## Androgen Effect on Genetic and Goldthioglucose-Induced Obesity

An observation that testosterone or androstanolone (5α-androstan-17β-ol-3-one) fed with the diet inhibited hepatic lipid synthesis in normal mice[1] prompted us to test the effects of dietary androgens upon mice with genetic and induced obesity. As shown in Figure 1, androstanolone (Mann, m.p. 178–182 °C; crystallized from methanol before use) at a concentration of 1% of the diet inhibited weight gain or caused marked weight losses in C57BL/6 mice homozygous for the obese (ob) or diabetes (db) mutation and in C57BL/6J mice made hyperphagic by treatment with goldthioglucose. The weight of normal C57BL/6J mice 6 weeks of age was stabilized between 20 to 23 g when they were fed 1% androstanolone while the weight of those fed the control diet increased to 30 g over a period of 4 months. The similarity in the stabilized weights of ob/ob and normal C57BL/6J mice fed androstanolone suggests that a maximum effect upon body weight was obtained when the steroid was fed at a concentration of 1% of the diet. At lower concentrations of androstanolone (0.5% or 0.25% of the diet) changes in the body weight of ob/ob mice were intermediate between those of the control group and the group fed 1% androstanolone. The effect of another androgen, testosterone (Mann, m.p. 155 °C, crystallized from methanol) at a concentration of 1% of the diet upon ob/ob mice was similar to that of androstanolone whereas cholesterol (1% of the diet) did not alter body weight or food consumption by ob/ob, db/db, and goldthioglucosetreated mice.

Figure 2 indicates that food consumption by ob/ob, db/db, and goldthioclucose-treated mice fed 1% androstanolone declined within 24 h to levels that were approximately normal for nonobese C57BL/6J mice. Food intake remained at this level as long as the steroid was fed and returned to the hyperphagic level within 24 h after the steroid was removed from the diet. When the concentration of androstanolone in the diet was lowered to 0.25%, food consumption was stabilized at a level higher than that for mice fed 1% androstanolone but lower than that for untreated controls. The effect of androstanolone upon food intake, as well as body weight, was not as great in db/db mice as in ob/ob or goldthioglucose-treated mice.

To determine whether the effect of the dietary androgens could be attributed to a change in the palatibility of the diet a comparable dose of androstanolone (10 mg in 0.25 ml of propylene glycol) was injected subcutaneously in the interscapular region. During the 24 hours after the injection food consumption by ob/ob, db/db, and goldthioglucose-injected mice fell from 5-6 g to 2–3 g per day. Thereafter it returned gradually over the ensuing 4 days to the usual hyperphagic level. Although the effect of androstanolone upon food consumption was clearly evident under these conditions, the injection of 0.25 ml of propylene glycol alone also depressed food consumption to some extent. During the 24 h after propylene glycol injection food intake by ob/ob mice fell from 5.3 g to 4.0 g; by goldthioglucose-treated mice, from 5.7 g to 4.6 g; and by db/

