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Increased glucose transfer in the rat jejunum after dietary potassium loading: effect of amiloride

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The glucose transfer across the jejunum was measured in Wistar rats under a high potassium diet (HKD). In 12 of 27 HKD animals the transfer coefficient for D-glucose was not significantly higher than in control ones, $(7.38 \pm 0.88) \cdot 10^{-5}$ s^{-1}. In the other 15 a clear increase in glucose transfer was observed, $(23.31 \pm 2.50) \cdot 10^{-5}$ s^{-1}. The D-glucose transfer in the first group ($n = 12$) was, as in the case of the control rats, insensitive to amiloride section (10^{-4} M), while D-glucose transfer became sensitive to amiloride in the second group (mean inhibition 94 ± 8%, $n = 14$). A smaller but significant increase in L-glucose and sucrose transfers was also observed when the D-glucose movement was increased. No differences in short-circuit current, transepithelial potential, resistance and mucosa to serosa Na^+ fluxes were observed between control and HKD rats and no effects of amiloride (10^{-4} M) on these parameters were observed either in control or in HKD animals. [^{3}H]Glucose uptake as also performed in brush-border vesicles prepared from rat jejunum, under control and HKD conditions. The specific and Na^+-dependent 'overshoot' in D-glucose concentration, in vesicles prepared from HKD rats, became sensitive to amiloride action (10^{-5} M). It is concluded that, besides the cellular adaptation induced in the distal portion of the nephron and large intestine, dietary potassium loading induces important modifications in glucose transfer in the rat jejunum.

Introduction

After dietary potassium loading, epithelia in distal portions of the nephron and large intestine show several adaptative changes [2,8,16,18,21]. These changes include an increase in transepithelial potential difference [3,4,19], an increase in Na,K-ATPase activity in the basolateral cell membrane [5], the appearance of amiloride-sensitive sodium channels in the apical border of the enterocyte [17] and an increase in potassium secretion [5]. At least part of these adaptative changes seems to be the consequence of the parallel development of high levels of aldosterone in blood [4].

In contrast to colon, the jejunum absorbs potassium in the basal state. Chronic potassium loading does not alter potassium transport in this tissue [4] and no changes were detected in transepithelial potential difference or Na,K-ATPase activity [4]. Nevertheless, when hyperaldosteronism is induced by Na^+ depletion, an amiloride-sensitive salt and fluid absorption appears in the rat small intestine [20].

We have now studied the effects of K^+ adaptation on a typical function of the small intestine: transepithelial glucose transport. Our results show an increase in glucose transfer under this condition. Simultaneously, this Na^+-dependent glucose transfer became sensitive to amiloride action.

Materials and Methods

Male Wistar rats weighing 250–300 g were maintained on ad libitum water and standard chow. Seven days before the experiments they were placed in individual cages and separated into two groups according to dietary intake. Rats of Group I were fed with a standard diet containing, by analysis, 0.2 mg of potassium per gram. The daily average intake was 4 mequivalents. Rats of Group II were fed with the same chow with KCl added up to a final concentration of 1.72 mequiv./g. The daily K^+ uptake was approx. 39 mequivalents. Tap water was supplied ad libitum in both groups.

