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Effect of Glucocorticoids on Metal Retention in Rats

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The absorption and retention of many non-monovalent metals and radionuclides are higher in the newborn and young organisms than in the adult ones (Barton, 1987). The phenomenon has been attributed to the immaturity of the intestinal mucosa, to its high pinocytotic activity and permeability, to the specific type of diet and particular physiology of the gut wall in the period of lactation. The concentration of total corticosterone in the rat plasma increase from 0.5 µg/dl (up to 12th day of age) to 5 µg/dl at the time of weanling. The treatment of juvenile animals with glucocorticoids, stimulating the production of endogenous corticosteroids, causes precocious gut closure and results in the maturation of metal absorptive process. Administration of glucocorticoid treatment to suckling rats reduced plutonium retention in the gut about 500 times and in the bone and liver about seven times (Sullivan and Gorham, 1982); reduced lead retention three to seven times (Keller and Doherty, 1980); caused higher elimination and lower retention values of ^{144}Ce and ^{95}Zr-^{95}Nb (Shiraishi and Ichikawa, 1972); suppressed significantly net magnesium and calcium absorptions from the small and large intestines (Ghishan and Meneely, 1982).

The purpose of this study was to investigate the effect of glucocorticoid treatment on toxic elements, which in suckling animals show very high retention values especially in the gut (cerium, mercury, cadmium), on the radiotoxic element strontium, which has no gut compartment, and on essential elements manganese and zinc. We also wanted to evaluate how glucocorticoid treatment affects distribution of administered radionuclides in the gastrointestinal tract.

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MATERIALS AND METHODS

The experiment was performed on 4-day-old suckling rats (about 8 g body weight). The radionuclides ^{141}Ce, ^{203}Hg, ^{115m}Cd, ^{85}Sr, ^{54}Mn and ^{65}Zn were administered orally in the form of chlorides (sp. act. about 18.5 MBq/mg Hg or Cd; the other radionuclides almost carrier free; all supplied by the Radiochemical Centre, Amersham, England). The method of administration was that of artificial feeding over 8 h in cow's milk (0.25) by means of a dropper (37-74 kBq of respective radionuclide per rat). Four-day-old sucklings were placed into three groups. First group received an intramuscular injection of 0.9% saline solution (0.02 ml) daily for three days. The second group received an intramuscular injection of 50 mg/kg body weight Methylprednisolone Sodium Succinate (Lemod-Solu, Inex Hemofarm - Vršac, Yugoslavia) for three days and the third group received also methylprednisolone but at a dose of 100 mg/kg body weight. On the fourth day of the experiment all the rats received one of the radionuclides and were killed six days later.

The radioactivity was determined in the carcass (whole body after removal of the gastrointestinal tract) and in the gut (the gastrointestinal tract content included) in a double-crystal scintillation counter (Tobor, Nuclear Chicago) and in the organs - liver, kidneys and femur in an automatic gamma counter (Nuclear Chicago). The gut was divided into six parts: the stomach (St), the small intestine subdivided into three segments of similar length - upper (S1), middle (S2) and lower (S3); and the large intestine subdivided into two segments - the caecum (L1) and the rest of the large intestine (L2). The radioactivity of each segment with the contents was determined in an automatic gamma counter (Nuclear Chicago).

All results were corrected for radioactive decay and geometry of the samples. The carcass, gut and organ retentions were expressed as percentages of the administered dose and presented as arithmetic means and standard errors of the means. The radioactivity in single segments of the intestine was expressed as a percentage of total gut radioactivity.

