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EFFECT OF INSULIN AND PREDNISOLONE ON TRANSPORT OF ORGANIC SUBSTANCES IN THE DOG KIDNEY

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In experiments on dogs a single injection of insulin in a dose of 1 unit/kg body weight caused an increase in the maximal reabsorption of glucose and secretion of diodone and reduced the excretion of sodium without any change in glomerular filtration. These effects depend on the direct action of insulin, for when it was injected directly into one of the renal arteries its action was manifested only in the kidney on the side of infusion. Prednisolone had no significant effect on glucose and diodone transport when given as a single injection (3-4 mg/kg) or over a period of 10 days (1.5-2 mg/kg daily).

KEY WORDS: Insulin; prednisolone; glucose reabsorption; tubular secretion; excretion of sodium by the kidney.

Insulin and glucocorticoids are among the main regulators of carbohydrate metabolism. Nevertheless, their effect on glucose transport in the kidneys has been inadequately studied. In experimental animals and in man both a decrease [5, 6] and an increase [3, 4] in glucose reabsorption have been observed under the influence of insulin. The action of glucocorticoids on glucose transport has virtually not been studied.

EXPERIMENTAL METHOD

Acute experiments were carried out on 23 dogs. A solution containing 0.8% sodium chloride, 0.03% potassium chloride, 0.7% inulin, 25% glucose, and 2% diodone was injected at a constant rate intravenously into the animals. The technique of the experiments and method of determining the various substances were described previously [1]. In 11 experiments prednisolone was injected intravenously in a dose of 3-4 mg/kg and in 12 experiments insulin was injected into the left renal artery at the rate of 0.1 unit/min. The injection continued for 30-40 min.

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TABLE 1. Effect of Insulin on Renal Function in Chronic Experiments on Dogs

Time after injection of insulin, min	Tm_{gl}, mg/min	Tm_d, mg/min	GFR, ml/min	Diuresis	E_{Na}, μeq/min
15	115±10,9*	29,4±4,6	56,9±5,4	1,3±0,17*	62±6,6*
30	120±11,7*	31,8±5,1	54,7±4,9	1,0±0,16*	58±5,4*
60	127±11,6*	39,4±6,3	53,4±4,3	0,8±0,12*	56±4,4*
120	134±8,8*	46,8±5,9*	54,3±4,1	0,7±0,08*	62±5,8*
180	126±8,6*	39,7±4,4*	55,3±4,2	0,9±0,15*	72±5,0*
300	98±3,3	30,6±6,4	60,2±3,7	2,1±0,10	90±9,6
Control	87±4,1	26,6±3,5	54,6±5,1	2,1±0,23	96±6,9

Legend. Here and in other tables: Tm_{gl}) maximal reabsorption of glucose, Tm_d) maximal secretion of diodone, GFR) glomerular filtration rate, E_{Na}) sodium excretion. Results differing significantly from control marked by asterisk.

In chronic experiments on six dogs with previously exteriorized ureters insulin was injected intravenously as a single dose of 1 unit/kg. Prednisolone was injected intramuscularly into five dogs in a dose of 1.5-2 mg/kg daily for 10 days.

EXPERIMENTAL RESULTS

In chronic experiments injection of insulin caused a sharp decrease in diuresis on account of increased reabsorption of fluid, for filtration remained unchanged (Table 1). The greatest changes were observed 30-60 min after injection of insulin. Reabsorption of glucose in the kidneys was increased from the first few minutes after injection of the hormone and the changes reached their maximum after 2 h. Diodone secretion rose gradually to reach a maximum simultaneously with glucose transport. Sodium reabsorption increased parallel with these changes.

In acute experiments on dogs, efforts were made to determine the extent to which insulin can act directly on the kidneys. For this purpose, insulin was infused into the artery of the left kidney and the urine was collected from the two kidneys separately. Under these circumstances the function of the right kidney served as the control. In the initial state the level of diuresis, the glomerular filtration rate, and the transport of organic materials were virtually the same in the two kidneys. Infusion of insulin was accompanied by a marked increase in the maximal reabsorption of glucose in the first few minutes of observation (Table 2). There was a parallel increase in the tubular secretion of diodone. Just as after intravenous injection of insulin, the diuresis fell rapidly as a result of increased reabsorption of fluid in the tubules, for there were no significant changes in filtration. Sodium excretion by the kidney was reduced. From 70 to 90 min after the end of infusion the renal function was largely restored to its original level. The exception was the secretion of diodone, which remained increased until the end of the period of observation. In the opposite kidney no visible changes were observed in its function.

