Glycogenolytic effect of vasopressin in the canine liver

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BERGEN, STANLEY S., JR., ROBERT SULLIVAN, JAMES G. HILTON, S. WARING WILLIS, JR. AND THEODORE B. VAN ITALLIE. Glycogenolytic effect of vasopressin in the canine liver. Am. J. Physiol. 199(1): 136-138. 1960.—The effect of synthetic vasopressin and oxytocin upon glucose flux across the liver was studied in fasted, unanesthetized dogs. Blood samples were obtained before and after hormone administration from portal and hepatic veins and aorta by means of catheters chronically implanted in these vessels. Responses to commercial Pitressin and Pitocin also were measured. Immediately following intraportal administration of 5-60 u of vasopressin (or Pitressin) an appreciable increment of glucose appeared in the hepatic vein, reaching a peak at 10 minutes and returning to base line levels within 30 minutes. During this time, glucose concentration in the portal vein failed to increase and in some instances decreased. Administration of 10-40 u of oxytocin (or Pitocin) failed to induce any change in hepatic vein glucose concentration.

FOR OVER FIFTY YEARS investigators have studied various aspects of the effect of posterior pituitary extracts on blood sugar. Indirect evidence, based on results in hepatectomized animals (1, 2) and animals depleted of liver glycogen (3), has suggested that vasopressin may elevate blood sugar by stimulating hepatic glycogenolysis. These results have been questioned because of the impure preparations used (4-7) and the lack of a direct approach to the problem.

The present report describes experiments in which the hepatic response to synthetic preparations of vasopressin and oxytocin was measured directly in the unanesthetized dog.

Twenty-two experiments were performed on 12 mongrel dogs weighing 22–31 kg. All the dogs were prepared, with slight modifications, according to the technique of Shoemaker et al. (8). This procedure consists of a one-stage abdominal operation with implantation of (12-gauge) Genflex catheters in the portal vein, an hepatic vein and aorta. The portal vein catheter is inserted via a splenic vein with visual and manual placement of the tip in the portal vein near the liver. The hepatic vein is catheterized by separating the natural plane between the left lateral lobe and left central lobe of the dog’s liver and inserting a catheter approximately 2 cm into the most cephalad vessel visible in the area. The aortic catheter is placed just below the renal arteries, with care taken not to occlude the iliac vessels.

Two to four days postoperatively, when the dogs had resumed normal eating habits, they were placed in a Pavlov-type sling without sedation or anesthesia. All experiments were performed after the dog had fasted for approximately 14 hours. Hepatic blood flow was estimated by the sulfobromophthalein (BSP) method of Bradley and co-workers (9). A priming dose of 0.08 mg/kg of BSP was given, followed by perfusion for 1 hour with a constant infusion pump. Plasma BSP was measured by the method of Seligson et al. (10). Glucose in whole blood was determined by the Nelson-Somogyi method (11) and plasma nonesterified fatty acids (NEFA) were measured by the method of Dole (12).

Two forms of vasopressin were used: a commercial preparation, Pitressin (Parke, Davis; 20 u/cc), and synthetic lysine vasopressin (kindly supplied by Dr. Vincent du Vigneaud). Similarly, Pitocin (Parke, Davis; 20 u/cc) and synthetic oxytocin were employed to study the effects of oxytocin. All substances tested were administered over a 2 minute period via the portal vein catheter. Samples of blood were obtained simultaneously from portal and hepatic veins and aorta immediately prior to hormone administration, and at 5, 10, 15, 30, 60 and, in some experiments, at 90 and 120 minutes after injection.

MATERIALS AND METHODS

Twenty-two experiments were performed on 12 mongrel dogs weighing 22–31 kg. All the dogs were prepared, with slight modifications, according to the technique of Shoemaker et al. (8). This procedure consists of a one-stage abdominal operation with implantation of (12-gauge) Genflex catheters in the portal vein, an hepatic vein and aorta. The portal vein catheter is inserted via a splenic vein with visual and manual placement of the tip in the portal vein near the liver. The hepatic vein is catheterized by separating the natural plane between the left lateral lobe and left central lobe of the dog’s liver and inserting a catheter approximately 2 cm into the most cephalad vessel visible in the area. The aortic catheter is placed just below the renal arteries, with care taken not to occlude the iliac vessels.

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Results

Vasopressin caused an immediate hyperglycemic response in the hepatic vein and aorta which reached a peak within 10 minutes followed by a return to control levels by 30 minutes (fig. 1). In this small series, height of the response was virtually the same irrespective of dose level. Sixty units of vasopressin induced an increase in hepatic blood glucose of 76 mg %, 40 u a rise of 80 mg % and 20 u a rise of 70 mg %, less marked increases were noted following administration of 5 and 10 u of vasopressin (table 1).

The hepatic-portal (H-P) glucose gradients during the first 15 minutes after vasopressin injection increased strikingly as compared with the control gradients (fig. 2). In contrast, the H-P gradient did not change significantly after injection of 20-40 u of oxytocin.

