Effects of Ouabain on Insulin Secretion in the Dog

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ABSTRACT
The mechanism of the previously reported hypoglycemic effect of ouabain was studied in dogs. Ouabain (1.0 μg/kg/min infused intravenously for 60 minutes) combined with insulin or propranolol caused a greater and more prolonged decrease in blood glucose than either of the drugs administered separately. In intact dogs, ouabain changed significantly portohepatic venous differences in plasma glucose from +6.6 to −13.6 mg/100 ml and in K+ from −0.03 to −0.4 mEq/liter. In pancreatectomized animals, ouabain did not cause any significant decrease in peripheral glucose level, and the portohepatic differences in plasma glucose changed from +5.3 to +30.2 mg/100 ml and the differences in K+ from −0.01 to +0.2 mEq/liter. These changes, indicating an increased release of glucose and K+ by the liver in the pancreatectomized dog, were also observed in isolated rat liver perfused with ouabain 10⁻⁶M. Glucose uptake of the hindlimb increased significantly during the infusion of ouabain in normal dogs, but did not change in pancreatectomized dogs. Ouabain caused a significant increase in plasma insulin in portal blood (+155%). These results demonstrate that the observed metabolic effects of ouabain in the dog are mainly mediated by insulin and that ouabain increases the secretion of insulin in intact dogs.

ADDITIONAL KEY WORDS hypoglycemia potassium cardiac glycosides glucose uptake insulin levels
Methods

The dogs were fasted for 18 hours before the experiment. Each animal was anesthetized with sodium pentobarbital, 35 mg/kg iv, and intubated with a cuffed endotracheal tube. They were mechanically ventilated with 100% O₂ at a rate and volume adjusted so as to maintain normal acid-base equilibrium and O₂ saturation in arterial blood throughout the experiment. Polyethylene catheters were inserted in the femoral vessels and in one jugular vein. Muscular relaxation was obtained with an initial dose of 4 mg succinylcholine chloride administered intravenously; an additional dose of 250 μg/min was infused at constant rate throughout the experiment. The animals were ventilated for at least 30 minutes following the administration of anesthesia and before the first samples were taken for control measurements. Following the control period, ouabain (1.0 μg in 0.1 ml of saline/kg/min) was administered intravenously for 60 minutes. The experiment was continued for 60 minutes following the end of ouabain administration.

In the first series of experiments, the hypoglycemic effect of ouabain in ten dogs was compared to that of ouabain combined with insulin or propranolol following a protocol previously described (12). Each animal served as his own control and was studied twice at a week’s interval. In one experiment, one group of dogs received insulin (75 mU/kg iv in 5 minutes) and the second group received propranolol (5 mg/kg iv in 5 minutes). In the following experiment, the animals received the same treatment combined with ouabain. At the end of each experiment, the dog received an intramuscular injection of antibiotics (streptomycin, 1 g; penicillin, 1 million I. U.) and the same dose the day after. All the animals survived the two experiments.

The second series of experiments was performed on 18 dogs, anesthetized and prepared as described previously (12). After laparotomy, a polyvinyl catheter was placed into the portal vein via one of the branches of the gastrosplenic vein; another catheter was inserted under fluoroscopy via the right jugular vein into a hepatic vein. A catheter was also placed into the left femoral artery and into the right femoral vein via a branch without disturbing the flow in the femoral vein. Samples for measurements of portohepatic and arteriovenous differences were taken from the corresponding vessels at the same time and rate. In some animals the right femoral artery was exposed and used for blood flow measurement. Blood pressure and pulse were recorded in all animals from the left femoral artery, and ouabain was administered through the left femoral vein. In this series, two groups of animals were used: (1) a group of ten normal dogs (with intact pancreas) and (2) a group of eight pancreatectomized dogs. Total pancreatectomy was performed by careful dissection of the gland from the surrounding tissue, preserving the vascular supply to the duodenum. The region was carefully examined for any remaining or aberrant pancreatic tissue. A polyvinyl catheter was implanted through one of the branches of the gastrosplenic vein into the portal vein and brought to the skin of the right side for subsequent blood sampling. After surgery the dogs received antibiotic treatment and the following day a continuous intravenous infusion of saline with sodium bicarbonate. The dogs were maintained on regular insulin given intramuscularly. The dose ranged from 2.5 to 4 U/day once or twice a day and was adjusted according to the blood glucose level. Insulin was withheld 24 hours before the experiment, which was performed 3 to 7 days after the surgery. Berson et al. (13) showed that injected insulin has a very short half time of disappearance (40 minutes). Davidson et al. (14) confirmed this finding in dogs and demonstrated that activity of serum insulin 48 hours after pancreatectomy is not significantly different from zero. All pancreatectomized dogs had high blood glucose levels ranging from 250 to 300 mg/100 ml and responded to insulin treatment.