RESULTS AND DISCUSSION

The administration of methylprednisolone to suckling rats caused reduction in the whole body, carcass and gut retentions of all the administered radionuclides (Table). The glucocorticoid effect was most prominent for cerium, followed by mercury and cadmium (whole body retentions reduced 16, 4 and 1.9 times respectively). It was very small for strontium while for manganese and zinc reten-

tion was mostly reduced in the carcass (1.6 and 1.3 times respectively). The effect was dose related and thus for all the radionuclides with the higher methylprednisolone dose lower retention values were observed. However, increasing methylprednisolone dose from 50 to 100 mg/kg b.w. caused, with the exception of cerium, only a minor further reduction in the retained dose of radionuclides. For toxic elements cadmium, mercury and cerium the main effect was the reduced retention in the gastrointestinal tract. With the higher methylprednisolone dose gut retentions of cerium, mercury and cadmium were reduced 40, 10 and 2 times respectively. For essential elements, manganese and zinc, this effect was reduced carcass retention. For all the administered radionuclides glucocorticoid treatment had a very small effect, or no effect at all, on organ retention. The treatment, however, slightly increased cadmium retention in the liver, kidneys and femur and strontium retention in the kidneys. Determination of radionuclide distribution in the gastrointestinal tract showed one pattern for cerium, mercury and cadmium and another one for manganese and zinc (Figure). Most of the ^{141}Ce, ^{203}Hg and ^{115m}Cd gut radioactivity was located in the lower part of the small intestine - ileum (segment S3) while for ^{54}Mg and ^{65}Zn it was distributed equally through the gut. For cadmium there was always more activity in the upper parts of the small intestine. The radionuclide distribution in the gut did not significantly change with the glucocorticoid treatment. Only for cadmium the dose retained in the large intestine and in the upper parts of the small intestine was slightly higher in the treated than in control group and for mercury there were slightly higher doses in the stomach and large intestine but the peak of activity was again in the ileum.

High values of metal and radionuclide retention in the suckling are due, for some metals, to very high retention in the gastrointestinal tract (Sullivan et al., 1985). Of the six metals administered cerium, mercury and cadmium had high gut retention - gut compartment (69-96 per cent of the whole body retention) while strontium, manganese and zinc had low gut retention. Metals are retained not only in enterocytes and on the brush border, but also within the crypts, lamina propria and muscularis (Sasser and Jarboe, 1977). Metal mucosal uptake and retention by gut tissues occur most prominently in those areas in which passive transport (pinocytosis or diffusion) is most prominent. Many metals absorbed by the immature intestine can be localized to pinocytotic vesicles (Inaba and Lengemann, 1972; Keller and Doherty, 1980). A sharp decline in pinocytotic activity, as measured by radioiodinated polyvinylpyrrolidone uptake (^{125}I-PVP) has been observed in rats between 18 and 21 days of age (Clarke and Hardy, 1971).

The developmental sequence of decreasing pinocytotic activity (gut closure) is closely correlated with the temporal pattern of decreasing metal absorption (Forbes and Reina, 1972; Keller and Doherty, 1980). Pretreatment of sucklings with cortisone has been reported to decrease intestinal pinocytotic activity as indicated by reduction of PVP uptake and results in precocious gut closure (Daniels et al. 1973). In the present study the glucocorticoid treatment significantly reduced retention of all the radionuclides administered. The effect of glucocorticoids on retention was very strong for the metals with high gut retention and much weaker for the ones without gut compartment. Thus, the strongest effect was observed for cerium, the element with the highest gut retention (gut compartment - 96 per cent of the dose retained was in the gut) and the smallest effect was observed for strontium, the element with the lowest gut retention. It is to be supposed that the effect of the glucocorticoid treatment was due to reduced pinocytotic activity - as was shown previously for lead, magnesium, calcium and iron (Keller and Doherty, 1980; Ghishan and Meneely, 1982; Loh and Kaldor, 1971). The administration of glucocorticoid treatment alters the morphology of the absorptive epithelium of the small intestine so that it resembles the one in adults and thus the permeability of the intestinal membranes is decreased. However, the administration even of a high cortisone dose (360 mg/kg) failed to reduce lead retention in sucklings to adult levels (Keller and Doherty, 1980).

The site of accumulation in the gut was for all the administered radionuclides the lower part of the small intestine - ileum. In suckling animals the pattern of metal distribution in the gut differs from that in adults (Kostial et al., 1983) whose accumulation sites are the large intestine and stomach. Glucocorticoid treatment significantly reduced radionuclide gut retention, especially for cerium, mercury and cadmium. However, it did not change their distribution in the gut - ileum remained the main site of their accumulation.

