Comparison of the pharmacological properties of pituitary and biosynthetic human growth hormone

Demonstration of antinatriuretic/antidiuretic and barbital sleep effects of human growth hormone in rats

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Abstract. Biosynthetic human growth hormone was compared with pituitary human growth hormone and pituitary 22 K in the weight gain and the tibia test. The three preparations were found to be equipotent. Furthermore, the growth hormones were compared in various pharmacological test systems. All three preparations were found to have a marked antidiuretic and antinatriuretic effect in the rat and to cause a significant shortening of the hexobarbital sleeping time in mice. Biosynthetic and pituitary preparations had the same diabetogenic activity in obese mice, and the growth hormones did not differ with respect to pharmacological profiles in the test systems applied.

Pituitary human growth hormone is a mixture of polypeptides, the major physiological component being a single-chain polypeptide of 191 amino acids with a molecular weight of 22,000 ("22K"-form). It has been reported that some of the minor components differ from the 22K-molecule in receptor binding characteristics and growth activities and in metabolic and possibly lactogenic effect (Lewis et al. 1980; Chawla et al. 1983; Closset et al. 1983).

Biosynthetic human growth hormone is a single component preparation consisting of 22K only.

In the present studies, the pharmacological properties of preparations of pituitary and biosynthetic human growth hormone were compared. Furthermore, a preparation of pituitary 22K isolated by purification was included.

The three growth hormone preparations were compared in hypophysectomized rats in the two most widely used bioassays for growth hormone, the weight gain test and the tibia test. In addition, general pharmacological studies were undertaken with the aim of gaining additional information on similarities and possible dissimilarities in the pharmacological profiles of the growth hormone preparations. The results presented are from those test systems in which effects were registered. The other tests performed are briefly mentioned under the Discussion.

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Materials and Methods

Hormones, drugs and chemicals

The growth hormone preparations used were manufactured by Nordisk Gentofte A/S, Denmark. Escherichia coli MC 1061 was used for expression of a growth hormone precursor which by means of a novel enzymatic method was converted to authentic human growth hormone (Dalbøge et al., manuscript accepted for publication).

The freeze-dried growth hormone materials were dissolved in distilled water to obtain isotonic solutions. Further dilutions were made with Nanormon buffer (a sodium bicarbonate buffer with glycine and mannitol).

The following preparations were used: Amylenhydraté (Gentofte Pharmacy, Denmark), Brielal® (metoheital, Lilly, Eli Lilly and Co Aps, Denmark), Tengesic® (buprenorfin, Reckitt & Colman Ltd, England), furosemide (DAK Laboratories A/S, Denmark), Vasopressin® (lypressin, Sandoz A/S, Denmark), and Decadron® (dexametason, Merck Sharp & Dohme, Denmark).
Hyphophysectomy

Female Wistar/Mol rats from Mollegaards Breeding Laboratory Aps, DK-4623 Li. Skensved, were housed at 21 ± 1°C, 60 ± 5% relative humidity, air change 16 times per hour and light on from 07.30 to 19.30 h. The animals had free access to drinking water and to Altromin diet (No. 1324, Chr. Pedersen Ltd, DK-4100 Ringsted) and were housed 5 per cage.

Hyphophysectomy was performed when the rats were 28–30 days old. The rats were anaesthetized with 4–5 ml/kg amylane hydrate (10% in 0.9% saline) in addition to 4–5 ml/kg Brietal® (10 g/l 0.9% saline) ip. The hyphophysectomy was performed with a special apparatus described by Illhardt (1971). After cutting the lower part of the ear, the rats were fixed in the apparatus for transauricular hypophysectomy. A cannula was inserted into the hypophyseal area, and the pituitary gland was sucked out with a vacuum of 200–400 mmHg. A cotton wool tampon was placed in the ear after the operation, and postoperatively the rats were treated for two days with twice daily injections of Temgesic® for analgesia.