In another series of experiments the effect of ouabain administration on glucose and potassium release by the isolated perfused liver of the rat was studied. The technique used was essentially that described by Miller (15). The perfusion medium consisted of modified Krebs-Ringer bicarbonate buffer (16) containing 50 μEq/liter of glycercer, 300 μEq/liter of sodium palmitate, 8 mM of glucose, and 3% bovine albumin. Washed rabbit erythrocytes were added to this medium to a final hematocrit which ranged from 12% to 15%. This diluted blood was equilibrated in a disc oxygenator with a mixture of 85% O₂ and 5% CO₂ so that the pH of the solution was 7.40. Temperature was maintained at 37°C, and the liver was perfused with a roller pump through the portal vein at the constant rate of 0.2 ml/g/min for 90 minutes. Seven experiments were performed, three controls and four with 10⁻⁵ M ouabain added to the perfusion medium. Effluent blood collected over three periods of 30 minutes was analyzed for glucose and K⁺ concentration. The results were expressed as micromoles of glucose and microequivalents of K⁺ released per gram of liver during 30 minutes of perfusion.

Mean blood pressure and pulse rate were continuously recorded with a Statham pressure transducer and a multichannel direct-writing recorder. The records were measured every 5 minutes, and the average of three measurements
was calculated. Midesophageal temperature was measured continuously and maintained constant within 1°C during the whole procedure by means of a heating pad. \( V_{O_2} \) was measured continuously by the closed-circuit method with a computer spirometer system designed by A. St. J. Lee (17). The blood flow was measured and continuously recorded by an electromagnetic blood flowmeter, Statham Model N-4000, using Statham Flow Probe Model 9 placed in good contact around the femoral artery. At regular intervals blood samples were collected anaerobically in heparinized cooled syringes, immediately analyzed for pH and \( P_{CO_2} \) (18, 19) and prepared for glucose (20) and electrolyte determinations. \( Na^+ \) and \( K^+ \) plasma concentrations were measured by flame photometry. All determinations were made in duplicate and the control measurements are averages of two samples. Plasma insulin levels, determined in 12 dogs, were quantitated by radioimmunoassay (21) and are expressed in terms of a porcine standard1 using a guinea pig antiserum which reacted essentially identically with porcine and canine insulin. After each collection of blood, a volume of dextran solution equal to the volume of blood withdrawn was administered to the animal, and a small amount of saline was infused to flush the arterial catheter. No heparin was used during the procedure except in the saline used to fill the catheters before their insertion at the beginning of the experiment. Ouabain, U.S.P. (Calbiochem Co.), regular insulin (Hletin, Eli Lilly and Co.), and propranolol (Ayerst Labs.) were used. The results were statistically analyzed by the Student t-test. The significance of the differences between paired measurements was calculated by the method of difference between correlated pairs.

Results

Effect of Ouabain and Insulin or Propranolol on Blood Glucose

Blood glucose levels decreased by 20% immediately after insulin administration. Shortly afterward glucose returned to control levels and at the end of the experiment was slightly elevated (Fig. 1). The same dose of insulin given during ouabain administration

\[ \text{FIGURE 1} \]

Changes in blood glucose level expressed as percent of control value. Insulin, 75 mIU/kg iv, was administered from 60 to 65 minutes. Ouabain, 1 \( \mu g/\text{kg/min} \), was infused intravenously from 30 to 90 minutes. Means \pm SE are given. Values marked by asterisks are significantly different (\( P < 0.05 \)) from those observed in the group of animals treated with ouabain alone.
produced a more pronounced and protracted decrease in blood glucose. When compared to the group of ten dogs that received ouabain alone, this decrease was significantly greater (40%, P < 0.05).