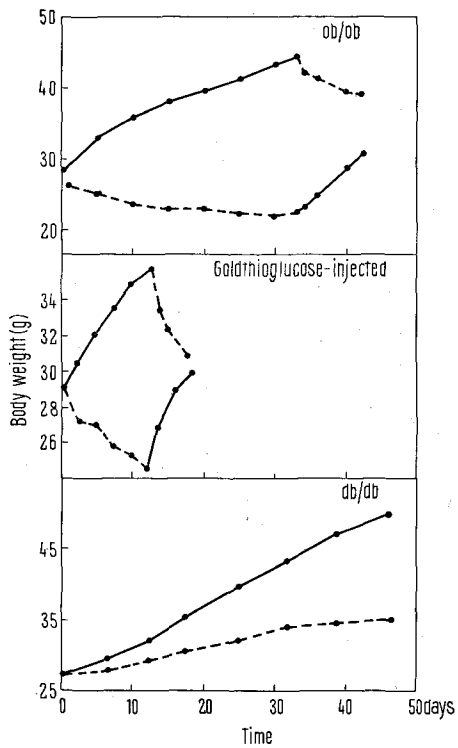


Fig. 1. The effect of dietary androstanolone on the body weight of obese (*ob*), diabetic (*db*) and goldthioglucose-treated mice. Mice, housed in individual cages, were fed ground Old Guilford laboratory chow alone (●—●) or containing 1% androstanolone (●---●). Male *ob* and *db* mice were approximately 6 weeks old at the beginning of the experiment. Obesity was induced in male C57BL/6J mice 4 months old by injecting them with goldthioglucose (600 μg/g body weight) three weeks before they were fed the experimental diet.

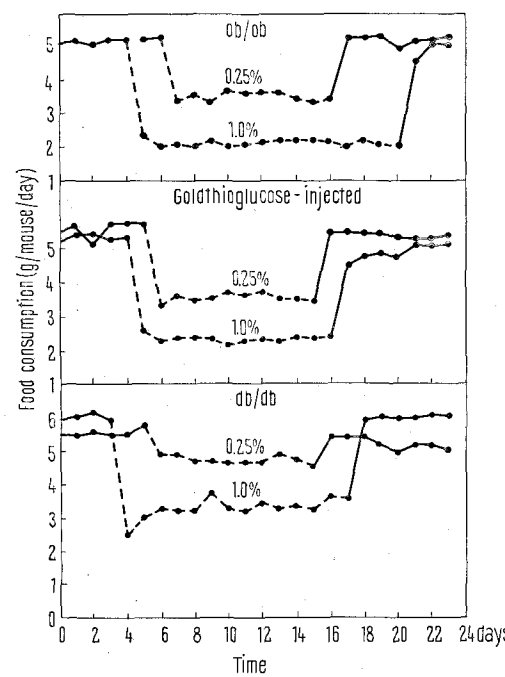


Fig. 2. Effect of dietary androstanolone on food consumption by obese mice. Male obese (*ob*) diabetic (*db*) and goldthioglucose-treated mice were fed the control diet alone (●—●) or containing 0.25% or 1% androstanolone (●---●) for the indicated periods of time.

[1] A. A. KANDUTSCH and R. N. PACKIE, Arch. Biochem. Biophys. *140*, 122 (1970).

db mice, from 5.8 to 3 g. The effect of propylene glycol alone on db/db mice on the first day after the injection was approximately as great as that of the steroid in propylene glycol. However, the return to hyperphagia in glycol injected mice occurred rapidly over the next 2 days whereas food consumption in db/db mice injected with androstanolone remained at the depressed level (about 3 g per day) for 3 more days.

Enlargement of seminal vesicles was evident in mice fed 1% androstanolone, whereas their livers appeared essentially normal in contrast to the enlarged fatty livers of ob/ob, db/db, or goldthioglucose-treated controls. Rates of fatty acid synthesis from acetate-1-$^{14}$C determined as described previously[2] in liver slices from young, moderately obese ob/ob, or db/db mice fed 1% androstanolone for 1 to 2 weeks were 30 to 80% lower than values for ob/ob and db/db controls. However, in untreated ob/ob and db/db mice rates of lipid synthesis from acetate per g liver declined with increasing obesity. This decline was counteracted by dietary androstanolone to such a degree that rates of lipid synthesis in older treated ob/ob or db/db mice were often equal to or higher than values for untreated controls. Rates at which $^{14}$C from either glucose-U-$^{14}$C or acetate-1-$^{14}$C appeared in the respiratory $CO_2$ of ob/ob and db/db mice were not significantly affected by the administration of a diet containing 1% androstanolone over a period up to 6 weeks. Blood sugar concentrations were stabilized at normal levels (140 to 150 mg/100 ml) in db/db mice fed 1% androstanolone whereas concentrations in untreated db/db controls rose to above 450 mg/100 ml as shown previously[3]. Blood sugar concentrations in untreated ob/ob controls were moderately elevated (200 to 300 mg/100 ml) and were normal or hypoglycemic (110 to 160 mg/100 ml) in ob/ob mice fed adrostanolone.

