# Utilization of Glucose by Hyperthyroid Isolated Rat Liver.* (22449)

STANLEY D. BURTON, EDWARD D. ROBBINS, AND SANFORD O. BYERS.
(With technical assistance of Tad Ishida.)
*Mount Zion Hospital, San Francisco, Calif.*

The marked stimulation by thyroxine of the utilization of carbohydrates by peripheral tissues and liver has been demonstrated by McEachern(1). *In vitro,* such stimulated tissues have markedly increased oxygen consumption and increased rate of glycolysis. It seemed that the behavior of the isolated perfused liver of a hyperthyroid rat should provide information concerning glucose metabolism in a simplified system but one which retains anatomical integrity lost with the use of liver slices. The present studies were undertaken to determine the effect of thyroxine on utilization of glucose by the liver.

*Materials and methods.* Male rats (Long-Evans strain) 16-20 weeks of age were used. These animals were fed stock laboratory diet† to which 0.1% thyroxine was added, for two weeks prior to time of sacrifice. Livers from these hyperthyroid animals were removed and perfused as isolated surviving organs for 6 hours according to previously described technic(2,3).‡ The glucose content of the perfusate was adjusted to contain an initial level of 650 mg % of glucose. Our previous experience, and that of other investigators, indicated that glucose utilization by the isolated liver preparation could not be demonstrated except at high initial glucose concentrations (4), and that entry of glucose into cells is facilitated by high glucose concentration(5). As controls, livers from untreated animals, fed standard laboratory maintenance diet, were removed and perfused in identical manner. Cellular elements and plasma, incorporated into perfusion fluid, were obtained from normal, untreated rats in all experiments with normal and with hyperthyroid livers. There were 8 perfusions of isolated livers from the hyperthyroid group, and 8 from control group. Glucose level of perfusate was determined by Nelson's modification of the method of Somogyi(6).

*Results. Group I—Control studies.* The average initial glucose concentration of the perfusate in this group was 641 mg % (range: 520-710 mg %); at the end of 6 hours of perfusion the glucose level had fallen an average of 22% of initial value. Hourly changes in glucose levels are given in Table I. Considerable irregularity in glucose level was observed from hour to hour, and from experiment to experiment, when normal livers were used. Indeed, at times the glucose concentration in the perfusate increased. (Table I).

*Group II—Hyperthyroid studies.* The average initial glucose concentration of the perfusate was 636 mg % (range: 580-710 mg %); the glucose level fell to an average of 52% of initial values at the end of 6 hours perfusion. Average hourly changes in glucose levels are given in Table I. The fall in glucose concentration was fairly regular and steady throughout the 6 hour perfusion.

*Discussion.* When the liver of a rat, which has been on daily intake of thyroxine, is perfused, glucose disappears from the perfusate rapidly, compared to rate of disappearance during perfusion of liver from an untreated animal. The data in these experiments thus indicate that the rate of utilization of glucose by the isolated hyperthyroid liver is markedly accelerated, and, in this respect, confirm in perfusion experiments the *in vitro* tissue slice studies of McEachern.

Using normal livers, it is difficult to demonstrate glucose utilization by the isolated rat liver perfusion experiments except when high

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† Simonsen Animal Farms, Gilroy, Calif., Maintenance Diet No. 2 consisting of ground wheat, corn, linseed meal, milk powder, meat and fish meal, alfalfa meal, yeast, vitamins and multiple salts supplement.

‡ The bovine albumin used in the perfusate for these experiments was kindly furnished by Dr. Sanford L. Steelman of Armour and Co.

TABLE I. Glucose Concentration of Perfusion Fluid. Expressed as avg % loss from initial concentration.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Group I. Livers from untreated rats—8 exp. | | | | | | | |
| Perfusion time in hr | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| % fall in glucose conc. | 0 | 11 | 14 | 24 | 28 | 20 | 22 |
| S.E. of mean* | + | ± 6.6 | ± 9.2 | ± 10.8 | ± 13.1 | ± 15.5 | ±14.2 |
| Group II. Livers from thyroxine-fed rats—8 exp. | | | | | | | |
| Perfusion time in hr | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| % fall in glucose conc. | 0 | 4.3 | 24 | 34 | 45 | 52 | 52 |
| S.E. of mean | ± | ± 6.8 | ±12.8 | ± 10.5 | ± 10.6 | ± 9.3 | ± 8.7 |
| S.E. of diff. between means† | | | | ± 5.5 | ± 6 | ± 6.4 | ± 5.9 |

* S.E. of mean $= \sqrt{\frac{\Sigma d^2}{N(N-1)}}$. † S.E. of difference between means $= \sqrt{\frac{6_1^2}{N_1} + \frac{6_2^2}{N_2}}$.

initial glucose concentrations of perfusate are employed(7).

It may well be that synthesis of glucose or glycogenolysis is adequate in the normal liver to supply glucose to the perfusion fluid in sufficient amounts to overbalance utilization by the perfusion system. Irregularities in such supply and utilization would account for irregularities observed in concentration of glucose in the fluid perfusing the normal liver. Presumably livers from thyroxine-treated animals are unable to supply sufficient glucose to overcome the steady utilization at the relatively rapid rate observed in our experiments. In contrast, the hyperthyroid liver effects a rapid disappearance of glucose from the perfusate when the initial glucose concentration is either at high or at physiologic levels(7).

The fate of the glucose which disappeared from the perfusate during these experiments cannot be determined from the present data. Some of the glucose which disappears from the perfusate during perfusion in all likelihood is converted into glycogen, since hyperthyroid livers uniformly show an increase in glycogen content after six hours of perfusion (8).

*Summary.* Perfusion of the isolated hyperthyroid rat liver results in a marked fall in the perfusate glucose level due to accelerated utilization of glucose by the hyperthyroid liver tissue in comparison with that of the isolated liver from euthyroid rats.

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