ORIGINALES

Reflex mechanism of potassium homeostasis regulation

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MECANISMOS REFLEJOS DE LA REGULACION HOMEOSTATICA DEL POTASIO

El efecto de la inyección intraportal de cloruro potásico al 1 % en la función renal ha sido estudiado en perros despiertos. Dicha inyección induce un aumento en la excreción de potasio y antidiuresis mediada por vasopresina. Las vías aferentes de la respuesta antidiurética reflejas parecen estar localizadas en la médula espinal, mien tras que aquéllas relacionadas con el cambio en la excreción de potasio están localizadas en las aferencias locales. Se discute el papel de los péptidos neurohipofisarios en el reflejo kaliurético.

Palabras clave: Potasio. Reflejos nerviosos. Hígado, riñones, infusión intraportal.

SUMMARY

Experiments in unanesthetized dogs showed that single intraportal injection of 1 % KCl solution evoked vasopressin-mediated antidiuresis and increase in potassium excretion. The data obtained suggest that the liver can store and release potassium. Afferent pathways of antidiuretic reflex response are mainly located in the spinal cord, but those changing potassium excretion are afferents of the vagal nerve. The role of neurohypophyseal peptides in the kaliuretic reflex is discussed.

Key words: Potassium. Reflex. Liver. Kidneys.

INTRODUCTION

Since McCance and Widdowson [32] discovered renal potassium secretion it was considered that the changes in potassium excretion rate were mainly dependent on the cation secretory process in distal nephron segments [20, 21, 22, 44, 52, 53, 54]. Such conclusion was based on the experiments with systemic infusions of KCL solutions. This maneuver results in increasing plasma potassium concentration and therefore the possibility of potassium direct action on distal nephron cells was arised [4, 5, 8, 11, 41, 42]. However the absorption of potassium from the gastro-intestinal tract did not usually cause an increment of K^+ concentration in systemic circulation, but at the same time the renal excretion of potassium did increase [2, 17, 38]. All these data make one suggest that at the border of the portal system and systemic circulation there is a receptory zone which being stimulated by absorbed potassium evokes reflex kaliuretic response maintaining potassium homeostasis.

In the present study we are concerned with the experimental examination of the existence of the reflex potassium homeostasis mechanism.

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METHODS

The investigations were carried out in unanaesthetized dogs of both sexes weighting 10-18 kg. All the animals two weeks prior the onset of experimental procedure were subjected to the operation of inserting gastric tube, putting out the part of the bladder with orifices of ureteres on the abdomen surface and inserting thin polyethylenic probe into the portal vein [16]. Cation concentration shifts in portal blood were attained by injection through the probe of 1 % KCL solution during one minute (0.75 ml/kg of body weight, i. e. 0.1 µmol/kg). In control experiments the solution was injected into the hindlimb vein. The study of the osmolality and ion concentration level in the portal blood during the intraportal infusion of KCL solution was carried out in chloralose anaesthetized dogs. At the same time the samples of hepatic tissue were taken to determine ions content in the liver. In order to analyse the afferent pathways of liver kaliuretic reflex two types of experiments in unanaesthetized dogs were made. The first group of animals was preliminary supradiaphragmatica-

lly vagotomized. In the second group the posterior spinal roots at the level of Th_5-Th_{12} were cut. The role of neurohypophyseal hormones in the kidney kaliuretic response was examined in unanaesthetized hypophysectomized dogs. The experiments were begun 3-5 days after the hypophysectomy was made.

All the animals had a free access to water and 12-18 hours before the experiment were deprived of food. After a period of training each dog was confined to Pavlov stand and by means of periodic administration of warm tap water through the gastric tube the diuresis was maintained within the level of 2.5-6.0 ml/min m^2 of body surface. Twenty minutes after urine flow rate was stable KCL solution was injected through the probe or intravenously. Urine was collected quantitatively at a 10 min intervals. Kidney response was observed during 1.5-2.0 h. The following parameters of kidney function were calculated: urine flow rate (V), glomerular filtration rate (GFR) as the endogenous creatinine clearance, fractional excretion of water (FE_{H_2O}), sodium excretion rate ($U_{Na}V$), potassium excretion rate (U_KV), fractional excretion of sodium and potassium (FE_{Na}, FE_K %). Ion concentration in plasma, urine and tissue was determined by flame fotometry (the tissue concentration after acid extraction stage in 0.75 N HNO_3), creatinine by the method of Bonsnes & Taussky [7], osmolality by the freezing point depression technique. For statistical analysis of the results t-Student test was used. Difference between mean values was considered significant at $p \leqslant 0.05$.

