

ORIGINAL ARTICLE

Histological features of the remodeling of rat submandibular salivary glands following the administration of a combination of monosodium glutamate, sodium nitrite, and Ponceau 4r

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ABSTRACT

Aim: To determine the dynamics of histological changes in the lobules of rat submandibular salivary glands under normal conditions and following the combined administration of the food additives monosodium glutamate, sodium nitrite, and Ponceau 4R.

Materials and Methods: Rats of the experimental group received sodium nitrite at a dose of 0.6 mg/kg, monosodium glutamate at a dose of 20 mg/kg, and Ponceau 4R at a dose of 5 mg/kg dissolved in 0.5 mL of distilled water and administered orally once daily. The animals were euthanized after 1, 4, 12, and 16 weeks of the experiment. Histological examination of the submandibular salivary glands was performed.

Results: Prolonged administration of the combination of food additives, including monosodium glutamate, sodium nitrite, and Ponceau 4R, resulted in stage-dependent morphological alterations. At the early stages, vascular-stromal disturbances and functional stress of the glandular epithelium predominated, accompanied by the development of persistent interstitial edema, hydropic degeneration, and ductal dysfunction. At later stages of the experiment, compensatory activation of a portion of glandular cells was observed in combination with dystrophic changes and microcirculatory imbalance. By the end of the study, these alterations manifested as chronic dystrophic remodeling, mucinous transformation of the secretory end pieces, desquamation of the ductal epithelium, and disruption of the structural integrity of the ductal system.

Conclusions: Administration of the combination of food additives leads to destructive and dystrophic changes in the structural components of the submandibular salivary glands and is accompanied by remodeling of the extracellular matrix components.

KEY WORDS: food additives, salivary glands, secretory end pieces, intercalated duct, striated duct, histological examination

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INTRODUCTION

Saliva formation and secretion constitute a complex physiological process ensured by the coordinated functioning of all parenchymal components of the salivary glands [1]. The secretory end pieces produce acinar fluid, referred to as primary saliva, which consists of water, ions, and secretory products of acinar cells and originates from the interstitial fluid formed through blood filtration from the surrounding capillaries. This fluid undergoes substantial modification while passing through the ductal system, which plays a crucial role in the processing and maturation of primary saliva [2, 3]. An integral component of the salivary glands is the interstitial compartment, which is filled with the ground substance whose physicochemical properties determine the transport processes occurring within it. Alterations in these properties may result in spatial reorganization of the pathways through which biological fluids are transported.

The functional activity of the salivary glands is influenced by numerous endogenous and exogenous factors. Therefore, the investigation of morphological alterations induced by environmental factors is of considerable scientific and practical importance [4]. Disturbances in saliva formation and secretion affect both the qualitative and quantitative composition of saliva, thereby influencing not only the maintenance of oral homeostasis but also the normal functioning of the digestive system as a whole. Consequently, histological examination, aimed at studying the microscopic architecture of tissues, remains one of the most informative approaches for assessing structural changes in salivary glands [5–7].

In recent years, increasing attention has been paid to the quality composition of industrially manufactured food products. To improve product appearance, extend shelf life, and compensate for the use of lower-quality raw materials, manufacturers increasingly