Although dietary androgens may affect body weight by altering metabolism-including protein and lipid metabolism – it seems likely that the marked weight losses as well as most of the metabolic alterations detected in mice fed androstanolone in the present studies were secondary to the dramatic and rapid reduction in food consumption. However, any attempt to account for the effect of androstanolone on the level of food intake must be speculative since we are not aware of any information bearing upon this question other than a finding that progesterone and estrogen influence food consumption in female rats[4,5]. It is possible that each of the three types of obesity involves some deficiency of the hypothalamic system as has been proposed for db/db mice[6]. Androstanolone may affect food consumption in these mice by raising the concentrations of circulating factors high enough to stimulate a relatively insensitive satiety center. Alternatively, it is conceivable that androstanolone acts directly upon neurons in the lateral or ventromedial hypothalamus to lower their threshold to satiety factors already present in the circulation[7].

*Zusammenfassung.* Es konnte gezeigt werden, dass die Gewichtszunahme bei genetisch oder durch Goldthioglukose induzierter Fettsucht von Mäusen durch Androstanolol oder Testosteron verhindert werden kann.

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[7] This work was supported in part by NIH Research Grants No. CA 02758 and No. CA 05873 from the National Cancer Institute, training grant No. GW-3957 from the National Science Foundation, and by grants from the Eloise and Richard Weber Foundation and the Elsa U. Pardee Foundation.

## The Effect of Calciferol, Parathormone and Calcitonin on the Biochemical Composition of Kidney

The influence of vitamin D and parathormone on the metabolic processes in kidneys, especially on calcium, phosphorus and citric acid, is a well known fact. The third factor which plays a role in the homeostasis of calcium is calcitonin. There is no agreement concerning its effect on the kidney and on the excretion of calcium, its main direct influence being that on the bone [1–5]. In our present paper we tried to compare the effects of all three calcium-influencing factors on the amount of calcium, phosphorus and citric acid in the different parts of the kidneys.

*Material and method.* 134 intact male rats of the Wistar strain (150–160 gg) were on a low calcium diet (wheat grain Ca 0.07%) 4 days previous to the experiment. 70 rats served as controls, of which 25 animals received, in case of the experiment with vitamin D, the corresponding dose of sunflower oil, 25 as controls for parathormone, 0.5 ml of

Table I. Values of citric acid, calcium and phosphorus in the serum

| | | Citric acid (mg/100 ml) | Calcium (mg/100 ml) | Phosphorus (mg/100 m |
|---|---|---|---|---|
| Controls | | 5.50 ± 0.54 | 10.8 ± 0.41 | 7.5 ± 0.55 |
| Calciferol | 300,000 U | 6.67 ± 1.15[a] | 12.4 ± 0.31[a] | 9.2 ± 0.77[a] |
| | 600,000 U | 9.75 ± 1.2[a] | 12.8 ± 0.33[a] | 7.6 ± 0.56 |
| | 900,000 U | 9.12 ± 0.82[a] | 12.8 ± 0.53[a] | 7.7 ± 0.12 |
| Parathormone (20 U) | 1 h | 7.70 ± 0.21[a] | 10.3 ± 0.68 | 5.7 ± 0.59[a] |
| | 3 h | 6.90 ± 0.33[a] | 10.2 ± 0.26 | 6.2 ± 0.36[a] |
| Calcitonin | 30 min | 4.38 ± 0.49[a] | 9.4 ± 0.50[a] | 7.0 ± 0.29 |
| 12 HIRSCH U. = 1,2 MRC U. | 60 min | 4.77 ± 0.34[a] | 8.1 ± 0.44[a] | 5.7 ± 0.33[a] |
| 2 × 12 HIRSCH U. | 60 min | 5.23 ± 0.11 | 7.2 ± 0.61[a] | 6.4 ± 0.25[a] |

[a] Statistical significance $P < 1\%$.