that oxytocin, unlike pitressin, does not release ACTH. Histamine as the dipicrate has been recovered from posterior lobe tissue (5,6) and a histamine-like substance has been reported present in this gland and also in neighboring hypothalamic structures(7). None of these data furnish conclusive evidence that a histamine complex of some sort is the active component of pitressin extracts but they are suggestive, and it seems not unreasonable to make such an assumption as a working hypothesis.

Summary. Commercial pitressin contains minute amounts of a histamine-like component apparently bound to the polypeptide but which can be concentrated and rendered capable of inducing physiological responses characteristic of histamine when pitressin is subjected to strong acid hydrolysis and the pressor activity destroyed. Extracts of commercial oxytocin contained but one-tenth the vasodepressor activity of pitressin extracts.

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Effects of Glucagon on Plasma Potassium.* (22220)

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Glucagon(1) has a selective action on liver in which the activity of phosphorylase is increased and this action may be the basis for increased hepatic glycogenolysis and hyperglycemia(2). The effects of glucagon mimic epinephrine action only in the liver. Glucagon has no glycogenolytic action on muscle, no cardiovascular effect(3), and no effect on hepatic vessels(4). These properties make glucagon a useful pharmacologic tool for studying the accompaniments of hepatic glycogenolysis. Our aim was to determine whether hepatic glycogenolysis was necessarily associated with increased blood potassium.

Although epinephrine hyperkalemia has been related to hepatic glycogenolysis, several facts appear inconsistent with this simple relationship. Subcutaneous epinephrine produces hyperglycemia without an associated hyperkalemia. Intravenous epinephrine produces hyperkalemia which persists for only 3 to 5 minutes(5) and hyperglycemia which continues for one-half to one hour. The relative potencies of sympathomimetic amines for the hyperkalemic effect are markedly different from their relative potencies for hyperglycemia(6,7). Dibenamine is effective in suppressing epinephrine hyperkalemia(7), but it is extremely weak as an antagonist to epinephrine hyperglycemia(8). Epinephrine hyperkalemia occurs in animals treated with phloridzin in order to deplete liver glycogen (9). Constrictor agents with weak hyperglycemic activity produce hyperkalemia(5, 10). These discrepancies were the basis for

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investigating blood potassium effects of glucagon, an agent which has hyperglycemic activity related in detail to the action of epinephrine but which has no vascular effect.

Methods. Cats, 1.85 to 3.0 kg were anesthetized with an intraperitoneal injection of 0.88 ml per kg of Dial with Urethane (each ml contains 0.1 g diallylbarbituric acid, 0.4 g urethane, and 0.4 g monoethylurea). Arterial blood samples and mean arterial pressure were obtained from a polyethylene catheter introduced into the right carotid artery and passed down into the region of the aorta. Arterial samples of approximately 3 ml were taken into heparinized syringes. Blood samples were cooled in an ice bath and the plasma separated in a refrigerated centrifuge. Control samples were taken 15 and 5 minutes before the injection. Plasma glucose was determined with the method of Nelson(11) and Somogyi(12) and plasma potassium was determined with a Beckman DU Spectrophotometer with flame attachment. Drugs were injected into a jugular or femoral vein. Glucagon‡ was an amorphous powder (Lot No. 208-158B-197) which contained approximately 50% glucagon and less than 0.05 unit of insulin per mg. In comparable experiments synthetic l-epinephrine bitartrate was used.

Results. Our data indicate that glucagon has an effect on plasma potassium similar to the effect of epinephrine. There is a marked, transient hyperkalemia followed by a slight hypokalemia of much longer duration. Glucagon induced an hyperglycemia which reached its peak much later than the hyperkalemia and hyperglycemia was present during the much longer period of hypokalemia.