Propranolol did not change blood glucose levels (Table 1). However, the same dose of propranolol given to dogs receiving ouabain decreased blood glucose concentration significantly more than ouabain alone (P < 0.05).

Metabolic Effects of Ouabain in the Pancreatectomized Dogs

In both normal and pancreatectomized dogs, mean blood pressure tended to increase during ouabain infusion, while heart rate decreased (P < 0.05). Throughout the experiment no significant changes were observed in femoral blood flow, oxygen consumption, and pH (Tables 2 and 3).

In normal dogs during and after ouabain infusion, the glucose level in arterial blood decreased from 103 to 80 mg/100 ml (−22%, P < 0.05). The control glucose level in pancreatectomized animals was much higher than in normal dogs, 270 mg/100 ml, and dropped during ouabain infusion by 14 mg/100 ml to 256 (5% decrease); this decrease was less than in normal animals and the change was not significant (Tables 2 and 3).

In four normal dogs the portalhepatic difference (+6 mg/100 ml) in plasma glucose during the control period indicates a small net

| TABLE 1 |
| Plasma Glucose Concentrations in Control Dogs (Infused with Saline) and in Dogs Treated with Propranolol, Insulin, and Ouabain |
|-----------------|---------------|---------------|---------------|---------------|---------------|
|                  | Control       | 60 min        | 90 min        | 120 min       | 150 min       |
| No. of expts.   |               |               |               |               |               |
| Control         | 5             | 103 ± 4       | 105 ± 5       | 102 ± 4       | 104 ± 3       | 104 ± 2       |
| Propranolol, 5 mg/kg | 2             | 102           | 97            | 104           | 108           | 103           |
| Insulin, 75 mU/kg | 5             | 108 ± 6       | 106 ± 5       | 80 ± 11       | 108 ± 8       | 114 ± 6       |
| Ouabain, 1 µg/kg/min | 10           | 104 ± 3       | 104 ± 4       | 80 ± 5        | 80 ± 6        | 85 ± 6        |
| Ouabain, 1 µg/kg/min, plus propranolol, 5 mg/kg | 5 | 105 ± 2 | 107 ± 2 | 101 ± 3 | 75 ± 6 | 67 ± 6 |
| Ouabain, 1 µg/kg/min, plus insulin, 75 mU/kg | 5 | 102 ± 4 | 102 ± 7 | 71 ± 7 | 61 ± 5 | 63 ± 6 |

Values are the means ± se and are given in milligrams per 100 ml. Ouabain was infused from 30 minutes to 90 minutes; propranolol and insulin were administered at 60 minutes.

| TABLE 2 |
| Effects of Ouabain, 1 µg/kg/min, Infused over Sixty Minutes in Eight Normal Dogs |
|-----------------|---------------|---------------|---------------|---------------|---------------|
|                  | Control 0 to 30 min | 30 to 60 min | 60 to 90 min | 90 to 120 min | 120 to 150 min |
| Mean blood pressure (mm Hg) | 137 ± 6 | 143 ± 6 | 151 ± 8 | 144 ± 7 | 124 ± 4 |
| Heart rate (beats/min) | 173 ± 11 | 165 ± 10 | 139 ± 12 | 142 ± 15 | 146 ± 17 |
| Femoral artery blood flow (ml/min) | 22.8 ± 5.3 | 24.8 ± 7.5 | 21.0 ± 4.5 | 18.0 ± 2.2 | 21.0 ± 4.5 |
| VO2 (ml/kg/min) | 7.07 ± 0.44 | 7.21 ± 0.46 | 6.97 ± 0.44 | 6.98 ± 0.52 | 6.87 ± 0.56 |
| Arterial pH | 7.38 | 7.38 | 7.38 | 7.34 | 7.32 |
| PaO2 (mm Hg) | 25.8 ± 1.3 | 25.7 ± 1.8 | 24.7 ± 2.2 | 25.2 ± 3.3 | 28.9 ± 3.5 |
| HCO3− (mEq/L) | 15.0 ± 0.7 | 14.5 ± 0.9 | 14.0 ± 0.8 | 12.9 ± 1.2 | 14.2 ± 1.2 |
| Blood glucose (mg/100 ml) | 103.1 ± 3.5 | 100.0 ± 5.2 | 84.7 ± 7.4 | 70.7 ± 9.3 | 55.7 ± 9.9 |

