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Isoproterenol-Induced Hypokalemia: Role of the Liver (40648)[1]

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In 1933, D'Silva and Bachromejew, working independently, reported the influence of the sympathetic nervous system on the potassium concentration, [K], of the blood (1, 2). D'Silva found that intravenous injection of epinephrine in the cat caused arterial serum [K] to increase temporarily, then to decrease slightly below the control value, and eventually to return to normal (3).

D'Silva (4) and others (5–8) presented evidence that the liver is the major source of the increase of arterial [K] caused by epinephrine. Other work indicates that the hypokalemia, caused subsequently by epinephrine, is due to the uptake of K by both skeletal muscle (8–12) and the liver (8, 9, 13). Kastello and Vick (13) found that the gut first took up K during the hyperkalemia, caused by epinephrine, and then released K during the hypokalemic phase.

Systemic infusion of the adrenergic β-receptor agonist, isoproterenol, causes only arterial hypokalemia (14, 15). Isoproterenol has been shown to cause an uptake of K by skeletal muscle during local infusion, and this uptake is not related to any change of blood flow (11, 12); investigators have postulated that β-receptor agonism alone may lead to gain of K by the liver (8). Castro-Tavares and Cardoso (16) stated that an isolated dog-liver preparation seems to have β-receptors, which, when stimulated, cause the uptake of K. Later, one of the same investigators reported that neither systemic infusion of isoproterenol, nor injection of the drug into the hepatic artery, affected liver K (17).

We have studied the role of hepatic tissue in the production of hypokalemia by isoproterenol, utilizing administration of the compound by constant infusion into the portal vein in the dog. Our results establish that the liver takes up K when adrenergic β-receptors are stimulated, and that the liver need not lose K for the uptake to occur.

Methods. Dogs that weighed between 12.5 and 29.5 kg and were not selected for sex or breed were anesthetized with pentobarbital sodium, 30 mg/kg iv. A cuffed endotracheal tube was inserted, and respiration was controlled by positive-pressure ventilation. The carotid arterial pressure and lead II of the ECG were recorded. A midline laparotomy was performed, and a double-lumen catheter was introduced through a splenic vein. The end of the catheter was advanced into the portal vein to a point just proximal to the liver; its position was confirmed by digital palpation. Isoproterenol was infused through the distal lumen of the catheter, and portal venous blood was collected through the proximal lumen. Another catheter was introduced through the right external jugular vein and guided by palpation to lodge in a hepatic vein. Then the laparotomy incision was closed. A short, nonoccluding catheter was placed in the left femoral artery to sample arterial blood.

Following surgery, a 30-min period was allowed for stabilization. After a subsequent 30-min control period, *dl*-isoproterenol hydrochloride was infused at a rate of 0.4 μg/kg body wt/min, calculated as the base, into the portal vein for 30 min, using a syringe-driver pump. Samples of blood were collected simultaneously from the femoral artery, the portal vein, and the hepatic vein, after specified intervals during the control period, the infusion period, and for 30 min after the infusion was finished. The samples were placed in heparinized tubes and centrifuged immediately. Plasma [K] was measured using an internal-standard flame photometer. Based on the assumption of a blood volume equal to 7.9% of body weight (18), no more than 6.6% of the blood of any animal was

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removed during any experiment. The total volume of solution administered to each animal was 6.9 ml.

To assess the significance of change of plasma [K] in a given vascular bed during and after the infusion of isoproterenol, the differences between each experimental sample and the sample at min 0 were taken, and Student's *t* test for paired data was applied. To assess the significance of the difference of plasma [K] between two vascular beds at a given time during or after the infusion of isoproterenol, analysis of variance was used to determine if differences were present among the group means. Duncan's new multiple range test was used to determine which group means were significantly different.

Results. In six dogs that were infused intraportally with isoproterenol, the mean arterial blood pressure did not change significantly. The heart rate was significantly greater throughout the period of infusion ($P < 0.01$).

The temporal courses of the portal venous, arterial, and hepatic venous plasma [K] are shown in Fig. 1. The patterns of the three are qualitatively similar; in each vessel, the plasma [K] increased slightly, but not significantly, at min 2. The arterial plasma [K] decreased significantly at mins 10 and 50 ($P < 0.02$) and from mins 15 to 40 ($P < 0.01$). Although the hepatic venous plasma [K] decreased from mins 10 to 40 ($P < 0.01$), and it was slightly lower than the arterial plasma [K] during the infusion, the differences between the two were not significant ($P > 0.2$).

The portal venous plasma [K] decreased significantly at mins 15 and 20 ($P < 0.05$), and mins 25 and 30 ($P < 0.02$). Although the temporal courses of the changes in plasma [K] in the two vessels were similar, the plasma [K] did not decrease as much in the portal vein as in the hepatic vein. The hepatic venous plasma [K] was significantly lower than the portal venous plasma [K] at mins 4 ($P < 0.05$), 10 ($P < 0.01$), 15 ($P < 0.02$), 25 ($P < 0.02$), and 30 ($P < 0.05$).

During the infusion of isoproterenol, the portal venous plasma [K] slightly exceeded the arterial plasma [K], yet the differences were not significant.

