MECHANISM OF THE CENTRAL ACTION OF INSULIN ON RENAL FUNCTION

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Evidence is accumulating in the literature that hormones, especially insulin, penetrate into the CSF [9, 12, 13]. However, there is very little information on the central action of insulin on carbohydrate metabolism [5, 6] and no reference could be found in the accessible literature on the effect of insulin on renal function after injection into the CSF.

Meanwhile insulin can involve central neurosecretory mechanisms in the regulation of renal function; as a peptide hormone it affects the function of glandular cells. Terminals of neurosecretory cells make contact with the glandular cells of the adenohypophysis and capillaries of the median eminence and posterior lobe of the pituitary and they penetrate into the cavity and recesses of the third ventricle [2, 4, 7, 8]. This paper describes a study of the central neurohumoral mechanisms of the effect of insulin on renal function when injected directly into the CSF of intact dogs.

EXPERIMENTAL METHOD

Experiments were carried out on female dogs with fistulas of the stomach and urinary bladder, into whose CSF insulin (0.1-0.3 U) was injected by suboccipital puncture. Animals into whose CSF 0.5 ml of physiological saline was injected served as the control.

The minute diuresis, glomerular filtration as reflected in insulin and endogenous creatinine clearance, the sodium and potassium concentrations in the blood plasma and urine (by flame photometry), and the osmolarity of the blood plasma and urine (by means of a semiconductor thermistor) were investigated. The sodium filtration fraction, relative reabsorption of water and sodium, reabsorption of sodium in the proximal and distal renal tubules, osmolar clearance (C_{osm}), and excretion of the osmotically free fraction of water (C_{H_2O}) and its reabsorption ($T^c_{H_2O}$) were calculated.

The experiments were conducted under conditions of spontaneous diuresis and hydration due to intravenous drip injection of physiological saline. The numerical results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

During spontaneous diuresis insulin has a central antidiuretic action and depresses sodium excretion as a result of activation of water and sodium transport in the renal tubules. Glomerular filtration and the filtration charge of sodium were unchanged under these circumstances. Diuresis was reduced because of a decrease in the excretion of osmotically bound water and a higher level of transport of osmotically free water ($T^c_{H_2O}$). The stimulating effect of insulin on transport of osmotically free water in the renal tubules was observed 30-60 min after its injection, whereas the decrease in the excretion of osmotically bound water was exhibited as early as 15 min after injection of the hormone (Fig. 1). Similar results were obtained when insulin was injected against a background of hydration.

The results thus indicate that after injection of insulin into the CSF against a background of spontaneous diuresis and hydration, besides an increase in tubular sodium transport, reabsorption of osmotically free water ($T^c_{H_2O}$) also increases. This effect is charac-

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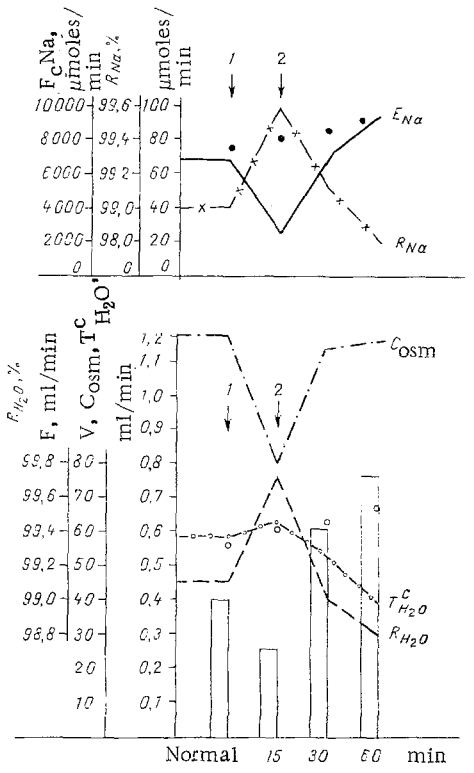

Fig. 1. Changes in electrolyte- and water-excretory function of the kidneys after intracisternal injection of the β-blocker inderal preceded by injection of insulin. Columns represent minute diuresis (V, ml/min); broken line shows tubular reabsorption of water (in %), broken line with empty circles shows transport of osmotically free water ($T^c_{H_2O}$, ml/min), line of dots and dashes shows osmotic clearance (C_{osm}, ml/min), empty circles — glomerular filtration (F, ml/min), filled circles — filtration charge of sodium (F_cNa, μmoles/min), continuous line — sodium excretion (E_{Na}, μmoles/ml), line with crosses — tubular reabsorption of sodium (R_{Na}, %). Arrows 1 and 2 indicate injection of insulin and inderal respectively.

teristic of the action of antidiuretic hormone (ADH). Data in the literature indicate that excitation of β-adrenergic receptors is accompanied by antidiuresis [1], increased neurosecretion, and liberation of ADH into the blood stream [1, 3, 4, 10, 11]. In order to discover whether β-adrenergic brain structures participate in the mechanism of action of insulin, insulin was injected after preliminary blocking of β-adrenoreceptors by inderal.