The rats were weighed before hypophysectomy and 14 days after. Only animals with a weight gain < 10 g or a weight loss < 4 g and in good health were used in the experiments.

Weight gain test

Biosynthetic human growth hormone (B-hGH), pituitary human growth hormone (Nanormon®), and pituitary 22K (P22K) were compared in a 10-day weight gain test at five dose levels. Each dosage was administered to a group of six rats in three different experiments. (270 rats totally). Furthermore, 36 rats were injected with placebo (Nanormon buffer). Nanormon® was injected in 24-h-dosages of 4, 8, 16, 32 and 64 µg of protein per rat, B-hGH in dosages of 5.06, 10.11, 20.22, 40.44 and 80.88 µg of protein, and P22K in dosages of 5.20, 10.41, 20.81, 41.62 and 83.24 µg of protein. The protein determinations were based on a quantitative GP-HPLC analysis comparing the areas of monomer 22K at 215 nm.

The treatments were randomly assigned to the groups. Half of the 24-h-dosages were administered at 07.00 h in 0.5-ml volumes sc in the neck, the other half at 16.00 h. The rats were weighed on days 1, 2, 3, 5, 7, 9 and 11, and sacrificed on day 11 by decapitation. The following organs were removed and weighed: the gastrointestinal tract (after washing with 0.9% saline), kidneys, liver, lungs, heart, thymus, and gastrocnemius muscles. Use was made of a Sartorius balance 1465 connected with an Epson HX-20 computer.

Tibia test

The three growth hormone preparations were tested at five dose levels and each dosage was administered to a group of ten rats in three different experiments (450 rats in all). Nanormon® was injected in 24-h-dosages of 4, 8, 12, 16 and 32 µg of protein per rat, B-hGH in dosages of 5.06, 10.11, 15.17, 20.22 and 40.44 µg of protein, and P22K in dosages of 5.20, 10.41, 15.61, 20.81 and 41.62 µg of protein.

The rats were injected sc in the neck for four days, once daily at 11.00 h, and about 21 h after the last injection they were sacrificed with CO₂. The tibia bones were dissected free of the accompanying soft tissue and split in the midsagittal plane. The bone halves (one half from each tibia) were washed for 5–10 min in distilled water, immersed in acetone for 10 min, washed in water again for 3 min, and placed in freshly prepared 2% silver nitrate for 2 min. They were then rinsed in water and exposed to strong light for 5–10 min, while under water. When the calcified portions became dark brown, they were placed on a microscope stage, and the width of the uncalcified epiphyseal cartilage was measured using a calibrated micrometer eyepiece. The average width of the two bone halves was used as the result for each individual rat.

Rat. Screening for diuretic and antidiuretic effects

The three growth hormone preparations were screened for effect on diuresis, essentially as described by Lipschitz et al. (1943). Male Wistar/Mol rats, 150 ± 5 g were used in the study. They were housed at 21 ± 1°C, 60 ± 5% relative humidity and light on from 07.30 to 19.30 h. They had free access to Altromin diet (No. 1324). The rats were deprived of food and water from 15.00 h the day before the experiment. Half of the rats were loaded with 25 ml/kg body weight of 0.9% saline po, the other half with 50 ml/kg distilled water po.

The treatments were randomly assigned to groups of six rats, which were treated with Nanormon®, 2.5 or 25 IU/kg, B-hGH, 2.5 or 25 IU/kg, P22K, 25 IU/kg, placebo (Nanormon buffer), furosemide, 15 mg/kg, or lypressin, 0.5 IU/kg. All dosages were administered sc at ~5 min, and the load of saline/water was administered at zero min. Thereafter the rats were placed individually in metabolism cages and the urine volumes excreted were measured at hourly intervals. Urine was pooled from each group of rats for the time periods 0–2 h and 2–6 h and Na, K and Cl concentrations were measured on the pooled samples. Na and K was measured with an FLM flamephotometer (Radiometer), Cl was measured using an ionselective electrode (Radiometer) after a 30-fold dilution with 0.1 mol NaNO₃.

