mean values of the heat-tests of variable duration it was necessary to transform individual curves to a common duration (the mean duration) and read off interpolated values. Statistical analyses were performed using Student's paired *t*-test, a *P* value of 0.05 or less was considered significant.

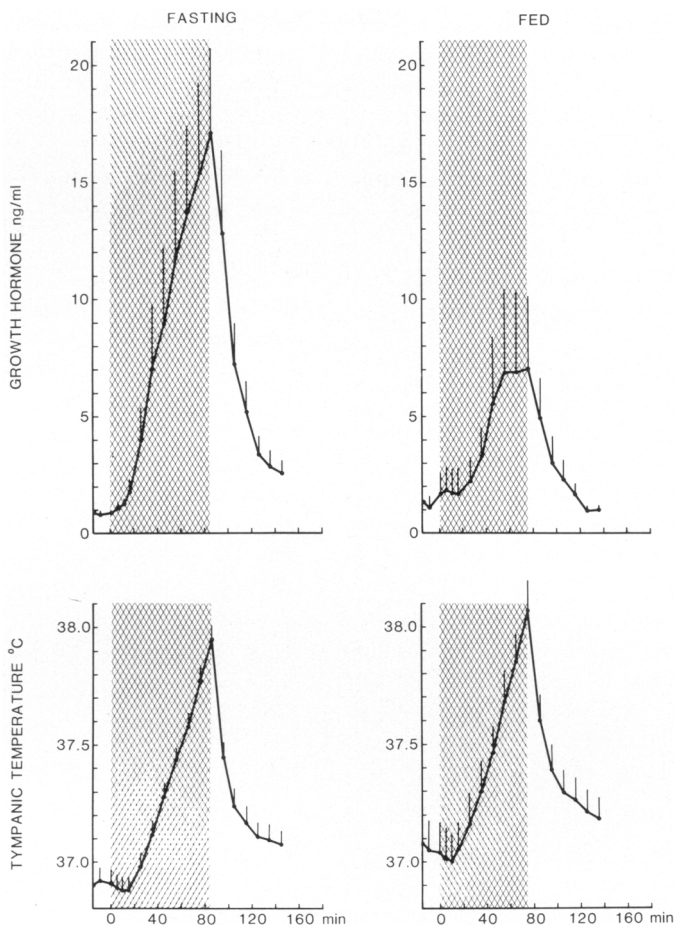


Fig. 1.

Average levels (\pm SEM) of tympanic temperature and plasma GH during external heating in 10 normal subjects. The abscissa gives the average time (shaded area) to reach an increment in temperature of 1°C (see text).

Results

1) Heat-test fasting (Fig. 1)

When the heat-test was performed during fasting all 10 subjects exhibited an increase in plasma GH lasting until termination of the stimulus. During the post-stimulus period base-line values were almost re-attained. Basal plasma GH levels ranged from 0.2 to 1.7 ng/ml, and the peak responses from 7.0 to 44 ng/ml. The blood glucose values did not show any significant variations during the test.

Mean tympanic membrane temperature (Fig. 1) started to rise after a lag of about 15 min, rose linearly from 36.81 ± 0.06 to $37.85 \pm 0.06^{\circ}\text{C}$, during the post-stimulus period the pre-level was nearly re-attained.

The mean pulse rate rose starting immediately after application of the heat-test, initially linearly, then leveling off (from 66.1 ± 2.7 to $98.2 \pm 3.6 \text{ min}^{-1}$).

Visible hidrosis was observed after approximately $\frac{1}{2}$ h of heating. Mean weight loss was 1.2 ± 0.1 kg. No correlations were found between the increments in plasma GH vs the duration of the stimulus or vs the weight loss or vs the increments in pulse rate.

2) Heat-test, non-fasting (Fig. 1)

All subjects attained lower plasma GH values than when studied during fasting. The plasma GH-response was above 5 ng/ml in 3 subjects only. The

blood glucose level was significantly elevated during test 2 compared with test 1 ($P < 0.01$).

The pre-stimulus mean tympanic membrane temperature was $36.94 \pm 0.13^{\circ}\text{C}$ compared to $36.81 \pm 0.06^{\circ}\text{C}$ in test 1. The slope and amplitude of the temperature rise during the heat stimulus was identical to those in test 1. The duration of the stimulus was not significantly shorter during test 2. The mean pulse rate rose from 71.4 ± 2.0 to $98.0 \pm 2.7 \text{ min}^{-1}$. Mean weight loss was $1.1 \pm 0.1 \text{ kg}$.

3) *Exercise-test, 22°C* (Fig. 2)

Mean plasma GH rose from pre-exercise concentration 0.81 ± 0.21 to $8.37 \pm 3.32 \text{ ng/ml}$ at the end of exercise. Four subjects responded to the test with peak GH concentrations exceeding 5 ng/ml . The blood glucose level was uninfluenced by the exercise load.

