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Laboratory Report

Ability of the Endocrine Pancreas to Attenuate the Increase of Plasma Potassium Caused by Succinylcholine

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Succinylcholine was infused (30 μg/kg/min) into acutely pancreatectomized (experimental) and non-pancreatectomized (control) dogs under morphine–pentobarbital anesthesia. During the infusion, plasma K^+ increased faster and to a greater extent in the pancreatectomized dogs; this exaggerated effect is attributed to the absence of pancreatic insulin. (Key words: Hormones: insulin; Metabolism: insulin; Ions: potassium; Neuromuscular relaxants: succinylcholine.)

SUCCINYLCHOLINE causes skeletal muscle to lose potassium (K^+) at a rate sufficient to increase the concentration of K^+ in the blood plasma.[1–3] Clinical data have shown that succinylcholine increases plasma K^+ more than normally in patients who have been traumatized or burned, who have neurologic surgery, or who have tetanus, and this augmented plasma K^+ may cause cardiac arrest.[4] Recent work has shown that succinylcholine also causes the release of insulin,[5] either directly, by acting on the pancreas, or indirectly, by increasing plasma K^+.[6–8] Insulin lowers plasma K^+,[9] and recent evidence indicates that this action of insulin may help to protect against increases in plasma K^+.[10–11] Thus, when succinylcholine is administered, the resulting secretion of pancreatic insulin should oppose the succinylcholine-induced increase of plasma K^+. To evaluate this possibility, we have compared the effects of succinylcholine on plasma K^+ in pancreatectomized dogs and in dogs with pancreas intact.

Methods

Healthy dogs not selected for sex or breed and weighing between 10 and 30 kg were fasted for 24 hours, with water *ad libitum*, then were anesthetized with morphine sulfate, 20 mg/kg, sc, and pentobarbital sodium, 5 mg/kg, iv. The trachea was cannulated to permit control of respiration by positive-pressure ventilation, and lead II of the electrocardiogram and arterial blood pressure were recorded. To prevent renal loss of K^+, both kidneys were exposed through bilateral, paralumbar incisions, and each renal artery, vein, and ureter was occluded in a mass ligature. Care was taken not to include the adrenal glands in the tie. The spleen was located through the incision on the left side, emptied by compression, and tied off to prevent sequestration or extrusion of erythrocytes during the experimental procedure.

The pancreas was reached through a midline abdominal incision. The caudal pancreaticoduodenal artery and vein and the pancreatic branches of the splenic artery and vein were ligated and cut. The cranial pancreaticoduodenal artery and vein were left intact, and every fragment of the pancreas was removed carefully by the avulsion method of Markowitz *et al.*[12] This procedure allowed removal of the pancreas without compromising blood

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TABLE 1. Verification of Completeness of Pancreatectomy by Infusing Isoproterenol

Condition	Number of Dogs	Arterial Plasma Insulin Concentration* (μU/ml)	
		Resting	Isoproterenol
Control	6	27.5 ± 7	72.3 ± 27.4
Pancreatectomy	9	1.4 ± 0.8	0.9 ± 0.1

* Mean ± SE.

flow in the duodenum. To check the completenesss of the pancreatectomies, we infused isoproterenol, which stimulates secretion of pancreatic insulin,[13] in acutely pancreatectomized dogs and in control dogs, and measured plasma insulin (see Table 1).

Other investigators have found the half-life of insulin in the dog to be of the order of 10 minutes.[14-15] To assure that plasma insulin had fallen to negligible levels, we waited at least 40 minutes after each pancreatectomy was completed before beginning our experiments. After an additional 30-minute control period, succinylcholine chloride (Sucostrin, Squibb), 30 μg/kg/min, calculated as the salt, was infused in a total volume of 15 ml, using a syringe-driver pump, through a nonoccluding catheter placed in the right femoral vein. Infusions lasted 30 minutes and were followed by a 60-minute recovery period. Additional control studies in which only NaCl solution was infused were done.

Samples of blood were taken from the left femoral artery at specified intervals throughout the experiments. A portion of each sample was collected in a heparinized tube for measurement of plasma K^+, and the remainder was collected in an EDTA tube for measurement of plasma insulin. All samples were centrifuged immediately after collection. Assuming a blood volume equal to 7.9 per cent of body weight in the dog,[16] no more than 6 per cent of any animal's blood was removed during any experiment. Plasma K^+ was determined using an internal-standard flame photometer. Plasma insulin was measured by radioimmunoassay, using the double-antibody system of Morgan and Lazarow.[17] The technique was modified by using porcine insulin as standard, ^{131}I-labelled porcine insulin as tracer, and dextran-coated charcoal instead of the second antibody.[18] Although insulin measurements obtained by this assay are porcine equivalents and do not represent absolute concentrations of dog insulin, it has been shown that this assay gives a valid representation of changes in canine β-cell activity.[7]

Results

Table 1 shows the mean concentrations of insulin in the arterial plasma of six control dogs, with pancreas intact, and nine pancreatectomized dogs, before and after infusion of isoproterenol, 2 μg/kg/min, for 10 minutes. These experiments show that pancreatectomy removed all significant sources of insulin secretion. Additional control studies in which NaCl, rather than succinylcholine, was infused in five pancreatectomized dogs and in seven dogs with pancreas intact were performed. After an initial increase in the pancreatectomized group after pancreatectomy, arterial plasma K^+ did not change significantly in either of these control experiments.