Values are the means ± se.
TABLE 3

Effects of Ouabain, 1 μg/kg/min, Infused over Sixty Minutes in Eight Pancreatectomized Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control 0 to 30 min</th>
<th>Ouabain infusion</th>
<th>90 to 120 min</th>
<th>120 to 150 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>125 ± 10</td>
<td>127 ± 12</td>
<td>134 ± 14</td>
<td>127 ± 16</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>182 ± 8</td>
<td>183 ± 12</td>
<td>168 ± 16</td>
<td>133 ± 22</td>
</tr>
<tr>
<td>Femoral artery blood flow (ml/min)</td>
<td>17.6 ± 4.3</td>
<td>17.3 ± 5.4</td>
<td>16.5 ± 3.6</td>
<td>16.3 ± 4.9</td>
</tr>
<tr>
<td>VO₂ (ml/kg/min)</td>
<td>7.26 ± 0.21</td>
<td>7.43 ± 0.21</td>
<td>7.17 ± 0.24</td>
<td>7.11 ± 0.35</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.38</td>
<td>7.37</td>
<td>7.36</td>
<td>7.34</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>27.1 ± 2.1</td>
<td>27.3 ± 2.5</td>
<td>25.8 ± 2.7</td>
<td>26.3 ± 2.7</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>15.8 ± 1.0</td>
<td>15.0 ± 1.1</td>
<td>13.9 ± 0.9</td>
<td>13.4 ± 0.9</td>
</tr>
<tr>
<td>Blood glucose (mg/100 ml)</td>
<td>270.3 ± 10.9</td>
<td>269.1 ± 11.4</td>
<td>250.7 ± 10.9</td>
<td>250.6 ± 10.0</td>
</tr>
</tbody>
</table>

Values are the means ± SE.

output of glucose by the liver, as should be expected in the fasting animal (Fig. 2). Following ouabain administration there was a significant change in the portohepatic difference (—13.6 mg/100 ml, P < 0.05), indicating a net glucose uptake by the liver. Changes in plasma K⁺ concentration paralleled glucose changes: the portohepatic difference was significantly decreased from control (—0.4 mEq/liter, P < 0.05). In five pancreatectomized dogs, as in normal ones, during the control period the portohepatic venous difference in plasma glucose (+5.3 mg/100 ml) indicated a net output by the liver. But after ouabain administration this portohepatic venous difference increased significantly (+30.2 mg/100 ml, P < 0.05), indicating a release of glucose from the liver. This increase in

FIGURE 2

Differences in glucose and potassium concentration between portal and hepatic vein blood in four normal and five pancreatectomized dogs following ouabain administration.

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TABLE 4

<table>
<thead>
<tr>
<th>Glucose Uptake by the Hindlimb in (A) Five Normal and (B) Six Pancreatectomized Dogs during Ouabain Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 0 to 30 min</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>A 1,069 ± 292</td>
</tr>
<tr>
<td>B 2,406 ± 438</td>
</tr>
</tbody>
</table>

Values are given in micrograms per minute.

* Significantly ($P < 0.05$) different from initial control measurement.

Portohepatic glucose difference was accompanied by a similar increase in $K^+ (+0.2$ mEq/liter, $P < 0.05$), also indicating a net output of $K^+$ during ouabain infusion in the pancreatectomized dog.

In five normal and six pancreatectomized dogs, blood flow in the femoral artery and the femoral arteriovenous difference in plasma glucose were measured simultaneously. The amount of glucose in $\mu$g/min taken up by the tissues of the hindlimb was calculated on the basis of these measurements (Table 4). Results were expressed as percent of control value for each dog (Fig. 3). The uptake of glucose in the hindlimb of normal dogs increased by 171% ($P < 0.05$) during ouabain infusion, and 60 minutes after the end of infusion returned to control values. No change in glucose uptake was observed during and after ouabain infusion in pancreatectomized dogs.

