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Hepatic Potassium Movements Induced by Sympathomimetic Amines Before and After Adrenergic Blockade[1] (38849)

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The intravenous injection of epinephrine produces an initial loss of K^+ from the liver followed in 1–2 min by a period of prolonged K^+ uptake (1, 2). Numerous investigators have sought to define the mechanism mediating these K^+ movements. The initial loss has been attributed either to the activation of α-adrenergic (3, 4) or both α and β-adrenergic receptors (5), while the delayed uptake was thought to result from the stimulation of β-receptors (5). Guthrie and Murphy demonstrated that β-adrenergic antagonism can attenuate arterial K^+ changes, in certain circumstances, by reducing splanchnic blood flow (6). Recent experiments, using an intraportal route for epinephrine injections to prevent significant changes in hepatic perfusion, have shown that neither α- nor β-adrenergic antagonism produces a significant blockade of the K^+ shifts (7). The present experiments, utilizing intraportal injections of specific adrenergic agonists and their respective blocking agents, were performed in a further attempt to classify the hepatic receptor mediating K^+ movements.

Methods. The experiments were performed on 18- to 20-kg male and female dogs. A catheter of polyvinyl chloride tubing covered with a graphite–benzalkonium–heparin anticoagulant surface (8) was inserted into a branch of the splenic vein and advanced into the portal vein until its tip lay 2–3 cm from the porta of the liver. The opposite end of the catheter was exteriorized between the scapulae. The animal was allowed to recover 1–2 wk before experiments were performed.

During experiments the animals were anesthetized with sodium pentobarbital (30 mg/kg iv) and ventilated through a cuffed endotracheal tube with an Air Shields Ventilator at a rate and depth sufficient to keep their arterial pCO_2 within the range of 35–38 mm Hg. A basket-tipped cardiac catheter was introduced into an external jugular vein and placed fluoroscopically in an hepatic vein. This catheter was attached to a Paley 7-place manifold to allow serial sampling of hepatic venous blood. Serial sampling of arterial blood was accomplished through a second manifold attached to a 20-gauge needle inserted percutaneously into the right femoral artery. Arterial blood pressure was measured with a Statham strain gauge attached to a needle in the left femoral artery. Celiac and superior mesenteric blood flows were measured in one dog with a Biotronix flow meter. Zero flow was obtained with inflatable occluders. Both the flow probes and the occluders were implanted under aseptic conditions 1 wk prior to experimentation. Blood flows, arterial blood pressure, and lead II ECG were recorded on a Gilson polygraph.

The adrenergic agonist, phenylephrine (Neosynephrine) 1:2500 (0.4 mg/ml) or isoproterenol (Isuprel) 1:25,000 (0.40 μg/ml) was injected into the portal vein over a 45-sec interval at a rate of 1 ml/9 sec. Just prior to the injection period, control samples were taken from the femoral artery and the hepatic vein. Beginning at the start of the injection period and ending 105 sec later sequential samples of 3-ml volume were withdrawn simultaneously from the artery and vein at a rate of 1 ml/5 sec. Six additional samples were taken, at 165–180 sec, 225–240 sec, 285–300 sec, 345–360 sec, 405–420 sec, and 465–480 sec after the start of the injection period. All blood samples were withdrawn in heparinized syringes and centrifuged immediately. Plasma was then analyzed photometrically for K^+ (Instrumentation Laboratories Flame Photometer).

Once a control series of samples was obtained in the manner described, an adrenergic blocking agent was administered and,

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TABLE I. MAXIMUM CHANGES IN ARTERIAL AND HEPATIC VENOUS K^+ INDUCED BY SYMPATHOMIMETIC AGENTS BEFORE AND AFTER ADRENERGIC BLOCKADE.[a]