RESULTS

As Table 1 shows injection of 1 % KCL solution into the portal vein provoked a pronounced antidiuretic response with a latent period of 6 ± 1 min and 53 ± 7 min duration. The average amount of fluid conserved was equal to 107 ± 17 ml. The fact of the absence of significant changes in GFR (excluding the first clearance period after injection) and diminishing fractional excretion of water was indicative of the reabsorptive mechanism of the response. In a parallel with the decrease of urine flow rate a distinct kaliuresis was observed. The mean value of potassium excretion rate increment compared to the basal level was 17.3 ± 4.5 μmol/min m^2 ($p < 0.002$). There was also an increase in frational excretion of potassium. The kaliuretic response was developed in a 15 ± 4 min latent period and prolonged during 48 ± 5 min.

In 8 out of 17 experiments the increase in potassium excretion was accompanied by augmented natriuresis with average duration of 47 ± 7 min. However it should be stressed that the latent period of natriuretic response was 13 ± 3 min longer than the kaliuretic one ($p < 0.01$) and maximum increasing in sodium excretion occured 11 ± 4 min later ($p < 0.05$) than the peak excretion of potassium. Moreover in 9 experiments sodium elimination with urine was not changed at all or even gradually decreased. Therefore statistical analysis of the results revealed significant increment in sodium excretion only in one clearance period. But allround response mean value of sodium excretion increment appeared to be nonsignificant (3.7 ± 3.3 mcmol/min m^2; $p > 0.1$).

Thus an administration of 0.1 mmol/kg KCL into the portal blood flow modified mainly diuretic and kaliuretic kidney function.

The kidney response could be the consequence of either direct action of potassium excess on renal tubules or reflex stimulation of liver receptors. As special experiments in conscious dogs showed, the intraportal injection of KCL solution produced the elevation of potassium concentration only in portal blood (by + 2.35 ± 0.22 mmol/l) without any changes in osmolality and potassium level in systemic circulation. Therefore it's worth while supposing in a most general form a reflex origin of kaliuretic kidney response. In order to test the hypothesis and evaluate the time course of kidney response to the hindlimb vein injection of KCL, 15 control experiments in 7 dogs were performed. Fig. 1 illustrates the average changes of renal function parameters in this experimental protocol. One can see that intravenous injection of KCL solution caused the tendency of diuresis decreasing with delayed and gradual onset (33 ± 5 min after injection, $p_c^* < 0.001$). Significant depression of urine flow rate

* p_c —here and somewhere else signs the probability of difference compared to the results obtained in the intact dogs with intraportal KCL injections.

