Western European Journal of Medicine and Medical Science
Volume 4, Issue 02, February 2026
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

EXPERIMENTAL STUDY OF BRUSH BORDER REMODELING OF ENTEROCYTES UNDER CHRONIC TOXIC-METABOLIC EXPOSURE

Azimova Masuda Karimovna, PhD
Associate Professor, Department of Human Anatomy and Clinical Anatomy
Tashkent State Medical University
2 Farabi Street, 100109, Tashkent, Uzbekistan

ABSTRACT

Background: Chronic exposure to toxic agents combined with metabolic disorders represents a significant pathogenic factor affecting the gastrointestinal tract. The small intestine, as a central component of the barrier–metabolic system, is particularly vulnerable to combined toxic–metabolic injury. Structural integrity of the enterocyte brush border plays a crucial role in maintaining effective membrane digestion and nutrient absorption.

Objective: To evaluate structural remodeling of the enterocyte brush border under chronic toxic–metabolic exposure in an experimental model.

Methods: The study was conducted on 36 adult Wistar rats divided into three groups: control, chronic pesticide intoxication, and chronic pesticide intoxication combined with alloxan-induced diabetes. Morphometric analysis of the jejunal mucosa was performed using the Kupriyanov staining method. Microvilli height, density, brush border thickness, and disorganization index were assessed. Statistical analysis was performed using Student's t-test ($p < 0.05$).

Results: Chronic toxic exposure resulted in moderate microvilli shortening (−17.6%) and reduced density (−16.5%) compared to controls. Combined toxic–metabolic exposure caused a more pronounced decrease in microvilli height (−34.3%) and density (−35.9%), along with a significant increase in brush border disorganization index. Structural alterations were associated with progressive reduction of the functional absorptive surface.

Conclusion: Chronic toxic–metabolic exposure leads to significant remodeling of the enterocyte brush border characterized by microvilli atrophy and spatial disorganization. The brush border may serve as a sensitive morphological marker of intestinal injury under combined toxic and metabolic stress conditions.

Keywords: Brush border; enterocytes; microvilli; chronic intoxication; alloxan-induced diabetes; toxic–metabolic exposure; small intestine; morphometric analysis; microangiopathy; experimental model

INTRODUCTION

Under conditions of increasing anthropogenic pressure, the problem of chronic toxic exposure has become particularly relevant. Prolonged intake of xenobiotics, including pesticides, in combination with metabolic disorders, leads to systemic structural and functional alterations of the digestive system.

The small intestine occupies a key position in this pathogenic cascade, functioning not only as an absorptive organ but also as an essential barrier component of the liver–intestine

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Volume 4, Issue 02, February 2026
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

axis. Chronic intoxication is accompanied by microcirculatory disturbances, tissue hypoxia, activation of inflammatory responses, and dystrophic changes in the epithelial layer.

The brush border of enterocytes represents a highly specialized structure composed of microvilli that ensure a substantial increase in the absorptive surface area. The structural integrity of microvilli directly determines the efficiency of membrane digestion, nutrient transport, and the barrier function of the intestinal mucosa.

Metabolic disorders, particularly alloxan-induced diabetes mellitus, aggravate toxic effects through the development of microangiopathy, increased oxidative stress, and impaired energy metabolism. Combined toxic-metabolic exposure may lead to remodeling of the apical complex of enterocytes; however, this aspect remains insufficiently investigated.

Therefore, the study of structural remodeling of the brush border under chronic toxic-metabolic exposure represents a relevant and promising direction in contemporary experimental morphology.

LITERATURE REVIEW

Contemporary experimental studies confirm that chronic toxic exposure combined with metabolic disturbances induces systemic remodeling of the digestive system, with the small intestine being particularly affected as a key component of barrier–metabolic regulation.

A stereological assessment of parenchymal and stromal cells in the small intestine of prepubertal rats exposed to heavy metals demonstrated marked changes in the volumetric relationships of tissue components [1]. A reduction in the relative volume of the epithelial layer along with an increase in the stromal component reflects the development of compensatory–dystrophic processes. These findings indicate a high sensitivity of the intestinal wall to chronic toxic stress and confirm the profound nature of structural remodeling.

