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EXPERIMENTAL ASSESSMENT OF ENTEROCYTE APICAL SURFACE REMODELING IN COMBINED TOXIC AND METABOLIC DAMAGE

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

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Abstract:

Background. Long-term exposure to toxic compounds together with metabolic imbalance exerts a substantial damaging influence on the gastrointestinal system. The small intestine is among the most vulnerable organs because its epithelial lining simultaneously performs absorptive, enzymatic, and barrier functions. Any disturbance of the enterocyte apical surface may therefore lead to a decline in digestive efficiency and nutrient transport.

Objective. To determine the morphological features of enterocyte apical surface remodeling in the jejunum under chronic toxic exposure combined with experimentally induced metabolic dysfunction.

Materials and methods. The investigation involved 36 adults male Wistar rats. Animals were assigned to three groups: intact control, chronic toxic exposure, and chronic toxic exposure combined with alloxan-induced diabetes. Histological specimens of the jejunum were processed by routine paraffin technique, and the apical border of enterocytes was visualized using the Kupriyanov method. Morphometric assessment included microvillus height, microvillus density, brush border thickness, and the degree of architectural disorganization. Statistical significance was evaluated with Student's *t*-test at $p < 0.05$.

Results. In the toxic group, moderate destructive changes were recorded, including shortening of microvilli and a reduction in their density. In the combined toxic-metabolic group, these disturbances became significantly more pronounced: the apical complex showed deeper structural simplification, lower compactness, and higher disorganization. The obtained data indicate a stepwise deterioration of the absorptive surface under the influence of combined pathological factors.

Conclusion. Chronic toxic exposure causes remodeling of the enterocyte brush border, while its combination with metabolic dysfunction aggravates the process and leads to marked ultrastructural and morphometric impairment of the absorptive apparatus. The brush border can be regarded as a sensitive morphological indicator of intestinal injury in complex toxic-metabolic states.

Keywords: small intestine, enterocytes, brush border, microvilli, chronic intoxication, alloxan diabetes, morphometry, experimental morphology.

INTRODUCTION

The growing impact of environmental and chemical stressors has intensified interest in chronic intoxication as a major factor of systemic tissue injury. Persistent exposure to toxic agents, especially when combined with metabolic disorders, may induce complex structural abnormalities in multiple organs and tissues. Within this context, the small intestine deserves special attention because it is not only responsible for digestion and absorption, but also serves as a key barrier between the external and internal environments of the organism.

The epithelial lining of the small intestine is particularly sensitive to pathological influences. Enterocytes possess a highly specialized apical domain represented by the brush border, which consists of closely packed microvilli. This structure enlarges the absorptive surface, supports membrane digestion, and contributes to mucosal barrier integrity. Damage to this delicate ultrastructural complex may therefore result in a decrease in digestive and transport capacity.

Metabolic abnormalities such as alloxan-induced diabetes intensify tissue damage by promoting oxidative

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stress, microangiopathy, trophic insufficiency, and cellular energy deficiency. When toxic injury develops on this background, epithelial disturbances may become deeper and more persistent. Despite the recognized significance of intestinal injury under such conditions, morphometric data specifically describing the state of enterocyte microvilli and the brush border remain limited.

For this reason, investigation of the enterocyte apical complex under combined toxic and metabolic stress is of clear scientific and practical interest. A detailed evaluation of brush border remodeling may improve understanding of the mechanisms underlying intestinal dysfunction and may help identify sensitive morphological markers of epithelial injury.

LITERATURE OVERVIEW

Splenectomy remains an important surgical intervention in hematological, traumatic, and portal hypertensive disorders; however, accumulating evidence indicates that removal of the spleen is associated with a wide range of systemic vascular and morphological consequences. One of the most extensively studied complications is portal vein thrombosis (PVT) and portal venous system thrombosis (PVST), which are recognized as major postsplenectomy adverse events. Contemporary reviews and meta-analyses have shown that splenectomy significantly increases the risk of thrombotic complications, especially in patients with cirrhosis, portal hypertension, hematologic diseases, and enlarged spleen volume. Recent state-of-the-art analyses emphasize that postoperative thrombosis is a multifactorial process involving platelet activation, altered portal hemodynamics, endothelial dysfunction, and hypercoagulability.