Mice. Narcomis potentiation

The effects of biosynthetic and pituitary human growth hormone preparations on hexobarbital sleeping time in mice were studied using male and female NMRI mice.
20 ± 2 g from Gl. Bomholtgaard, Ry, Denmark. The mice were housed at 20 ± 1°C, 60 ± 5% relative humidity and light on from 07.30 to 19.30 h. They had free access to Altromin diet (No. 1324) and drinking water until they were used in the experiment. Dosages of 0.25, 2.5 and 25 IU/kg body weight were administered sc in the neck in volumes of 10 ml/kg body weight to groups of 10 mice ½ h or 2 h before the ip administration of 0.5 ml-volumes of 100 mg/kg hexobarbital (a 0.4% solution of hexobarbital in distilled water was prepared, adding approximately 10 ml 5 N NaOH per l). The treatments were randomly assigned to the groups and a placebo group receiving Nanormon buffer was included each experimental day.

During the narcosis, the mice were placed on a heated operating table (37°C), and the time from disappearance to reappearance of righting reflex was registered as the sleeping time.

**Obese (ob/ob) mice. Diabetogenic activity**

The effects of the three human growth hormone preparations on fasting blood glucose concentrations and glucose tolerance in obese mice were investigated.

Female obese (ob/ob, C57BL/6) mice were purchased from Olac Ltd, Shaw’s Farm, England. The mice were housed at 20 ± 1°C, 60 ± 5% relative humidity and light on from 07.30 to 19.30 h. The animals had Altromin diet (No. 1324) and drinking water ad libitum.

The experimental design was essentially as described by Reagan (1978). The mice were randomly assigned to groups of 7 mice checked for matching body weight.

All groups were injected with placebo (Nanormon buffer) sc in the neck at 09.00 h for three consecutive days. On the fourth day, each mouse was given 2 µg of dexamethasone in 0.2 ml sc at 07.00 h and fasted for 6 h. After fasting, a glucose tolerance test (GTT) was performed: 1 g/kg glucose was administered ip at zero min. From the orbital plexus, 25-µl blood samples (in duplo) were taken at −5, 20, 40, 60, 90, 120 and 180 min for glucose determinations. The glucose analyses were performed on a Technicon Autoanalyzer using Mercks gluc-DH-method.

Seven days after the beginning of placebo treatment, the same groups of mice were treated for three days (day 8–10) with one out of the three growth hormone preparations at a dose of 0.5 IU or 2.0 IU sc per day or with placebo in 1.0-ml volumes. The treatments were randomly assigned to the groups. On day 11, a treatment with dexamethasone was followed by a glucose tolerance test as described above.

![Graph](image-url)

**Fig. 1.**

Log dose response lines for pituitary human growth hormone (Nanormon® †—+), biosynthetic human growth hormone (B-hGH 0—+) and pituitary 22K (P22K •—+) in the weight gain test. The figure shows means ± SEM (N = 18). The data were fitted to straight lines by linear regression (applying the least square method).
Results

Weight gain test

Fig. 1 illustrates the log dose response lines for the three human growth hormone preparations in the weight gain test. The lines were tested for parallelity and found to be parallel \((P < 0.05)\). B-hGH was found to have 109.2% of the potency of Nanormon\(^\circledR\) (95\% confidence limits: 83.9–119.1\% of stated potency). P22K had 105.6\% of the potency of Nanormon\(^\circledR\) (95\% confidence limits: 83.1–120.4\%) and 93.2\% of the potency of B-hGH (95\% confidence limits: 82.9–120.6\%). The correlation coefficients and regression coefficients were as follows: For B-hGH, \(r = 0.99, a = 3.553, b = 6.267\); for Nanormon\(^\circledR\), \(r = 1.00, a = 3.787, b = 6.000\) for P22K, \(r = 1.00, a = 5.404, b = 5.552\). The \(\lambda\)-values as indexes of precision \((\lambda = s/b)\) were 0.61, 0.47 and 0.70, respectively.