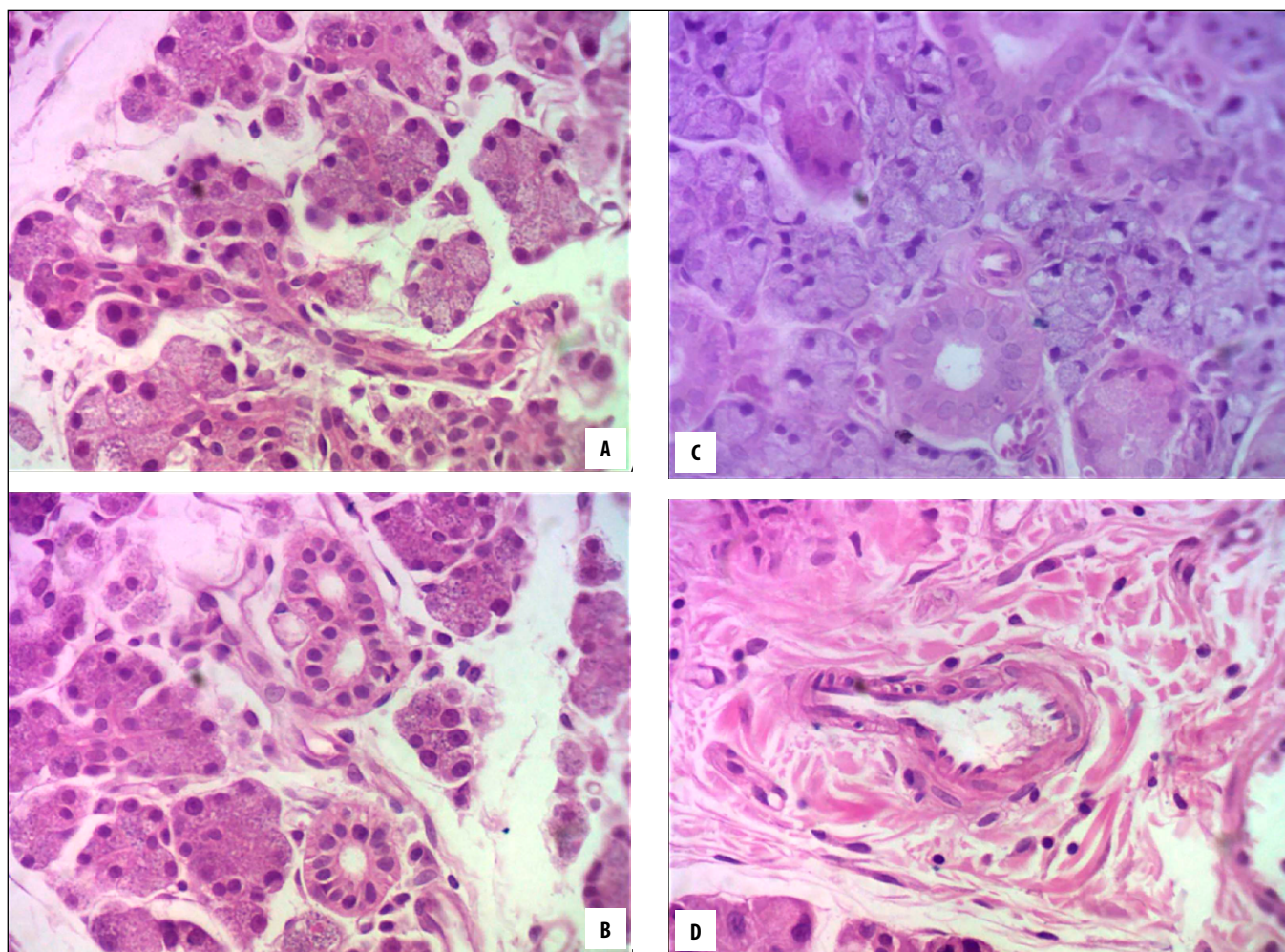


Fig. 1 a). Secretory end pieces and intercalated ducts. B). Striated ducts and the periductal capillary network. C). Vessels of the microcirculatory bed. D). Interlobular interstitial connective tissue of the submandibular salivary glands of rats in the control group. Photomicrograph. Hematoxylin and eosin staining. Magnification $\times 400$

Picture taken by the authors

employ various food additives. Analysis of commercially available food products has demonstrated that monosodium glutamate, sodium nitrite, and Ponceau 4R are among the most commonly used additives. Previous studies have not provided a definitive explanation for the variability in human susceptibility to the effects of these substances, while data concerning their combined action remain limited [8, 9].

Importantly, the combination of the most frequently used food additives includes compounds characterized by different potential mechanisms of tissue injury. Experimental studies have associated monosodium glutamate with oxidative stress and dystrophic alterations in various organs, including the submandibular salivary gland [10, 11]. However, no consensus has yet been reached regarding the safe dosage of monosodium glutamate, and the mechanisms underlying its pathogenic and

tissue-damaging effects remain insufficiently understood.

Sodium nitrite has been shown to enhance the generation of reactive oxygen species, disrupt antioxidant homeostasis, and induce histological alterations in salivary glands [12]. Nevertheless, studies investigating its effects on the organs of the digestive system are scarce, and many aspects of its biological action remain inadequately explored [13].

Ponceau 4R, a synthetic azo dye, has demonstrated potential cytotoxic and genotoxic properties in certain experimental models, although its toxicological profile largely depends on dosage, duration of exposure, and the biological system under investigation [14, 15]. The combined exposure to these substances, even at doses below the maximum permissible levels, may impose a cumulative burden on antioxidant defense mechanisms, vascular regulation, epithelial metabolism, and the extracellular matrix.