Glucose excretion was measured in urine collected over 30 minute-periods by means of an urethral catheter and expressed as micrograms of glucose per kilogram of body weight. The amount of glucose eliminated in the urine during the control period averaged 91.8 $\mu$g/kg in normal dogs and did not change significantly during ouabain infusion. In pancreatectomized dogs an average of 6,050 $\mu$g/30 min/kg of glucose was excreted in the control period; glucose elimination increased steadily during and 30 minutes after the ouabain infusion (+194%, $P < 0.05$). In the last 30-minute period after the ouabain infusion the rate of glucose excretion returned almost to preinfusion levels (Fig. 4).

The direct effect of ouabain on glucose and potassium output by the liver was tested in isolated perfused rat liver (Table 5). When ouabain was added to the perfusion medium to a final concentration of $1 \times 10^{-6}$M, glucose and potassium output by the liver was significantly greater than in the control experiments.

Effect of Ouabain on Plasma Insulin Level

Plasma insulin levels in portal blood during

![Graph showing glucose uptake](http://circres.ahajournals.org/)

**FIGURE 3**

Glucose uptake in the hindlimb of five normal and six pancreatectomized dogs during ouabain administration. Femoral artery blood flow and femoral arteriovenous differences in plasma glucose were measured and glucose uptake in $\mu$g/min calculated. The results are expressed as percent of control values for each dog.

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Ouabain and Insulin Secretion

Ouabain infusion increased significantly (by 155%, P < 0.02) in comparison with the control group and tended to return back to control values 1 hour after the infusion (Table 6). Similar results from this laboratory have been reported in detail recently (22).

Discussion

The greater and more protracted fall in blood glucose when insulin is combined with ouabain than when either of the drugs is administered separately indicates a possible interaction between ouabain and insulin and also that the sympathetic nervous system may participate in these changes. It is known that decrease in blood sugar is a stimulus for the release of catecholamines which in turn counteract the hypoglycemia (23-25). The greater decrease in blood glucose observed when ouabain was combined with insulin or propranolol might then be ascribed to the inhibitory effect of ouabain on the action of catecholamines described previously (12). The antiadrenergic property of ouabain was also demonstrated in vitro (10, 11) and is supported by observations of Ho (26) who

### Table 5

<table>
<thead>
<tr>
<th></th>
<th>Glucose (mmol/g)</th>
<th>Potassium (μEq/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to 30 min</td>
<td>30 to 60 min</td>
</tr>
<tr>
<td>Control</td>
<td>32.37 ± 0.68</td>
<td>27.48 ± 3.38</td>
</tr>
<tr>
<td>Ouabain</td>
<td>63.33 ± 12.05*</td>
<td>51.28 ± 6.20*</td>
</tr>
</tbody>
</table>

Values are the means ± SE and are given in micromoles and microequivalents per gram of liver per 30 minutes. In three experiments control measurements were made; in four others the liver was perfused with \(10^{-5}\)M ouabain added to the perfusion medium.

*Significantly different from control experiments.

### Table 6

<table>
<thead>
<tr>
<th></th>
<th>Infusion</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45 min</td>
<td>60 min</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>% Change</td>
</tr>
<tr>
<td>Control</td>
<td>16.2 ± 8.0</td>
<td>17.2 ± 3.2</td>
</tr>
<tr>
<td>Ouabain</td>
<td>26.1 ± 13.7</td>
<td>66.8* ± 15.5</td>
</tr>
</tbody>
</table>

Values are the means ± SE and are given in microunits per milliliter.

*Significantly higher (P < 0.02) than the value before infusion.
showed in vitro that ouabain inhibits the formation of cyclic 3',5'-AMP and by our observation of the competitive inhibition exerted by ouabain on epinephrine-stimulated lipolysis (27). Furthermore, in vitro ouabain in concentrations at least 100 times higher (10^{-6} to 10^{-4}M) than those used in dogs increased glycogen content of the muscle, and under certain conditions also increased glucose uptake (28).

The circulatory changes observed during ouabain infusion were the same in both groups of animals (intact and pancreatectomized) and are in general agreement with those reported by others using a similar dose (29-33).

The release of glucose by the liver observed during ouabain infusion in pancreatectomized dogs is caused by a direct effect of ouabain since the same phenomenon was observed in isolated rat liver perfused with ouabain in the concentration of 10^{-4}M. The mechanism of this effect is not clear, but it could be related to the known inhibitory action of ouabain on Na^+ and K^+-dependent ATPase which in turn results in a loss of intracellular potassium. In pancreatectomized dogs, as in the perfused liver, the output of glucose during ouabain infusion was accompanied by loss of potassium from the liver. While glucose output from the liver was increased during ouabain infusion in pancreatectomized dogs, no similar change occurred in muscle. This difference could be accounted for by the presence of glucose-6-phosphatase in the liver cell and its absence in the muscle (34, 35). However, further work is required to clarify the mechanism of the direct action of ouabain in the liver.