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Measurement of transepithelial D-glucose, L-glucose, sucrose and sodium transfer in sac preparations. The rat jejunum was removed and two pieces 5 cm long, adjacent to the duodenum, were flushed with standard saline (mequiv./l: Na^+ 140, Cl^- 110, K^+ 5, Ca^{2+} 5, HCO_3^- 25, glucose 25 mM (pH 7.4)) and mounted. The proximal end of each fragment was attached to a glass tube, while the distal one was closed. These jejunum sacs were filled with standard saline (250 μl) and immersed in test tubes containing the same solution, bubbled with O_2 95%/CO_2 5%. The tubes were placed in a thermostated bath (37°C). D-[^{3}H]Glucose and L-[^{14}C]glucose or D-[^{3}H]glucose and [^{14}C]sucrose were added to the inner solution at a final activity of 1 μCi/ml at the beginning of the experiment. In other experiments [^{3}H]glucose and ^{22}Na fluxes were simultaneously tested. The jejunum sacs were then transferred every 5 min to new test tubes containing non radioactive tracers. The ^{3}H, ^{14}C and/or ^{22}Na activities accumulated in the serosal bath were determined by liquid (^{3}H, ^{14}C) or solid (^{22}Na) scintillation counting (with appropriated corrections for reinjection and quenching). Because the real membrane surface is not easy to estimate in the jejunum, D-glucose, L-glucose, sucrose and Na^+ permeabilities were expressed by the transfer coefficient K, representing the fraction of the total radioactive molecules present in the mucosal bath transferred per minute in each jejunum fragment. Determinations were not cumulative and the back flux remained negligeable in all cases. The specific activity inside the sac was recalculated after each 5-min period, taking into account the previous transfer of radioactivity.

Electrical parameters and D-glucose fluxes in flat preparations. In other series the jejunum was mounted as a flat sheet between two twin-barrel lucite chambers. These experimental conditions allowed to control mucosal and serosal bath compositions in a more complete form. In these experiments transepithelial potential difference (PD), short-circuit current (I_{SC}) and resistance (R) could also be determined. Voltage electrodes consisted of agar bridges connected to calomel half-cells and placed adjacent to the epithelium. The PD could be short-circuited through current-passing electrodes (Ag-AgCl wires) located at the rear of each half-chamber [13]. Transepithelial D-[^{3}H]glucose fluxes were simultaneously measured at 5-min intervals as previously described [13]. The tracer was added to the mucosal bath and the serosal bath volume was completely removed and counted every 5 minutes during at least 12 consecutive periods.

Glucose uptake by brush-border vesicles. Brush-border vesicles were isolated from the rat jejunum by the precipitation technique according to Kessler et al. [10], with the substitution of $CaCl_2$ by $MgCl_2$. D-Glucose and L-glucose uptakes were carried out by the Millipore filtration technique [7,10]. The vesicles were formed in a 'preparative buffer' containing 50 mM mannitol, 10 mM Hepes-Tris, 0.1 mM paramethylsulfoxide, 0.01% NaN_3 (sodium azide), (pH 7.4). They were then equilibrated for 60 min in an 'equilibration buffer' (the preparative buffer plus 100 mM KCl in the presence of $2 \cdot 10^{-6}$ M valinomycin). Uptakes were initiated by addition of 20-μl aliquots of membrane suspension to 150 μl of the 'transport medium' (100 mM NaCl re-

