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Age Dependent Activity of Brush-border Enzymes in BALB/c Mice*

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Intestinal lactase-phlorizin hydrolase, sucrase-isomaltase and maltase-glucoamylase are brush-border hydrolases important for the digestion of carbohydrates. Alkaline phosphatase is generally used as a marker of epithelial cell maturation. Expression of these enzymes during postnatal development has been characterized, but the effect of ageing on disaccharidase activity is still poorly understood. The aim of this study was to determine the effect of ageing on disaccharidase and alkaline phosphatase activities. Age related changes in 3-, 6- and 12-month-old BALB/c mice were studied. The results of this study showed a statistically significant decrease in all studied enzyme activities, proportional to ageing (P<0.05). Horizontal patterns of disaccharidase and alkaline phosphatase activities were not affected by age. The age related decline in studied enzymes in BALB/c mice could be associated with reduced nutrient absorption and increased incidence of malnutrition in elderly mice. Hence, dietary regulation may be useful for appropriate intestinal absorption with ageing.

Keywords
ageing
disaccharidases
alkaline phosphatase
BALB/c mice

INTRODUCTION

Intestinal digestion is mainly carried out by enzymes bound to the microvillus membrane of absorptive cells. Major mechanisms associated with absorptive cells are the digestion and transport of nutrients from the small intestine into the circulatory system.[1] Intestinal disaccharidases are membrane glycoproteins synthesized in the membrane-bound polysome. They are located on or within the microvilli and protrude on the outer luminal surface of the intestinal cell membrane.[2]

Intestinal lactase-phlorizin hydrolase (LPH) (EC 3.2.1.23, 3.2.1.62), sucrase-isomaltase (SI) (EC 3.2.1.48, 3.2.1.10) and maltase-glucoamylase (MG) (EC 3.2.1.20, 3.2.1.3) are the three main brush membrane hydrolases. These disaccharidases play an important role in carbohydrate digestion. Lactase-phlorizin hydrolase digests lactose, sucrase-isomaltase digests all the sucrose and about 80 % of dietary maltose, whereas maltase-glucoamylase digests the remaining maltose.[3]

Development of intestinal microvillus membrane hydrolases during fetal life is an essential maturational

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event, which enables proper uptake of nutrients after birth.[4] In humans, in the 12th week of gestation, sucrase and maltase show about half of their activity normally present in newborns, while between the 28th and 34th weeks they reach nearly 70 % activity.[5] Lactase activity remains very low during the entire gestational period and increases in the last week. In the 28th and 34th weeks it has 30 % of activity found in newborns where at the gestational age of 35th–38th weeks the activity amounts to 70 %.[5,6] Two distinct lactase phenotypes have been recognized in humans: persistent high lactase activity and adult-onset lactase decline.[7,8] Adult-onset lactase decline, distinct from the rare congenital lactase deficiency, is characterized by a 90 % decline in lactase activity at the age of 5–7 years compared to earlier activities.[9] This pattern is similar to the post-weaning decline observed in other mammals, including rats and rabbits.[10,11] In rats, lactase specific activity is high at birth and declines during weaning, whereas sucrase specific activity is undetectable at birth and increases to adult levels during weaning.[12,13] These enzymatic changes coincide with the transition from the milk-based diet, in which the primary carbohydrate is lactose, to the diet of solid foods.[9]

Alkaline phosphatase (ALP, EC.3.1.3.1.), a metalloenzyme containing Zn and Mg in its active centre, is generally used as a marker of epithelial cell maturation.[14] Intestinal ALP is a nonspecific phosphomonoesterase usually linked to the external cell surface *via* glycosylphosphatidylinositol.[15] ALP hydrolyzes monophosphate esters at an alkaline pH.[14] The activity of this brush border enzyme can be detected in the 10th week and rises until the 23rd week of gestation.[16,17]

Disaccharidases and alkaline phosphatase are important constituents of the microvillous membrane and changes in their activities could result in reduced absorption of nutrients.[18] Little information is currently available about the disaccharidase and ALP activities in BALB/c mices. No systematic report on the activity of the brush-border enzymes in this species has been published to date, and there is no description of how they change with ageing.

The aim of this study was to determine the influence of age on disaccharidase and ALP activities in five segments of the gastrointestinal tract of 3-, 6- and 12-month-old BALB/c mice. The results will provide the basis for understanding the site and age-dependent absorption of nutrients in the intestine. The knowledge of these processes is crucial for creating specific diets for the elderly as well as introducing various food supplements.