Results of this study with those obtained for other metals and radionuclides indicate that pinocytosis is one of the mechanisms involved in metal absorption in sucklings. However, decreasing pinocytosis alone cannot account for the decrements in metal absorption observed with age and/or glucocorticoid treatment. Many other maturational phenomena (in addition to dietary changes) also occur which affect the microanatomy, enzyme complements, permeability and luminal milieu of enterocytes (Herbst and Sunshine, 1969; Ghishan and Meneely, 1982) and thus influence metal and radionuclide absorption and retention.

The effect of methylprednisolone on metal retention in suckling rats

		Whole body		Carcass		Gut		Gut (% WB)		Liver		Kidneys		Femur	
^{141}Ce	C	45.3±3.2[a]		1.6±0.2		43.7±3.2		96.0±0.7		0.20±0.02		0.03±0.003		0.03±0.004	
	E_1	8.4 0.6	5.4[b]	1.3 0.1	1.2	7.1 0.6	6.2	83.7 1.8	1.1	0.21 0.02	0.1	0.04 0.004	0.8	0.02 0.001	1.5
	E_2	2.9 0.4	15.6	1.8 0.2	0.9	1.1 0.3	39.7	35.7 3.7	2.7	0.15 0.002	1.3	0.03 0.002	1.0	0.01 0.001	3.0
^{203}Hg	C	76.0 1.5		23.3 0.6		52.7 1.3		69.3 0.8		4.24 0.12		3.42 0.15		0.64 0.003	
	E_1	25.4 2.5	3.0	15.8 1.9	1.5	9.6 0.9	5.5	38.6 2.1	1.8	2.84 0.33	1.5	3.20 0.42	1.1	0.04 0.005	16.0
	E_2	19.3 2.2	3.9	13.7 1.7	1.7	5.5 0.8	9.6	29.2 2.9	2.4	2.36 0.28	1.8	2.91 0.44	1.2	0.04 0.005	16.0
^{115m}Cd	C	99.2 2.3		4.7 0.3		94.5 2.5		95.2 0.4		2.40 0.13		0.38 0.01		0.01 0.001	
	E_1	59.7 3.7	1.7	8.3 0.3	0.6	51.4 3.7	1.8	85.6 0.9	1.1	3.89 0.15	0.6	0.63 0.04	0.6	0.02 0.002	0.5
	E_2	51.6 3.1	1.9	7.9 0.3	0.6	43.7 3.0	2.2	84.4 0.8	1.1	3.83 0.15	0.6	0.66 0.02	0.6	0.02 0.002	0.5
^{85}Sr	C	79.6 1.4		79.4 1.4		0.13 0.01		0.17 0.01		0.013 0.001		0.007 0.0003		1.49 0.03	
	E_1	74.7 2.3	1.1	74.6 2.3	1.1	0.09 0.01	1.4	0.12 0.01	1.4	0.015 0.004	0.9	0.026 0.007	0.3	1.27 0.03	1.2
	E_2	69.0 0.7	1.2	68.9 0.7	1.2	0.08 0.01	1.6	0.11 0.01	1.5	0.012 0.003	1.1	0.069 0.007	0.1	1.19 0.02	1.3
^{54}Mn	C	84.4 2.3		71.6 2.0		12.8 0.7		15.1 0.7		7.65 0.36		1.70 0.03		0.45 0.02	
	E_1	61.0 2.2	1.4	52.0 2.0	1.4	9.0 0.6	1.4	14.8 0.9	1.0	6.31 0.44	1.2	1.15 0.04	1.5	0.31 0.02	1.5
	E_2	54.0 3.1	1.6	44.8 2.7	1.6	9.2 0.5	1.4	17.0 0.4	0.9	6.46 0.56	1.2	1.08 0.08	1.6	0.22 0.01	2.0
^{65}Zn	C	76.4 1.0		72.0 1.0		4.4 0.1		5.7 0.2		7.20 0.20		0.76 0.02		0.56 0.01	
	E_1	66.4 1.7	1.2	61.4 1.6	1.2	5.1 0.2	0.9	7.6 0.2	0.8	7.23 0.24	1.0	0.81 0.04	0.9	0.46 0.02	1.2
	E_2	59.9 1.4	1.3	55.3 1.3	1.3	4.6 0.2	1.0	7.7 0.3	0.7	6.78 0.31	1.1	0.78 0.04	1.0	0.49 0.01	1.1

