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Treatment of Cardiac Sensitivity to Hyperkalemia with Aldosterone, Renin, or Insulin[1] (39482)

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In a previous study of transmembrane K^+ transfer in pancreatectomized (pancx)–nephrectomized (nephx) dogs K^+-loaded by an infusion of 2 mEq KCl/kg/hr, an unexpected change in the cardiac effect of K^+ was observed; the cardiotoxic concentration of serum K^+ (compared to controls) fell by more than 2 mEq/liter to the level previously found in adrenalectomized (adrenx) dogs (1). In the present investigation it was found that treatment with aldosterone, renin, or insulin significantly decreased cardiac sensitivity to K^+ and restored prelethal serum K levels to the control range.

Methods. Data were compiled from 33 dogs of either sex that weighed between 15.5 and 26.0 kg and were fasted for 18 hr before an experiment. All were anesthetized with 30 mg/kg sodium pentobarbital iv, connected to a Harvard respirator, and infused with about 25 ml/hr of 0.15 *M* NaCl. Thirty of the animals were bilaterally nephrectomized through a midline abdominal incision. Twenty-seven were pancreatectomized by the avulsion method (2) before loading with K^+; 12, 2 to 6 days before an experiment (diabetes was controlled with regular insulin until 18 h before infusion was commenced), and 15, immediately after bilateral nephrectomy. Dogs were loaded with K^+ by discontinuing NaCl infusion and connecting them to a Harvard peristaltic pump that delivered 30 ml/hr of a KCl solution of such concentration that each animal received 2 mEq/kg/hr in a cephalic vein. During infusion, dogs were connected with a Hewlett-Packard ECG machine and Lead II monitored at frequent intervals; KCl was administered until prelethal ECG changes appeared—ventricular bradycardia of <20 beats/minute, bizarre QRS, or ventricular flutter.

The dogs were divided into five groups (Table I). Group A, the control group consisted of nine animals; six were infused with KCl 2 hr after nephrectomy, and three were infused 2 to 6 days after pancreatectomy. Group B comprised 8 nephrectomized–pancreatectomized dogs; five were pancreatectomized 2 to 6 days before nephrectomy and KCl infusion, while three were pancreatectomized immediately following nephrectomy and K^+-loaded 70 min later, when serum insulin levels are well below normal or even unmeasurable (3). Group C was made up of six nephrectomized–pancreatectomized dogs that were treated with infusions of KCl and 3 μg aldosterone acetate/kg/hr (in 30 ml/hr of ~1 ml of a 0.05% ethanol solution in 240 ml ion-free water); the latter was started in the opposite cephalic vein immediately after nephrectomy (i.e., about 2 hr before KCl infusion) and continued for nearly 4 hr, to the end of the experiment. Group D, six pancreatectomized–nephrectomized dogs that were treated with infusions of KCl and 5 U insulin with 20 μg glucagon (each/kg/hr); infusion of the hormones in 30 ml/hr ion-free water was started immediately after nephrectomy and continued for about 5½ hr to the end of the experiment. When serum glucose fell below 50 mg/100 ml, 10 ml doses of a 50% glucose solution in water were injected iv. Group E included four

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TABLE I. INFUSED TO PRELETHAL LEVEL WITH 2 mEq KCl/kg/hr.

Group	Total K^+ infused (mEq/kg)	Prelethal serum K^+ (mEq/liter)
A (9)[a] nephx (6) or pancx (3)	4.2 ± 0.9 1.2 ± 0.1	9.94 ± 0.16[b] 10.01 ± 0.11
B (8) nephx-pancx	2.20 ± 0.06	7.68 ± 0.18
P (A, B)		<.001
C (6) nephx-pancx, aldosterone	2.71 ± 0.06	9.84 ± 0.22
P (B, C)		<.001
D (4) nephx-pancx, insulin	5.4 ± 0.09	9.26 ± 0.26
P (B, D)		<.001
E (6) nephx-pancx, renin	3.4 ± 0.05	9.51 ± 0.1
P (B, E)		<.001
Adrenx (12)[c]	1.89 ± 0.14	7.59 ± 0.09
P[d] (B, adrenx)		NS

[a] Number of dogs.
[b] Mean and SEM.
[c] Previously reported (1).
[d] $P > 0.05$ not significant: *t* test.

pancreatectomized-nephrectomized dogs in which K^+-loading was accompanied by infusion of enough of a saline solution of hog renin to raise mean blood pressure by 30 mmHg: renin infusion was begun immediately after nephrectomy and continued for about 4 hr to the end of KCl administration.

Venous blood samples were obtained from an exposed femoral vein immediately after anesthesia, before KCl infusion was begun, at half-hour intervals as it proceeded and when it was discontinued, i.e., when prelethal ECG changes appeared ("end point"). Serum K^+ was determined with an Instrumentation Laboratories Flame Photometer using lithium as an internal standard. In the pancreatectomized and nephrectomized-pancreatectomized dogs serum insulin was measured by the method of Morgan and Lazarow (4), and blood glucose by a rapid glucose oxidase method (5). In four nephrectomized-pancreatectomized dogs arterial blood pH and serum Ca were also measured; the former with Radiometer Acid-Base Analyzer, the latter with a Perkin-Elmer Atomic Absorption Flame Photometer.

