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Insulin Potentiating Action of Tolbutamide in Eviscerated Cats. (26080)

JOOP MADSEN (Introduced by G. Asboe-Hansen)
Institute of Medical Physiology, University of Copenhagen, Denmark

An increase in glucose uptake of hepatectomized rats, rabbits and dogs has been produced by injection of tolbutamide(1,8,9). The author has shown the same in hepatectomized cats(5). He explained this effect as probably due to a "potentiation" of insulin secreted in the animals. This explanation is supported by the present experiments.

Methods. Nembutal anaesthetized cats were eviscerated and nephrectomized. Glucose was then infused *i.v.* at a constant rate sufficient to keep the blood sugar level nearly constant. Groups of 6-7 animals were treated as follows: Two groups were injected with insulin 0.01 unit/kg *i.v.* One of these received tolbutamide 100 mg/kg *i.v.* 5 minutes before insulin injection. A third group received only tolbutamide 100 mg/kg *i.v.* The fourth group served as controls, which were injected with a volume of 0.9% saline similar to that of the tolbutamide injection in the 2 preceding groups. Blood sugar level was followed at 10 to 20 minute intervals for 2 hours before and 3 hours after injections. Blood sugar determinations were made by the Somogyi-Nelson technic(7) on heparinised plasma obtained from arterial blood samples immediately after bleeding.

Results. The results are shown in Fig. 1 and 2 giving average values of the 4 groups, blood sugar concentrations being expressed as percentages of the level at zero hour. Absolute blood sugar values at this time varied between 82 and 160 mg %.

Fig. 1 demonstrates how the hypoglycemic effect of insulin (0.01 unit/kg) is reinforced by tolbutamide. T-tests shows that corresponding points in the 2 curves differ significantly 40 minutes after the medication ($P<0.05$). After 60 minutes P was less than 0.01. It kept this value during the rest of the experiment except 75 and 120 minutes after the injections, where $0.01<P<0.05$.

Fig. 2 shows a slight effect of tolbutamide given without insulin to eviscerated, nephrectomized cats. The difference between the curves is not statistically significant at the 5% probability level. The blood sugar rises slightly in the last half of the experimental period when only saline is injected, while it remains practically unaltered during the 5 hours of the experiments when tolbutamide is given.

Comparing corresponding differences in the pair of curves in Fig. 1 and 2 it is found that the hypoglycemic effect of tolbutamide is 2½-6 times as pronounced when given with insulin as when given alone. This clearly indicates an insulin "potentiating" effect, although the difference between the tolbutamide effects in Fig. 1 and 2 can not be proved statistically at the 5% probability level with the present number of experiments. The insulin potentiation appears partly as a more pronounced, partly as a more sustained hypoglycemia than when insulin is given alone.

Discussion. The mechanism of this insulin potentiation is obscure, but the maintained hypoglycemia could be explained by an inhibited insulin degradation, as proposed by Mirsky(6). If this is the case, the feeble effect seen in eviscerated animals not given insulin (Fig. 2) might be due to preservation of small amounts of insulin remaining in the animals from before the evisceration. This possibility is at present under investigation

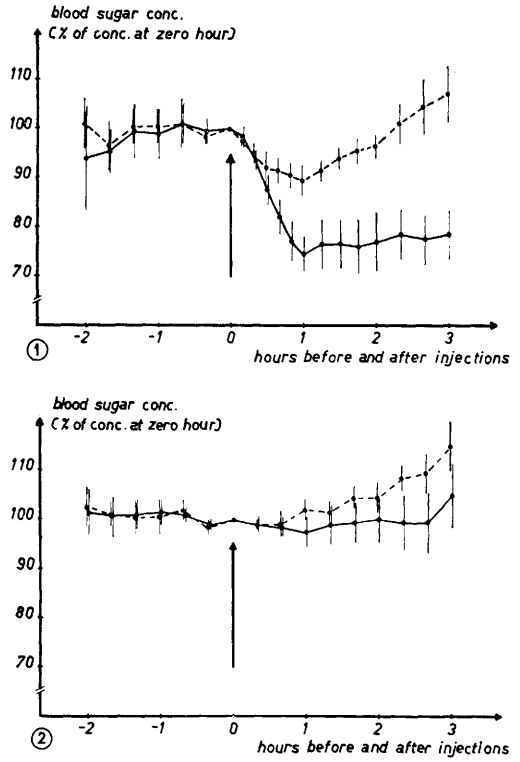

FIG. 1. Blood sugar response of eviscerated cats to insulin 0.01 unit/kg i.v. (dotted curve—avg of 7 animals) and to tolbutamide 100 mg/kg + insulin 0.01 unit/kg i.v. (solid curve—avg of 6 animals). Injections at the arrow. S.E. of mean indicated by vertical lines.

FIG. 2. Course of blood sugar conc. after inj. of saline (dotted curve—avg of 7 animals) and tolbutamide 100 mg/kg i.v. (solid curve—avg of 7 animals). Injections at the arrow. S.E. of mean indicated by vertical lines.

on cats pancreatectomized 2 days before evisceration.

Several investigators(2,3,4,10) including the author(5) have reported that tolbutamide is without effect in eviscerated animals. In some of these works, including the author's, lack of control experiments may have concealed a possible effect of the tolbutamide, as the constant glucose uptake in eviscerated animals injected with tolbutamide gives the impression that tolbutamide has no effect.

The results reported here are in accordance with the findings by Houssay *et al.*(3) of a hypoglycemic effect of tolbutamide in eviscerated dogs continually infused with glucose and insulin.

Summary. An insulin potentiating action of tolbutamide in eviscerated, nephrectomized cats is reported.

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Delayed Monoarthritis in Rabbits Induced by Means of Avian Nephrotoxic Serum.* (26081)

CONSTANTIN V. TEODORU AND BRUNO W. VOLK
(With the technical aid of Alice Einhorn)
Isaac Albert Research Institute, Jewish Chronic Disease Hospital, Brooklyn, N. Y.

In a series of experiments in which Duck Anti-Rabbit Kidney Serum (DARKS) was injected into rabbits by various routes other than intravenous, the specific affinity of the serum for kidney tissue appeared doubtful. Based on a pathogenetic concept suggested by these experiments, small amounts of DARKS were injected repeatedly into the stifle of rab-

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