Figure 1 illustrates the results of infusing succinylcholine at a rate of 30 μg/kg/min in six pancreatectomized dogs and in six dogs with pancreas intact. Data were calculated as difference from time 0 for each animal. The increase of plasma K^+ which occurs after pancreatectomy is related to the morphine used in the anesthesia and is discussed below. After the infusion of succinylcholine was begun, plasma K^+ increased in both groups of animals, but the increase was greater in the pancreatectomized group. The normalized values of the two groups were significantly different at minutes 30 ($P < 0.01$), 40, 50, 70, and 80 ($P < 0.05$).

Discussion

Morphine-pentobarbital anesthesia was chosen for these studies because, with this combination, normal arterial blood pressure, heart rate, and heart rhythm (*i.e.*, normal sinus arrhythmia) are retained. Morphine has the disadvantage of causing release of pancreatic insulin by stimulating medullary vagal nuclei[19-21] and by producing hyperglycemia, secondary to the release of epinephrine from

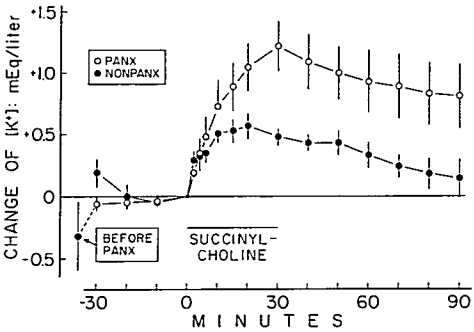

FIG. 1. Effects of infusing succinylcholine chloride, 30 μg/kg/min, on arterial plasma K^+ in six acutely pancreatectomized (PANX) dogs, with spleen and kidneys removed, and in six dogs with spleen and kidneys removed but pancreas intact (NONPANX). Total elapsed time between taking sample before pancreatectomy and minute −30 is time for operation plus 40 minutes recovery period. Data are mean differences (±SE) from minute 0.

the adrenal medulla.[22-23] In other studies, we found that basal plasma insulin in dogs subjected to similar morphine–pentobarbital anesthesia was 27 ± 7 μU/ml. This contrasts with levels in unanesthetized dogs, which Hiatt *et al.*[7] found to be 14 ± 2 μU/ml. Thus, we assume that, in the present studies, plasma insulin and background levels of catecholamine were increased to above normal by the action of morphine. Insulin and epinephrine both cause the uptake of K^+ by tissues[9,24-26] and probably were responsible for the low values of plasma K^+ in our anesthetized animals. Removal of the pancreas in these animals removed essentially all plasma insulin, permitting plasma K^+ to return toward values found in unanesthetized animals.

According to conventional theory, K^+ moves out of the cell along a chemical activity gradient and into the cell along an electrical gradient and as a result of the expenditure of metabolic energy.[27] Acetylcholine and succinylcholine both increase the conductance of small cations, but not of anions, at the motor end-plate.[28] Both substances increase the influx of Na^+ along its activity and electrical gradients, depolarizing the cell, reducing the electrical gradient acting on K^+, and permitting K^+ to leave the cell, along its activity gradient. It has been estimated that succinylcholine can cause the loss of about 1 per cent of total muscle K^+,[2] and this efflux should cause a transient and localized increase of extracellular K^+ in the area of the end-plate, contributing to further depolarization of the end-plate region.[29,30] In fact, it has been observed that the end-plate potential is decreased by succinylcholine to the greatest extent soon after application, and, as interstitial K^+ is washed away, the potential increases again to a steady level about halfway between the resting value and maximum depolarization.[31] Influx of K^+ into these partially repolarized tissues may account for some of the decline of plasma K^+ after the infusion of succinylcholine was stopped (fig. 1).

The increase of plasma K^+ that occurs during the infusion of succinylcholine in the group of pancreatectomized dogs appears to follow an exponential time course (fig. 1). By contrast, the time course of the increase of plasma K^+ in the nonpancreatectomized group is more erratic. These data support the hypothesis that, in the nonpancreatectomized animals, plasma K^+ first increases rapidly and triggers release of pancreatic insulin, which lowers plasma K^+ by stimulating tissue uptake of K^+. Plasma insulin decreases, and plasma K^+ begins to increase again, causing more insulin to be released, which, once again, causes plasma K^+ to decrease. This interplay between insulin and K^+ may account for the erratic time course of plasma K^+ seen (fig. 1) during the initial stages of the infusion of succinylcholine in the nonpancreatectomized dogs. The exponential increase of plasma K^+ in the pancreatectomized group supports the hypothesis that in this group tissue uptake of K^+ from the

extracellular space is altered; an exponential time course would be expected if K^+ were exchanged passively between extracellular and intracellular spaces along an electrochemical gradient.

The observation that succinylcholine causes an abnormally large increase of plasma K^+ in patients and animals after muscle denervation with loss of motor function has been attributed to an increased area of succinylcholine-sensitive membrane in such muscle,[22] *i.e.*, succinylcholine depolarizes the entire sarcolemma, rather than merely the area of the motor end-plate, thus causing greater loss of K^+ from the muscle. It has been pointed out that the hyperkalemic effect of succinylcholine in traumatized patients without neurologic damage may be related, in fact, to muscle atrophy caused by prolonged bed rest.[23] The present study demonstrates that in animals the kalemotropic effect of succinylcholine is enhanced by removal of the pancreas. Hyperkalemia, in a clinical sense, did not occur. However, these results support the prediction that the hyperkalemic effect of succinylcholine might be exaggerated in diabetic patients.

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