In alloxan-induced diabetes, impairment of intestinal carbohydrate digestion has been reported [2]. The identified functional disturbances indicate decreased activity of enterocyte enzymatic systems, indirectly suggesting potential structural alterations of the brush border and microvilli. Metabolic decompensation is accompanied by impaired mucosal trophism and compromised energy supply of epithelial cells.

Under conditions of acute pesticide intoxication on the background of alloxan-induced diabetes, pronounced alterations of vascular and tissue structures of the small intestine have been described [3]. These include blood stasis, perivascular edema, and dystrophic changes in the epithelial layer. The combination of toxic and metabolic factors enhances tissue injury through microangiopathy and tissue hypoxia.

Similar evidence has been obtained in studies of chronic pesticide intoxication [6], which demonstrated persistent changes in the hemocirculatory bed, thickening of vascular walls, and disruption of mucosal architecture. The chronic nature of exposure results in structural instability of the intestinal wall and reduces its adaptive capacity.

Exposure to the pesticide “Omayt-57E” in animals with alloxan-induced diabetes revealed progressive disturbances of microcirculation and tissue organization in the small intestine [8]. These data indicate intensification of ischemic processes and dystrophic changes of the epithelial component under combined toxic–metabolic exposure.

An investigation of the gastric microcirculatory bed during intoxication with pesticides of different classes confirmed disorganization of the vascular network, reduced capillary density, and development of ischemic tissue injury [7]. These changes reflect the universal

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character of vascular disturbances under toxic stress and allow extrapolation of similar mechanisms to the small intestine.

In acute erosive-ulcerative lesions of the gastric and duodenal mucosa of various etiologies, structural alterations of the apical epithelium associated with impaired barrier function have been reported [5]. Damage to the superficial layer leads to disruption of intercellular contacts and reduced epithelial resistance to aggressive factors.

Systemic endocrine disorders also exert a pronounced effect on the morphology of digestive organs. In hypothyroidism, structural changes of the pancreas have been documented [4], emphasizing the significance of metabolic imbalance in the development of morphological alterations of the digestive system as a whole.

Overall analysis indicates that most studies have focused on the vascular component and general tissue organization of the mucosa under toxic and metabolic disturbances. The role of microcirculatory disorders, tissue hypoxia, and dystrophic processes in intestinal wall remodeling has been substantiated.

However, the available literature provides insufficient coverage of the condition of the enterocyte brush border and microvilli remodeling as a key structural–functional element of the small intestinal mucosa under chronic toxic–metabolic exposure. Detailed morphometric data characterizing alterations of the enterocyte apical complex under combined toxic injury and metabolic dysfunction remain limited.

Thus, the existing gap in understanding the structural organization of the enterocyte brush border determines the scientific relevance of further experimental studies aimed at assessing morphological remodeling of microvilli under chronic toxic–metabolic exposure.

MATERIALS AND METHODS

The experimental study was conducted on 36 adults male Wistar rats weighing 180–220 g. The animals were maintained under standard vivarium conditions at a temperature of 22–24 °C, relative humidity of 55–60%, and a natural light cycle. Rats had free access to water and a standard pelleted diet. All experimental procedures were performed in accordance with generally accepted ethical guidelines for laboratory animal research.

The animals were randomized and divided into three equal groups of 12 animals each. The first group served as the control and consisted of intact animals. The second group represented a model of chronic toxic intoxication induced by prolonged pesticide exposure. The third group included animals with chronic toxic intoxication combined with metabolic disturbances caused by alloxan-induced diabetes.

Metabolic disorders were induced by a single intraperitoneal injection of alloxan at a dose of 150 mg/kg body weight. Blood glucose levels were measured 72 hours after injection using a glucometer. Animals with glycemia ≥ 11 mmol/L were included in the study.

The model of chronic intoxication was established by oral administration of the pesticide at a subtoxic dose corresponding to 1/10 LD50 for 30 consecutive days. This protocol corresponded to a commonly accepted model of chronic toxic exposure.

On day 31 of the experiment, animals were euthanized by anesthetic overdose. A 1–1.5 cm segment of the jejunum was excised from the middle portion of the small intestine. The collected tissue was immediately fixed in 10% neutral buffered formalin for 24 hours.