Results. The dogs pancreatectomized 2 to 6 days before, seemed the same as any other animals subjected to operation of similar scope, but all were frankly diabetic, with blood glucose greater than 250 mgm/100 ml, urine glucose 1–2 g/100 ml (Clinitest), no acetonuria (Acetest), and serum insulin <2.5 μU/ml. The dogs pancreatectomized 70 min before were not yet diabetic (6) at the time of KCl infusion, i.e., they had no hyperglycemia, glycosuria, or acetonuria, although insulin levels averaged only approximately one-third normal. In four nephrectomized-pancreatectomized dogs serum Ca and arterial pH were within normal limits. Neither pancreatectomy, nephrectomy, nor pancreatectomy-nephrectomy significantly altered the mean normal (preinfusion) level of serum K^+ (4–5 mEq/liter).

Group A (controls), nephrectomized or pancreatectomized and KCl infusion (Table I). The end point was similar in both sets of dogs. The mean serum K concentration at which prelethal ECG changes appeared differed by less than 0.3 mEq/liter from the average (10.2 mEq/liter) determined in eight dogs previously reported (three each of these were normal or bilaterally ureterligated, while two were ligated-pancreatectomized animals (7, 8)). In the pancreatectomized dogs serum insulin was always <2.5 μU/ml and blood glucose over 250 mg/100 ml.

Group B, nephrectomized-pancreatectomized, with KCl infusion 70 min to 6 days after pancreatectomy (Table I). In all members of the group there was a highly significant increase of sensitivity to hyperkalemic cardiotoxicity: prelethal ECG changes appeared at a mean serum K concentration ~2.3 mEq/liter below that of dogs that were either pancreatectomized or nephrectomized. The blood glucose response was not uniform—it was consistently >250 mg/100 ml in those with pancreatectomy of 2 to 6 days duration, but within normal limits (90–120 mg/100 ml) in those pancreatectomized 70 min before; however, during KCl infusion serum insulin was <2.5 μU/ml in all specimens from both. Increased sensitivity to K^+ cardiotoxicity was almost identical in hyperglycemic and normoglycemic dogs. In the four animals in which arterial pH and serum Ca were measured, these were within usual limits during the entire course of KCl infusion; calcium varied between 9.1 and 10.6 mEq/100 ml—pH between 7.24 and 7.43.

Group C, nephrectomized-pancreatecto-

mized, infused with KCl 70 min later and treated with aldosterone (Table I). Aldosterone treatment abolished cardiac sensitivity to hyperkalemia; mean prelethal concentration of serum K^+ rose by almost 2.2 mEq/liter to nearly the same level found in dogs that were either nephrectomized or pancreatectomized. Blood glucose stayed within normal limits but serum insulin was consistently <2.5 μU/ml during KCl administration.

Group D, nephrectomized-pancreatectomized, infused with KCl from 70 min to 6 days after pancreatectomy and treated with insulin and glucagon (Table I). Insulin treatment markedly decreased cardiac sensitivity to hyperkalemia—mean prelethal serum K^+ (as in aldosterone treated dogs) was highly significantly greater than in untreated nephrectomized-pancreatectomized dogs. Serum insulin was not measured; blood glucose tended to fall, but was kept in the normoglycemic range by the injection of two to three, 10 ml doses of a 50% glucose solution. In two nephrectomized-pancreatectomized dogs treated with glucagon alone, there was moderate hyperglycemia and no suggestion of improved cardiac sensitivity to K.

Group E, nephrectomized-pancreatectomized, infused with KCl 70 min later and treated with renin (Table I). Treatment with renin almost completely restored cardiac sensitivity to K^+. Mean prelethal serum K was only about 0.4 mEq/liter less than in the control animals of Group A. During KCl infusion serum insulin was <2.5 μU/ml and blood glucose between 90 and 120 mg/100 ml in all specimens.

Discussion. In dogs infused with 2 mEq KCl/kg/hr after simultaneous nephrectomy and pancreatectomy, there was a highly significant ($P < 0.001$) increase of cardiac sensitivity to elevated serum K^+. Since neither nephrectomy nor pancreatectomy alone produced any substantial change of cardiac sensitivity to hyperkalemia, it was entirely unclear why sensitivity should be so remarkably augmented when the operations were combined. The only clue was the previous finding that dogs infused with 2 mEq KCl/kg/hr 4 hr after bilateral adrenalectomy (with and without nephrectomy) had an almost identical increase of cardiac sensitivity to hyperkalemia (1, Table I). Functional adrenalectomy due to adrenal exhaustion was considered, but the scope and duration (<1 h) of the operative procedure made it unlikely. The usual serum Ca and arterial blood pH levels (in those nephrectomized-pancreatectomized dogs in which they were measured) ruled these out as causes of increased cardiac sensitivity.

