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Hepatic Sodium–Potassium Exchange Induced by Adrenomimetic Amines[1] (39156)

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Epinephrine causes a transient elevation in the serum K^+ followed by a prolonged hypokalemia, which is primarily the result of an initial loss and subsequent uptake of K^+ by the liver (1, 2). There has been a question as to whether or not there are accompanying changes in serum Na^+. In the present study this is examined by noting the electrolyte composition of the hepatic venous blood following the direct intraportal injection of adrenergic agonists.

Methods. Male and female mongrel dogs weighing 18–20 kg were used in these experiments. The methods for implanting a portal vein catheter and for serial sampling of arterial and hepatic vein blood are described in detail elsewhere (3). One to 2 weeks after the portal vein catheter had been placed, the animals were anesthetized with sodium pentobarbital and ventilated through a cuffed endotracheal tube at a rate and depth sufficient to maintain their $PaCO_2$ within a range of 35–38 mm Hg. Catheters were then placed to allow sampling of arterial and hepatic venous blood. Arterial blood pressure was measured with a Statham strain gauge.

The adrenergic agonists, epinephrine (1:100,000), norepinephrine (1:50,000), phenylephrine (1:2,500), or isoproterenol (1:25,000) were injected intraportally over a 45-sec interval at a rate of 1 ml/9 sec with a Sage infusion pump. Just prior to injection of an agonist, samples were taken from the artery and the hepatic vein. Beginning with the injection period and ending 105 sec later, sequential arterial and venous samples of 3 ml volume were withdrawn simultaneously at a rate of 1 ml/5 sec. Additional samples were taken at 165–180, 225–240, 285–300, 345–360, 405–420, and 465–480 sec after the start of the intraportal injection. All blood samples were collected in heparinized syringes and centrifuged immediately after withdrawal. The plasma was then analyzed photometrically for Na^+ and K^+ (Instrumentation Laboratories Flame Photometer).

Once a control series of samples was obtained, an adrenergic blocking agent was administered and, after the appropriate time interval, the injection of the agonist and the sampling procedures were repeated. The β-adrenergic blocking agent, propranolol (Inderal, 0.5 mg/kg), was administered intravenously, and 20 min later, the injection of the agonist was repeated. One hour elapsed following α-adrenergic blockade with *N,N*-dibenzyl-β-chloroethylamine (Dibenamine, 15 mg/kg) before repeating the injection of the agonist. Simultaneous α- and β-blockade was achieved by giving propranolol 40 min after Dibenamine, and 20 min later repeating the injection of the agonist. The doses of the blocking agents were sufficient to effect adrenergic blockade as the propranolol blocked isoproterenol induced cardiac acceleration, and the Dibenamine blocked the pressor response of phenylephrine.

The changes in arterial and hepatic venous K^+ and Na^+ before and after adrenergic blockade were compared using Student's *t* test for the difference between the means of paired observations. Each animal was used in several such experiments with at least 1 week intervening between individual trials.

Results. Thirty experiments were performed on seven dogs. Six animals received isoproterenol before and after propranolol; six received phenylephrine before and after Dibenamine; six received epinephrine before and after Dibenamine; four received epinephrine before and after simultaneous

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α- and β- blockade; four received norepinephrine before and after simultaneous blockade; and four received isoproterenol plus phenylephrine before and after simultaneous blockade.

Each adrenergic agonist produced an initial hyperkalemia, defined as a rise above the preinjection level, and a subsequent hypokalemia, defined as a fall below the preinjection level. Since only the magnitude and not the duration or the time of appearance of these phases varied with the different agonists, the data from all experiments were combined. The maximum value for hepatic venous K^+, which averaged 5.35 ± 0.6 mEq/liter above the preinjection level, was observed during the 45–60-sec sampling interval (Fig. 1, below). Hepatic venous K^+ had fallen 0.86 ± 0.2 mEq/liter below its preinjection level by the 225–240-sec interval, and it remained significantly ($P < 0.01$) below that level through the eighth, and final min of observation.

Each adrenergic agonist produced a fall in hepatic venous Na^+. The minimum value to which the hepatic venous Na^+ fell (5.30 ± 0.8 mEq/liter below the preinjection level) was observed during the 45–60-sec interval, and while it returned toward its resting value, it remained significantly ($P < 0.01$) below that level and significantly ($P < 0.05$) below arterial Na^+ through the eighth min of observation (Fig. 1, above). The relative potencies of the agonists for producing these changes in hepatic venous K^+ and Na^+ were: epinephrine, 1; norepinephrine, 1/2; isoproterenol, 1/25; phenylephrine, 1/40. In Fig. 2 the adrenergically-induced maximum elevation of hepatic venous K^+ is plotted against the maximum decrease in hepatic venous Na^+ for the 30 individual experiments prior to adrenergic blockade. In every instance, the maximum changes in K^+ and Na^+ appeared during the same sampling interval.

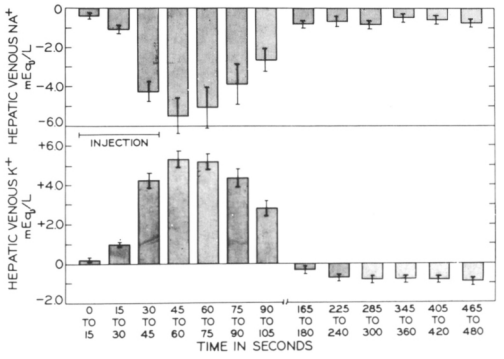

FIG. 1. Effects of intraportally injected adrenomimetic amines on hepatic venous Na^+ (above) and K^+ (below). Values are the means ± SE of 30 experiments in seven dogs following the intraportal injection of 5 ml of epinephrine 1:100,000, or norepinephrine 1:50,000, or isoproterenol 1:25,000, or phenylephrine 1:2500, or isoproterenol plus phenylephrine.