TABLE 1

CHANGES OF THE RENAL FUNCTION PARAMETERS AFTER INJECTION OF 1 % KCL SOLUTION INTO V. PORTA

(M ± SE) n = 17

Time min.	Urine flow rate ml/min. m^2 (V)	Glomerular filtration rate ml/min. m^2 (F)	Fractional excretion of water % (FE_{H_2O}) $\frac{V \cdot 100\ \%}{F}$	Potassium excretion rate μmol/min. m^2 (U_KV)	Sodium excretion rate μmol/min. m^2 ($U_{Na}V$)	Fractional excretion of potassium % (FE_K) $\frac{U_K \cdot V}{F \cdot P_K}$ 100 %	Fractional excretion of sodium % (FE_{Na}) $\frac{U_{Na} \cdot V}{F \cdot P_{Na}}$ 100 %
						Increment above the basal level	
basal line	3.7	0.3	58	3	6.5	0.5	26	4	31	9	10.7	2.1	0.34	0.09
	KCL	injection												
10	2.8	0.3*	49	3*	5.5	0.5	+ 6	2*	+ 1	2	+ 5.1	2.0*	+0.06	0.03
20	1.4	0.3*	50	4	3.1	0.6*	+ 19	6*	+ 1	3	+ 9.3	2.7*	+0.04	0.03
30	1.2	0.2*	52	4	2.6	0.5*	+23	7*	+ 7	7	+10.0	2.6*	+0.12	0.07
40	1.6	0.2*	58	3	2.9	0.4*	+29	8*	+11	5*	+ 9.7	2.5*	+0.14	0.07
50	2.2	0.3*	58	4	4.0	0.4*	+21	6*	+10	7	+ 7.8	2.5*	+0.10	0.07
60	3.5	0.2	64	4	5.7	0.4	+15	5*	+ 3	5	+ 3.4	1.2*	+0.01	0.06
70	6.3	0.3	61	3	8.8	0.4	+13	6	− 7.5	5	+ 2.7	1.0*	−0.07	0.06

* The difference is statistically significant compared to the basal level.

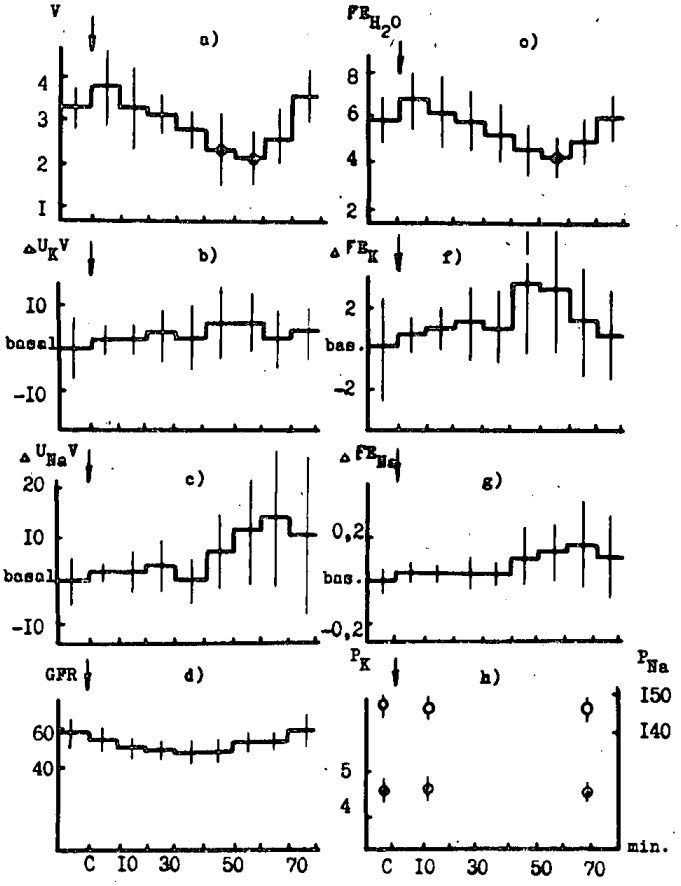

Fig. 1.—*Changes of renal function parameters after injection of 1 % KCL solution into systemic circulation. Abscissa-time in 10– – min intervals. Arrows show the moment of KCL solution injection. Vertical lines— ± t SE. Points mark significantly different results compared to the basal level. a) Urine flo rate, ml/min m^2; b) $U_K V$, mcmol/min m^2; c) $U_{Na} V$, mcmol/min m^2; d) GFR, ml/min m^2; e) FE_{H2O} %; f) FE_K %; g) FE_{Na} %; h) potassium (black circles) and sodium (open circles) plasma concentration, μmol/l. Parameters b, c, f, g were calculated as an increment above the basal level.*

was developed only in the 50-th minute and lasted 20 minutes. During this period 57 ± 9 ml ($p_c < 0.02$) of fluid were retained. The lack of significant changes of GFR and decrease in fractional excretion of water demonstrated the reabsorptive mechanism of the oliguric response. In 10 experiments delayed and coincided in time with antidiuresis (the increase in ions excretion was observed). The mean increment of potassium and sodium excretion above base-line was only 3.6 ± 2.7 μmol/min m^2 ($p > 0.1$; $p_c < 0.02$) and 6.5 ± 2.7 μmol/min m^2 ($p > 0.1$; $p_c > 0.1$) respectively. Substantial changes in ions concentration in both plasma and whole blood were not registrated.

