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Effect of Ergotamine Tartrate Upon Systemic and Peripheral Blood Sugar in Rats.* (20835)

RACHEL COSGROVE. (Introduced by Raymond W. Cunningham.)

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Shepherd and Buchanan(1) have reported the lowering of blood sugar values by ergotamine tartrate. Their blood sugar determinations were made on peripheral blood samples obtained from the tip of the rat tail. Evidence has been obtained in this laboratory to the effect that the tail blood (peripheral blood) sugar level after ergotamine tartrate treatment is not representative of the systemic blood sugar level.

In the course of blood sugar determinations on rats treated with ergotamine tartrate, it was noted that the powerful vasoconstrictive action of this agent made it difficult to bleed the rats from their tails. To overcome this difficulty blood samples were obtained by cardiac puncture. It was found that the blood sugar determinations from heart blood samples differed greatly from determinations on blood taken from the tail. Comparisons were then made between tail blood and heart blood samples taken at the same time. The results indicated a great divergence in the blood sugar level of systemic and peripheral blood. Komrad and Loew(2) have suggested that certain other vasoconstrictive agents such as Pitressin, Pitocin, and ephedrine may possibly cause a lowering of epinephrine-induced hyperglycemia by prevention of an even distribution of this hyperglycemia due to circulatory changes.

Methods. All animals used in these experiments were normal adult male Wistar rats ranging in weight from 182 to 355 g. No animal was used more than once. After a fasting period of 16 hours, the animals were placed in bleeding cages, warmed by means of a heating lamp to facilitate bleeding, and control samples taken using potassium oxalate as an anticoagulant. Control blood samples were taken only from the tail, because the high incidence of mortality following cardiac puncture outweighed the information obtained by heart blood controls. Moreover, the lack of significant difference between heart and tail blood samples subsequently demonstrated in the starch control group justified this procedure. The animals were divided into groups of 8 or 9 rats for treatment. One and one-

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TABLE I. Effect of Ergotamine Tartrate, Insulin, and 2% Starch Solution on Blood Sugar Values in the Rat. 8 rats in each group.

Compound	Avg blood sugar in mg %: Control,† Tail blood	1½ hr after treatment: Tail blood	1½ hr after treatment: Heart blood
Ergotamine tartrate	92.4±4.3*	37.4±3.5*	101.0±3.6*
Insulin (control)	81.9±4.7	37.5±3.6	46.3±3.7
2% starch sol. (control)	92.4±3.3	82.4±2.5	93.5±2.8

* Stand. error of mean.
† Blood sample taken after 16 hr fast, before administration of compound.

half hours after the treatment, blood samples were taken by both methods. Blood sugars were determined by the Shaffer-Hartman-Somogyi method(3). The effect of ergotamine tartrate *per se* on blood sugar levels was investigated as follows. Three groups comprised this experiment. One group was given intraperitoneally 2.5 mg/kg of ergotamine tartrate suspended in 2% starch solution. Two groups served as controls: one group received 0.75 units/kg of insulin intraperitoneally as hypoglycemic controls, while the other was treated with 0.5 ml/100 g intraperitoneally of the starch suspending vehicle. Two groups of rats were used to investigate the effect of ergotamine tartrate on the hyperglycemic response to epinephrine. One group received 2.5 mg/kg intraperitoneally of ergotamine tartrate suspended in 2% starch solution, followed after a 20-minute absorption period by 0.2 mg/kg of epinephrine hydrochloride subcutaneously. The control group received 1.0 ml/100 g of 2% starch solution intraperitoneally, followed by 0.2 mg/kg of epinephrine hydrochloride subcutaneously 20 minutes later.

Results. The effects of ergotamine tartrate, insulin, and starch upon tail and heart blood sugar values are summarized in Table I. The control blood sugar values of the 3 groups do not differ at the P = 0.01 level of significance(4). With ergotamine tartrate treatment no difference of statistical significance could be demonstrated between control tail blood and 1½ hour heart blood sugar determinations. The 1½ hour tail blood was significantly less than both at the P = 0.01 level of significance.