Histological processing included standard paraffin embedding followed by preparation of serial sections 5–7 μm thick. The Kupriyanov staining method was applied to visualize the brush border of enterocytes, allowing clear identification of the apical complex and microvilli.

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Morphometric analysis was performed at ×1000 magnification using an ocular micrometer and digital microphotography. The following parameters were evaluated: microvilli height (µm), microvilli density (number per 1 µm of apical surface), brush border thickness, and disorganization index (graded on a 0–3 scale). At least 50 enterocytes were analyzed per specimen to ensure representativeness of the data.

Statistical analysis was performed using parametric methods. Data were presented as mean ± standard error of the mean (M ± m). Intergroup differences were assessed using Student's t-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

General Morphological Characteristics

In the control group, the small intestinal mucosa exhibited preserved architecture. The villi were well defined, the epithelial layer was continuous, and no signs of dystrophy or desquamation were observed. The brush border of enterocytes demonstrated a uniform linear structure, with microvilli densely packed and strictly parallel to one another, forming a compact apical complex.

In the toxic group, moderate structural alterations of the brush border were observed. These included shortening of microvilli, partial rarefaction, and focal loss of parallel orientation. In some areas, uneven staining of the apical layer was detected, indicating early dystrophic changes.

In the toxic-metabolic group, structural disturbances were markedly pronounced. Microvilli were significantly shortened, locally fragmented, and their density was reduced. Areas of partial desquamation of the superficial epithelium were noted, along with uneven brush border thickness and severe disorganization of the apical complex.

Table 1. Microvilli Height of Enterocytes (µm)

Group	Height (M ± m)
Control	1.08 ± 0.03
Toxic	0.89 ± 0.04*
Toxic-Metabolic	0.71 ± 0.05**

** $p < 0.05$ vs. control*
*** $p < 0.05$ vs. toxic group*

The mean microvilli height in the control group was 1.08 µm, reflecting normal structural organization of the apical complex. In the toxic group, a statistically significant decrease to 0.89 µm was observed, corresponding to a 17.6% reduction compared with controls. This indicates the development of moderate microvilli atrophy under chronic toxic exposure.

In the toxic-metabolic group, microvilli height decreased to 0.71 µm, representing a 34.3% reduction compared to the control group and a 20.2% decrease compared to the toxic group. These findings demonstrate that the combination of toxic exposure and metabolic dysfunction significantly intensifies structural reduction of microvilli. Shortening of microvilli directly correlates with a reduction in the absorptive surface area of the intestinal mucosa.

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Table 2. Microvilli Density (per 1 µm of Apical Surface)

Group	Density (M ± m)
Control	28.4 ± 1.1
Toxic	23.7 ± 1.3*
Toxic-Metabolic	18.2 ± 1.5**

** p < 0.05 vs. control*
*** p < 0.05 vs. toxic group*

In the control group, microvilli density was 28.4 per 1 µm of apical surface, indicating high compactness and functional integrity of the brush border.

In the toxic group, density decreased by 16.5%, reflecting a reduced number of microvilli per unit surface and partial disorganization of the apical complex.

In the toxic-metabolic group, microvilli density decreased by 35.9% compared to controls. The statistically significant reduction relative to the toxic group confirms pronounced structural damage under combined exposure. Reduced density exacerbates functional deficiency by decreasing the number of active absorptive units.

Table 3. Brush Border Disorganization Index (score)

Group	Index (M ± m)
Control	0.4 ± 0.1
Toxic	1.6 ± 0.2*
Toxic-Metabolic	2.7 ± 0.3**

** p < 0.05 vs. control*
*** p < 0.05 vs. toxic group*

In the control group, the disorganization index remained minimal and corresponded to physiological structural integrity.

In the toxic group, the index increased more than fourfold, indicating moderate disruption of parallel microvilli orientation and partial fragmentation of the apical layer.

In the toxic-metabolic group, the index reached 2.7 points, reflecting severe spatial disorganization of the brush border. Disruption of microvilli arrangement strongly correlated with reductions in their height and density.

Comparative analysis of the three groups demonstrates a progressive increase in structural disturbances. Chronic intoxication alone induces moderate microvilli reduction, whereas its combination with metabolic disorders results in pronounced atrophy, rarefaction, and disorganization of the apical complex.