Thus the kidney response to the intravenous injections of KCL contrary to the intraportal ones was weak and delayed.

One could suppose that the response was arised in connection with the vein receptors stimulation which located near the place where KCL solution had been infused. First it seemed true, since earlier studies demonstrated that infusions of potassium chloride solutions into isolated vein but with nerves intact caused afferent discharges affected respiration and circulation variables [10, 28, 30]. However another version can not be ruled out according to which potassium being infused into systemic circulation was sorbed and deposited in the liver and in the long run produced the similar type of response which used to develop after the intraportal infusions but it was less intensive and more delayed.

The kidney response turned out to be absent after KCL solution perfusion of the humorally isolated subcutaneous vein of the limb [17]. Accordingly the periferal vein interoreceptors don't take part in potassium excretion regulation.

To further define the problem, the ability of the liver to deposit potassium was studied. In this kind of experiments chloralose anaesthetized dogs were utilized. Infusions of 0.1 μmol/kg of body weight of KCL during 5 minutes into v. porta brought about the rise of potassium plasma level in portal blood from 4.7 ± 0.1 mmol/l to 7.1 ± 0.4 mmol/l ($p < 0.001$) (Fig. 2). At the same time cation concentration in hepatic veins remained practically unchanged. Liver tissue analysis at the end of the infusion revealed a marked increase in hepatic potassium concentration by 2.9 ± 0.4 mmol/100 g of tissue dry weight and a parallel reduction of sodium content by 2.3 ± 0.5 mmol/100 g of tissue dry weight ($p < 0.002$). It should be noted that the quantity of sodium released by the liver had a negative correlation with reyained potassium. This connection is expressed by the following regression equation: $Y = -0.92 X$; $r = -0.85 \pm 0.09$. Water content in the liver during the infusion was not changed.

Thus the liver possesses potassium depositive ability and by means of retaining absorbed cation prevents hyperkaliemia in the systemic circulation. On the other hand potassium accumulated in the liver could stimulate the specific receptors and start reflex kidney response.

An experimental analysis of information pathways of the afferent link of potassium homeostatic control reflex was performed in the dogs with partial liver denervation. The first step included 22 experiments in 7 dogs with bilateral vagotomy. Fig. 3 (A) presents the results of this series of experiments. Intraportal injections of KCL solutions to the vagotomized animals caused an antidiuretic response not considerably differed from the pattern which took place in intact dogs (Fig. 3 A [a].). However the case with ionuretic kidney function was somewhat different. In 18 experiments there were no ionuretic responses at all and only in 4 experiments transitory and slight increment of ion excretion rate was observed. Statistical processing of the data has proved that potassium excretion did decrease as compared to the basal level by 9.9 ± 2.7 μmol/min m^2 ($p < 0.01$; $p_c < 0.001$).

Thus the absence of kaliuresis in vagotomized dogs obviously indicated that kaliuretic response in normal dogs originated due to reflex mechanism with receptors located in the liver and afferent pathways which were an organic part of vagus nerves.

Another type of liver deafferentation was performed by means of cutting the posterior spinal roots at the level of Th_5-Th_{12}. Such animals responded in a contrast way than the vagotomized ones. As Fig. 3 B (a) showed there was a marked reduction of the magnitude of the antidiuretic response. The quantity of fluid retained was only 70 ± 22 ml. The latency of the response prolonged up to 34 ± 6 min ($p_c < 0.001$) and duration of antidiuresis decreased to 34 ± 4 min ($p_c < 0.002$). As far as potassium excretion is concerned the pattern of the ionuretic response did not essentially differ from that in intact dogs. Moreover duration and intensity of kaliuresis in such type of liver denervation even increased (Fig. 3 B [b]).