Agonist	Blocking agent	No. of dogs	Time	Arterial K^+				Hepatic Venous K^+			
				Max increase[c] (meq/liter)		Max decrease[c] (meq/liter)		Max increase[c] (meq/liter)		Max decrease[c] (meq/liter)	
				C	E	C	E	C	E	C	E
Ph	D	4	1 hr	0.8 ±0.1	1.1 ±0.3	−0.3 ±0.1	0.0 ±0.0[d]	4.53 ±0.4	3.45 ±0.3	−0.6 ±0.1	−0.4 ±0.1
Is	P	4	20 min	0.4 ±0.1	0.3 ±0.1	−0.7 ±0.1	−0.6 ±0.1	1.4 ±0.3	0.9 ±0.2	−1.1 ±0.2	−1.0 ±0.2
Ph + Is	D + P	3	1 hr/20 min	1.5 ±0.2	1.2 ±0.4	−0.5 ±0.1	0.0 ±0[d]	7.9 ±0.6	6.9 ±0.5	−1.3 ±0.2	−1.1 ±0.4

[a] Ph: Phenylephrine. Is: Isoproterenol. D: Dibenamine. P: Propranolol.

[b] Time: Interval after blocking agent before agonist injection was repeated.

[c] Maximum changes in K^+ as compared to the values prior to agonist injection before blocking agent (C) and after blocking agent (E).

[d] K^+ change after blocking agent (E) significantly different from that before blocking agent (C) at $P < 0.001$ level.

after an appropriate time interval, injection of the agonist and sampling procedures were repeated. The β-adrenergic antagonist propranolol (Inderal, 0.5 mg/kg) was dissolved in 0.9% saline and injected intravenously. The intraportal injection of isoproterenol was repeated 20 min after the propranolol. The α-adrenergic antagonist *N*,*N*-dibenzyl-β-chloroethylamine (Dibenamine, 15 mg/kg) was dissolved in propylene glycol and diluted to 50 ml with 0.9% saline before being injected intravenously over a 5-min interval. Phenylephrine injections were repeated 1 hr after Dibenamine. Simultaneous α and β blockade was achieved by giving propranolol 40 min after Dibenamine. Twenty minutes later the isoproterenol plus phenylephrine injection was repeated.

All values cited in the text and in Table I for arterial and hepatic venous K^+ during adrenergically induced hyperkalemia are the means ± SE of the maximum increase in K^+ above that present before the injection of the agonist. The values cited during the delayed hypokalemic phase are the means ± SE of the maximum fall in K^+ below that present before the injection of the agonist. The latter values are indicated as negative. The data obtained before and after adrenergic blockade were compared using Student's *t* test for the difference between the means of paired observations.

Results. The maximum changes in arterial and hepatic venous K^+ caused by intraportal injection of phenylephrine are summarized in Table I. The maximum rise in arterial K^+ occurred during the 75- to 90-sec sampling interval while the peak hepatic venous K^+ value appeared during the 60- to 75-sec interval. The maximum fall in arterial and in hepatic venous K^+ appeared during the 465- to 480-sec interval. Mean arterial blood pressure rose 20 ± 5.1 mm Hg and splanchnic blood flow (sum of celiac and superior mesenteric flows), measured in one dog, fell from a resting value of 750 ml/min to 140 ml/min at 70 sec after the start of the phenylephrine injection. Splanchnic flow gradually returned to resting levels at 480 sec. Hepatic venous pO_2 measured at 180 sec was 9 mm Hg below its preinjection value ($P < 0.01$).

After α-blockade phenylephrine produced elevations in arterial K^+ which were slightly greater than those in control experiments (136%, $P > 0.3$) while hepatic venous K^+ rose 78% ($P > 0.3$) of control levels (Table I). The maximum K^+ elevations occurred during the same time intervals as in control experiments. The maximum decrease in hepatic venous K^+, which now appeared in the 285- to 300-sec interval, was 72% of that in control experiments ($P > 0.3$). No hypokalemic phase was observed in arterial blood ($P < 0.001$). Intraportal injection of phenylephrine after α-blockade produced no detectable changes in mean arterial blood pressure, splanchnic blood flow, or hepatic venous pO_2.