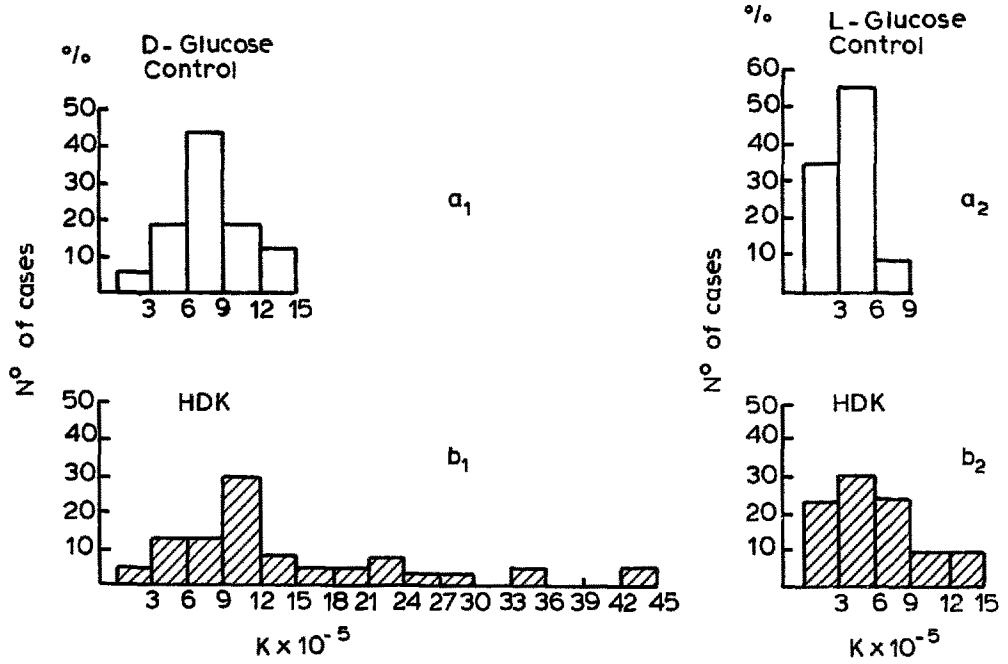

Fig. 1. D-Glucose and L-glucose transfer in the rat jejunum. Distribution of the observed values in control (a_1, a_2) and HKD rats (b_1, b_2). Ordinate: percentage of the total observations. Abscissa: transfer coefficient K (s^{-1}).

placed KCl in the equilibration buffer) plus 0.1 mM glucose, 1 μCi/ml L-[^{14}C]glucose and 1 μCi/ml D-[^{3}H]glucose. Control uptakes were made in the absence of Na^+ (100 mM KCl in the medium).

Statistical analyses. All results are reported as the arithmetic mean ± the standard error of the mean (S.E.). Statistical analyses were performed using paired or unpaired Student's *t*-test with a value of $P < 0.05$ chosen as the level of statistical significance.

Results

Transepithelial D-glucose and L-glucose fluxes in jejunum sacs

Figs. 1a and 1b show the distribution of the observed values for D-glucose and L-glucose transfers across jejunum sacs in control rats and in rats that were fed, during 7 days, with a high potassium diet. It is evident that the high potassium diet did not increase glucose transfer in all cases even when the mean increase was significantly different (Table I). In the following paragraphs, we will call 'K-adapted rats' those rats in which the D-glucose transfer was higher than $13.2 \cdot 10^{-5}$ s^{-1} (the mean value observed for control animals plus two times the standard deviation ($7.39 \pm (2.92 \times 2) = 13.2$).

Fig. 2 shows the time course of the D-glucose and L-glucose transfers across the jejunum in control and HKD rats (sacs experiments). Data from HKD rats were divided in two groups: (1) jejunum sacs showing D-glucose transfers in the level of control animals ($\bar{x} \pm 2$ S.D.) and (2) jejunum sacs from 'K-adapted rats'. As expected, addition of amiloride (10^{-4} M) did not modify D-glucose or L-glucose movements in control animals (Fig. 2a). In the case of HKD rats, a clear difference was observed, concerning amiloride action, between those animals that showed D-glucose transfers in the control range and those showing a clear increase in this parameter. The first group (Fig. 2b) was, as the control one, non sensitive to this diuretic. The second group that showed a small but significant increase in L-glucose movement, developed a clear sensitivity to amiloride (Table I). This agent (10^{-4} M) reduced both D-glucose and L-glucose transfer to control values (Table I). The inhibition was also important at 10^{-5} M ($-75 \pm 11\%$, $n = 6$). It was not observed at 10^{-6} M ($+20 \pm 12\%$, $n = 6$).

In other experimental series D-glucose and sucrose transfers were simultaneously measured in control and 'K^+-adapted rats'. The obtained results showed that sucrose transfers values are similar to those observed in L-glucose transfers (Table I).