A number of clinical studies have attempted to identify predictors of thrombosis after splenectomy. These include postoperative thrombocytosis, splenic vein diameter, portal vein blood flow changes, liver cirrhosis severity, and the underlying non-traumatic disease for which splenectomy is performed. Prospective and retrospective investigations demonstrated that platelet count elevation after splenectomy is not merely a laboratory phenomenon, but may reflect deeper changes in vascular reactivity and coagulation balance. Reactive thrombocytosis, in particular, has been repeatedly described as a common postsurgical response that may contribute to thrombogenesis, especially when combined with endothelial injury and venous stasis.

Systematic reviews and meta-analyses published in recent years further strengthened the evidence that patients after splenectomy constitute a specific risk group for portal venous thrombosis. Risk stratification models and predictive scoring systems have therefore been proposed to identify patients requiring early anticoagulant prophylaxis. Several authors reported that long-term prophylactic anticoagulation may reduce the incidence of portal vein thrombosis in cirrhotic patients after splenectomy, although the optimal duration, timing, and safety of such prevention remain under discussion. Despite this progress, prevention of postoperative portal/splenic vein thrombosis is still regarded as an unresolved clinical issue.

Beyond thrombotic complications, splenectomy appears to affect vascular remodeling on a broader level. Experimental evidence indicates that removal of the spleen modifies thrombus-associated vascular wall responses and changes the character of vascular remodeling. This suggests that the spleen plays a regulatory role not only in immune surveillance and blood filtration, but also in maintaining the balance between coagulation, endothelial integrity, and reparative vascular processes. In addition, reviews have pointed to a possible association between splenectomy and pulmonary hypertension, supporting the idea that splenic removal may induce long-term hemodynamic and vascular disturbances extending beyond the portal circulation.

Experimental morphological studies also provide important insight into the systemic effects of splenectomy. Reports devoted to the liver hemomicrocirculatory bed in rats after experimental splenectomy demonstrated significant changes in microvascular architecture, blood filling, and tissue trophics. Other morphological works describe that splenectomy influences the course of pathological processes in parenchymal organs, indicating that structural reorganization after loss of the spleen may involve not only vascular channels but also stromal and cellular components. Investigations in aged white rats further suggest that splenectomy may alter immune status and affect longevity, indirectly confirming the long-term biological significance of the spleen in systemic homeostasis.

At the same time, although the vascular, thrombotic, and general morphological consequences of splenectomy have been actively studied, much less attention has been paid to the fine ultrastructural changes occurring in the digestive tract epithelium after splenic removal, particularly under conditions of combined pathological influence. Most available studies focus either on portal hemodynamics, thrombosis risk, liver morphology, or broad immunological consequences. Considerably fewer investigations address how splenectomy may modulate epithelial

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integrity, absorptive surfaces, and barrier-specialized structures of the small intestine.

This issue becomes especially important in the context of combined toxic and metabolic injury. Under such conditions, the intestinal mucosa is exposed to hypoxia, microcirculatory disorders, oxidative stress, and trophic imbalance. If splenectomy additionally modifies vascular remodeling, coagulation, and systemic immune responses, it may intensify structural damage in the intestinal wall, including the apical region of enterocytes. However, detailed morphometric and ultrastructural studies devoted specifically to brush border remodeling under these combined conditions remain scarce.

Therefore, analysis of the available literature indicates that splenectomy is associated with significant thrombotic, vascular, and morphological alterations, but the structural-functional state of the enterocyte apical surface under combined toxic-metabolic damage after splenectomy remains insufficiently explored. This gap justifies targeted experimental investigation aimed at clarifying the degree of microvillar remodeling, epithelial injury, and absorptive dysfunction in the small intestine under these conditions.

MATERIALS AND METHODS

The study was carried out on 36 mature male Wistar rats weighing 180–220 g. The animals were kept under standard vivarium conditions with free access to water and a regular pelleted diet. Temperature and humidity were maintained within conventional laboratory ranges, and all procedures were conducted in accordance with accepted ethical principles for animal experimentation.

