ON THE HYPOGLYCEMIC ACTION OF ALLOXAN

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Jacobs (1) observed that an intravenous injection of alloxan in rabbits produced a fall in the blood sugar level leading to hypoglycemic convulsions. This was confirmed by Dunn and McLetchie (2), Bailey and Bailey (3), Hughes et al. (4), Brunschwig et al. (5), Goldner and Gomori (6), and Kennedy and Lukens (7). If the animals were given intravenous injections of glucose so as to counteract the effect of hypoglycemia, they survived and developed hyperglycemia and glycosuria. The cause of this transient hypoglycemia has been differently explained. Dunn and McLetchie (2) think that hypoglycemia is due to the stimulating action of alloxan on the islands of Langerhans, whereby an increased quantity of insulin is released into the circulation. The cells of the islands of Langerhans become necrosed, being exhausted from overwork, leading to the symptoms of diabetes mellitus. Hughes et al. (4), on the other hand, consider that this fall in the blood sugar level is due to the liberation of preformed insulin from the necrosed cells of the islands of Langerhans and that there is no overproduction of insulin. They came to this conclusion because they observed that the hypoglycemic action of alloxan could be simulated by the injection, in the form of protamine zinc insulin, of that amount of extractable insulin which is known to be present in the pancreas of a normal rabbit. However, they admit that this evidence is not conclusive. Ridout et al. (8) studied the insulin content of the pancreas of dogs killed at different times after the injection of alloxan. They did not notice any significant change in the insulin content of the pancreas up to 8 hours after the injection, by which time the hypoglycemia becomes most marked in dogs and rabbits (7, 8). They therefore consider that the hypoglycemia is not due to overproduction of insulin. This observation, however, may not be contrary to the overproduction theory, because it might be argued that insulin as soon as formed by overstimulation is released into the circulation and consequently there is no increase in the insulin content of the pancreas. Ridout et al. (8) also reported that alloxan could not produce hypoglycemia in depancreatized dogs and in dogs made diabetic by previous injection of alloxan. This observation was also confirmed by Kennedy and Lukens.

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(7) in rabbits. These investigators think that this is also evidence against the overproduction theory. This argument does not seem to be valid, owing to the fact that if there is no normal islet tissue left, by previous injection of alloxan or by the removal of the pancreas, alloxan cannot produce this action.

In order to elucidate the mechanism of alloxan hypoglycemia, I partially pancreatectomized rabbits and studied the blood sugar curve after injection of alloxan. The amount of pancreatic tissue left after operation was just sufficient to maintain the normal fasting blood sugar level. The idea was that if the action of alloxan is that of stimulation, so that the islet cells are necrosed due to overactivity, the remnant of the pancreas in the partially pancreatectomized rabbits would release enough insulin to cause hypoglycemic convulsions in these animals. On the other hand, if alloxan only releases the preformed insulin by its necrosing action on the islets, the blood sugar will be lowered to a lesser extent because the amount of insulin released from the pancreatic remnant will be much less. The experimental results obtained are presented in this paper.

EXPERIMENTAL

Nine healthy male Himalayan rabbits of weights varying between 800 and 1450 gm. were used. All the animals were fasted overnight. Six were anesthetized with ether and about a half of the pancreas was removed by a
median longitudinal abdominal incision. 3 hours after the operation three of the partially pancreatectomized rabbits and three others with intact pancreas were given a single intravenous injection of a 10 per cent solution of alloxan (200 mg. per kilo). Samples of blood were drawn at intervals from the ear vein. Blood sugar was estimated according to the method of Hagedorn and Jensen (9). The blood sugar curves are shown in Fig. 1.

Three partially pancreatectomized rabbits not injected with alloxan were placed in separate metabolism cages and their urine was collected under toluene. The fasting blood sugar level was estimated next morning and the urine was examined for the presence of sugar with Benedict's reagent. The blood sugar values were 100, 110, and 116 mg. per 100 cc.; the urine showed a trace of sugar.

Results

In three of the rabbits with intact pancreas, the blood sugar fell rapidly, after a transient rise, following the injection of alloxan and all the animals died of hypoglycemic convulsions. The three partially pancreatectomized rabbits similarly treated not only did not develop marked hypoglycemia but also survived and showed hyperglycemia and glycosuria on the following day (Fig. 1). The three partially pancreatectomized rabbits not injected with alloxan excreted only traces of sugar, while the fasting blood sugar values were normal.

Discussion

Alloxan could not produce hypoglycemic convulsions in the partially pancreatectomized rabbits. The amount of pancreatic tissue left in these rabbits was just sufficient to maintain the normal fasting blood sugar level. If the injection of alloxan produced stimulation of the pancreatic remnant to such an extent as to cause death of the islet cells as a result of overwork, sufficient insulin should have been liberated to produce marked hypoglycemia. This, however, was not observed in our experiments. The slight hypoglycemia observed in the alloxan-treated, partially pancreatectomized rabbits appears to be due to the release of a smaller amount of preformed insulin from the necrosed islets of the pancreatic remnant into the circulation. Thus the hypoglycemic action of insulin seems not to be due to the overproduction of insulin. It is, however, to be noted that the hypoglycemic action of alloxan is not a constant phenomenon in rhesus monkeys (10).

Summary

1. Hypoglycemic convulsions were not observed when alloxan (200 mg. per kilo) was injected intravenously into three partially pancreatectomized rabbits.
2. All the three animals survived and developed hyperglycemia and glycosuria on the following day.

3. Three normal rabbits with the pancreas intact died of hypoglycemic convulsions within varying periods after the intravenous injection of alloxan.

4. The cause of the alloxan hypoglycemia is suggested to be due to the release of preformed insulin from the necrosed islets and not to stimulation of the islet tissue.

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