L-Glucose or sucrose transfers probably showed the paracellular movement [13], plus the eventual leak due to dead or damaged cells. The difference between D-glucose and L-glucose or sucrose would be the transcellular transfer across the specific pathway. To estimate the 'leaky path', jejunum fragments were incubated at 4°C for 3 h. Trans L-glucose transfer was measured, in two fragments of the same jejunum, at 4°C and 37°C. The remaining L-glucose flux at low temperature only repre-

TABLE I

D-Glucose, L-glucose and sucrose transfer coefficients (K and ΔK in 10^{-5} s^{-1}) in control and HKD rats: effects of amiloride (10^{-4} M)

Non-adapted are those animals with $K < 13.2 \cdot 10^{-5}$ s^{-1} and adapted are those with $K > 13.2 \cdot 10^{-5}$ s^{-1}

	K, control (1)	*K*, HKD			*ΔK*		
		all (2)	non-adapt (3)	adapt (4)	2 vs. 1	3 vs. 1	4 vs. 1
D-Glucose	7.39 ± 0.91 ($n = 12$)	13.75 ± 2.50 ($n = 27$)	7.38 ± 0.83 ($n = 12$)	23.31 ± 2.50 ($n = 15$)	6.36 ± 2.66 ($P < 0.02$)	0.01 ± 1.23 (n.s.)	15.92 ± 2.56 ($P < 0.01$)
D-Glucose + amil.	7.19 ± 0.75 ($n = 12$)	8.08 ± 0.88 ($n = 27$)	7.50 ± 0.88 ($n = 12$)	9.00 ± 0.95 ($n = 15$)	0.89 ± 1.16 (n.s.)	0.31 ± 1.16 (n.s.)	1.81 ± 1.21 (n.s.)
ΔK	0.20 ± 1.20 (n.s.)	5.67 ± 2.65 ($P < 0.02$)	0.12 ± 1.21 (n.s.)	14.31 ± 2.67 ($P < 0.01$)			
L-Glucose	3.22 ± 0.77 ($n = 12$)	4.97 ± 0.75 ($n = 27$)	3.55 ± 0.50 ($n = 12$)	7.93 ± 0.81 ($n = 15$)	1.75 ± 1.04 (n.s.)	0.33 ± 0.92 (n.s.)	4.71 ± 1.12 ($P < 0.01$)
L-Glucose + amil.	4.18 ± 0.92 ($n = 12$)	3.77 ± 0.58 ($n = 27$)	4.08 ± 0.47 ($n = 12$)	3.72 ± 0.39 ($n = 15$)	0.41 ± 1.09 (n.s.)	0.10 ± 1.03 (n.s.)	0.46 ± 0.99 (n.s.)
ΔK	0.96 ± 1.20 (n.s.)	1.20 ± 0.95 (n.s.)	0.53 ± 0.69 (n.s.)	4.21 ± 0.89 ($P < 0.01$)			
Sucrose	3.47 ± 0.52 ($n = 4$)	–	–	6.88 ± 0.70 ($n = 4$)	–	–	3.41 ± 0.87 ($P < 0.02$)
Sucrose + amil.	3.15 ± 0.28 ($n = 4$)	–	–	3.68 ± 0.55 ($n = 4$)	–	–	0.53 ± 0.62 (n.s.)
ΔK	0.32 ± 0.59 (n.s.)	–	–	3.20 ± 0.89 ($P < 0.02$)	–	–	