Mean tympanic temperature rose from 36.56 ± 0.09 to $37.36 \pm 0.08^{\circ}\text{C}$ reached at the end of the

exercise period. During the post-stimulus period temperature returned towards pre-stimulus values. The mean pulse rate rose sharply at initiation of exercise from $65.2 \pm 2.0 \text{ min}^{-1}$, leveled off and reached $115.8 \pm 2.8 \text{ min}^{-1}$ at the end of exercise, and then immediately returned towards resting levels. Mean weight loss was $0.7 \pm 0.1 \text{ kg}$.

4) *Exercise, 4°C* (Fig. 2)

The mean GH values during the exercise period were significantly lower when compared to the pre-values ($P < 0.01$). At the termination of exercise a rebound in plasma GH was observed. The blood glucose level was uninfluenced by exercise and identical to that of test 3.

Mean tympanic temperature rose from basal level of 36.56 ± 0.08 to $36.83 \pm 0.15^{\circ}\text{C}$ reached after 25 min of exercise, and was followed by a continuous drop in temperature lasting until 40 min after termination of exercise when the minimum temperature $36.29 \pm 0.11^{\circ}\text{C}$ was reached.

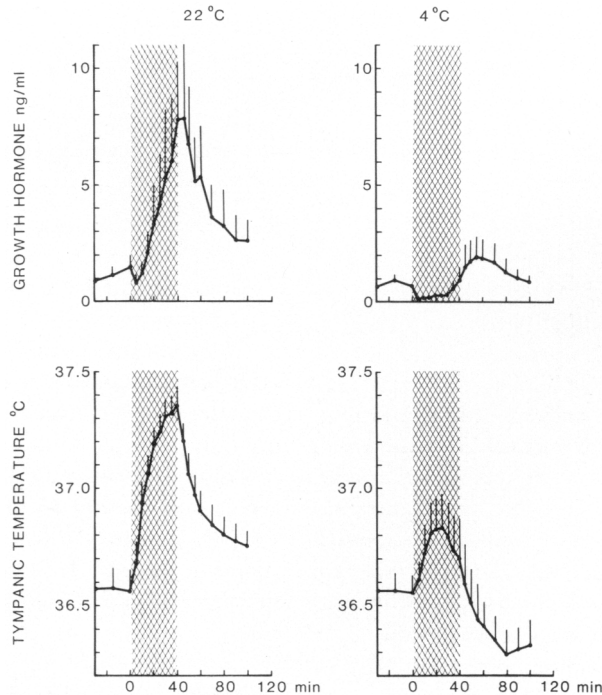


Fig. 2.

Average levels (\pm SEM) during exercise (450 kpm/min) for 40 min (shaded area) of tympanic temperature and plasma GH in the 10 normal subjects studied in Fig. 1.

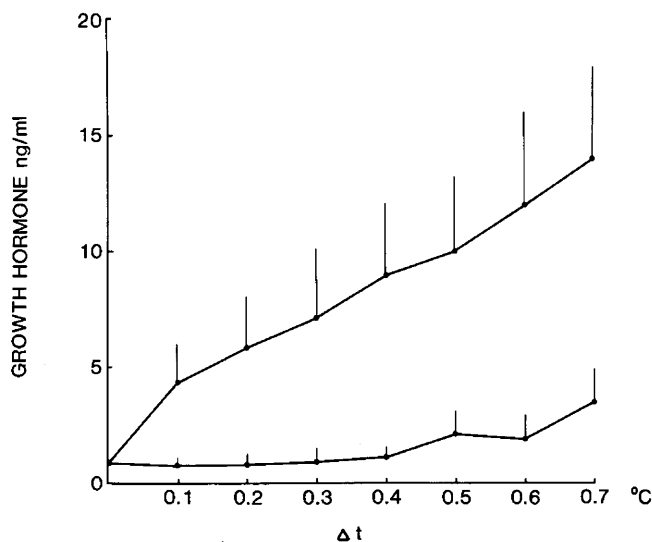


Fig. 3.

Average increases in plasma GH (\pm SEM) per 0.1°C increase in tympanic temperature in 10 normal subjects during external heating (upper curve) and exercise (lower curve). Two subjects did not reach an increase in temperature above 0.7°C in the exercise experiments.

Discussion

Mean basal pulse rate was $61.6 \pm 1.6 \text{ min}^{-1}$, rose to $104.2 \pm 3.9 \text{ min}^{-1}$ after 50 min of exercise and stayed at a plateau during the rest of the exercise period, whereupon it rapidly decreased to resting values. Mean weight loss was $0.5 \pm 0.04 \text{ kg}$.

Growth hormone response in test 1 vs test 3.

In Fig. 3 the average GH values in test 1 and test 3 (lower curve) are given, expressed per tenth of one degree centigrade.