EXPERIMENTAL

Animals

The study was carried out on three groups of male 3-, 6- and 12-month-old BALB/c mice. Each group consisted of ten mice. Mice were housed in plastic cages, fed standard pellet food (MK, Complete Diet for Laboratory Rats and Mice, Slovenia) and given tap water *ad libitum*. The animals were maintained under a 12/12 h dark/light cycle at constant temperature (20 ± 1 °C) and humidity (50 ± 5 %).

Experimental Procedure

Mice were put to death by cervical dislocation. To avoid diurnal variability, all operations were performed between 8:00–9:00 a.m. The gastrointestinal tract was isolated, washed with saline and separated into five segments (duodenum, jejunum, ileum, colon, rectum). Each segment was weighed and its length was measured. Segments were placed on ice-cold glass plates and cut longitudinally. The mucosa was scarped from segments with a glass microscope slide. Brush border membrane fractions were prepared from mucosal scrapings according to Ahnen *et al.*[19] The aliquots were stored at –80 °C for further assays of enzyme activities.

Enzyme Assay

Enzyme activities for disaccharidases were measured by the Dahlqvist method.[20] The homogenate was incubated with the substrate (lactose or sucrose). The glucose achieved during the disaccharidase hydrolysis was measured using the GOD Period method. ALP activity was determined at 30 °C in 0.9 mmol dm^{-3} 2-amino-2-methyl-1-propranolol buffer (pH = 10.5) with 10 mmol dm^{-3} Mg^{2+} and 16 mmol dm^{-3} *p*-nitrophenylphosphate as supstrate.[21] Each assay was repeated. Enzyme activities were expressed as the amount of substrate hydrolised per minute per 1 g of protein (μmol $min^{-1}g^{-1}$) under the assay conditions. Protein concentrations were determined according to Lowry *et al.*[22] using bovine albumin serum (Sigma) as standard.

Statistical Analyses

Values presented in the text and figures are expressed as mean +/– standard deviation (SD). Data were subjected to one-way ANOVA followed by the Tukey HSD test. The value of $P<0.05$ was taken as the critical level of significance.

RESULTS

Lactase-phlorizin hydrolase (LPH), sucrase-isomaltase (SI) and maltase-glucoamylase (MG) specific activities were determined in five segments of the gastrointestinal tract in 3-, 6- and 12-month-old BALB/c mice in order to characterize the changes in disaccharidase activities with age. All analyzed enzymes showed a marked decrease in their activity, in strong correlation with ageing.

Lactase activity in five intestinal segments relative to age is shown in Figure 1. The highest lactase activity in 3-, 6- and 12-month-old mice was found in the jejunum. The lowest lactase activity was found in the colon and rectum where no activity was detected in 6- and 12-month-old mice. Statistically significant differences in

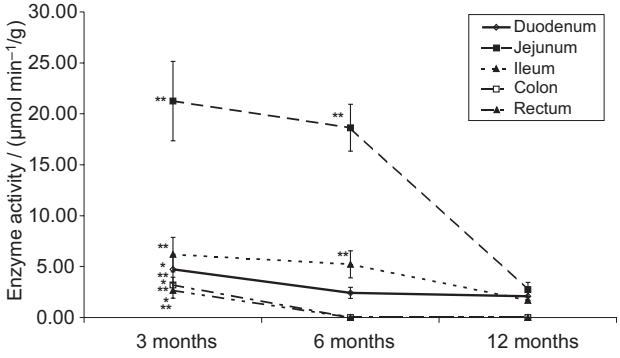

Figure 1. Lactase-phlorizin hydrolase (LPH) activity in five locations of the gastrointestinal tract in 3-, 6- and 12-month-old BALB/c mice. (Mean ± SD; $n = 10$ for each group). *P<0.05: statistically significant difference compared to 6-month-old mice. **P<0.05: statistically significant difference compared to 12-month-old mice.

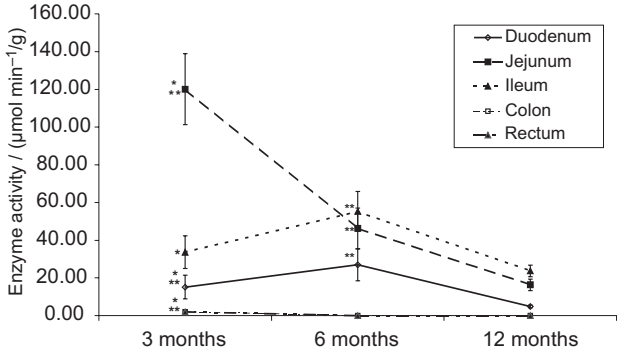

Figure 2. Sucrase-isomaltase (SI) activity in five locations of the gastrointestinal tract in 3-, 6- and 12-month-old BALB/c mice. (Mean ± SD; $n = 10$ for each group). *P<0.05: statistically significant difference compared to 6-month-old mice. **P<0.05: statistically significant difference compared to 12-month-old mice.

