ABNORMAL EXPRESSION OF Dipeptidylpeptidase IV ACTIVITY IN ENTEROCYTE BRUSH-BORDER MEMBRANES OF CHILDREN SUFFERING FROM COELIAC DISEASE

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SUMMARY

Dipeptidylpeptidase IV (DPP IV) activity has been shown cytochemically to decrease significantly in enterocytes of children suffering from coeliac disease. This decrease is due to a halving of the time available for enterocytes to express DPP IV in their brush-border membranes during development. This effect is compared with previous results showing coeliac disease to inhibit disaccharidase activities selectively.

INTRODUCTION

The ability of human enterocytes to express different peptide- and disaccharide-splitting enzymes in their brush-border membranes has already been shown to vary selectively in patients suffering from coeliac disease (Lojda, 1981). More recent cytochemical analysis of this effect shows the rate and duration of enzyme appearance to vary independently for different disaccharide-splitting enzymes (Phillips, Smith & Walker-Smith, 1988). The main aim of the present work was to provide similar information on the possible ways in which coeliac disease might affect peptidase expression by enterocytes from patients with the disease. Results obtained are discussed in relation to an earlier suggestion that relative lack of a particular peptidase in coeliac disease might hinder hydrolysis of gliadin peptides (Frazer, 1956).

METHODS

Biopsies of the proximal small intestine were performed as part of the routine management of each child with fully informed parental consent. Most of the tissue obtained was used for diagnostic purposes, the remainder being frozen for quantitative cytochemistry. Six children were diagnosed as having coeliac disease (three male, three female; median age 75 months) and ten children were found to have no gastrointestinal cause for their symptoms (six male, four female; median age 19-5 months). Samples from both coeliac and control patients were coded in London before being analysed for enzyme activities in Babraham.

Cytochemical determination of dipeptidylpeptidase IV (DPP IV), lactase and alkaline phosphatase activities involved incubating 10 µm frozen sections of intestine at 37 °C with different colour-producing substrates specific for each enzyme assayed. All reactions took place under initial-rate conditions. Final estimates of the amounts of enzyme reaction products present in the brush-border membrane of villus enterocytes were obtained by scanning microdensitometry. Further details of the methods are given by Phillips et al. (1988) for lactase and alkaline phosphatase, and by Gutschmidt & Gossrau (1981) for DPP IV.
RESULTS

Maximal enzyme activities recorded for controls and patients with coeliac disease are summarized in Table 1. Results showing lactase but not alkaline phosphatase activity to be reduced significantly in coeliac disease confirm previously published findings (Phillips et al. 1988). The maximal activity of DPP IV was also inhibited significantly in tissue taken from coeliac patients, but this effect was less noticeable than for lactase. Positional profiles describing how these maximal values are reached are shown in Fig. 1A.

Enterocytes migrating from crypts show more DPP IV activity in control tissue than in diseased tissue. Both activities then increase to maximal values which remain constant. In controls the distance over which the increase occurs is however only half that found in coeliac patients. Enterocytes migrate from hyperplastic crypts in coeliac disease three times more quickly than from control crypts (Wright, Watson, Morley, Appleton & Marks, 1973). Using this value to plot data produces profiles shown on a real-time scale in Fig. 1B.

The age of enterocytes emerging from crypts (9.5 and 9.1 h) and the rates at which DPP IV activity increases subsequently in control tissue and tissue taken from coeliac patients (6.7±0.8 and 9.4±1.3 arbitrary units/h) are not significantly different (P > 0.1). The time during which this increase takes place is however twice as long in control tissue (10 compared with 5 h).

Table 1. Maximal values for brush-border hydrolase activities measured cytochemically in proximal small intestinal tissue taken from controls and patients with coeliac disease. Values are means±SEM. The statistical significance of differences noted in enzyme activities was assessed using Student's unpaired t test.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Controls n</th>
<th>Coeliac disease n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>223±15</td>
<td>190±14</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dipeptidyl-peptidase IV</td>
<td>228±14</td>
<td>156±37</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lactase</td>
<td>137±16</td>
<td>20±17</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DISCUSSION

Present work with DPP IV and previous work with alkaline phosphatase and different disaccharidases (Phillips et al. 1988) show that the time over which enzyme activities increase once enterocytes have passed the crypt–villus junction is consistently halved in coeliac disease compared with controls. The rates of increase during this reduced time span can, however, rise (alkaline phosphatase), fall (lactase), or remain constant (DPP IV, α-glucosidase) (Phillips et al. 1988 and present work). The occurrence of three different adaptive responses to a disease state within a single cell disproves the often reiterated, but rarely tested, statement that increases in crypt cell proliferation lead to the production of uniformly immature enterocytes (Dowling, 1982).
COELIAC DISEASE AND ENTEROCYTE DEVELOPMENT

Fig. 1. Developmental profiles for DPP IV appearance in human enterocytes. DPP IV activities determined cytochemically along villi of control (○, ●) and coeliac disease (□, ■) tissue are related to position on villus (A) or age of enterocyte (B). Open and closed symbols show, respectively, rising and plateau phases for DPP IV appearance. Straight lines are fitted by linear regression.

The original suggestion that patients suffering from coeliac disease might completely lack a single peptidase able to hydrolyse gliadin components has not been substantiated by later assays of brush-border peptidases (Bruce, Woodley & Swan, 1984). Other evidence, however, suggests that endopeptidase is inhibited more than dipeptidases with aminopeptidases being least affected in coeliac disease (Lojda, 1981). It would now be worthwhile examining these findings further using quantitative cytochemistry to investigate the possible clinical significance of an additional level of selective disease-induced effects on enterocyte development.

REFERENCES


