SENSITIVITY OF PARTIALLY PANCREATOMIZED RATS TO INSULIN

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Injection of insulin in a dose of 4 i.u./100 g body weight into partially pancreatectomized rats 6 and 18 h after operation induces convulsions and a comatose state which are not found if the hormone is injected into intact or pseudopancreatomized animals. Injection of insulin 1 h after partial pancreatectomy, which is not accompanied by the clinical manifestations mentioned above, prevents their development in response to a second injection of hormone into the same rats 18 h after the operation. A single injection of insulin 24 h before partial pancreatectomy likewise abolishes the clinical effect of the hormone at the above times after this operation.

Rats are known to show good tolerance to single and repeated injections of comparatively large doses of insulin, which induce hypoglycemia without any appreciable accompanying clinical manifestations [3, 9, 10]. However, under some experimental conditions the sensitivity of the animals to insulin can be increased, so that the hormone in doses usually well tolerated by intact animals induces the appearance of convulsions and a comatose state [5, 6]. The development of increased sensitivity to an exogenous hormone in these cases may be due to a change in the production of both insulin and of anti-insulin factors as well as to changes in the equilibrium between the two processes [1, 2, 12].

On these grounds it was assumed that the production of insulin deficiency in rats by resection of the splenic portion of the pancreas, which is rich in insular tissue, may induce a decrease in the activity of anti-insulin factors and thus lead to the development of increased sensitivity to insulin. To test this hypothesis the clinical response of animals to insulin was studied in the early period after partial pancreatectomy, when deficiency of the production of this hormone had not yet had time to be compensated by regeneration of the residual organ.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 230-250 g. The animals of one group acted as the control. The rats of the second group underwent partial pancreatectomy, with removal of the splenic part of the organ weighing about 300-350 mg. The animals of the third group were subjected to a mock operation. All the rats received an intraperitoneal injection of a solution of commercial crystalline insulin in a dose of 4 i.u./100 g body weight. The animals were examined for the appearance of a clinical response for 4-5 h after injection of the hormone. Insulin was injected into the partially pancreatectomized animals 1, 3, 6, 18, 24, 32, 48, 72 and 96 h after the operation.

EXPERIMENTAL RESULTS AND DISCUSSION

Injection of insulin into intact rats evoked a clinical response in only one of the 10 rats, even though the doses of insulin used are known to induce hypoglycemia in rats [9, 10]. In partially pancreatectomized rats 6 and 18 h after the operation, insulin regularly (in all five and in 25 of the 26 rats respectively) induced adynamia (so that the rats lay on their side), severe periodic convulsions with opisthotonus, and death of the animals between 30 min and 4 h after its injection. This type of response was found inconstantly (in two of

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the five rats) 3 h after partial pancreatectomy, but it was completely absent 1 h after the operation and was not manifested 24 and 32 h thereafter. Injection of insulin 18 h after the mock operation gave rise to no visible clinical manifestations of the action of the hormone. Although injection of insulin into partially pancreatectomized animals 1 h after the operation did not give rise to clinical symptoms, it did have the effect that when a second injection of insulin was given to the same animals 18 h after the operation, it induced convulsions in not more than 1 of the 6 experiments. The absence of this response in all 6 partially pancreatectomized animals 18 h after the opeation also was found if the animals initially received a similar dose of insulin 24 h before the operation.

These results show that removal of the splenic portion of the pancreas increases the sensitivity of rats to insulin for a certain period of time. The increase in sensitivity to the hormone is not, however, the result of the nonspecific operative trauma or of the anesthetic, for it was not found at the corresponding times in the pseudopancreatectomized animals.

The appearance of increased reactivity to insulin in partially pancreatectomized animals may be due to a decrease in their ability to inactivate large quantities of exogenous insulin, for example by complex formation with serum or other proteins, and also under the influence of specific anti-insulin factors. The activity of the anti-insulin factors after the operation may be reduced adaptively after the appearance of insulin deficiency, the presence of which has been demostrated by investigations of the insulin-like activity and sugar concentration in the blood of rats during the first day after pancreatectomy [11]. The possibility cannot be ruled out that the desensitizing effect of preoperative or early postoperative loading of animals with insulin to the repeated injection of the hormone may be due to an increase in the activity of anti-insulin factors through the action of preliminary injection of insulin [7, 8]. Prevention of the increased sensitivity of partially pancreatectomized rats to insulin in this way is essentially reminiscent of the reports in the literature of a decrease in the effect of insulin on various physiological and biochemical processes when injected repeatedly into animals [4, 9, 10]. The phenomenon of a transient and marked increase in the sensitivity of partially pancreatectomized rats to insulin, and also the simple method of their desensitization, can be used, in the authors' opinion, to study the biochemical and physiological effects of this hormone.

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