The effects of glucagon (50 μg/kg i.v.) on the potassium and glucose of the arterial blood plasma are shown in Fig. 1. This is a graph of the averages of 5 experiments of similar duration. In a total of 8 experiments the average rise in plasma potassium one minute after the glucagon was administered was 2.20 mEq./l. (range 1.28-3.50) from an average control level 3.63 mEq./l. (range 3.14-4.31). The control plasma potassium and the effect of glucagon on plasma potassium were not proportional to the control plasma glucose nor to the rise in glucose. Both fasted and nonfasted cats were used. Control plasma glucose levels were from 73 to 198 mg%.

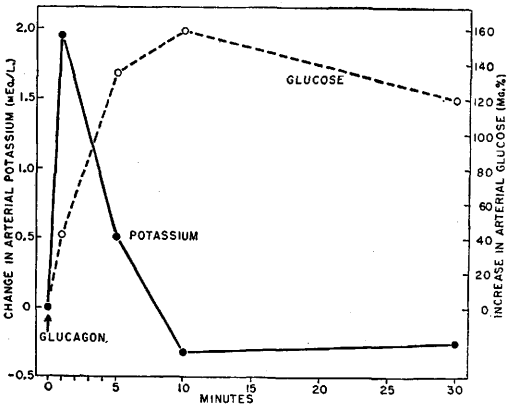

FIG. 1. Effects of glucagon (50 μg/kg) on arterial plasma potassium and glucose concentrations. Points indicate averages of 5 experiments in cats anesthetized with Dial.

Similar hyperkalemic and hyperglycemic effects were obtained with epinephrine 10 μg/kg i.v. Epinephrine produced its characteristic pressor action, whereas glucagon had no effect on the blood pressure, on the heart rate, or on the electrocardiogram. In control experiments there were no changes in arterial potassium one minute after the intravenous administration of saline or of glucagon-free insulin‡ (50 μg/kg).

With the exception of the hyperkalemic effect of glucagon, which does not appear to have been observed previously, our results confirm previous data in the literature. The subsequent hypokalemia would be expected as a consequence of the hyperglycemia which can induce a discharge of insulin and a greater tissue storage of potassium.

Discussion. It appears that glucagon, as well as epinephrine, produces a transient rise in arterial plasma potassium (presumably derived from the liver) during the activation of hepatic glycogenolysis. Since epinephrine and glucagon have the same effect on liver glycogenolysis, but only epinephrine has a vasoconstrictor action(13), it appears reason-

‡ Glucagon and glucagon-free insulin were obtained through the kind cooperation of Dr. W. R. Kirtley, Lilly Research Laboratories, Indianapolis, Ind.

able to conclude that there may be some relation of the hyperkalemic effects of these agents to hepatic glycogenolysis rather than to any vascular action. There are still several facts which do not appear to be consistent with this simple relationship. Some of these have been noted in the introduction. Although hyperkalemia and hyperglycemia appear to be associated responses, the former is completed in a few minutes while the latter persists. More related in time are the duration of hyperkalemia and the rising phase of hyperglycemia. The possibility exists that potassium loss from the liver occurs during the activation of phosphorylase, a process which occurs in less than four minutes(14), and which, under present experimental conditions, may be restored to the resting state in less than 10 minutes.

The repeated release of potassium from the liver was demonstrated by D'Silva(9) at intervals of 3 minutes. These experiments involved the repeated injection of epinephrine at 3 minute intervals and the withdrawal of arterial samples one minute after each injection. Since the liver has completed its release of potassium and may be reabsorbing potassium 3 minutes after an injection of epinephrine, D'Silva's data do not necessarily represent a continuous release of potassium.

The simultaneous loss of potassium and glycogen from the liver would appear to be in accord with Fenn's concept that there is a relation between the storage and loss of glycogen and potassium in tissues(15). However, the loss of potassium is rapid, but transient, and there is replenishment of hepatic potassium during the extended period of hyperglycemia. More information on hepatic phosphorylase activity may explain this curious situation.

Summary. In the cat, glucagon has an effect on arterial plasma potassium like that of epinephrine. It produces a transient, marked hyperkalemia followed by a much longer, but milder hypokalemia. Thus, glucagon is similar to epinephrine in that it elevates blood potassium and glucose and dissimilar in that it has no cardiovascular effects.

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