It was noteworthy that following administration of vasopressin the glucose concentration in portal vein blood failed to increase and actually showed a decrease in some instances, while glucose levels were rising in hepatic venous and arterial blood (fig. 2). This decrease in portal vein blood glucose lasted for approximately 15 minutes and remained unexplained. Hepatic blood flow, estimated by BSP extraction, increased by 120-200 cc/min. following vasopressin administration. Plasma levels of nonesterified fatty acids fell by approximately 40% during the ninety minutes after vasopressin was given.

When large doses of vasopressin were given, the dogs displayed an immediate reaction which lasted 10-15 minutes and consisted of restlessness, tachycardia, hyperventilation and passage of a loose watery stool. Hyperventilation alone occurred after 20 u or less of the hormone. In one dog, in which arterial pressure was measured directly, a mean elevation of 20 mm of saline followed administration of 60 u of Pitressin.

Discussion

In 1958 Borchardt (13) demonstrated hyperglycemia in rabbits following injection of infundibular hypophyseal extracts. Subsequently posterior pituitary extracts were shown to protect experimental animals from insulin hypoglycemia (14-16) and to induce hyperglycemia in the dog (17, 18), rabbit (17) and cat (19). These results were variously interpreted as being due to 'circulatory changes' (6), interference with insulin release, or simply 'manipulation' (7).

In 1927, Lambie (2) demonstrated that removal of the liver from circulation abolished the protective effect of Pituitrin in insulin-induced hypoglycemia in the cat. Further studies have revealed that Pituitrin-induced hyperglycemia fails to occur when liver glycogen is depleted (3) and in heptatectomized animals (1).

The present studies confirm the occurrence of an immediate hyperglycemic response following administration of vasopressin. Use of synthetic hormones has eliminated the possibility of contamination with other substances affecting blood glucose and reveals vasopressin and not oxytocin to have hyperglycemia inducing
TABLE 1. Changes in Hepatic Vein Glucose Concentration and in Hepatic-Portal Glucose Gradients Following Intraportal Administration of Posterior Pituitary Hormones

<table>
<thead>
<tr>
<th>Dose*</th>
<th>Weight, kg</th>
<th>Preparation</th>
<th>Dose, U</th>
<th>Glucose Change, mg %</th>
<th>Hepatic vein increment, † after hormone</th>
<th>Hepatic-portal gradient, † before hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>22.7</td>
<td>Pitressin</td>
<td>5</td>
<td>9.0</td>
<td>8.2</td>
<td>50.0</td>
</tr>
<tr>
<td>7</td>
<td>28.1</td>
<td>Vasopressin</td>
<td>10</td>
<td>(29.8)</td>
<td>18.6</td>
<td>51.0</td>
</tr>
<tr>
<td>6</td>
<td>22.7</td>
<td>Vasopressin</td>
<td>20</td>
<td>70.0</td>
<td>19.3</td>
<td>77.1</td>
</tr>
<tr>
<td>5</td>
<td>22.4</td>
<td>Pitressin</td>
<td>40</td>
<td>80.0</td>
<td>38.0</td>
<td>132.0</td>
</tr>
<tr>
<td>3</td>
<td>22.4</td>
<td>Vasopressin</td>
<td>60</td>
<td>(26.6)</td>
<td>14.0</td>
<td>87.7</td>
</tr>
<tr>
<td>11</td>
<td>24.8</td>
<td>Oxytocin†</td>
<td>10</td>
<td>(−5.7)</td>
<td>10.1</td>
<td>8.3</td>
</tr>
<tr>
<td>13</td>
<td>9.5</td>
<td>Pitocin</td>
<td>20</td>
<td>(−20.6)</td>
<td>5.3</td>
<td>7.0</td>
</tr>
<tr>
<td>18</td>
<td>29.0</td>
<td>Oxytocin†</td>
<td>40</td>
<td>(−8.4)</td>
<td>3.7</td>
<td>11.1</td>
</tr>
</tbody>
</table>

* Representative experiments. † Synthetic. ‡ Maximal response.

The glycogenolytic effect of vasopressin in the liver could occur directly or via another glycogenolytic agent such as glucagon or epinephrine. It is doubtful that vasopressin stimulates release of epinephrine in quantities sufficient to produce the observed responses. Epinephrine raises plasma NEFA (20) and in these experiments, plasma NEFA fell uniformly after vasopressin. Epinephrine tends to inhibit the rate at which blood glucose is removed by peripheral tissues (21); following vasopressin-induced hyperglycemia the blood sugar level fell rapidly. Last, vasopressin is known to induce hyperglycemia in dogs and cats pretreated with dihydroergotamine (22).

The possibility has not been ruled out that vasopressin induces glycogenolysis by stimulation of glucagon release. Nevertheless, it seems likely from the rapidity of the hyperglycemic response that the effect is a direct one involving the rate-limiting enzyme hepatic phosphorylase.

REFERENCES