Growth hormone insufficient patients

The two GH-deficient patients studied according to test 1 conditions did not exhibit any GH-increase.

Local heating of anterior truncus

When the two subjects were warmed at the anterior truncus by an electric heating pad, but otherwise uncovered, the tympanic membrane temperature did not rise and plasma GH-levels were unaltered. Skin temperature measured on abdomen rose maximally 9.1 and 6.3°C in the two subjects. These delta values were higher than those obtained during the heating test: 3.8 and 3.3°C, respectively.

The present study explores the possibility, as suggested recently by Weeke & Gundersen (1983), of a GH-release test utilizing the pronounced stimulatory effect of increases in body temperature induced by external heating. In a series of preliminary experiments comprising more than 60 subjects we noted that heating constantly and reproducibly induced large GH-responses in normal subjects who had fasted overnight (unpublished). In these experiments we also attempted to develop a procedure somewhat more practical and acceptable than previous ones which utilized the hot air of saunas (Brandenberger et al. 1979; Leppäluoto et al. 1975; Okada et al. 1972) or submersion into hot water (Buckler 1973; Jurcovicová et al. 1980; Weeke & Gundersen 1983; Wehl et al. 1981) and which were not suitable for a clinical test. We ended up with the simple technique described here in which the subjects are placed between two heating blankets with a flow of thermostatically controlled hot water and covered by highly heat-reflecting aluminium foil (rescue blankets).

In previous studies the question remained whether the heat-induced GH-release is evoked by an increase in core temperature by the blood reaching

the hypothalamus or through cutaneous heat-receptors. In the present study no increase in plasma GH was found in experiments in two subjects who had attained a much higher but local increase in temperature of the anterior skin of thorax and abdomen without increased core temperature, supporting the idea that it is mainly the latter which determines the GH-release. On the other hand, the present results do not exclude the possibility that the GH stimulation observed during external heating and the suppression occurring in the cold room might be mediated through changes in the firing rate of cutaneous cold receptors, which have a hypothetical inhibitory effect of GH-release. The heating pad covered a comparatively small area of skin and cold receptors in other areas might still be active enough to suppress GH-release. However, the previous experiments of Weeke & Gundersen (1983) seem to rule out the hypothesis, since they observed no increase in plasma GH in subjects submerged for 90 min in water of 36°C under which circumstances core temperature was constant and cutaneous cold receptors were obviously inactive.

It appears also, that alterations in blood glucose, pulse rate, body fluid balance, and 'stress' were hardly involved in the different patterns of plasma GH obtained in the four tests.

From a physiological point of view it would be of interest to understand to what extent the temperature-dependent GH-release is involved in some of the multitude of situations which influence GH-secretion.

Obvious candidates for such a study would be the well-known changes in GH-release activity through the menstrual cycle, which incidentally appear to fit with the alterations in body temperature (Hansen & Weeke 1974). Speculatively, the so-called sleep-induced nocturnal plasma GH peaks (Takahashi et al. 1968) may also be related to changes in hypothalamic temperature setting. However, more evident perhaps it is to try to estimate a possible participation in the exercise-induced GH-secretion (Hansen 1970, 1972).

An exercise load (i.e. about 200 kpm/min) which would induce a similarly slow rise in core temperature as that attained in the present external heating experiment will interestingly induce no GH-release at all in reasonably fit young subjects (Hansen 1972). We therefore used the greater work-load of 450 kpm/min, which by 40 min will stimulate GH-secretion in most (Hansen 1972). Surprisingly,

despite the almost 2-fold steeper increase in temperature per time unit, the exercise-induced GH-release was appreciably lower than that attained during external heating. Expressed as plasma GH increase per increase in tenths of degrees centigrade the difference was striking (Fig. 3). It is therefore tempting to suggest that exercise in some way inhibits the GH-release induced by the concomitant rise in core temperature. This view is borne out by the virtually complete inhibition of 'exercise-induced' GH-release, when the work-load was performed in the cold room where rises in core temperature were almost abolished. The finding is in accordance with the results of Galbo et al. (1979) who studied GH-responses to swimming in cold and neutral water, but is at variance with that of Buckler (1973) who in a single subject found that heat-induced GH-release was smaller than that obtained during exercise with comparable increase in body temperature.

In conclusion, increase in core temperature is a powerful GH-stimulus in normal weight, fasting, normal adult. It is, however, less effective in the non-fasting state as is the case in other GH-stimulation tests. Weeke & Gundersen (1983) found that it is inversely correlated to percentage of ideal weight, and we found very inhibited responses in grossly obese subjects (unpublished). The procedure used here appears to be well-suited as a test for pituitary function, a fact that may have clinical interest especially in children and adolescents in whom responses to traditional tests are often less dependable than in adults.

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