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EFFECT OF THYROXINE ON CHONDRO-Osseous COMPLEX RESORPTION IN THE RAT

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INTRODUCTION

The direct effects of various hormonal agents on bone are poorly known, with the exception of parathormone. By direct is meant an effect not requiring the presence of another hormone. There is much basic disagreement over specific effects, for example, the effect of hydrocortisone on bone resorption. In an attempt to understand in experimental situations what the direct effects of hormonal agents are, we did a simple, conceptual thing: instead of seeking to understand the effects of a given hormone on bone, we elected to look for agents which altered rates of formation and resorption of bone. This has proven to be a more readily solved problem.

In this text the effects of thyroxine on resorption rate are described.

MATERIALS

A pure strain of Norwegian white rat obtained from Holtzman Rat Company, Wisconsin was studied. Animals were kept in cages in an air-conditioned room with controlled temperature, humidity and cycling of light and darkness. They were fed water and complete rat diet ad libitum.

METHODS

Chondro-osseous complex physiology is discussed elsewhere. The experimental site observed in this study was the chondro-osseous complex of the proximal tibial epiphysis. The animals observed were first kept under control conditions for seven days, being weighed and having x-rays of the tibias in standard positions taken at the beginning and end of this period.

Following this baseline period of observation, the animals were given 20 micrograms of T₄ (tetraiodothyronine, given to us courtesy of Upjohn Co., Kalamazoo, Mich.) parenterally daily. The weights of the normal animals when administration of the drug was begun averaged 100 gm, while the weights of the hypex (hypophysectomized) animals averaged 70 gm. at this time.

At the conclusion of seven days on T₄ the animals were again weighed and x-rays of the tibias in standard positions again taken. After formalin fixation, longitudinal hematoxylin and eosin stained decalcified sections were prepared through the proximal tibial epiphyses. Observations of the length of the chondro-osseous complex, and of the transverse width of its trabeculae or of their transverse density on x-ray, were made from the above x-ray and histological material.
From left to right are the x-rays of the right tibia of a normal female rat. The leftmost film is the tibia at the start of the period of observation. The middle film is the appearance of this bone the day T4 was started. The rightmost film is the appearance at the end of 7 days of 20 ugm. T4 daily. Note the increase in resorption under the proximal epiphyseal plate, manifested by an increase in radiolucency. There has also been a spurt in growth in this animal, indicating that the resorption rate was increased more than the rate of formation of new material that occurs with an increase in growth.

Control animals were run with the experimental animals, being treated alike in every way except that they were not given any injections during the experimental period. The bones of the control animals were studied in similar fashion to the experimental.

Four experiments using eight normal animals, half of them being controls, were run. An additional four experiments using eight hypex animals each, half being controls, were run. Two experiments combining T4 with growth hormone and two combining T4 with growth hormone and cortisone acetate were also run on hypex rats. The experiments were rerun after a ten month period to ensure reproducibility.

Measurements of growth rate were made on the x-rays which in effect were tele-roentgenograms, the ratio of tube to film and bone to film distances exceeding 100.

**RESULTS**

The results are presented in summary form.

A) T4 increased the rate of resorption of the chondro-osseous complex in normal and in hypophysectomized rats.
Hypophysectomized rat. The left x-ray shows the appearance of the proximal tibial epiphysis the day $T_4$ injections were started. The right x-ray shows the appearance after 7 daily injections. There is a slight difference in the x-ray techniques, accounting for the apparently increased density on the right.

Note that the longitudinal length of the chondro-osseous complex is less on the right than on the left, although as in figure 3, there has been a visible spurt in growth during the experiment. The growth spurt of necessity involves faster production of chondro-osseous complex. If resorption of the complex had not increased, the longitudinal length of the complex would have increased. This is not the case.

If resorption had increased in proportion to formation, then the proportional length of the chondro-osseous complex would remain the same during the experiment. This is not the case. The necessary conclusion is that resorption was increased more than formation.

**B)** $T_4$ increased the rate of growth in length in about 0.3 of the animals, had no significant effect in 0.3, and led to slight retardation in growth in about 0.3.

**C)** As has been noted by others, hypex rats tolerate $T_4$ very poorly; to complete a 7 day experiment it was necessary to reduce the dosage of the preparation we used to 5 meg/day.

**D)** We gained the impression that corticoids opposed the $T_4$ effect on resorption. Cortisone definitely improved the tolerance of the hypex animals to $T_4$.

**E)** See figures 1-7.

**DISCUSSION**

The evaluation of $T_4$ on resorption was in a sense a test of the validity of the methods used in evaluating the effects of estrogen and corticoids on resorption. There
Figure 3

Longitudinal, hematoxylin and eosin stained section through the proximal tibial epiphysis of a normal rat, control. The plate is at the top, the chondro-osseous complex immediately below it and filling the lower two thirds of the illustration.
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Figure 4

Section similar to figure 3 but from a rat given T4 20 ugm/day for 7 days prior to sacrifice. Note the wider intertrabecular spaces compared to figure 3. This is the result of increased resorption.
Another thyroxine treated, normal rat, revealing increased resorption of the chondro-osseous complex under the epiphyseal plate.
Figure 6
The proximal tibial epiphysis in longitudinal section of a hypex rat given no treatment. Note in comparison with figure 3 the much thinner zone of trabeculation under the plate, which is characteristic of hypex rats. The cartilage sequences are also abnormal.
Section from hypex rat given 5 ugm. T4 daily for 7 days. There has been almost complete resorption of the chondro-osseous complex under the epiphyseal plate, leading to the radiolucency seen on the x-rays. Note also the better cartilage sequences, a frequent occurrence in hypex rats given T4 but not a constant one. This means an increase in growth and in the face of this increase the lack of chondro-osseous complex is even more significant.
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can be little doubt that thyroxine accelerates resorption in both man and animal because of the multiplicity of studies in which this conclusion, while not the attention of the studies, is necessitated by the studies.

For example, thyrotoxics develop osteoporoses rapidly and in the presence of often tremendous negative nitrogen balances and hypercalcuias. Since other work indicates that the normal adult skeleton resorbs about 0.2 gm. of calcium per day, a negative calcium balance in excess of 200 mg./day suggests that the absolute rate of resorption has been increased to account for this. Negative balances larger than this have been recorded.

Note that in this and companion studies the mechanisms of the effect of various hormones on bone have not been elucidated. Specifically, it is not known if the effect of T₄ on resorption is a direct action on osteoclasts, or an action on the balance between calcium absorption and loss which in turn somehow affects osteoclasts. For the present purpose this aspect is immaterial, but in the next stage of the investigation it should be important.

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REFERENCES