Although there is no obvious connection between adrenalectomized dogs and those with simultaneous pancreatectomy and nephrectomy, the similar cardiac responses to hyperkalemia suggested a possible relation. In work to be published we found that cardiac sensitivity to K returns to the normal range in K^+-loaded adrenalectomized dogs that are nephrectomized and treated with 3 μg aldosterone/kg/hr. The same treatment proved effective in nephrectomized-pancreatectomized animals—an infusion of 3 μg aldosterone/kg/hr, started before and continued during K^+ loading, consistently restored prelethal serum K^+ to control levels (Table I). This observation suggested that nephrectomized-adrenalectomized and nephrectomized-pancreatectomized dogs were equivalent preparations in which KCl failed to provoke aldosterone secretion; in the former because of actual absence of the adrenals, in the latter possibly because of functional inability to stimulate secretion of the hormone—thus making them both aldosterone deficient.

There is evidence that mineralocorticosteroids are involved in maintenance of the normal resting membrane potential of myocardial fibers in rats, and of their sensitivity to K^+ in dogs. Following adrenalectomy both are diminished, and each is improved by treatment with mineralocorticoids (1, 9, see above).

K^+ salt infusion acts on the adrenal to stimulate aldosterone secretion in intact and nephrectomized dogs (10). In these and in pancreatectomized animals (absence of insulin alone does not influence K^+ cardiotoxicity (Table 1)) normal cardiac sensitivity to K^+ suggests adequate aldosterone secretion in response to KCl infusion. However, in nephrectomized-pancreatectomized dogs aldosterone secretion seems inadequate—there

is a highly significant diminution of cardiac sensitivity to K^+ unless exogenous hormone is administered or the animals are treated with renin or insulin. While the cardioprotective effect of the former may stem from its ability to stimulate aldosterone secretion, insulin with no such property may exert its cardioprotective effect in nephrectomized–pancreatectomized dogs by mediating the stimulation of aldosterone secretion by KCl (nephrectomized animals become hyporeninemic in about 30 min (10)). K^+ salts stimulate aldosterone secretion, apparently by transfer of K^+ to intracellular fluid (ICF) of the zona glomerulosa (11) and insulin has a powerful ability to transfer infused K^+ to ICF (7, 8). Endogenous insulin stimulated by KCl infusion (7) may perform the same office in K^+-loaded nephrectomized dogs. At any rate, it has been noted clinically that elevation of serum K^+ may be associated with hypoaldosteronism in hyporeninemic diabetics (12).

On the other hand, all of our results can be adequately explained if nephrectomy–pancreatectomy reduces cardiac sensitivity to K by activation of a sensitizing substance that is in turn inactivated by infusion of excess aldosterone, insulin or renin. Furthermore, our observations may stem from myocardial effects of insulin (13) or angiotensin II (14). However, the validity of this latter notion is rather impaired by our finding that treatment with insulin or renin is totally ineffective in adrenalectomized–nephrectomized dogs—dogs in which cardiac sensitivity to K^+ is completely restored by treatment with aldosterone (to be published).

There are centers (not our own at present) where numbers of hyporeninemic diabetics with low aldosterone levels are well known. In these, it may be possible to demonstrate the role of insulin in the response of aldosterone to KCl infusion. The results could be of considerable value clinically—for at present there are many anephric diabetics, and these are prone to cardiac complications (15).

K^+ infused into a dog not only serves to raise serum K^+, but it also provides for urinary K^+ loss (pancreatectomized dogs of Group A) and transmembrane K^+ transfer. In the present experiment there is no discernible relation between total K^+ infused and prelethal serum K^+ concentration (Table I).

Cross circulation experiments should help clarify the mechanism of increased cardiac sensitivity to K^+ while assay of serum aldosterone should establish the importance of insulin in mediating stimulation of aldosterone secretion by KCl infusion, in nephrectomized–pancreatectomized dogs.

Summary. In pancreatectomized or nephrectomized dogs K^+-loading by infusion of 2 mEq KCl/kg/hr produces ECG evidence of prelethal hyperkalemic cardiotoxicity when serum K^+ reaches about 10 mEq/liter. If, however, the operations are combined and the KCl infused into nephrectomized–pancreatectomized animals, there is a highly significant increase in cardiac sensitivity to hyperkalemia; prelethal ECG changes appear when mean serum K^+ is ~7.7 mEq/liter ($P < 0.001$), a level almost identical with that found in dogs loaded with K^+ 4 hr after bilateral adrenalectomy. Treatment of nephrectomized–pancreatectomized dogs with aldosterone, renin, or insulin decreases cardiac sensitivity to K^+ and raises the prelethal cardiotoxic level of serum K^+ to the range found in controls. The results suggest the possibility of a role for insulin in stimulation of aldosterone secretion by KCl infusion.

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