In the other group of experiments the action of intravenous injection of prednisolone on kidney function was studied. As Table 3 shows, the diuresis showed no significant change whether during or 3.5 h after the end of administration of the drug. Filtration remained constant almost throughout the period of observation, and fell only a little 2.5-3 h after the end of injection of prednisolone. Maximal reabsorption of glucose remained at the initial level during the period of administration of prednisolone and also during the next hour of

TABLE 2. Function of Left Kidney in Dogs after Injection of Insulin into Renal Artery

Index studied	Initial state	Infusion of insulin	After infusion		
			30 min	90 min	120 min
Diuresis	1,21±0,09	0,52±0,04*	0,74±0,06*	0,91±0,12	0,95±0,07
GFR, ml/min	16,2±0,8	16,3±0,7	17,0±0,9	16,8±0,9	16,7±0,9
Tm_{gl}, mg/min	93±3,7	116±4,2*	108±4,6*	99±3,2	96±3,3
Tm_d, mg/min	11,4±0,5	16,8±0,9*	17,5±1,0*	13,8±0,5*	14,2±0,3*
E_{Na}, μeq/min	78±3,4	40±2,1*	63±4,4*	76±6,4	

TABLE 3. Kidney Function in Dogs after a Single Injection of Prednisolone

Index studied	Initial state	Infusion of prednisolone	After infusion, min			
			40—60	80—110	120—150	150—200
Diuresis	4,4±0,24	4,3±0,36	4,3±0,7	4,4±0,66	4,1±0,55	4,6±0,71
GFR, ml/min	44,7±2,2	44,4±2,3	44,8±2,7	45,0±2,4	41,6±2,6	40,4±2,0
Tm_{gl}, mg/min	166±6,9	171±7,1	164±6,6	156±7,1	148±6,5	137±8,0*
Tm_{d}, mg/min	30,2±2,4	29,7±2,5	29,7±3,0	29,4±2,6	28,4±3,3	26,0±2,0
E_{Na}, μeq/min	298±47	293±44	316±53	350±60	382±66	418±63

observation. It then began to fall gradually, and 2.5-3 h later glucose transport differed significantly from its initial level. It is important to note that maximal diodone secretion was reduced a little at this same time. These small changes in kidney function were perhaps not connected with the action of prednisolone but were the result of the prolonged (over 6 h) infusion of the hypertonic solution. This explanation is supported by some increase in the sodium excretion with the urine.

In chronic experiments on dogs the effect of a single dose of prednisolone was studied, and the drug continued to be given to these animals for a further 9 days. To avoid prolonged infusion of the hypertonic solution, intravenous injection began 3 h after the injection of prednisolone, i.e., at a time when in the acute experiments the indices of kidney function were lowered. Experiments carried out two days previously served as the control. The results of experiments with a single injection of prednisolone are given in Table 4 (the column headed "after 3 h"). As the results given in Table 4 show, the indices of kidney function were virtually indistinguishable from the original values. Sodium excretion increased a little, although not significantly. This result confirms the above suggestion that the decrease in kidney function was due to prolonged infusion of the hypertonic solution and it suggests that prednisolone has no effect on the transport of organic substances when injected in a single dose.

During and after the course of prednisolone injections into these same dogs the state of their kidney function was tested on the 4th, 8th, and 10th days on administration of the drug and again on the 6th and 14th days after the end of the injections. It will be clear from the data in Table 4 that the rate of glomerular filtration was virtually unchanged throughout the period of observation. The diuresis changed irregularly, but sometimes significantly. Maximal glucose reabsorption showed no significant changes during the injections of prednisolone and likewise did not differ from the initial level when tested later in the course of the investigation. The tubular secretion of diodone was a little raised, although not significantly, after 8 days of prednisolone injection and approached the initial level in the second week after stopping the drug. Sodium excretion in these experiments remained at almost the same level throughout the period of observation, the same as the initial values.