Injection of insulin into the CSF after preliminary injection of inderal was found not to inhibit diuresis. Under these conditions, 15 min after injection of insulin a diuretic response actually was observed and it continued for 90 min. Glomerular filtration remained

TABLE 1. Effect of Insulin on Water-Excreting Function of the Kidneys when Injected into the CSF after Preliminary Blocking of β-Adrenoreceptors by Inderal (M ± m)

Parameter of renal function	Initial data	15 min after injection of inderal	Time after injection of insulin, min			
			15	30	45	90
Minute diuresis (V), ml/min	0,472±0,028	0,408±0,021	0,609±0,039	0,803±0,091	0,897±0,091	0,606±0,056
P		>0,1	<0,001	<0,001	<0,001	<0,001
Glomerular filtration (F), ml/min	65,1	60,9	57,8	57,7	62,5	59,2
	1,8	3,4	2,3	2,2	2,5	1,6
P		>0,1	>0,1	>0,1	>0,1	>0,1
Tubular reabsorption of water (R_{H_2O}), %	99,276±0,045	99,326±0,034	98,931±0,085	98,611±0,161	98,686±0,115	98,956±0,100
P		>0,1	<0,001	<0,001	<0,001	<0,001
Osmotic clearance (C_{osm}), ml/min	1,284±0,067	1,074±0,118	1,321±0,065	1,293±0,16	1,404±0,093	1,498±0,085
P		>0,1	<0,05	>0,1	<0,02	<0,01
Transport of osmotically free water ($T^c_{H_2O}$), ml/min	0,812±0,042	0,706±0,057	0,711±0,122	0,369±0,064	0,508±0,072	0,725±0,059
P		>0,1	>0,1	>0,002	<0,02	>0,1

TABLE 2. Effect of Insulin on Electrolyte-Excretory Function of the Kidneys when Injected into the CSF after Preliminary Blocking of β-Adrenoreceptors by Inderal (M ± m)

Parameter of renal function	Initial data (n = 10)	15 min after injection of inderal (n = 10)	Time after injection of insulin, min			
			15	30	45	90
Filtration charge of sodium (F_cNa), μmoles/min	8146±246	8248±198	7838±193	7806±297	8450±354	7948±257
P	—	<0,1	<0,1	<0,1	<0,1	<0,1
Reabsorption of sodium (R_{Na}), %	99,209±0,045	99,291±0,062	98,799±0,095	98,740±0,132	98,715±0,139	98,825±0,174
P	—	<0,1	<0,001	<0,002	<0,001	<0,02
Excretion of sodium (E_{Na}), μmoles/min	69,5±4,0	65,5±5,2	91,3±6,6	101,4±9,3	109,0±9,4	91,4±8,8
P	—	<0,1	<0,002	<0,001	<0,001	<0,02
Excretion of potassium (E_k), μmoles/min	17,41±1,07	14,0±1,6	15,1±3,2	21,5±3,5	29,8±4,6	16,2±1,7
P	—	<0,1	<0,1	<0,05	<0,001	<0,1

unchanged but tubular reabsorption of water was significantly reduced (Table 1). Sodium and potassium excretion was significantly increased after inderal compared with its initial level because of a decrease in cation reabsorption in the renal tubules, for the filtration charge of sodium was unchanged (Table 2). Clearance of osmotically bound water was increased, but 60 min after injection of inderal the transport of osmotically free water in the renal tubules was reduced (Table 1).

In another series of experiments, in which inderal was injected after preliminary injection of insulin, increased diuresis was found. The peak of the diuretic response occurred 60-75 min after injection of the β-blocker. Under the influence of inderal, the increase in water absorption induced by insulin in the renal tubules was reduced, whereas glomerular filtration was unchanged. After preliminary injection of inderal the excretion of osmotically bound water was increased and reabsorption of osmotically free water was reduced, and these coincided with the peak of the diuretic response. After injection of inderal the inhibition of sodium excretion by insulin also disappeared and the excreted sodium fraction increased because of a fall in tubular reabsorption of sodium. Parallel with the sodium excretion, the potassium excretion with the urine also increased (Fig. 1).

The stimulating action of insulin, injected into the CSF, on sodium and water transport in the renal tubules is thus evidently effected through β-adrenergic brain structures. The possibility likewise cannot be ruled out that secondary activation of secretion of vasopressin and its release into the blood also takes place through these structures. Vasopressin can cause the blood cAMP level to rise [14, 15], and this increases the permeability of the renal tubules for water and inhibits diuresis.

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