Thus cutting the dorsal spinal roots without having affected the trend of ionuretic response resulted in significant decreasing water retention.

The presence of different channels for transmission of afferent signals to regulate hydro— and kaliuresis seems to be indicative of a complex arrangement of liver receptory field. Under physiological conditions only full information directed to the central nervous system by two channels caused two component ionregulating reflex with augmented potassium excretion and reduced diuresis.

The study of the efferent link of potassium-regulating reflex was carried out in hypophysectomized dogs. This approach

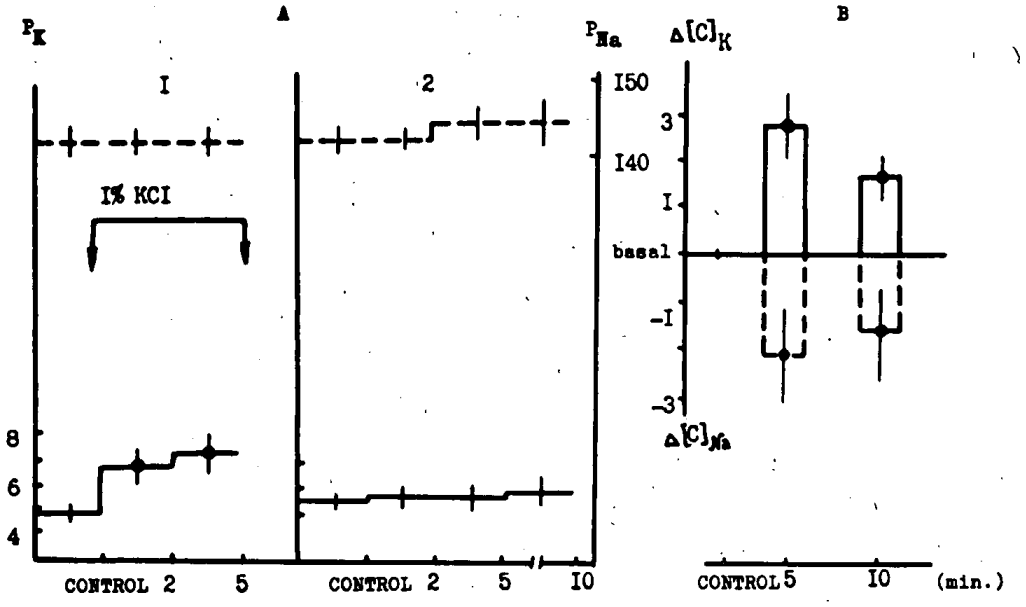

Fig. 2.—*Changes of plasma potassium and sodium concentration (A) in portal blood (1), hepatic veins (2) and liver tissue (B) during the infusion of 0.75 ml/kg of 1 % KCL solution into the portal blood flow. Solid line-plasma potassium concentration, μmol/l. Dashed line-plasma sodium concentration, μmol/l. Bars— changes of ions concentration in liver tissue (difference with the basal level), μmol/100 g of tissue dry weight. The rest symbols are the same as at the Fig. 1.*