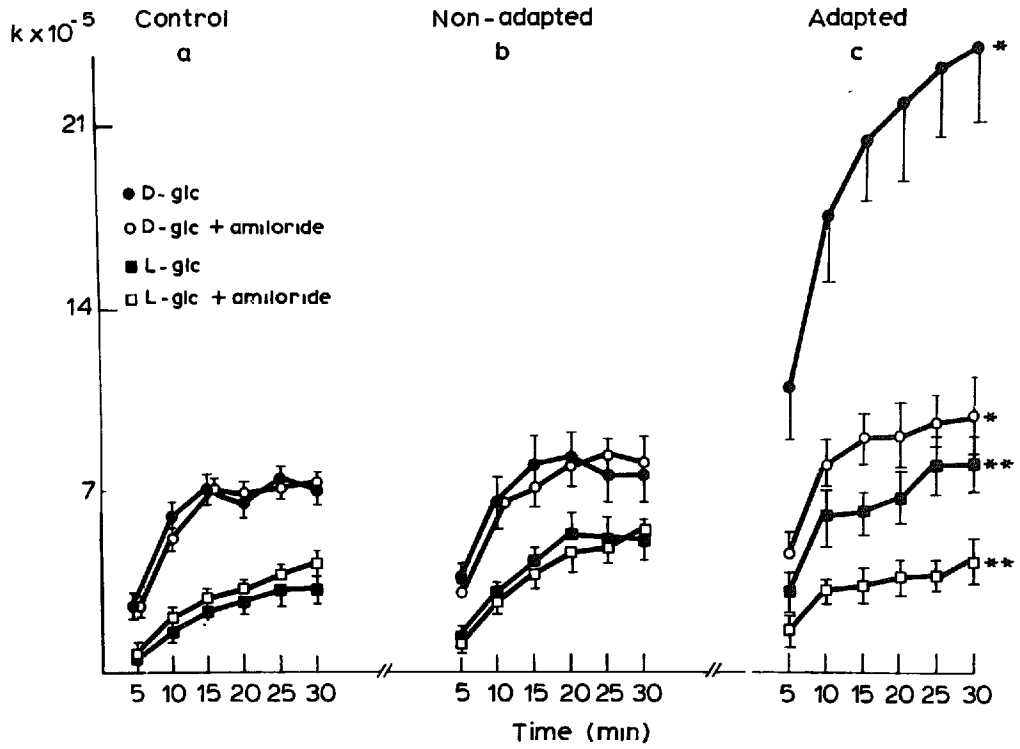

Fig. 2. D-[^{3}H]Glucose and L-[^{14}C]glucose transfer coefficients K, as a function of the time in the rat jejunum. (a) Control rats, (b) non-adapted HKD rats and (c) adapted HKD rats. Effect of amiloride (10^{-4} M). Radiotracers were added at zero time in the mucosal bath (see Methods). * $P < 0.01$ (Student's t-test for paired data, $t = 5.36$, $n = 15$), ** $P < 0.01$ ($t = 4.73$, $n = 15$).

sented $8.0 \pm 3.1\%$ ($n = 4$) of the L-glucose observed in control rats and $6.0 \pm 2.5\%$ ($n = 3$) in HKD rats.

The role of Na^+ in the observed phenomena

The effect of mucosal Na^+ removal on D-glucose transfer in control rats was tested in 'flat sheet experiments'. At these conditions the transfer coefficients (K) for -glucose and L-glucose dropped, in absence of Na^+, from $(13.0 \pm 1.1) \cdot 10^{-5}$ to $(4.7 \pm 0.7) \cdot 10^{-5}$ s^{-1} (in absence of Na^+) and from $(2.7 \pm 0.7) \cdot 10^{-5}$ to $(2.0 \pm 0.7) \cdot 10^{-5}$ s^{-1}, respectively. The differences were, in both cases, significative for paired data ($P < 0.01$ and $P < 0.05$, respectively, $n = 5$).

The transepithelial potential difference, short-circuit current and transepithelial resistance observed in control and HKD animals (flat experiments) are presented in Table II. No significant differences were detected in these parameters between both experimental conditions.

TABLE II

Transepithelial PD, short-circuit current and membrane resistance in the jejunum of control and HKD rats ($n = 6$)

		Control	HKD	Δ
PD (mv)	no amiloride	1.7± 0.4	1.2± 0.2	0.5± 0.4 (n.s.)
	+amiloride	1.4± 0.3	1.2± 0.2	0.2± 0.4 (n.s.)
	Δ	0.3± 0.5	0.0± 0.3	
		(n.s.)	(n.s.)	
I_{sc} (μA/cm^2)	no amiloride	11.4± 3.2	9.5± 3.4	1.9± 4.0 (n.s.)
	+amiloride	10.1± 2.0	9.4± 3.2	0.7± 4.0 (n.s.)
	Δ	1.3± 3.8	0.1± 4.8	
		(n.s.)	(n.s.)	
R (Ω·cm^2)	no amiloride	169 ±13	178 ±83	9 ±26 (n.s.)
	+amiloride	169 ±11	188 ±38	19 ±39 (n.s.)
	Δ	0.0±17	10 ±44	
		(n.s.)	(n.s.)	