Discussion. The plasma [K] during the control period in these experiments was lower than normal, perhaps due to the background

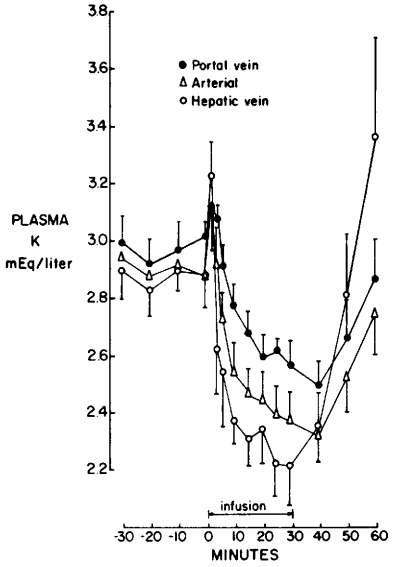

FIG. 1. Effects of constant infusion of isoproterenol into the portal vein on portal venous, arterial, and hepatic venous plasma [K]. Infusion at a rate of 0.4 μg/kg/min began at min 0 and ended at min 30. Mean ± SE of six experiments.

sympathetic activity, which was made greater by the surgery (19). Vick and Todd have suggested that normal sympathetic activity may exert an influence on the arterial plasma [K] (20). Since the initial increase in arterial plasma [K] caused by epinephrine is short lasting, sustained sympathetic function during stress is expected to act to reduce plasma [K]. Moreover, the use of pentobarbital as an anesthetic may have caused a decrease of the plasma [K] during the control period in the present experiments. Other investigators have observed a reduction in the plasma [K] during the use of a variety of anesthetics (21, 22), pentobarbital included (23).

It is assumed that the general response seen in the present experiments, which utilized *dl*-isoproterenol, would have been similar if *l*-isoproterenol had been used, although the magnitude of the response resulting from an equivalent dosage may have been different. During the period of hypokalemia caused by the infusion of isoproterenol, net movement of K from the plasma to the liver is indicated, as plasma [K] in the portal vein was significantly greater than that in the hepatic vein during most of the period of infusion. Although the differences between the arterial

plasma [K] and the hepatic venous plasma [K] were not statistically significant, there was a trend toward a greater arterial concentration. Assuming that plasma [K] in both the portal vein and the hepatic artery exceeded that in the hepatic vein, these data establish that the liver takes up K under the influence of adrenergic β-receptor stimulation, and that the liver need not lose K immediately beforehand, as occurs during the infusion of epinephrine, for the uptake to occur. However, it is conceivable that increased sympathetic discharge during surgery, as mentioned earlier, might have been associated with an initial release of K before the experimental period began.

Although the differences between the arterial plasma [K] and the portal venous plasma [K] during the infusion of isoproterenol are not significant, the data indicate a slight release of K into the plasma in the mesenteric bed at the same time that the liver takes up K. These opposing actions of the liver and of the gut on the plasma [K] also have been observed during the period of hypokalemia caused by systemic infusion of epinephrine (13).

The decrease of arterial plasma [K] during the infusion of isoproterenol reflects the cumulative uptake of K not only by the liver, but also by the skeletal muscle, if the isoproterenol recirculates sufficiently. The concentration of the drug which reached skeletal muscle beds is not known. Apparently, not enough of the isoproterenol escaped inactivation by the liver to decrease mean arterial pressure, although enough of the drug reached the heart to increase the heart rate during the period of infusion.

After the infusion of isoproterenol was completed, the hepatic venous plasma [K] exceeded the plasma [K] in the portal vein and in the hepatic artery, which suggests that, under the influence of isoproterenol, the liver took up more K than it could retain. This outflow of K from the liver would act to restore arterial plasma [K] to a normal level.

In other investigations, isoproterenol has been shown to cause an early increase in arterial plasma [K] (14, 24). The hyperkalemic effect is not constant, and the response is negligible in some animals, even with high doses. Todd and Vick (15) reported no significant increase of mean arterial plasma [K] in dogs infused with isoproterenol at a rate of 2 μg/kg/min in the femoral vein. In the present experiments, although a slight increase of plasma [K] occurred at min 2, it was not significantly different from the control value.

Intraportal infusion of isoproterenol at the rates of 0.1 to 0.4 μg/kg/min does not increase the portal venous blood flow significantly (25) (unpublished observations), although other investigators (26–28) have found that isoproterenol dilates the hepatic arterial vessels. Effects on the intrahepatic portal venous bed are unclear. Hanson (26) found an inconsistent response of the portal vessels to the isoproterenol which was infused through the hepatic artery, and, portal vessels dilated in some perfused dog liver preparations *in situ*, but in some others, they did not. Green (29) suggested that pentobarbital sodium, used for anesthesia, may have diminished the resting tone of the intrahepatic portal vessels, and, thus, prevented further dilation caused by the isoproterenol.

The mechanism by which β-receptor agonism causes the uptake of K by the liver is not known. Since the liver need not lose K beforehand, which might establish a passive gradient for the uptake to occur, we need to postulate some type of active transport mechanism that is stimulated by isoproterenol. Dockry *et al.* (30) have suggested that isoproterenol causes muscle to take up K by stimulating an electrogenic Na "pump." Porte (31) demonstrated that isoproterenol can stimulate the pancreas to secrete insulin. Although insulin can lower plasma [K] (32), Pettit and Vick (33) found that the actions of the catecholamines on the plasma [K] do not depend on the release of pancreatic insulin. These authors postulated that the β-receptor activity might increase the amount of insulin the pancreas secretes, while simultaneously counteracting the peripheral action of insulin on tissue uptake of K.

Summary. Constant infusion of isoproterenol into the portal vein of the dog produces a sustained decrease of the plasma [K] in the femoral artery, the hepatic vein, and the portal vein. During the hypokalemia, the hepatic venous plasma [K] falls significantly below the portal venous plasma [K], which indicates a net uptake of K by the liver; at the same

time that the liver takes up K, the gut releases a slight amount of K. A preceding loss of K by the liver is not essential to the occurrence of the uptake; therefore, the data suggest that isoproterenol acts directly to increase the uptake of K by the liver.

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