The weight gain in the placebo group during the administration period was 0.500 ± 0.392 g.

At autopsy it was found that the dose-related increases in the absolute organ weights were similar for all three growth hormone preparations (not shown). All dosages of the three preparations caused significant increases compared with placebo in the organ weights registered \((P < 0.001, \text{ Student's } t\text{-test})\). As for the relative organ weights, no dose-dependent changes were seen. However, the relative thymus weight was lower for the placebo group (0.29\%) than for all other groups (0.34–0.43\%).

Tibia test

The width of epiphyseal cartilage in hypophysectomized rats receiving only placebo treatment (Nanormon buffer) was 133.6 ± 3.8 \(\mu\)m. The Nanormon\(^\circledR\) batch used was compared in the tibia test with the international standard for growth hormone, human, for bioassay (NBSB) and found to have an activity of approximately 2.9 IU/mg protein.

The log dose response curves obtained with the three preparations in the tibia test are shown in Fig. 2.

The lines were tested for parallelity and found to be parallel \((P < 0.05)\). B-hGH had 86.6\% of the activity of Nanormon\(^\circledR\) (95\% confidence limits: 65.8–113.9\% of stated potency). P22K had 54.5\% of the activity of Nanormon\(^\circledR\) (95\% confidence limits: 38.7–76.8\%) and 61.5\% of the activity of B-hGH (95\% confidence limits: 43.7–86.7\%). The correlation and regression coefficients were as follows: For B-hGH, \(r = 0.89, a = 116.1, b = 16.7\); for Nanormon\(^\circledR\), \(r = 0.89, a = 167.6, b = \).
TabU

1. Effect on diuresis in rats; 25 ml/kg body weight 0.9% saline was administered po at 0 min. Drugs were administered at −5 min to groups of 6 rats.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses per kg body weight sc</th>
<th>Excretion**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–2 h</td>
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<tr>
<td></td>
<td>µl urine</td>
<td>µmol Na</td>
</tr>
<tr>
<td>Placebo*</td>
<td>–</td>
<td>7875</td>
</tr>
<tr>
<td>Nanormon®</td>
<td>25 IU</td>
<td>2840</td>
</tr>
<tr>
<td>Biosynthetic human growth hormone</td>
<td>25 IU</td>
<td>4380</td>
</tr>
<tr>
<td>Pituitary 22K</td>
<td>25 IU</td>
<td>2965</td>
</tr>
<tr>
<td>Furosemide</td>
<td>15 mg</td>
<td>48 765</td>
</tr>
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</table>

* Means of two groups are shown. ** Urine pooled from 6 rats.

17.4; for P22K, r = 0.87, a = 173.7, b = 11.4. The λ-values (λ = s/b) were 1.02, 0.70 and 1.73, respectively.

Rat. Screening for diuretic and antidiuretic effects

B-hGH, Nanormon®, and P22K had a significant antidiuretic effect at the doses administered, i.e. 2.5 and 25 IU/kg body weight. Tables 1 and 2 show the effects on pooled urine volumes and on the Na, K and Cl excretion. The antidiuretic effect was accompanied by a marked antinatriuretic effect. Furthermore, a decrease in excretion of chloride was observed. The duration of the effect, estimated on the basis of individual urine volumes excreted during the various time periods (not shown), was up to 6 h after sc administration.

Table 2.