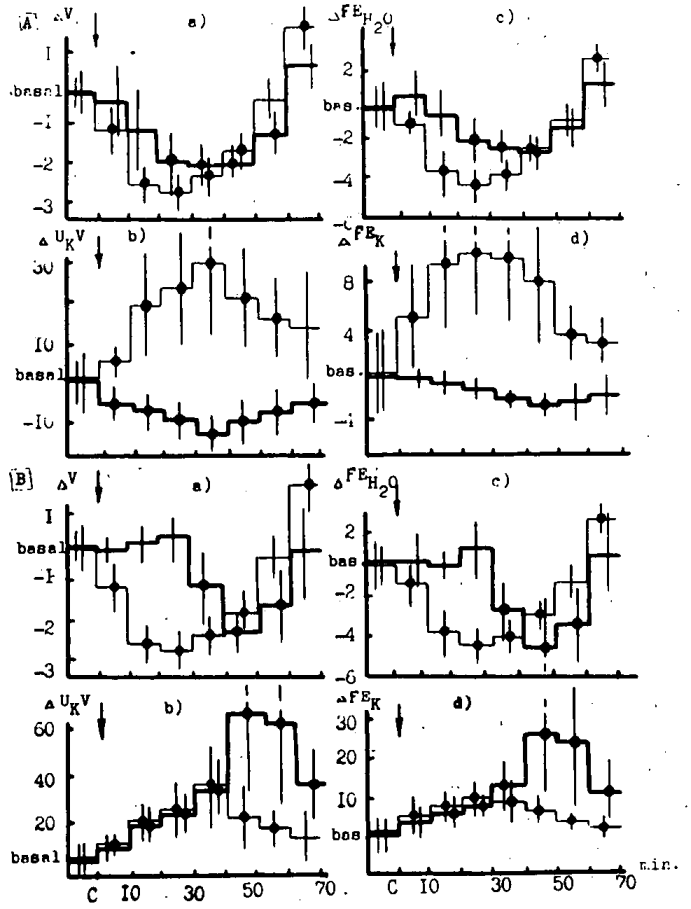

Fig. 3.—*Changes of renal function parameters after the intraportal injection of KCL solution in the dogs with bilateral vagotomy (A) and cutting of dorsal spinal roots (B). Thin lines-results of the experiments in intact dogs. Thick lines-results obtained in the dogs with liver deafferentation. a) Urine flow rate, ml/min m²; b) U_KV, mcmol/min m²; c) FE_{H2O} %; d) FE_K %. The rest symbols are the same as at Fig. 1.*

seemed to be usefull since it had been clearly demonstrated not only the antidiuretic action of neuropeptides [24, 37, 50] but also the kaliuretic one [9, 14, 27, 29]. Fig. 4 represents the results of some experiments in hypophysectomized animals. In 8 out of 12 experiments intraportal injection of KCL solution in the dogs with removed hypophysis did not change hydro— and ionuretic kidney function (Fig. 4/2/). The mean value of potassium excretion changes from the basal level was -0.13 ± 3.0 μmol/min m². However 4 experiments demonstrated the kaliuretic response (Fig. 4/4/) ($+ 9.7 \pm 2.9$ μmol/min m² above the baseline) though oliguria was absent. The lack of antidiuresis was indicative of the fact that vasopressin had not been released in blood. The manifestation of the increased potassium excretion suggested that some additional factors appeared in blood to cause the kaliuresis.

Summing up there is a point in considering that neurohypophyseal hormones take part and are necessary for the realization of potassium-regulating reflex. However some additional efferent mechanisms appear to exist.

DISCUSSION

In the discussion of the results obtained one should first of all dwell on the question concerning the type of receptors responded to a potassium concentration shift. The absence of changes in portal blood osmolality after the infusions of KCL solutions made hardly probable the role of liver osmoreceptors in the response observed. The possibility of baroreceptors involvement has been rejected on the basis of the experiments with blood serum or Ringer solution infuaions into hepatic vascular bed [48]. Moreover it appeared that a marked potassium excretion could not be stimulated by NaCL intraportal injections [1]. With the foregoing information as a background we can consider that in the portal system there exist a specific receptory apparatus the adequate stimulant of which are potassium ions. Apparently these selectively potassium-sensitive receptors can not be attributed by their nature to the previously described chemoreceptors of vessels and inner organs which are widely represented throughout the organism [10, 28, 30]. The experiments which did not find out the kaliuretic response during the infusions of KCL solution into the right atrium [1] and humorally isolated limbvein [17] proved this thesis. Obviously, it's worth while assuming that the liver has the specialized potassium-sensitive receptors which give an impetus to the potassium-regulating reflex, the receptors being stimulated. This assumption has resently been confirmed [46, 47].

