The Participation of the Adrenal and Thyroid in Fat Metabolism in Hypophysectomized Baboons *(Papio ursinus)*

The weight of hypophysectomized baboons can be manipulated within limits by appropriate treatment with cortisone or with adrenocorticotropic hormone (ACTH) and thyroxin[1]. Since these weight changes are linked with an increase or a decrease in depot fat, the role of the adrenal and of the thyroid in regulating fat metabolism in baboons has been further investigated.

The present report is based on results obtained from 30 baboons including 3 normal females, 5 hypophysectomized animals (1 adult male and 4 adult females, of which 1 was also thyroidectomized), 9 adrenalectomized females and 13 thyroidectomized animals, 3 of which were males. ACTH and cortisone were administered daily in 2 divided doses to hypophysectomized baboons on a body weight basis, namely, 1 mg cortisone per kg per day and 1 unit ACTH per kg per day. All hypophysectomized baboons, irrespectively of body weight, received 0·5 mg thyroxin 3 times per week.

Bilateral adrenalectomy in the baboon leads to progressive depletion of the fat depots with a loss of body weight, indicating first, that an intact adrenal is essential for maintenance and expansion of the fat depots, and secondly, that mobilisation of fat from the depots can be achieved in the absence of the adrenal. It is to be recalled in this connection that adrenalectomy prevents the fatty liver in rats known to result from poisoning with phosphorus or following injections or extracts of anterior pituitary gland[2], and this in the face of active fat synthesis said to occur in liver slices obtained from adrenalectomized rats[3].

Complete thyroidectomy of male and female baboons is not associated with the development of a fatty liver even when observed over a four-year period. In this respect the baboon behaves differently from the dog[4].

Removal of the pituitary can be followed by a steady gain in weight attributable largely to expansion of intra-abdominal and subcutaneous fat depots, provided the dietary whims of the animals are gratified. The gain in weight would appear to be of the kind demonstrated in hypophysectomized rats after forced feeding[5] and confirms the suggestion made by RUSSELL[6] that accelerated removal of carbohydrate by hypophysectomized animals, in the face of a high respiratory quotient and a low metabolic rate, is indicative of active fat synthesis in excess of utilisation. Unlike the dog[4], the hypophysectomized baboon fails to develop a fatty liver even at the end of 8 months after operation.

Treatment of hypophysectomized baboons with cortisone or ACTH leads at first to a decrease in body weight which continues for 7 to 14 days[1]. Thereafter, the marked improvement in appetite is attended by a steady gain in weight, particularly noticeable in baboons treated for more than 26 days. In the initial stages of treatment, a mild periportal fatty infiltration occurs in the liver. As the weight increases, fat disappears from the liver, as revealed by serial puncture biopsy specimens, but accumulates in massive quantities in the subcutaneous tissues of the neck, axilla, breast, pericardium, retro-abdominal tissues and in the mesentery, the greater omentum alone weighing over 900 g in one animal.

During the early stages of treatment with cortisone or ACTH the loss of body weight is apparently due to tissue catabolism and would explain, in rats, the inhibition of lipogenesis from carbohydrates and acetates both by cortisone and ACTH[3]. The subsequent gain in weight of hypophysectomized baboons is in accordance with the well-known clinical observations in man that long-continued treatment with ACTH or cortisone can promote the deposition of fat in various parts of the body. The observations in baboons also confirm the initial catabolic effect of treatment with cortical hormones in "normal" rats and the finding that fat storage may be favoured in those animals which survive the preliminary treatment[7]. Accumulation of fat in the depots of hypophysectomized baboons subsisting on high carbohydrate diets in response to prolonged treatment with ACTH or cortisone more than suggests that the fat is derived from carbohydrate sources. Furthermore, both cortisone and ACTH can promote synthesis and deposition of fat in a thyroidectomized-hypophysectomized baboon. It still remains to be established whether a similar effect can be induced by these hormones in pancreatectomized baboons.

The second-stage effect of cortisone on body weight in hypophysectomized baboons can be counteracted by the simultaneous administration of adequate amounts of thyroxin. Arrest or reduction of body weight is accompanied also by a reduction in the blood lipids. Withdrawal of cortisone and thyroxin is followed within 14 days by the progressive deposition of fat in the liver which eventually becomes as severe as that described in the livers of malnourished infants[8]. The mechanism underlying the development of this type of fatty liver is now being investigated.

The experiments in baboons cited above indicate that despite depression of adrenal activity following hypophysectomy, sufficient adrenal function persists to maintain life and, probably in conjunction with insulin, to promote a measure of synthesis and deposition of fat from carbohydrates and possibly from protein precursors. This synthesis and increase in the fat depots can be intensified by the administration of cortisone or ACTH and counteracted by thyroxin.

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Zusammenfassung

1. Im Gegensatz zum Hund entwickelt sich beim Pavian keine Fettleber nach Hypophysektomie oder Thyreoidektomie oder nach einer Kombination dieser beiden Eingriffe.

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2. Thyroxin wirkt als Antagonist hemmend auf die Fettbildung, die durch Cortison beim hypophysektomierten Pavian angeregt wird.