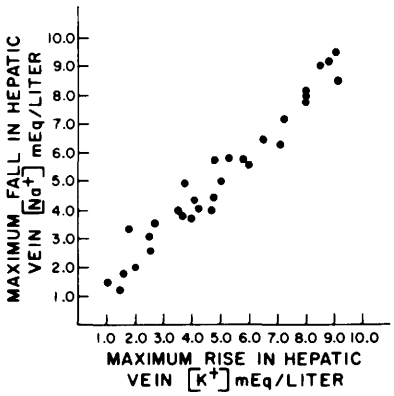

FIG. 2. Maximum fall in hepatic venous Na^+ plotted against the maximum rise in hepatic venous K^+ in 30 individual experiments following the intraportal injection of epinephrine, norepinephrine, isoproterenol, phenylephrine, or isoproterenol plus phenylephrine. In each experiment the maximal changes in Na^+ and K^+ were recorded during the same sampling interval (45–60 sec after the start of the agonist injection).

After adrenergic blockade, whether with separate agents or combined α- and β-blockade, the changes in arterial and hepatic K^+ and Na^+ induced by the agonists varied by less than 13% from those induced before the blockade. Furthermore, adrenergic blockade did not alter the duration or time of appearance of the electrolyte changes.

Discussion. In his studies on the epinephrine-induced changes in serum K^+, D'Silva was unable to detect concomitant alterations in serum Na^+ (2, 4). Subsequently, investigators did note hyponatremia accompanying the hyperkalemia (5, 6, 7). This was not a consistent finding, however, and not all adrenergic agonists which produced changes in systemic serum K^+ also altered Na^+ concentrations. Studies on the liver have also failed to produce consistent results. Elliot *et al.* administered epinephrine

to perfused, hypothermic rabbit livers and observed a rise in effluent K^+ and a fall in Na^+ (8). Craig, however, reported a decrease in both hepatic venous K^+ and Na^+ following administration of epinephrine to perfused frog livers (9). More recently, Haylett and Jenkinson, using guinea-pig liver slices, observed that norepinephrine reduced intracellular K^+ and raised intracellular Na^+ in a ratio of approximately 1:1.7 (10). The direct application of these later observations to the intact animal is difficult, however, owing to the marked alterations in the resting intracellular ionic compositions exhibited by their tissue slices.

The data obtained in the present experiments indicate that catecholamines provoke a loss of hepatic K^+ in exchange for Na^+ in a 1:1 ratio. While all catecholamines studied gave this result, epinephrine and norepinephrine appear much more efficient than either specific adrenergic agonist. Haylett and Jenkinson consider such ion shifts the consequence of a transient increase in hepatic cellular membrane permeability to K^+ (10). They would limit the change in cation permeability to K^+ since they observed hyperpolarization of the hepatic cells during the periods of Na^+/K^+ shifts, indicating that the membrane was moving closer to the K^+ equilibrium potential. It should be pointed out, however, than an increase in membrane permeability to Na^+ could also occur. As long as the increase in K^+ permeability was significantly greater than the increase in Na^+ permeability, hyperpolarization still results.

Finally, some mention should be made of the potential significance such rearrangements of intracellular ionic composition might have. The original suggestion of D'Silva (2) and of Fenn (11) that the epinephrine-induced release of glucose and K^+ were related, was discarded after the experiments of Ellis and Eusebi (12, 13) which appeared to demonstrate that these two processes were mediated by different adrenergic receptors. It is now clear that catecholamine-induced ion movements and glycogenolysis possess the characteristic of relative nonspecificity in terms of strictly defined adrenergic receptors (3, 14, 15). There is, therefore, no reason to separate these processes on the basis of the mechanisms which mediate them. Cahill *et al.* (16) demonstrated a 400% increase in epinephrine-induced phosphorylase activation, glycogen breakdown, and glucose release in a high Na^+ medium as opposed to a high K^+ one. In fact, only small increases in the Na^+/K^+ ratio produced maximal stimulation of these processes. In the present experiments, while the initial loss of hepatic K^+ is rapidly followed by K^+ uptake, the accumulation of Na^+ by the liver is not reversed by the eighth min of observation, which is well into the time when the liver is known to be releasing glucose. These results suggest that catecholamines, in order to effect the most productive environment for glycogenolysis, might induce membrane permeability changes that would result in an increased intracellular Na^+/K^+ ratio.

Conclusions. The effects of catecholamines on hepatic K^+ and Na^+ movements were studied in anesthetized dogs by measuring systemic arterial and hepatic venous electrolyte composition following intraportal injections of adrenergic agonists. All catecholamines studied caused the initial loss and subsequent uptake of K^+ by the liver. The loss of hepatic K^+ was accompanied by an uptake of Na^+ at a 1:1 ratio. This accumulation of Na^+ continued, although at a slower rate, for at least 8 min. Epinephrine and norepinephrine were much more potent in these effects than either phenylephrine or isoproterenol. Neither α- nor β-adrenergic blockade, singly or in combination, had an appreciable effect on the magnitude or duration of the observed ion shifts. It is concluded that the predominant effect of catecholamines is to produce a net accumulation of hepatic Na^+, and that the mechanism governing hepatic ion movements is nonadrenergic as defined by stimulation by specific adrenergic agonists and inhibition by specific adrenergic antagonists.

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