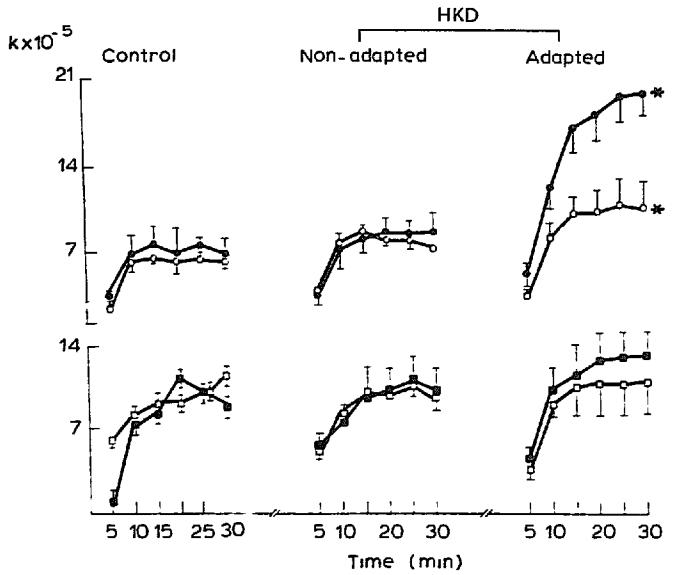

Fig. 3. D-[^{3}H]Glucose and ^{22}Na transfer coefficients as a function of the time in the rat jejunum. (a) Control rats, (b) non-adapted HKD rats and (c) adapted HKD rats. Radiotracers were added at zero time in the mucosal bath. ●, D-[^{3}H]Glucose; ○, D-[^{3}H]glucose plus amiloride (10^{-4} M); ■, ^{22}Na; □, ^{22}Na plus amiloride. * $P < 0.01$ (Student's t-test for paired data, $t = 3.26$, $n = 7$).

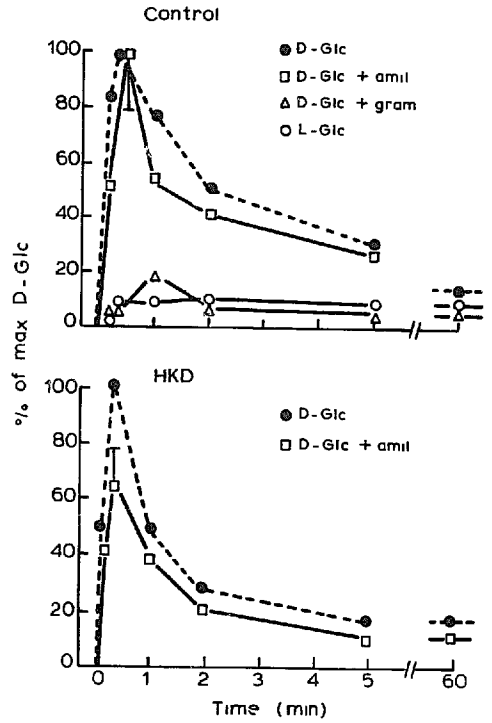

Fig. 4. Glucose uptake by brush-border vesicles prepared from control (upper figure) and HKD (lower figure) rats, in different experimental conditions. Effect of amiloride and gramicidin.

It was of importance to measure sodium transfer together with glucose transfers, as well as the effect of amiloride on these parameters, in jejunum sacs from HKD rats showing D-glucose transfers higher than 13.2 $\cdot 10^{-5}$ s^{-1}. Fig. 3 shows the obtained results. It can be observed that while amiloride reduced the D-glucose uptake, it did not modify Na^+ movements in these preparations.

D-Glucose uptake in brush-border vesicles

Fig. 4a shows the classical overshoot in D-glucose concentration inside the vesicles observed with material from control rats. As expected, the glucose overshoot (41 ± 11 pmol/mg vesicular protein) was stereospecific, and not observed with L-glucose. Furthermore the 'overshoot' collapsed when the Na^+ gradient (the driving force for D-glucose entry) was short circuited by gramicidin channels [15]. To complete these control series it was observed that the D-glucose uptake was not sensitive to amiloride action (10^{-4} M).