Insulin thus has a stimulating effect on transport of organic substances regardless of the fact that the active mechanisms of glucose and diodone transport are localized on opposite cell membranes in the epithelium of the proximal tubules. Meanwhile the transport of fluid and sodium reabsorption were intensified. The fact that these changes were parallel and in the same direction points to the universal action of insulin through stimulation of key metabolic reactions, increasing the energy potential of the cells. These effects of insulin are direct, for if the hormone is injected into one renal artery they are found only in the kidney on the side of injection.

Glucocorticoids probably have no appreciable effect on glucose transport in the kidneys. The absence of any significant effect of prednisolone on the diuresis and sodium excretion does not contradict the results of previous investigations showing an increase in these indices after injection of prednisolone into dogs [2], for

TABLE 4. Kidney Function in Dogs during and after Administration of Prednisolone for 10 Days

Index studied	Initial state	During administration of prednisolone				After end of administration	
		after 3 h	4th day	8th day	10th day	6th day	14th day
Diuresis	3,8±0,57	3,3±0,62	2,5±0,44	4,4±0,69	2,2±0,35*	3,8±0,55	3,7±0,42
GFR, ml/min	54,0±2,8	54,5±2,2	51,2±5,3	56,2±1,9	53,1±2,8	54,2±2,7	54,6±2,6
Tm_{gl}, mg/min	178±13,7	179±8,8	192±4,0	159±11,8	161±12,3	182±7,7	171±4,2
Tm_{d}, mg/min	38,8±0,8	37,7±1,7	38,8±2,9	45,0±3,1	41,8±2,3	44,9±2,8	37,5±1,0
E_{Na}, μeq/min	349±50	440±64	325±90	338±126	350±97		

the present experiments were carried out not under conditions of spontaneous diuresis, but during infusion of a hypertonic solution of glucose, and this could weaken the diuretic response to the glucocorticoid.

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EFFECT OF INTRAVENOUS INJECTIONS OF CALCIUM CHLORIDE ON EFFECTIVENESS OF INFUSION THERAPY OF ACUTE MASSIVE BLOOD LOSS

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Acute experiments on 70 dogs showed that in the late stage of response of the animal to acute massive blood loss neither blood transfusion nor infusions of calcium-free gelatinol or 0.9% NaCl could prevent death of the animals. Intravenous injections of 10% $CaCl_2$ solution immediately after the above infusion therapy led to survival of most of the animals.

KEY WORDS: infusion therapy; hemorrhagic shock in dogs; injection of $CaCl_2$.

In the late stages of the response of the body to acute blood loss, blood transfusions or infusion of colloidal and salt solutions do not always prove successful [8-10].

Considering that calcium ions play an important role in the regulation of cardiac activity [4, 7, 12, 14, 15], have the ability to increase the tone of the vagus nerves [1], and have a significant effect on heart muscle [3, 4], and the mechanism of transmission of nervous impulses and on enzyme systems [3], it seemed likely that intravenous injections of $CaCl_2$ solution would make the infusion therapy of acute massive blood loss more effective. To test this hypothesis the experiments described below were undertaken.

EXPERIMENTAL METHOD

Experiments were carried out on 70 unanesthetized dogs of both sexes and of different weights. Bleeding took place from the femoral artery for 3-5 min until the blood pressure had fallen to 40-45 mm Hg. The mean volume of the blood loss was 35 ml/kg body weight. In the course of the experiment the arterial and central venous pressures, heart rate, respiration rate, rectal and subcutaneous temperatures (electrothermometer), EEG (unipolar derivation with needle electrodes), ECG (standard lead II), and EMG (using needle electrodes from the posterior cervical muscles) were recorded. The indices were recorded on a four-channel 4ÉÉG-01 electroencephalograph; changes in spontaneous activity and the effect of photic stimulation (10 flashes/sec) and acoustic stimulation (1000 Hz) were analyzed. At the critical stages of the experiments the conjunctival vessels were photographed (with the MBS-2 microscope), and the erythrocyte count, hemoglobin concentration, hematocrit index, cardiac output (by the dye dilution method with T-1824) and the blood flow rate (by the lobeline method) were investigated. On the basis of these parameters the dynamics of the posthemorrhagic reaction could be assessed objectively. The main criteria of the efficacy of treatment were the survival rate and life span of the animals. A 10% solution of $CaCl_2$ was injected in a dose of 50 mg/kg at the rate of 2-3 ml/min after blood transfusion or infusions of plasma-substitute solution in the late stage of hemorrhagic shock.

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