The maximum changes in arterial and hepatic venous K^+ produced in four dogs

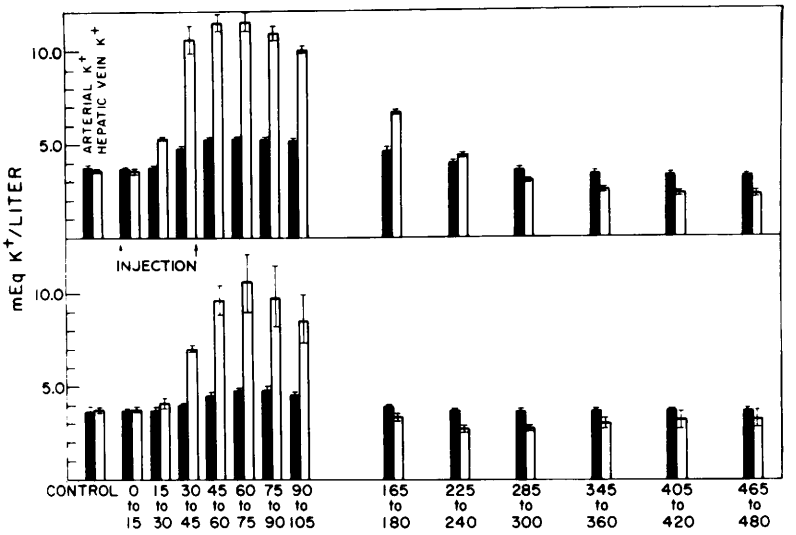

FIG. 1. Effects on arterial and hepatic venous K^+ of intraportal injections of phenylephrine (1:2500, 5 ml) plus isoproterenol (1:25,000, 5 ml) before (above) and after (below) simultaneous α and β adrenergic blockade (Dibenamine plus propranolol).

receiving intraportal injections of isoproterenol are summarized in Table I. After β-blockade isoproterenol produced elevations in arterial and hepatic venous K^+ which were 72% ($P > 0.3$) and 69% ($P > 0.3$), respectively, of those attained in the control experiment. The magnitude of the hypokalemic phase in both arterial and hepatic venous blood, and the sampling intervals during which the maximal K^+ changes appeared were unaffected by propranolol.

The maximum changes in arterial and hepatic venous K^+ produced by an intraportal injection of isoproterenol plus phenylephrine before and after simultaneous α and β blockade are illustrated in Fig. 1. This combined adrenergic blockade produced no significant changes in the magnitude or time course of the K^+ changes (Table I). Hepatic venous pO_2 at 180 sec was 9 mm Hg ($P < 0.01$) below the preinjection value. No splanchnic flows were measured in these dogs.

Discussion. In the classical studies the designation of an adrenergic receptor as being either α or β depended upon its activation by a specific agonist or upon agonist inhibition by a specific antagonist (9–12). Previous investigations in this laboratory have shown that neither α nor β blockade, singly or in combination, could modify the epinephrine-induced release or subsequent uptake of K^+ by the liver when effects of alterations in splanchnic blood flow were largely eliminated (6, 7). It was tentatively concluded, therefore, that epinephrine-induced hepatic K^+ movements were not dependent upon the activation of α or β receptors. The present experiments, utilizing specific adrenergic agonists to produce hepatic K^+ movements are in agreement with this conclusion.

Phenylephrine is thought to stimulate α receptors primarily (10). O'Brien *et al.* produced a modest arterial hyperkalemia with this drug (13) as did Todd and Vick (5). These observations, combined with reports that α blockade can diminish the arterial hyperkalemia caused by an intravenous injection of epinephrine (4), are the basis for the argument that hepatic K^+ release requires the activation of α-receptors (11). Our finding that Dibenamine fails to block the effects of phenylephrine administered intraportally does not support such a suggestion. In numerous investigations it has been reported that phenylephrine was from $\frac{1}{2}$ to $\frac{1}{10}$ as effective as epinephrine in producing a variety of α-receptor-mediated effects on smooth muscle and metabolic processes (9, 11, 14). In the present study a dose of phenylephrine 40 times that of epinephrine (7) was required to produce an equivalent hyperkalemic response.

The intraportal injection of isoproterenol produced a modest hyperkalemic response. Its effectiveness was approximately 1/25th that of epinephrine. When tested on other systems isoproterenol and epinephrine demonstrate much more nearly equivalent potencies (10, 15). Propranolol did not block the effects of intraportally administered isoproterenol. It would, therefore, be difficult to argue that activation of β-receptors is necessary for hepatic K^+ release.