Brush-border vesicles prepared from animals adapted to a high potassium diet accumulated D-glucose similarly to the control ones (mean value at the peak of the overshoot 53 ± 14 pmol/mg of vesicular protein). Nevertheless the D-glucose uptake became sensitive to amiloride in HKD rats (Fig. 4b). The represented points are the mean of seven different experiments, each one being a pool of 4 to 6 animals). The mean percentual inhibition was, at the peak of the overshoot, −37 ± 11%, $t = 3.36$, $P < 0.01$. The non specific uptake (in the absence of Na^+) was, in HKD rats, non significantly different from the one observed in control animals.

In an additional experiment with HKD rats, the D-glucose transfer was tested in a jejunum fragment while the rest of the jejunum mucosal were scraped and frozen. Only material from animals showing D-glucose transfers higher than 13.2 $\cdot 10^{-5}$ s^{-1} (four animals) was then processed to prepare brush-border membrane vesicles. The obtained results are showed in Fig. 5. It can be remarked that in these vesicles, obtained from HKD-adapted animals, the effect of amiloride was clearly observed.

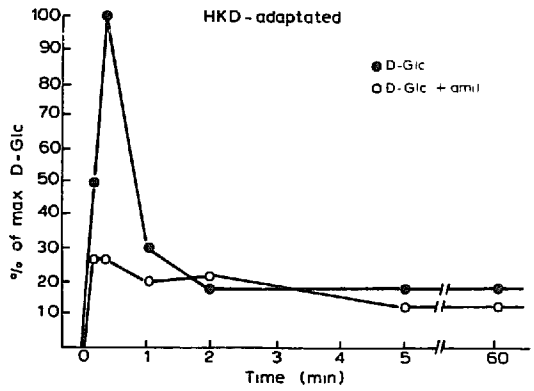

Fig. 5. D-Glucose uptake by brush-border vesicles prepared from HKD rats showing D-glucose transepithelial transfers higher than 13.2 $\cdot 10^{-5}$ s^{-1}. Effect of amiloride.

Discussion

Previous works on K^+-adapted animals have shown important adaptative changes in the distal portion of the nephron and large intestine. We report here an increase in D-glucose transepithelial transfer across the jejunum of HKD rats. This increase was quite variable in different animals and in many cases D-glucose transfer remained in the control range (Fig. 1). Due to this situation we had differentiated animals under a high potassium diet from 'K^+-adapted' ones. We consider in this second group only those showing glucose uptakes higher than $13.2 \cdot 10^{-5}$ s^{-1}. We have employed 5-cm long fragments of jejunum in our experiments and, on average, no significant differences in weight were observed between control and adapted rats. Nevertheless, we can not discard that the observed increase in D-glucose transfer is related to an increase in the membrane surface of the brush-border per unit of length. The increase in D-glucose transfer was accompanied when observed, by an also significative increase in L-glucose or sucrose movements (Fig. 2a, b, c, Table I).

D-Glucose entry into the intestinal cells is coupled to Na^+ transfer [6,9], and Na^+ influx is mediated by at least three different transport mechanisms [14]: (1) An electroneutral Na^+/Cl^- symport; (2) solute coupled transporters (glucose, amino acids); and (3) a Na^+/H^+ exchange mechanism. Furthermore the paracellular pathway must represent a significant fraction of the Na^+ entry into this leaky epithelium [12]. It was then not unexpected that an important increase in the glucose/Na^+ entry was not reflected in the Na^+ total transfer. Confirming previous results [3], we have not observed significant changes in short circuit current, membrane potential or Na^+ influx in the jejunum of HKD rats.

The effect of amiloride

It is evident that the here reported effects of amiloride are rather unexpected results. This pirazine diuretic inhibits two general classes of Na^+ transport mechanisms: (1) a conductive Na^+ entry pathway found in electrically high resistance epithelia; and (2) a Na^+/H^+ electroneutral exchange system found in different epithelia such as the renal proximal tubule and small intestine. Much higher concentration of amiloride are required to inhibit the exchange pathway than those required to inhibit the Na^+ entry pathway [15].

