

23

DEVELOPMENT OF COLONIC TRANSPORT PROCESSES IN EARLY CHILDHOOD:
EVIDENCE OF REDUCED ANION EXCHANGE
H R JENKINS AND P J MILLA

Institute of Child Health & Hospital for Sick Children, London WC1

Studies of colonic electrolyte transport in adults and children suggest that anion movement in vivo is only in part mediated by $\text{Cl}^-/\text{HCO}_3^-$ exchange mechanism. Using the technique of non-equilibrium dialysis of the rectum we have investigated anion exchange by incubating solutions of differing electrolyte composition in children (2 premature infants and 1 neonate, age 33-42 weeks gestation = A, and 3 children aged 5-18 months = B). Using a plasma-like solution, absorption of Cl^- and HCO_3^- was greater in A compared with B (see table). As in B HCO_3^- secretion might have been expected, we investigated the effect of the electrochemical gradient on HCO_3^- movement by using a Cl^- free solution to remove anion exchange, and a Na^+ free solution to remove the electrical drive for HCO_3^- absorption. With a Cl^- free solution HCO_3^- absorption increased in both A and B. With no electrical gradient, Cl^- absorption decreased in both groups but only in B did HCO_3^- secretion occur. These data support our previous view that anion exchange is poorly developed in infancy, only accounting for 15% of Cl^- absorption in infants and accounting for virtually no Cl^- absorption in the preterm neonate. In addition it is clear that, in vivo, Cl^- is absorbed by electrical coupling as well as anion exchange.

	(A) Cl^-	HCO_3^- (\pm SEM)	(B) Cl^-	HCO_3^-
Plasma-like	+318(\pm 46)	+40(\pm 9)	+184(\pm 43)	+22(\pm 17)
Cl^- free	-67(\pm 12)	+63(\pm 6)	0	+48(\pm 11)
Na^+ free	+270(\pm 89)	+26(\pm 5)	+142(\pm 26)	-27(\pm 9)

(nmols/min/cm²)

24

THE EFFECTS OF SOMATOSTATIN ON JEJUNAL SECRETION IN PATIENTS WITH SEVERE SECRETORY DIARRHOEA (SSD)

W M BISSETT, H JENKINS, I W BOOTH, P J MILLA

Institute of Child Health & Hospital for Sick Children, London WC1

Isolated reports suggest that somatostatin may be effective in patients with (SSD). We have assessed the effect of parenterally administered somatostatin on the secretory function of the jejunum in 4 patients with (SSD) due to a variety of conditions. Using a steady state perfusion technique we have measured jejunal H₂O and ion movement from a glucose (G2 + 0.56mM) electrolyte solution both before and after the infusion of somatostatin (3.5ug/kg stat + 3.5ug/kg/hr).

Where villous structure and function was intact net secretion of water was reversed following somatostatin from -62(G2mM) +10 (0.56mM) to +3(G2mM) +31.5(0.56mM) ul/min/cm. In 2 patients with severe villous atrophy somatostatin was of little or no benefit. [PRE -19(G2mM) -32(0.56mM) POST -13(G2mM) -3(0.56mM)]. In a patient with a morphologically normal mucosa populated with poorly differentiated enterocytes somatostatin exacerbated the secretion and the symptoms. [PRE -19(G2mM) -96(0.56mM) POST -119(G2mM) -323(0.56mM)]. Glucose absorption was unaffected and Na^+ and Cl^- movement followed that of water. These data show that in (SSD) if absorptive processes, particularly Na^+ coupled Cl^- absorption, are intact somatostatin is helpful in reducing secretion in keeping with its known alpha adrenergic agonist like action but where villous absorptive mechanisms are disrupted it is of little use and may exacerbate symptoms.

25

SELECTIVE INHIBITION OF BRUSH BORDER HYDROLASE DEVELOPMENT IN COELIAC DISEASE (CD) AND COW'S MILK PROTEIN INTOLERANCE (CMPI) MW Smith*, AD Phillips, JA Walker-Smith. Queen Elizabeth Hospital for Children, London & *AFRC Inst of Animal Physiology, Cambridge.

Brush border hydrolase activities increase as enterocytes migrate from crypts towards villous tips. Recently this process has been studied at the cellular level using quantitative cytochemistry (1). This technique is now applied to alkaline phosphatase (AP), a-glucosidase (a-G), and lactase (L) development in controls (n=6), and children with CD (n=6) and CMPI (n=5).

In controls AP, a-G, and L activities increased over the first 120 μm from the crypt-villous junction (142 to 270; 102 to 147; 78 to 138 absorbance units [AU] respectively) and changed little thereafter. The development pattern in CMPI was similar for AP (115 to 263 AU) but a-G & L levels were lower (49 to 100; 31 to 91 AU). The pattern of development in CD was again similar for AP (110 to 208 AU); a-G activity was initially low and the subsequent increase was reduced (48 to 84 AU); L activity remained low throughout (19 to 26 AU).