The rats were divided into three equal groups:

1. Control group — intact animals.
2. Toxic group — animals exposed to chronic pesticide intoxication.
3. Toxic-metabolic group — animals exposed to chronic pesticide intoxication in combination with alloxan-induced diabetes.

Metabolic disturbance was induced by a single intraperitoneal administration of alloxan at a dose of 150 mg/kg. Blood glucose was measured after 72 hours, and only animals with glycemia of at least 11 mmol/L were included in the diabetic model. Chronic toxic exposure was reproduced by oral administration of the pesticide in a subtoxic dose equal to 1/10 LD50 for 30 consecutive days.

On day 31, the animals were euthanized by anesthetic overdose. A 1–1.5 cm fragment from the middle portion of the jejunum was collected and fixed in 10% neutral buffered formalin for 24 hours. Tissue samples were embedded in paraffin, and serial sections 5–7 μm thick were prepared. The Kupriyanov staining method was used to visualize the enterocyte brush border.

Morphometric analysis was performed at ×1000 magnification using ocular micrometry and digital microphotography. The following parameters were measured: microvillus height, microvillus density per 1 μm of apical surface, brush border thickness, and disorganization index scored from 0 to 3. At least 50 enterocytes were analyzed in each specimen. Statistical processing was carried out by parametric methods, with results expressed as M ± m. Differences between groups were assessed using Student's *t*-test, and significance was accepted at $p < 0.05$.

RESULTS

In intact animals, the jejunal mucosa demonstrated well-preserved architectural organization with clear differentiation of its structural layers. The villi were elongated, regularly shaped, and uniformly distributed along the mucosal surface. The epithelial lining remained continuous without signs of desquamation, and the brush border exhibited a homogeneous, sharply delineated linear contour. Ultrastructural examination showed that microvilli were densely packed, strictly parallel, and formed a highly organized and compact apical surface, which is indicative of optimal absorptive capacity and functional integrity of enterocytes.

In the toxic exposure group, moderate morphological alterations were detected. Although the general villous architecture remained relatively preserved, the apical surface of enterocytes showed early signs of structural disorganization. Microvilli appeared shortened and partially deformed, their parallel arrangement became irregular, and intermicrovillar spaces slightly increased. In addition, uneven staining of the apical cytoplasm suggested the development of dystrophic processes, likely associated with impaired intracellular metabolism and early degenerative changes.

The most severe structural damage was observed in the toxic-metabolic group. In these animals, the jejunal mucosa exhibited pronounced degenerative alterations affecting both the epithelial lining and its apical specialization. Microvilli were markedly shortened, fragmented, and unevenly distributed, with a substantial decrease in their density. In several areas, focal desquamation of superficial epithelial cells was noted, exposing the underlying layers. The brush border lost its uniform thickness and appeared irregular and discontinuous. The spatial organization of the apical complex was severely disrupted, indicating deep remodeling of the absorptive apparatus and significant impairment of enterocyte functional capacity.

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Table 1. Microvillus 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

Analysis of microvillus height revealed a clear progressive decrease across experimental groups. In the control group, the mean value of 1.08 μm corresponded to normal ultrastructural organization and optimal functional state of the brush border.

Under chronic toxic exposure, microvillus height decreased to 0.89 μm, representing a statistically significant reduction of 17.6% compared to controls. This finding indicates moderate atrophic remodeling of the apical surface and suggests impairment of membrane digestion and nutrient absorption processes.

In the toxic-metabolic group, the parameter further declined to 0.71 μm. This corresponds to a 34.3% decrease relative to control values and a 20.2% reduction compared to the toxic group. Such pronounced shortening reflects severe structural regression of microvilli and confirms that metabolic disturbances significantly aggravate toxic-induced damage, leading to deeper impairment of the absorptive machinery.

Table 2. Microvillus 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*

The density of microvilli showed a similar decreasing trend, reflecting progressive disruption of brush border compactness.

In intact animals, the density value (28.4 per μm) indicated tightly packed microvilli and preserved structural organization of the apical surface.