3. Starke Leberverfettung entsteht bei hypophysektomierten Pavianen nach gleichzeitiger Entziehung von Cortison und Thyroxin.

Effect of Hormonal and Dietary Treatments on Lipogenesis from Acetate in Hereditarily Obese Hyperglycemic Mice[1]

In a series of publications (e.g. BATES, MAYER, and NAUSS[2]; BATES, ZOMZELY, and MAYER[3]; MAYER and ZIGHERA[4]) it has been shown that mice with the hereditary obese hyperglycemic syndrome were characterized by an increased rate of acetate incorporation into fatty acids over their non obese litter mates, even under conditions of paired feeding, restricted feeding or fasting. Under such conditions, goldthioglucose obese mice, hypothalamic hyperphagic rats and hypothalamic mice do not exhibit such an increase. Under conditions of *ad libitum* intake lipogenesis from acetate in obese mice can reach four times the normal value.

A possible explanation of the mechanism of development of the hereditary obese hyperglycemic syndrome has been offered (MAYER, ANDRUS, and SILIDES[5]). It was suggested that these animals were characterized by hypersecretion of a pancreatic hyperglycemic hormone, presumably glucagon and a secondary hypersecretion of insulin. It was further suggested that growth hormone may be trophic to the hyperglycemic factor. It has since been demonstrated (WRENSHALL, ANDRUS and MAYER[6]) that mice with the syndrome did in fact show hyperplasia of the islets of Langerhans, and an increased pancreatic insulin content, in spite of degranulation of cells, consistent with a picture of hypersecretion. As for the possibility of increased glucagon secretion, it has been shown that the mice show a considerably increased rate of glycogen turnover (SHULL and MAYER[7]), corresponding increased liver phosphorylase activity (SHULL, ASHMORE, and MAYER[8]) and a sixfold increase in pancreatic glucagon content after treatment with growth hormone (CLARKE, WRENSHALL, and MAYER[9], to be submitted). Normal mice do not show this increase. Growth hormone induces hyperglycemia in obese mice (MAYER and SILIDES[10]; SHULL and MAYER[7]) and obese mice are particularly sensitive to glucagon (SHULL and MAYER[7]). In view of these considerations, it appeared of particular interest to see how insulin, insulin combined with hyperglycemia, growth hormone and glucagon affected acetate incorporation in mice with the obese hyperglycemic syndrome and their controls. Because these obese mice on a high fat diet, unlike goldthioglucose (MARSHALL and MAYER[11]) and hypothalamic (MAYER *et al.*[12]) obese mice, are considerably slowed down in their rate of weight gain (MAYER and JONES[13]), it appeared worthwhile to compare effects of this diet on the acetate incorporation into fatty acids in obese and non obese animals.

Methods. The animals used were hereditarily obese hyperglycemic mice, and their non obese litter mates, 4 to 6 months of age. The weight of the obese mice were in the 40 to 60 g range, that of the non obese 20 to 30 g. All animals were housed in individual cages for at least 3 days prior to the experiment. Unless otherwise noted they were fed Purina Laboratory chow *ad libitum*. Fasted animals were subjected to an 18 h fast. The animals on the high fat diet were fed for the 10 days preceeding the experiment the carbohydrate free diet previously described (MAYER and JONES[13]). The C^{14} carboxyl labeled acetate was given intraperitoneally in 0·5 cm^3 water solution in measured doses of approximately 10^6 c.p.m. in the case of the obese animals and 10^6 c.p.m. in the case of the non obese. Hormones and glucose were given intraperitoneally in 0·25 cm^3 solution. Doses are given in the Table. In the case of the studies using insulin, insulin alone, or insulin with glucose, these injections were given 15 min before labeled acetate administration. In the experiment in which both insulin and glucose were given blood glucose determinations showed that the non obese animals were hyperglycemic (levels of 200 mg % or more) for at least 20 min following injections. The blood glucose levels were back at pretreatment levels after 30 min. Control saline injections had no such effect. Glucagon was injected 10 min before acetate was given. The animals were sacrificed 30 min after acetate administration. The procedure used to determine counts retained in liver and carcass (defined as body *minus* liver) fatty acids has been described in detail previously (BATES, MAYER, NAUSS[3]; BATES, ZOMZELY, MAYER[4]). The significance and limitations of the method have been discussed in a recent paper (BATES, ZOMZELY and MAYER).

Results and discussion. The results, expressed in percent counts retained multiplied by 10^3, are given in the Table. Significance of the differences with the untreated animals, calculated by Student's "t" method, are included. It is readily seen that insulin considerably increases lipogenesis from acetate both in non obese and in obese animals. The fact that the level reached in the carcass of the obese animals is hardly higher than that reached by the non obese animals may indicate that the upper limit is set by factors other than circulating insulin or that, alternately, the dose of insulin given is very large in comparison to the amount of circulating insulin. Liver synthesis was increased proportionately less than peripherial synthesis. The effect of growth hormone, studied at two time intervals because of the observed delay in the hyperglycemic action in obese mice (SHULL and MAYER[7]), shows that growth hormone

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