The hyperkalemia produced by phenylephrine plus isoproterenol was slightly greater than the sum of that produced by each agent alone, with a rise in arterial K^+ of 125% ($P > 0.3$) and in hepatic venous K^+ of 130% ($P > 0.3$) of the sums of those produced by the individual agonists. Todd and Vick (5) reported that intravenous infusions of phenylephrine plus isoproterenol produced an arterial hyperkalemia averaging three times the sum of that produced by these agents given singly. The simplest explanation for this, they proposed, was that the release of hepatic K^+ required the activation of both α and β receptors. An alternate explanation, they suggested, was that the β agonist, by producing vasodilatation and increased cardiac output, facilitated the egress of K^+ from the liver after its release from parenchymal cells. Our results favor this second explanation. Furthermore, since combined α and β-blockade did not attenuate the hyperkalemia evoked by intraportal injections of phenylephrine plus isoproterenol it is difficult to maintain that these agents act on the liver through true adrenergic receptors to induce K^+ loss.

Heretofore, the delayed phase of hepatic K^+ uptake was thought to be due to stimulation of hepatic β receptors (5). In a previous study, utilizing the present technique of intraportal injections and hepatic vein sampling, we demonstrated that the delayed uptake of K^+ by the liver induced by epinephrine could not be blocked with adrenergic antagonists (7). In experiments reported here, it is demonstrated that specific α and β agonists were capable of inducing delayed hepatic K^+ uptake, and that this reponse, as indicated by hepatic venous hypokalemia, was not blocked by adrenergic antagonists. This uptake of K^+ by the liver was not accurately reflected in the arterial samples in two series of experiments (phenylephrine after Dibenamine and phenylephrine plus isoproterenol after combined blockade). In previous studies (6, 7) a disparity between arterial and hepatic venous K^+ values was associated with reduced splanchnic blood flow. With phenylephrine plus isoproterenol after combined blockade hepatic venous pO_2 at 180 sec was reduced, indicating intrahepatic stasis or impaired splanchnic blood flow. This suggests that failure to observe an arterial hypokalemia was due to poor hepatic perfusion. This was not the case with phenylephrine after Dibenamine, and in this instance the failure to observe an arterial hypokalemic phase cannot be explained. However, since phenylephrine caused hepatic venous K^+ to fall below preinjection values roughly the same amounts before and after Dibenamine, it cannot be concluded that α-blockade significantly interfered with hepatic K^+ uptake. It is possible that Dibenamine affects arterial K^+ through a redistribution of extracellular K^+ as is known to occur after α blockade with this agent (16).

The present investigation demonstrates that specific adrenergic agonists are capable of producing an initial loss and subsequent uptake of K^+ by the liver. Relatively high doses of these agonists are required and specific adrenergic blocking agents do not seriously interfere with these responses. Hepatic K^+ movements share with hepatic glycogenolysis this characteristic that adrenergically induced responses are nonspecific. Sherline *et al.* demonstrated that both α- and β-adrenergic agonists could stimulate phosphorylase activity and glycogenolysis and that these responses could be blocked by either α- or β-adrenergic antagonists (17). The results of the present study, combined with our previous investigations (6, 7), suggest that the mechanism responsible for hepatic K^+ movements is particularly sensitive to epinephrine but is essentially nonadrenergic as defined classically by responsiveness to specific adrenergic agonists and inhibition by specific adrenergic antagonists.

Summary. The hepatic K^+-mobilizing effects of phenylephrine and isoproterenol were studied in dogs equipped with chronic in-

dwelling portal vein catheters. Animals anesthetized with sodium pentobarbital, received intraportal injections of these sympathomimetic amines, alone or in combination, before and after α, or β, or combined adrenergic blockade. Hepatic K^+ movements were assessed by measuring systemic arterial and hepatic venous K^+ levels. It was concluded that adrenergic blockade exerted no significant influence on the ability of these agents to provoke the initial release and subsequent uptake of K^+ by the liver.

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