Effect on diuresis in rats; 50 ml/kg body weight distilled water was administered po at 0 min. Drugs were administered at −5 min to groups of 6 rats.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses IU/kg body weight sc</th>
<th>Excretion**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–2 h</td>
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<tr>
<td></td>
<td>µl urine</td>
<td>µmol Na</td>
</tr>
<tr>
<td>Placebo*</td>
<td>–</td>
<td>32 140</td>
</tr>
<tr>
<td>Nanormon®</td>
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<td>30 540</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>22 470</td>
</tr>
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<td>29 890</td>
</tr>
<tr>
<td>Pituitary 22K</td>
<td>25</td>
<td>25 050</td>
</tr>
<tr>
<td>Lypressin</td>
<td>0.5</td>
<td>11 380</td>
</tr>
</tbody>
</table>

* Means of two groups are shown. ** Urine pooled from 6 rats.
Table 3.
Hexobarbital narcosis in mice. GH was administered 30 min before hexobarbital.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Doses IU/kg body weight sc</th>
<th>Male mice N</th>
<th>Duration of narcosis (min) ( \bar{x} \pm \text{SEM} )</th>
<th>Female mice N</th>
<th>Duration of narcosis (min) ( \bar{x} \pm \text{SEM} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-</td>
<td>25</td>
<td>38 ± 3</td>
<td>20</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Nanormon®</td>
<td>25</td>
<td>20</td>
<td>28 ± 2**</td>
<td>10</td>
<td>25 ± 5*</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>10</td>
<td>21 ± 2***</td>
<td>10</td>
<td>26 ± 3*</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>10</td>
<td>22 ± 3**</td>
<td>10</td>
<td>31 ± 3</td>
</tr>
<tr>
<td>B-hGH</td>
<td>25</td>
<td>10</td>
<td>24 ± 3**</td>
<td>10</td>
<td>20 ± 3**</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>10</td>
<td>26 ± 5*</td>
<td>10</td>
<td>28 ± 4</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>10</td>
<td>28 ± 3</td>
<td>10</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>P22K</td>
<td>25</td>
<td>10</td>
<td>17 ± 3***</td>
<td>10</td>
<td>27 ± 4*</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>10</td>
<td>25 ± 5*</td>
<td>10</td>
<td>15 ± 1***</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>10</td>
<td>26 ± 3*</td>
<td>10</td>
<td>31 ± 3</td>
</tr>
</tbody>
</table>

* \( P < 0.05 \). ** \( P < 0.01 \). *** \( P < 0.001 \) (Student's t-test).

Fig. 3.
Effect of Nanormon®, B-hGH and P22K on the glucose tolerance of obese (ob/ob) mice. Groups of 7 mice were treated with placebo for three days and tested for glucose tolerance (control period ——). Thereafter, they were treated for three days with Nanormon®, 2 IU/day, B-hGH, 0.5 IU/day or P22K, 2 IU/day and retested (experimental period ——). The figure shows means ± SEM (N = 7) * \( P < 0.05 \), ** \( P < 0.01 \) (method of paired comparisons).
Furosemide had a significant diuretic effect which was accompanied by a natriuretic effect and an increase in excretion of chloride. The effect lasted up to about 2 h during which period more than the load was excreted. Lypressin had an antidiuretic effect which lasted from about 0.5 h till 2 - 3 h after administration, and an increase in the excretion of Na and Cl was observed.

No drug-induced changes in urinary pH were observed.

Mice. Narcosis potentiation
Table 3 shows the duration of hexobarbital narcosis in male and female mice after administration of placebo or the three human growth hormone preparations. All three preparations had a significant shortening effect on the hexobarbital sleeping time. Effects were observed even after 0.25 IU/kg body weight - nearly therapeutic doses. The effect did not differ between male and female mice. In all groups, the onset of narcosis was within a few minutes after ip injection of hexobarbital, and this was not changed by the previous administration of growth hormones. However, when the growth hormones were given 2 h prior to the hexobarbital injection, the effects of growth hormone was practically absent (not shown). This means that the effect is of rather short duration.

Obese (ob/ob) mice. Diabetogenic activity
The three human growth hormone preparations caused a mild glucose intolerance in the ob/ob mice. Fasting blood glucose levels were not elevated after treatment for three days with the growth hormones. However, a decrease in their tolerance to administered glucose was observed. Fig. 3 shows examples of the glucose tolerance curves obtained after treatment with placebo or growth hormones. The fasting blood glucose levels in the mice treated with P22K were low, but the rise in levels was comparable to that in the other groups, when they had been given growth hormone.