The results with insulin on the other hand may be taken as a true blood sugar lowering effect. In this group the 1½ hour tail and heart blood sugar values are not different at the P = 0.01 level of significance, but both are significantly less than the control blood sugar values. At 1½ hours, the tail blood sugar determinations of rats receiving 2.5 mg/kg of ergotamine tartrate and rats injected with 0.75 unit/kg of insulin are the same; but the insulin heart blood sugar differs significantly at P = 0.01 from both its ergotamine and starch controls.

Neither tail nor heart blood sugar values differ significantly from the control determination in the group receiving only the 2% starch solution.

The effect of 0.2 mg/kg of epinephrine hydrochloride on the blood sugar picture of rats treated with 2.5 mg/kg of ergotamine tartrate in 2% starch solution is summarized in Table II. It is quite evident that inferences regarding the effect of ergotamine tartrate on epinephrine-induced hyperglycemia depend greatly on the source of the blood sample. The hyperglycemic response of the heart blood was significantly greater than the pretreatment control at the P = 0.01 level of significance, but was only barely significantly less than the corresponding starch controls at P = 0.05. With respect to systemic blood, inhibition of epinephrine hyperglycemia by ergotamine tartrate was not very striking.

In contrast to heart blood, tail blood sugar levels appeared to indicate a complete blockade by ergotamine tartrate of the hyperglycemic response to epinephrine. The 1½ hour blood sugar level was less than the pretreatment control, and was very significantly less than the corresponding starch controls at the P = <0.001 level of significance. In the starch-treated group, the epinephrine-induced hyperglycemia was identical in both tail and heart blood.

Summary. Under the conditions of this experiment, 2.5 mg/kg of ergotamine tartrate, intraperitoneally, had a differential effect on the peripheral and systemic blood sugar level of rats. Tail blood sugar levels were low, while blood obtained from the same animals

TABLE II. The Effect of Ergotamine Tartrate and 2% Starch Solution on Epinephrine-Induced Hyperglycemia in the Rat.

Compound	No. of rats/group	Avg blood sugar in mg %: Control,† tail blood	1½ hr after epinephrine‡: Tail blood	1½ hr after epinephrine‡: Heart blood
Ergotamine tartrate	9	86.1 ± 2.6*	53.7 ± 4.8*	154.0 ± 5.0*
2% starch sol. (control)	8	85.3 ± 3.7	212.1 ± 10.6	230.8 ± 10.1

* Stand. error of mean.
† Blood sample taken after 16 hr fast, before admin. of compound.
‡ Dose 0.2 mg/kg of epinephrine hydrochloride subcut. 20 min. after admin. of ergotamine tartrate or 2% starch sol.

by cardiac puncture exhibited normal glycemic levels. This discrepancy is probably related to the prolonged vasoconstrictive action of ergotamine tartrate and the resultant interference with normal peripheral circulation. It would appear that 0.2 mg/kg of epinephrine hydrochloride had little effect on the rat peripheral circulation since the hyperglycemic response in the starch-treated controls was equally distributed between systemic and peripheral blood. The results with insulin indicated that a true hypoglycemic agent lowered both tail and heart blood sugar values to the same extent. Slight inhibition of epinephrine-induced hyperglycemia by ergotamine tartrate was evident in heart blood, but appeared complete in tail blood, a reflection no doubt of the impairment of peripheral circulation by ergotamine tartrate. These results indicate very strongly that systemic, not peripheral blood, is the better indicator of drug effects on the blood sugar level.

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In vitro Study of Antifungal Activity of Nitrostyrenes.* (20836)

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The discovery by Elson(1) of the fungistatic activity of propamidine (p,p'trimethylenedibenzamidine) against a number of pathogenic fungi led to further confirmatory investigations of other aromatic diamidines(2-6) such as pentamidine (p,p'-pentamethylenedibenzamidine) and stilbamidine (p,p'-stilbenedicarboxamidine) and to clinical trials in the treatment of systemic mycotic infections (7-12). Singular success was obtained with the use of stilbamidine in the therapy of North American blastomycosis. Curtis and Harrell(10) described 2 cases of North American blastomycosis that responded to treatment by large doses of diethylstilbestrol and noted the similarity of the chemical structures of stilbamidine and diethylstilbestrol. It was considered worthwhile to screen for antifungal activity other compounds with

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