The analysis of the afferent pathways of potassium-regulating reflex revealed that the information necessary to produce kaliuresis was transmited along vagus nerves. According to Passo et al. [36] vagotomy also eliminates the possibility of increasing sodium excretion in response to the sodium load. The

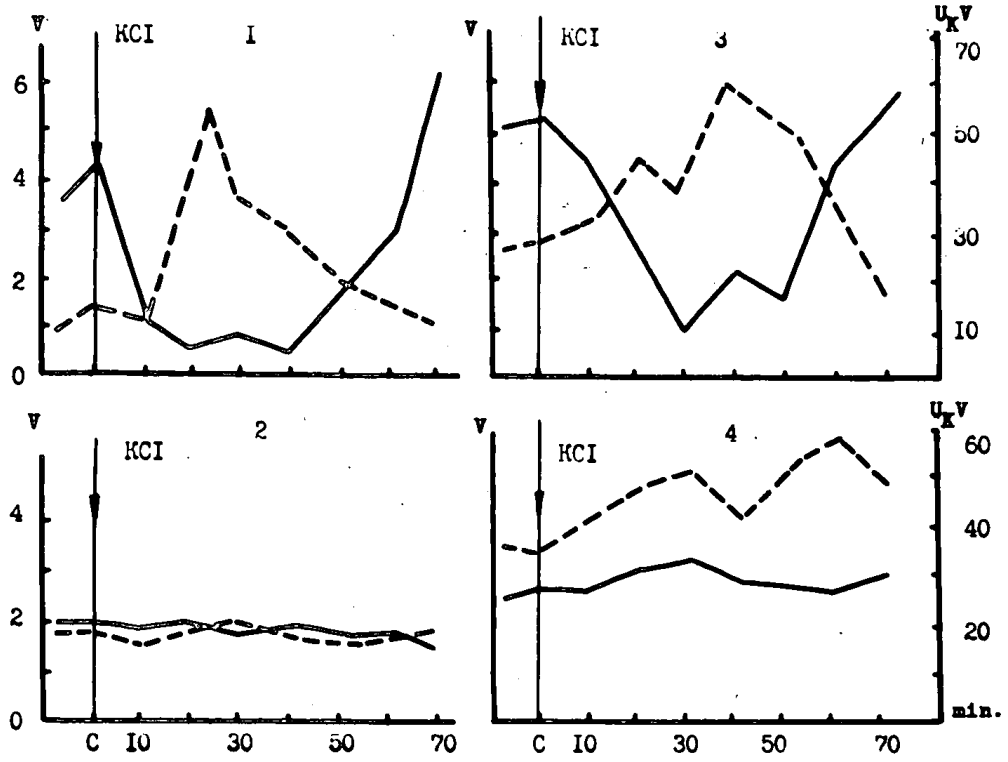

Fig. 4.—*Changes of diuresis and kaliuresis after intraportal injections of 1 % KCL solution in intact (1, 3) and hypophysectomized (2, 4) dogs. Solid line-diuresis. Dashed line-U_KV.*

absence of substantial changes in the trend of antidiuretic response in vagotomized dogs compared to the intact ones could be accounted for by the nonspecific depolarizative action of potassium on liver osmoreceptors the information from which used to drive along the spinal cord. Indeed as it was stated [49] chordotomy at the level of Th_3-Th_8 made the development of the antidiuresis after stimulation of hindlimb osmoreceptors impossible. The slight oliguric response that can be observed in the dogs with interrupted posterior roots might arise as a result of liver antidiuretic principle secretion [15, 31] or stimulation of n.vagi endings which produced antidiuretic hormone release [26, 33]. Comparing the data obtained with the data available in the literature and summarizing all the results one should conclude that liver possesses at least 5 sorts of receptors of different specificity. Among them there are sodium—, potassium—, magnesium-sensitive receptors, volume— and osmoreceptors [18, 19, 25, 35, 36, 45, 48].