The findings indicate a synergistic effect of toxic and metabolic factors, leading to progressive reduction of functional absorptive surface area. The degree of structural remodeling appears directly proportional to the severity of toxic-metabolic exposure.

Thus, the identified morphometric alterations confirm significant structural destabilization of the enterocyte brush border under chronic toxic-metabolic conditions.

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DISCUSSION

The obtained results indicate progressive structural remodeling of the enterocyte brush border in the small intestine under chronic toxic–metabolic exposure. The statistically significant decrease in microvilli height and density, together with the increase in the disorganization index, reflects profound morphofunctional alterations of the apical complex.

Isolated chronic intoxication was accompanied by moderate microvilli reduction. Similar changes have previously been described under toxic exposure associated with microcirculatory disturbances and tissue hypoxia [3,6,8]. In this context, microvilli shortening may be interpreted as an adaptive–dystrophic response to prolonged injury.

The most pronounced alterations were observed in the toxic–metabolic group. The combination of pesticide intoxication with alloxan-induced diabetes resulted in a synergistic enhancement of destructive processes. These findings are consistent with data highlighting the role of microangiopathy and vascular disturbances in mucosal remodeling [3,7]. Diabetic microangiopathy contributes to reduced mucosal perfusion, development of hypoxia, and impaired trophic support of enterocytes.

Stereological studies of the small intestine under toxic exposure [1] have demonstrated alterations in the ratio of parenchymal and stromal components, indicating deep tissue remodeling. The present data complement these findings by showing that destructive changes involve not only general mucosal architecture but also its key functional element — the brush border.

Impaired intestinal carbohydrate digestion in alloxan-induced diabetes [2] indirectly confirms reduced functional activity of enterocytes. The reduction in microvilli height and density observed in the present study morphologically explains the development of enzymatic insufficiency and decreased membrane digestion.

The increase in the disorganization index reflects disruption of microvilli spatial orientation and fragmentation of the apical complex. A probable underlying mechanism involves damage to the actin cytoskeleton of microvilli under oxidative stress conditions. Chronic hyperglycemia enhances the generation of reactive oxygen species, leading to damage of enterocyte membranes and structural proteins.

Systemic metabolic imbalance also plays an important role. Structural alterations of digestive organs under endocrine disorders [4] confirm that hormonal and metabolic regulation are closely linked to the morphological state of the intestinal mucosa.

Thus, the present findings suggest that the brush border may serve as a sensitive morphological marker of toxic–metabolic injury. The pronounced reduction in microvilli height (34.3%) and density (35.9%) under combined exposure indicates a substantial decrease in functional absorptive surface area and suggests a potential risk of malabsorption syndrome.

Comparative analysis demonstrates that metabolic disturbances significantly potentiate toxic injury, supporting the concept of an integrated interaction between vascular, metabolic, and epithelial components in the development of structural remodeling of the intestinal wall.

CONCLUSION

The present study demonstrated that chronic toxic–metabolic exposure is associated with significant structural remodeling of the enterocyte brush border in the small intestine. These alterations are characterized by a pronounced decrease in microvilli height and density, indicating disruption of the morphofunctional organization of the apical complex.

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Isolated chronic intoxication resulted in moderate microvilli reduction and partial brush border disorganization. However, the combination of toxic exposure with alloxan-induced diabetes markedly intensified the degree of morphological destruction, confirming the synergistic interaction of toxic and metabolic components.

It was established that under toxic–metabolic conditions, microvilli height decreased by 34.3% and microvilli density by 35.9% compared to control values. These findings reflect a substantial reduction in the functional absorptive surface area of the small intestine and suggest a potential risk of malabsorption syndrome.

The increase in the disorganization index indicates progressive disruption of microvilli spatial orientation and destabilization of the enterocyte apical complex. The identified alterations confirm the important role of microangiopathy and metabolic dysfunction in the development of structural remodeling of the intestinal mucosa.

Thus, the enterocyte brush border may be considered a sensitive morphological marker of toxic–metabolic injury to the intestinal wall in experimental models, providing a foundation for further investigation into the mechanisms of intestinal dysfunction under systemic intoxication and metabolic disorders.

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