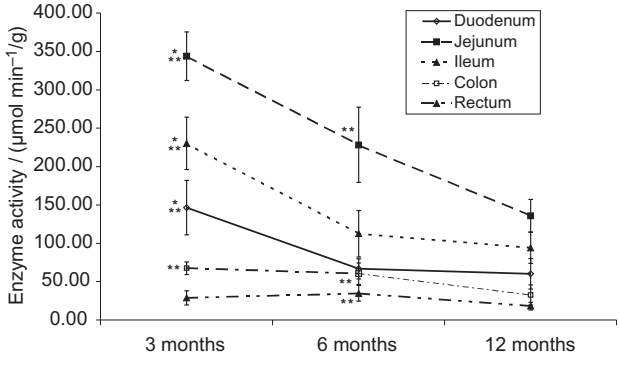

Figure 3. Maltase-glucoamylase (MG) activity in five locations of the gastrointestinal tract in 3-, 6- and 12-month-old BALB/c mice. (Mean ± SD; $n = 10$ for each group). *P<0.05: statistically significant difference compared to 6-month-old mice. **P<0.05: statistically significant difference compared to 12-month-old mice.

lactase activity were found in all segments of the gastrointestinal tract in 12-month-old mice compared to 3-month-old mice (P<0.05). The most conspicuous decrease in lactase activity was detected in the jejunum, showing a statistically significant decrease in activity in 12-month-old compared to 6-month-old mice (P<0.05). On the other hand, no statistically significant difference was found in the jejunum between 3- and 6-month-old animals. In the colon and rectum, low lactase activity was recorded in 3-month-old mice, but it was statistically significantly higher compared to 6- and 12-month old mice where no activity was detected. The same situation was found in the duodenum, but with higher lactase activity in 6- and 12-month-old animals than in the colon and rectum.

Sucrase activity varied throughout the gastrointestinal tract, having the highest activity in the jejunum in 3-month-old mice (Figure 2). No sucrase activity was detected in the colon and rectum in 6- and 12-month-old mice. A statistically significant decrease in sucrase activity was determined in all intestinal segments when comparing 3- and 6-month-old animals (P<0.05). When comparing 6- and 12-month-old animals, the decrease in sucrase activity was statistically significant in the duodenum, jejunum and ileum (P<0.05). The differences between sucrase activities in 3- and 12-month-old mice were found to be statistically significant (P<0.05) in all the intestinal segments except in the ileum.

A very consistent age-dependent decrease in maltase activity was observed (Figure 3). The highest maltase activity was found in the jejunum of 3-month-old mice. Duodenal, jejunal and ileum activities in 3-month-old mice were significantly higher than in the same segments of 6-month-old mice (P<0.05). When comparing maltase activity in 3-month-old to 12-month-old BALB/c mice, it was significantly higher (P<0.05) in all the segments except in the rectum. Unlike sucrase and lactase, maltase activities were detected in the colon and rectum of 6- and 12-month-old animals.

Influence of location and age was most notable in the ALP activity (Figure 4). ALP activity accompanied the longitudinal arrangement of the anatomical parts of the gastrointestinal tract, having the highest activity in the duodenum and the lowest in the rectum of all age groups. Thereafter, it showed an intense age-dependent attitude. A conspicuous age-dependent decrease in ALP activity through the analyzed locations of the gastrointestinal tract was observed. ALP activity was the highest in the duodenum of 3-month old mice. The ALP activity in 3-month-old mice was significantly higher in all locations compared to 12-month-old BALB/c mice (P<0.05). When comparing 3- and 6-month-old animals, a statistically significant decrease in the ALP activity was found in the duodenum, jejunum and ileum in 6-month-old mice (P<0.05).