It has been previously reported that hyperaldosteronism is associated to potassium adaptation [4] as well as to sodium depletion [19]. In this last condition the development of an amiloride-sensitive salt and fluid absorption has been described in the rat jejunum [20]. We are now reporting that the sodium-dependent glucose transfer observed in the small intestine becomes sensitive to amiloride in rats adapted to a high K^+ diet, while we have not observed a decrease neither in short circuit current nor in ^{22}Na transfer. These results indicate a clear difference with the situation described in animals adapted to a low Na^+ diet [20]. The experiments showed in Fig. 3 point out that even in those cases in which the increase in D-glucose transfer was of importance, no effect of amiloride on the Na^+ movement was observed.

Our experiments with brush-border vesicles were preliminary ones. They were designed to give us a first approach to the subcellular localization of the amiloride action. The sensibility to amiloride of D-glucose transport, observed in HKD rats, could be reproduced in this preparation. The obtained results seem to localize, at least in part, the adaptative changes in the mucosal border.

It must be remarked that Fig. 4 shows experiments with vesicles material pooling 4 to 6 HKD rats (probably including 'K^+-adapted' and 'non-adapted' animals). When the glucose transfer was previously tested, screening 'HKD-adapted' rats, the effect of amiloride became much more important.

An amiloride sensitive Na^+/glucose transporter?

Two alternative hypotheses can explain the here reported results: (1) the well known sodium-glucose cotransporter becomes sensitive to amiloride under high K^+ diet.

(2) The observed results are indirect consequences of the amiloride action on other transport systems present in the mucosal border.

Cook and coll. [1] have reported that amiloride inhibits the Na^+-dependent hexose uptake in a clone of pig kidney cells (LLC-RK_1/CL4). This effect was only observed at high amiloride concentrations (4.5 mM) and low levels of sodium in the medium (< 15 mM). The authors give solid evidence showing that amiloride is interacting with the Na^+ site of the hexose transporter, in a competitive way. In our experiments the inhibitory action was observed at lower amiloride concentration (10^{-4} M) and at higher sodium levels (150 mequiv./l). If we accept a direct effect on the glucose transporter, the affinity of amiloride for the glucose transport would be higher than in the case of the pig kidney cells.

Alternatively, our results could be a secondary effect related to amiloride action on the Na^+/H^+ exchange. This mechanism represents a minor fraction of the mucosal entry of Na^+ [11]. This can explain why we have not observed a significant increase in Na^+ transfer in K^+-adapted rats. This hypothesis, that must be experimentally tested, can give a possible interpretation for amiloride action on glucose transfer, based on secondary effects related to changes in intracellular pH.

The L-glucose and sucrose transfers

The experiments at low temperature showed that the

'leaky pathway' was very low. Then, most of L-glucose and sucrose transfers probably represent paracellular movements. The importance of the 'solvent drag' of not charged molecules, drived by the active transport of solute, has been recently stressed [12]. According to this hypothesis, the increase in D-glucose transfer, via the Na^+-associated transporter, would induce the secondary increase of L-glucose or sucrose here observed. This mechanism also explains the effect of amiloride: once the specific and transcellular transfer of D-glucose was reduced, the secondary and paracellular movements of L-glucose and sucrose were also affected. Vesicles experiments confirm this hypothesis. In this subcellular preparation, where the paracellular path disappeared, the transfer of L-glucose was very low and insensitive to amiloride action.

It is evident that our results open the road to a series of new experiments, necessary to clarify the underlying mechanisms. The real status of sodium transport in the small intestine of animals adapted to a high potassium diet [4] must be carefully reinvestigated. It must be also studied if hyperaldosteronism has a significant role in the here described phenomena, and if amiloride (directly or indirectly) extends its action to other sodium-coupled transfers.

Acknowledgements

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