As it was mentioned above neurohypophyseal hormones are necessary to realize the ionregulating reflex. However the mechanism of the hormones kaliuretic action still remains unclear. Further work is in order to settle this question. A number of suppositions may be advanced to explain the cause of the kaliuresis, but none of them are exhaustive. Firstly, perhaps ADH exerts a direct action on distal potassium secretion [14]. However this mechanism could not be considered as a single one because in some experiments on hypophysectomized dogs the kaliuretic response was observed. Moreover neurohypophyseal hormones could be kaliuretic due to the stimulation of ACTH secretion [3, 23] and consequently to the increment of gluco and mineralcorticoids level in blood. In fact the direct radioimmunoassay determination of aldosterone concentration in systemic blood after intraportal injection of 1 % KCL solution showed significant increase in hormone level (by 44.6 ± 16.1 pg/ml) [13]. Besides that oxytocin exerting a central action [37, 40] could stimulate or inhibit the release of hypothetical humoral factors which by itself or via other neurohormonal mechanisms influenced potassium transport in renal tubules. Up to date there is a strong evidence of natriuretic hormone existence [34]. Therefore one could speculate that a kaliuretic hormone might be released to modify potassium excretion by the kidneys.

At the end of the discussion we should like to present a simplified scheme of reflex potassium homeostasis regulation (Fig. 5). As a rule potassium concentration shifts during the absorption of cation from the gastro-intestinal tract used to be within the limits of portal vasculature due to the liver ability to elicit ion excess from the blood. The retaining potassium caused

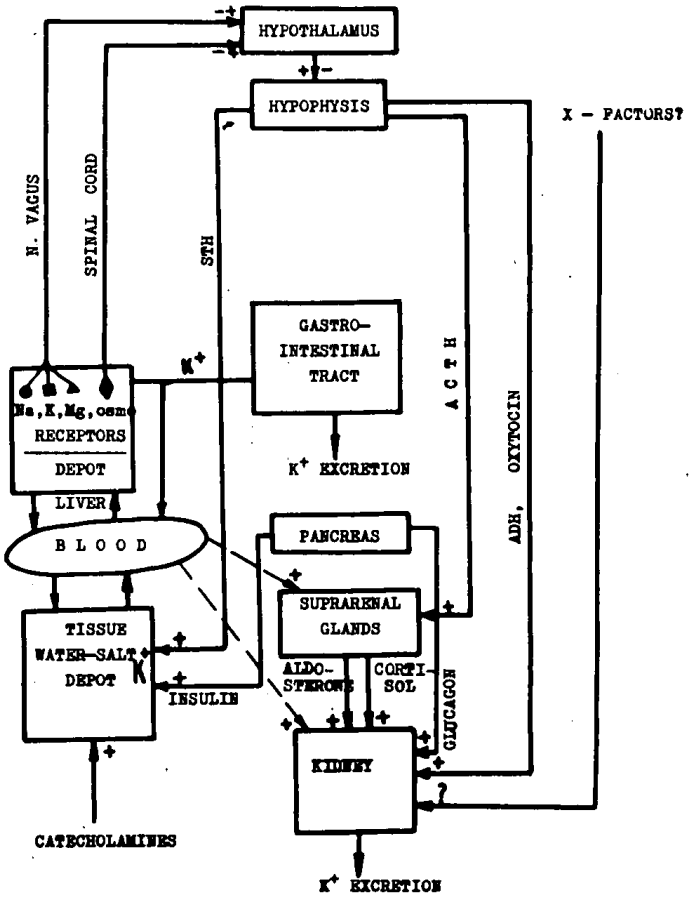

Fig. 5.—*The scheme of potassium homeostasis regulation system.*

an excitation of receptors and as a consequence afferent discharges along the spinal cord and n.vagi towards the hypothalamic nuclei. Released neurohypophyseal peptides and some unknown principles resulted in antidiuretic and physiologically expedient kaliuretic response.

The stability of plasma potassium level in spite of its increased excretion can be achived due to gradual liver output of retained ion into the general blood flow.

Parallel with reflex mechanism the direct action of potassium on the kidney to cause kaliuresis under hyperkaliemia state is apparently not be excluded.

Besides that, extrarenal mechanisms of potassium homeostasis regulation can operate. Ion deposition in the various tissues (skeletal muscle, connective tissue, etc.) which can be regulated by somatotropin, insulin and other hormones and cation excretion via gastro-intestinal tract seems to be involved [6, 12, 39, 43, 51].

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