DISCUSSION

Lactase-phlorizin hydrolase (LPH), sucrase-isomaltase (SI) and maltase-glucoamylase (MG) are the main brush-border enzymes involved in carbohydrate digestion. Their accurate activity is important for proper nutrient absorp-

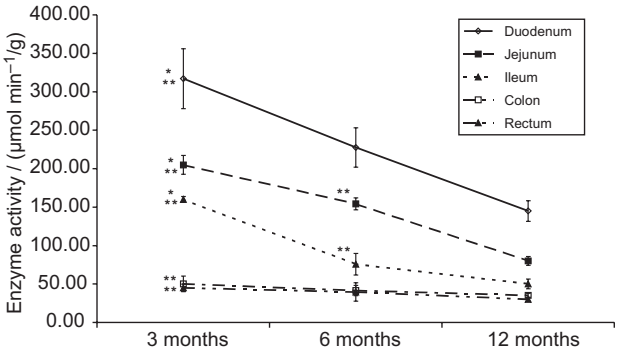

Figure 4. Alkaline phosphatase (ALP) activity in five locations of the gastrointestinal tract in 3-, 6- and 12-month-old BALB/c mice. (Mean ± SD; $n = 10$ for each group). *P<0.05: statistically significant difference compared to 6-month-old mice. **P<0.05: statistically significant difference compared to 12-month-old mice.

tion. Our aim was to determine and clarify the age-related changes in disaccharidase and ALP activities in BALB/c mice.

Lactase, sucrase, maltase and ALP specific activities were determined in five segments of the gastrointestinal tract in 3-, 6- and 12-month-old BALB/c mice. We characterized the relationship between ageing and brush-border membrane enzymes in the intestines of adult and senescent mice using a multiple-sampling technique that quantifies total intestinal enzymatic activity. The same pattern of distribution was found in 3-, 6- and 12-month-old mice: the highest activities were always determined in the jejunum and ileum, while the lowest in the colon and rectum (Figures 1, 2, 3).

The presented data revealed that total intestinal lactase, sucrase, maltase and ALP activities decline significantly with age (P<0.05). Meanwhile, the horizontal patterns of disaccharidase and ALP activities were not affected by age. The results of our study are in agreement with previously reported studies in rats, which showed that specific disaccharidase activities in jejunum decrease significantly with ageing.[23,24]

Decreased enzymes activities in aged BALB/c mice that we observed could result in reduced digestion and absorption of intraluminal nutrients. Consequently, an increased incidence of malnutrition in elderly mice could occur. The magnitude and timing of age-related changes result from dietary inputs interacting with genetic determinants.[25] Correspondingly, age-related changes do not occur at the same time for all species or for the various digestive functions.[26] Functional changes are dramatically illustrated by a pattern of expression of disaccharidase enzymes in the small intestine.[26,27]

The mammalian small intestinal epithelium is composed of a continuously renewable population of cells where multipotent stem cells give rise to enterocytes and villous components to be eventually extruded into the intestinal lumen.[28] During the passage of intestinal cells from the crypt to the villus tip, morphological, biochemical and functional changes occur, which are a function of cellular differentiation.[29] Small intestinal development is determined both by the rate of crypt cell division and the lifespan of the villus cells. It changes during normal development and in response to various hormonal and dietary factors as well as in conditions such as diabetes or starvation.[28,30,31]

Numerous previous studies have shown that disaccharidase maturation in the small intestine is characterized by parallel changes of enzyme activity, protein expression and the corresponding mRNA.[26,32] Lee *et al.*[26] showed that intestinal disaccharidase activity in rats declined significantly with age, but this decrease was not paralleled by a decline in lactase and sucrase mRNA. The decrease in lactase and sucrase activities along the small intestine may be a result of differences in mRNA translation mechanisms, increase in protein degradation and inactivation of disaccharidase activity rather than reduced transcriptional rate or stabilization of mRNA.[27,33]

There are two major events that could influence the amount of digestive brush-border hydrolyses: the first is an increased rate of cellular renewal along the crypt villus axis of the intestinal epithelium and the second could be an increased number of anaerobic bacteria in the small intestine correlated with age, since it is well known that anaerobic bacteria can produce proteases that interfere with disaccharidases in the brush-border membrane.[25,34] The villus cells number, villus height and cell migration rates do not change with ageing.[35] Older rats have an increased number of crypt cells, crypt cell proliferation rates and zone of proliferation within the crypt compared to young animals. Increase in the crypt cell population could result in a delay in cellular differentiation along the crypt-villus axis, which is manifested by less differentiated cells at the base of the villi in senescent animals.[36]