By contrast, in normal dogs the glucose uptake by muscle and liver significantly increased during ouabain infusion. This increased glucose uptake by the liver and muscle may well account for the decrease in peripheral blood glucose occurring during ouabain infusion in normal dogs. Since these changes were not present in pancreatectomized dogs, the hypoglycemic effect of ouabain in normal dogs seems to be mediated through insulin. The significant increase in insulin levels in portal vein following administration of ouabain in intact animals confirms this interpretation. This would agree with the known effect of insulin on glucose metabolism in the liver and muscle (36-46).

If the hypoglycemic effect of ouabain in normal dogs is mediated by insulin, one would expect that blood glucose levels in pancreatectomized animals would not change. However, a slight decrease in blood glucose did occur during ouabain infusion in the pancreatectomized dogs and, in addition, was accompanied by increased output of glucose by the liver and unchanged glucose uptake by the muscle. In an attempt to find an explanation for these results, urine glucose excretion was measured before, during, and after ouabain infusion in some animals of both groups. Glucose loss in the urine of pancreatectomized dogs was approximately 100 times higher than in normal dogs and increased nearly three times during ouabain infusion. In normal dogs the amount of glucose eliminated in the urine was very small and did not change significantly throughout the experiment. The increased loss of glucose in the urine in pancreatectomized animals during ouabain infusion is in agreement with Czakó's finding of decreased maximum tubular excretory capacity for glucose (TmG) in dogs after high doses of ouabain (47). In normal dogs during ouabain infusion the depression of TmG by ouabain was not sufficiently marked to increase loss of glucose in the urine because of the normal blood glucose concentration which remained below the glucose threshold. Hence the effect of ouabain on glucose tubular reabsorption should not participate in the hypoglycemic effect of ouabain in normal animals. By contrast, in pancreatectomized dogs which have high blood glucose levels, the decrease in glucose tubular reabsorption caused by ouabain resulted in increased glucose loss in urine. This observation itself deserves further experimental and clinical consideration. From the present data it is not possible to relate quantitatively the increased glucosuria and the fall in blood glucose observed in these animals.
The hypoglycemic effect of ouabain seems to be mainly mediated by insulin, either through direct interaction or its increased secretion. Bihler and Sawh (48) showed that ouabain significantly increases the penetration of methylglucose in the presence of a small dose of insulin, indicating an interaction of ouabain and insulin. Measurements of plasma insulin showed that ouabain also causes an increase in insulin plasma concentration (22). This increase might be due to the following mechanisms: redistribution of cardiac output in such a manner that more blood would drain the pancreatic tissue, resulting in higher insulin plasma levels; decreased rate of insulin inactivation; or increased insulin secretion. The first mechanism has to be investigated. The second mechanism is ruled out mainly by the observation of a smaller increase in plasma insulin levels in peripheral blood than that observed in portal blood which indicates that the increase in plasma insulin levels during ouabain administration is not due to a change in the rate of inactivation of insulin by the liver. An increase in plasma insulin levels as the result of increased insulin secretion is in agreement with Milner and Hales's report (49) that ouabain increased insulin secretion in pancreatic tissue in vitro. Whether this is related to an effect of ouabain on sodium and potassium active transport as postulated by Milner, or to an effect of the sugar molecule, which is part of the glycoside, or to a direct effect of ouabain on one of the enzymes which regulates cyclic 3',5'-AMP level in the cell remains to be established.

It has been reported that cardiac glycosides administered in vivo distribute preferentially in heart, kidney, liver, and pancreas (50) and only to a limited extent in other tissues. It is possible that the concentration of ouabain in the pancreas following in-vivo administration of the dosage used in the present experiments is high enough to affect membrane ATPase. If this hypothesis was substantiated, the metabolic effects of ouabain in vivo as well as in vitro could be mediated by that same enzyme system which is present in adipose tissue, muscle, and pancreas.

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