Discussion
On the basis of the two bioassays, the three human growth hormone preparations are evaluated as being equally potent. P22K turned out to be less potent in the tibia test, however, the precision index (λ) being poor for this assay, 1.73. It is the overall impression from the present studies that the weight gain test is more accurate than the tibia test. However, the rats in the weight gain test were given two daily doses for a 10-day period, whereas the rats in the tibia test were given one daily dose for four days only. The correlation coefficient between the two methods was r = 0.86 (P < 0.001).

The weight gain in the hypophysectomized rats treated with growth hormone was compared with that in rats of the same age, strain, and sex and housed in the same environments, but not hypophysectomized and not receiving growth hormone. It was found that the weight gain in the hypophysectomized rats treated with 64 µg of Nanormon® was the same as that in the normal rats (28 - 29 g) during the 10-day treatment period, only the level on day 1 was lower, about 70 g in the hypophysectomized animals and 130 g in the normal rats of the same age.

B-hGH, Nanormon®, and P22K had a marked antidiuretic effect in the rat test system. This effect has not been described in the literature on human growth hormone. As for the mechanisms of action, it is obvious that growth hormone does not act in the same way as lypressin. Growth hormone produced an antinatriuretic effect, whereas lypressin gave an increase in Na excretion. Possible mechanisms of action are a decrease in atrial natriuretic peptide levels and an increase in aldosterone levels, perhaps secondary to an increase in renin-angiotensin levels. Growth hormone may have a direct effect on the sodium transport in the kidney. Further experiments are required to clarify the mechanism of action of growth hormone in the rat kidney. The clinical significance is probably small, as no adverse effects of human growth hormone on the diuresis have been reported from the clinic. The doses of growth hormone used in the present study are approximately 15 and 150 times the therapeutic human dosage.

All three human growth hormone preparations caused a significant shortening of the hexobarbital sleeping time in mice. This effect has not previously been reported in the literature. Since the other pharmacological results we obtained do not in any way support a central stimulating action of growth hormone, other explanations may be that growth hormone promotes redistribution of hexobarbital from the brain to other tissues or perhaps causes an induction of the microsomal enzymes in the liver responsible for
the oxidative metabolism of barbiturates. This warrants further investigation.

It is known from the literature that pituitary human growth hormone has a diabetogenic effect (Lewis et al. 1980; Lostroh & Krahl 1974; Reagan 1978). A number of investigators have suggested that the diabetogenic substance of the pituitary gland is a fragment of growth hormone, rather than intact human growth hormone (Lewis et al. 1980). However, others claim that it has not been possible to dissociate diabetogenic activity completely from highly purified growth hormone preparations (Reagan 1978; Hart et al. 1984).

Our studies show that highly purified pituitary as well as biosynthetic growth hormone causes a mild glucose intolerance in obese (ob/ob) mice. This means that the diabetogenic effect presumably is linked to the 22K-molecule, and that B-hGH can be expected to cause the same glucose intolerance as pituitary growth hormone in man.

Besides the tests reported above, the three human growth hormone preparations were compared in several in vivo and in vitro test systems. Studies of effects on naive behaviour, spontaneous activity, coordinated movements, and temperature regulation were performed on mice. Neuromuscular transmission and blood coagulation parameters were studied in rats. Cardiovascular effects and effects on ECG, respiration and ganglionic transmission were studied in anaesthetized cats. At doses of 2.5 and 25 IU/kg body weight, the growth hormones had no effects in these tests. A dose of 50 IU/l had no effect on the autonomic nervous system or the smooth muscle of the isolated guinea-pig ileum or vas deferens.

In conclusion, B-hGH, Nanormon® and P22K were equipotent in the bioassays and did not differ with respect to pharmacological effects in the test systems applied.

References


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