Reduced brush border enzyme activities in aged animals suggest the possibility of serious deterioration of membrane, reduced digestion of carbohydrates and absorption of nutrients. The observed lower total intestinal sucrase activity in aged mice could be caused by the cumulative effect of a reduced number of villus enterocytes synthesizing sucrase. The same mechanism might also explain the lower lactase activity in 12-month-old mice. Although lactase is detected before birth in species such as rat and mouse, sucrase does not develop until the time of weaning.[10,12] These enzymatic changes, accompanied by profound modifications of intestinal morphology and transport functions, coincide with the transition from a milk-based diet, in which the primary carbohydrate is lactose, to a diet consisting of solid foods.[9,26] Our results confirm the well-known reciprocal shift in the intestinal activities of lactase and sucrase.[37]

The age-related changes presented in this work could be further explained by intestinal adaptation to environmental stimuli.[38] Dietary nutrients induce functional or morphological changes of the intestine. Depending on the nutrients available, the intestine adapts to variations in dietary load and composition.[39] Dietary alternations result in a reprogramming of the developing enterocytes in the crypts. Ageing results in a higher proliferative rate of crypt cells, which could reduce the number of transporting enterocytes and lead to reduced nutrient absorption and finally contribute to poor nutritional status.[38] Ferraris *et al.* showed that the adaptive increases in carbohydrate uptake in the aged group of mice were not only reduced but also restricted to more proximal regions of the small intestine.[40] Although aged mice possess adaptive mechanisms to the diet that are similar to those in young mice, the effectiveness of these mechanisms may be impaired with age. This may result in malabsorption symptoms so prevalent in the elderly.

Alkaline phosphatase (ALP) is localized mainly in the brush border area on the external side of the microvili.[16] It is an important constituent of the microvillus membrane which could be involved in dephosphorylation synthesis of cellular protein, differentiation of the cell and glycosilation of the membrane.[18] ALP is often used as a marker of enterocyte differentiation.[14,41]

The results of our study in mice showed significantly lower ALP activities in all the intestinal segments when comparing 3- and 12-month-old BALB/c mice ($P<0.05$). These findings are in agreement with the results reported by Jang *et al*.[18] showing a decreased ALP activity in older mice. The ALP activity decrease in our study showed a very coherent site- and age-dependence, where the ALP activity decreased progressively along the intestine. The same ALP activity pattern was found in all age groups, but definitely decreased with ageing. Variations in ALP activity during normal development may be due to the diet, age, or structural and enzymatic modifications during growth.[16] Some of these variations may be induced by hormones [30] and conditions such as diabetes or starvation.[42]

CONCLUSION

Age is an important factor that influences the brush-border enzyme activity. All analyzed enzymes (lactase, sucrase, maltase and ALP) showed a marked decrease in their activity, in a strong correlation with ageing. Horizontal patterns of disaccharidase and ALP activities were not affected by age. The age related decline in the studied enzymes in BALB/c mice could be associated with reduced nutrient absorption and an increased incidence of malnutrition in elderly mice. Knowledge of these processes is crucial for creating specific diets for the elderly as well as introducing various food supplements. Hence, dietary regulation may be useful for appropriate intestinal absorption with ageing.

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SAŽETAK

Utjecaj starenja na aktivnost enzima sluznice tankoga crijeva u BALB/c miševa

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Crijevna laktaza-florizin hidrolaza, saharaza-izomaltaza i maltaza-glukoamilaza su hidrolaze sluznice tankoga crijeva važne za probavu ugljikohidrata. Alkalna fosfataza rabi se kao pokazatelj sazrijevanja epitelnih stanica. Poznat je izražaj navedenih enzima tijekom postnatalnoga razvoja, međutim, još nije dovoljno istražen utjecaj starenja na aktivnost disaharidaza. Cilj ovog istraživanja bio je utvrditi utjecaj starenja na aktivnost disaharidaza i alkalne fosfataze. Proučavane su promjene vezane za starenje u 3, 6 i 12 mjeseci starih BALB/c miševa. Rezultati ovoga istraživanja ukazuju na značajno sniženje aktivnosti istraživanih enzima (P<0,05), proporcionalno sa starenjem. Starenje nije utjecalo na horizontalnu distribuciju aktivnosti disaharidaza i alkalne fosfataze. Sniženje aktivnosti istraživanih enzima tijekom starenja može se povezati sa smanjenom apsorpcijom hranjivih sastojaka te povećanom učestalošću pothranjenosti starijih miševa. Dobiveni rezultati ukazuju na potrebu prilagodbe prehrane, u svrhu regulacije apsorpcije nutrijenata kod starijih populacija.