In the toxic group, this показатель decreased to 23.7 per μm, corresponding to a 16.5% reduction, which suggests partial loss of structural integrity and early disorganization of the absorptive surface.

In the toxic-metabolic group, density dropped to 18.2 per μm, which is 35.9% lower than control values and significantly reduced compared to the toxic group. This substantial decrease indicates a marked loss of functionally active microvilli and reflects a severe decline in absorptive efficiency due to combined pathological воздействие.

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*

The brush border disorganization index demonstrated a consistent and statistically significant increase from control to experimental groups.

In intact animals, the low value (0.4) reflected minimal structural variability and preserved architectonics of the apical surface.

In the toxic group, the index increased to 1.6, indicating moderate disorganization of microvillar structure and partial loss of apical uniformity.

The highest value (2.7) was observed in the toxic-metabolic group, representing a marked increase in structural disorder. This finding confirms severe disruption of apical architectonics, including fragmentation, irregular distribution, and loss of coordinated orientation of microvilli.

SUMMARY OF MORPHOMETRIC FINDINGS

Overall, the obtained data demonstrate a stepwise progression of structural damage in the enterocyte apical surface from control to toxic and toxic-metabolic conditions. While toxic exposure alone induces moderate atrophic and disorganizational changes, the addition of metabolic dysfunction significantly amplifies

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these alterations, leading to pronounced degeneration of the brush border.

These results indicate that combined toxic-metabolic injury exerts a synergistic effect on enterocyte ultrastructure, resulting in severe impairment of absorptive and barrier functions of the small intestine.

DISCUSSION

The obtained findings demonstrate that the enterocyte brush border undergoes progressive structural remodeling under conditions of chronic toxic and combined toxic–metabolic stress. The statistically significant reduction in microvillus height and density, together with the increase in the disorganization index, indicates a pronounced impairment of the apical membrane complex and, consequently, of the absorptive capacity of the intestinal epithelium.

Under isolated chronic intoxication, the observed alterations were moderate and primarily manifested as shortening and partial rarefaction of microvilli. These changes can be interpreted as adaptive–dystrophic responses of enterocytes to prolonged exposure to toxic agents. At this stage, the epithelial layer still retains partial structural integrity, suggesting the presence of compensatory mechanisms aimed at maintaining functional activity.

In contrast, the combination of toxic exposure with metabolic disturbance (alloxan-induced diabetes) led to substantially more severe damage. The marked decrease in microvillus parameters, along with significant architectural disorganization, reflects a breakdown of adaptive capacity and the development of deeper degenerative processes. This may be explained by the synergistic effect of toxic injury and metabolic imbalance, including oxidative stress, microcirculatory disturbances, impaired trophic supply, and cellular energy deficiency.

The progressive loss of microvillar organization observed in this study is of particular importance, as the brush border plays a key role in membrane digestion and nutrient absorption. Disruption of this structure inevitably leads to decreased enzymatic activity and impaired transport processes. Therefore, the morphometric parameters of microvilli can be considered reliable indicators of functional impairment in the small intestine.

These findings are consistent with previously reported data indicating that chronic intoxication and metabolic disorders adversely affect intestinal morphology, primarily through vascular, hypoxic, and dystrophic mechanisms. However, the present study provides a more detailed morphometric characterization of the enterocyte apical surface, highlighting its sensitivity as a target of combined pathological воздействия.

CONCLUSION

1. Chronic toxic exposure induces structural remodeling of the enterocyte brush border, manifested by a reduction in microvillus height and density.
2. The combination of toxic and metabolic factors leads to a significant aggravation of these changes, resulting in pronounced disorganization of the apical surface.
3. The morphometric parameters of microvilli (height, density, and disorganization index) serve as objective and sensitive markers of intestinal epithelial damage.
4. The enterocyte brush border can be considered a key structural indicator for assessing the severity of pathological processes in the small intestine under complex toxic–metabolic conditions.
5. The obtained results expand current understanding of intestinal epithelial remodeling and may contribute to the development of diagnostic and prognostic criteria for gastrointestinal disorders associated with chronic intoxication and metabolic imbalance.

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