Cells migrate more rapidly and have considerably shortened life spans in CD and CMPI yet they still manage to attain the same maximal AP activity, presumably through adaptation. The failure of enterocytes to respond in a similar way when expressing a-G and L probably represents a specific and selective disease-induced lesion.

(1) Smith MW (1985) Ann Rev Physiol 47: 247-260

26

DEFECTIVE POSTTRANSLATIONAL PROCESSING OF SUCRASE-ISOMALTASE (SI) IN CONGENITAL SUCRASE-ISOMALTASE DEFICIENCY

H.Y. Naim, E.E. Sterchi, H.P. Hauri, J. Schmitz and M.J. Lentze

Dept. Gastroenterology, Univ. Children's Hospital, CH-3010 Berne and Biocenter Basel, Univ. of Basel, CH-4056 Basel, Switzerland; Hôpital des Enfants Malades, 149, rue de Sèvres, F-75730 Paris, France

Three cases of congenital sucrase-isomaltase deficiency in man were investigated by pulse-labelling of biopsy specimen in organ culture with ³⁵S-methionine and by measurement of enzyme activity. Sucrase activity was either completely absent or drastically reduced. Isomaltase activity was in all cases 1/10 of that found in normals. Pulse-labelling followed by immunoprecipitation of SI with monoclonal antibodies revealed only the high-mannose precursor forms. In fact, the polypeptides precipitated from the 30 min and 4 h labelled biopsies were equally sensitive to endoglycosidase H (endo H). In normal controls, the complex glycosylated, endo H-insensitive form of SI was the predominant species after 4 h pulse.

Conclusions: These findings suggest that SI is synthesized but did not acquire complex carbohydrates in the Golgi and consequently is not further transported to the microvillus membrane. These results correlate well and extend those found by immunoelectronmicroscopic localization of the SI precursors in one of the biopsies studied here.

27

BIOSYNTHESIS OF TRANSFERRIN-RECEPTOR IN HUMAN SMALL INTESTINAL CELLS

M.J. Lentze, E.E. Sterchi and H.Y. Naim

Dept. Gastroenterology, University Children's Hospital, CH-3010 Berne, Switzerland

Biopsies from human small intestine were studied in organ culture by labelling newly synthesised proteins with ³⁵S-methionine for 6 hours continuous pulse or for 10 minutes pulse followed by chase with excess of cold methionine for different time intervals. Biopsies were further processed by immunoprecipitation with monoclonal antibodies (OKT 9) against human transferrin receptor (TR). Electrophoretic analysis of the precipitates by SDS-PAGE in normal mucosa revealed immature TR-precursor with apparent molecular weight of 87 Kd after 50 minutes of chase. At 80 minutes of chase the mature form of TR with an apparent molecular weight of 90 Kd was noted. When iodinated transferrin (¹²⁵I) was incubated with microvillar membrane fraction and crosslinked with dimethyl-3-3'-dithiodispropionimide two bands were visible on SDS-PAGE under nonreducing conditions: one representing the transferrin and the second corresponding to the transferrin-TR-complex. The organ culture of totally flat mucosa from a patient with untreated celiac disease for 6 hours continuous pulse demonstrated no TR molecule on SDS-PAGE in contrast to normal mucosa. Conclusion: TR is synthesised in human intestinal mucosa within 50 minutes in organ culture. TR is absent in acute celiac disease suggesting that this defect might play a role in the pathogenesis of iron deficiency in this condition.

28

ALTERATION OF SURFACE MEMBRANE GLYCOPROTEIN SYNTHESIS IN THE SMALL INTESTINE OF RATS WITH NUTRITIONAL IRON DEFICIENCY (NID). J.P. Buts, J. Vamecq, Fr. Van Hoof. Laboratory of Pediatric Gastroenterology, Univ. of Louvain, Brussels, Belgium.

We studied the activity and kinetic parameters of brush border membrane (BBM) enzymes in villus cells and the concentration of the secretory component (SC) of p-IgA in subcellular fractions of crypt cells in 35 day old rats with NID and in controls. In rats with NID, the specific and the total activities of sucrase, maltase, lactase, aminopeptidase and diamine oxidase were decreased from -17 to -66% (p<0.05) compared to the controls. The lower activity of sucrase in the BBM of rats with NID (2.26 times) was associated with much slower enzyme synthesis rate (2.19 times) than in controls. K_m of sucrase determined in villus cells was identical in rats with NID and controls but the V_{max} was reduced proportionally to the enzymatic activity (1.21 and 1.24 times lower than control values). Electron microscopy of epithelial villus cells from rats with NID revealed a rarefaction of transport vesicles without structural changes of BBM or of the cellular organelles. In villus and crypt cells of rats with NID, SC was reduced to a level about one-half (p<0.05) that of the controls. When SC was measured in subcellular fractions of crypt cells, SC content in each fraction was 2 to 3 times lower in rats with NID than in controls. In conclusion, the decrease in disaccharidases and in SC in the small intestine of NID rats is due to an alteration of the synthesis with reduced transport of these glycoproteins to the BBM.