C - control animals received 0.9% saline (0.02 ml) during three days before radionuclide administration.
E - experimental animals received intramuscularly 50 mg/kg (E_1) or 100 mg/kg body weight (E_2) methylprednisolone sodium succinate during three days before radionuclide administration.
[a]Arithmetic mean ± SE of 9-12 animals in each group.
[b]Ratio control/experimental group.

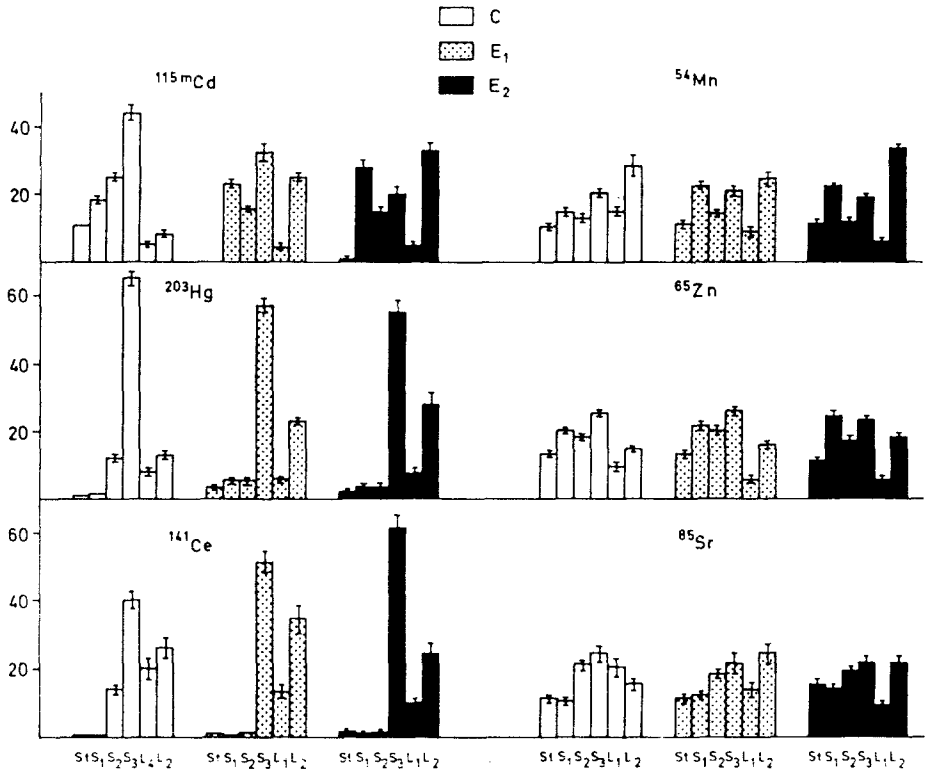

Figure. Intestinal retention of ^{141}Ce, ^{203}Hg, ^{115m}Cd, ^{85}Sr, ^{65}Zn and ^{54}Mn in suckling rats. The results are expressed as percentages of the total radioactivity of the gastrointestinal tract (contents included): stomach (St); upper, middle, and lower small intestine (S_1, S_2, S_3); caecum (L_1); and remaining large intestine (L_2). They are presented as arithmetic means and standard errors of the means. C - control animals received 0.9% saline; E_1 - 50 mg/kg body weight methylprednisolone and E_2 - 100 mg/kg b.w. methylprednisolone for three days.

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