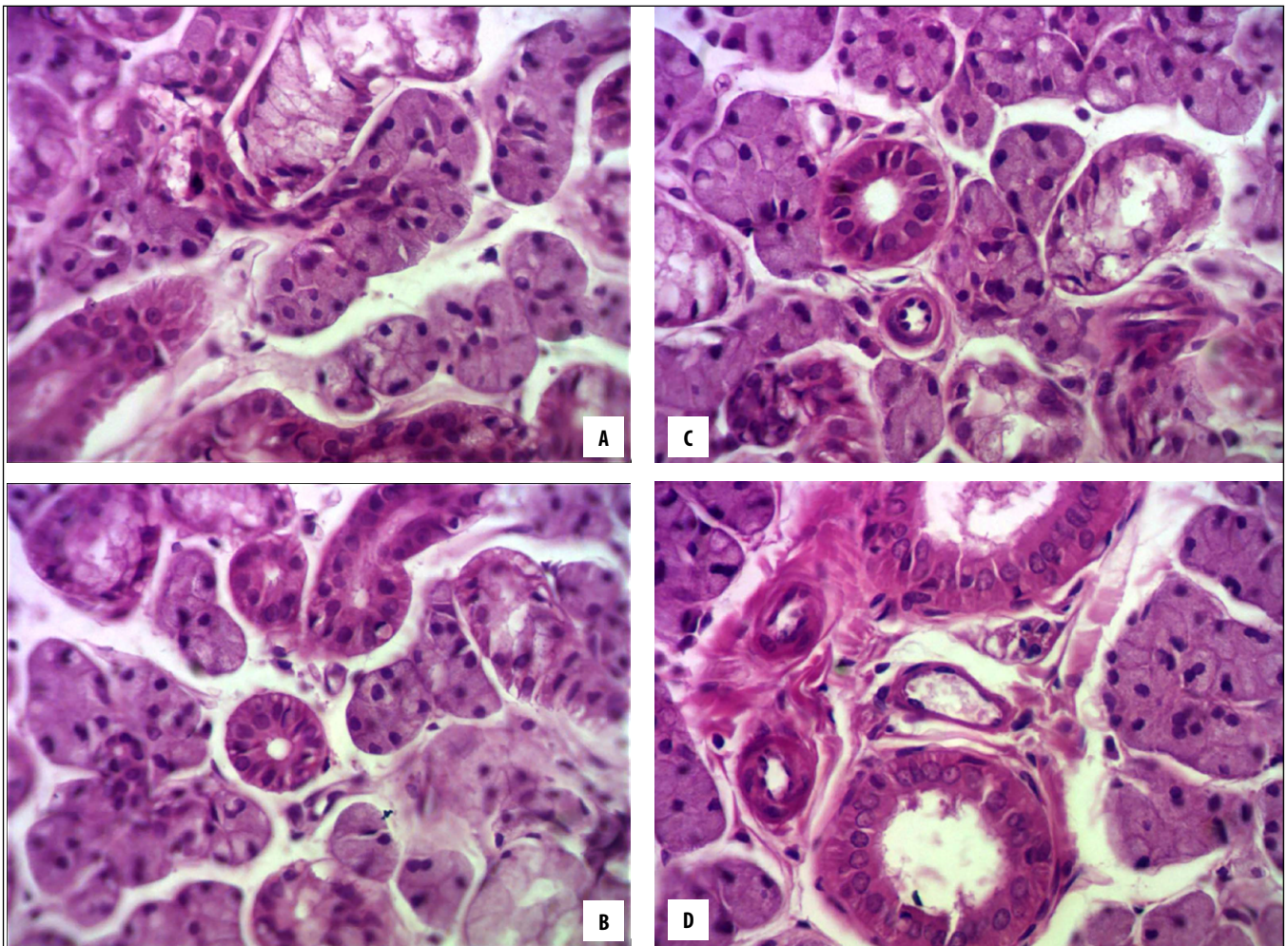


Fig. 2 A). Alterations in the tinctorial properties of the cytoplasm of seromucous cells of the secretory end pieces and reactive changes in the epithelium of the intercalated ducts. B). Initial stages of periductal edema formation around the striated ducts. C). Arteriolar spasm and signs of depletion of the exchange microvascular vessels. D). Expansion of the nodal interstitial compartments of the submandibular salivary glands of rats after 1 week of administration of the combination of monosodium glutamate, sodium nitrite, and Ponceau 4R. Photomicrograph. Hematoxylin and eosin staining. Magnification $\times 400$

Picture taken by the authors

AIM

The aim of the present study was to determine the dynamics of histological changes in the lobules of rat submandibular salivary glands under normal conditions and following combined exposure to the food additives monosodium glutamate, sodium nitrite, and Ponceau 4R.

MATERIALS AND METHODS

The study was conducted on 84 adult male rats. Animals in the control group had free access to drinking water and received physiological saline orally. Rats in the experimental group, under conditions of unrestricted access to water, were administered sodium nitrite at a dose of 0.6 mg/kg, monosodium glutamate at a dose of 20 mg/kg, and Ponceau 4R at a dose of 5 mg/kg dissolved in 0.5 mL of distilled

water once daily by oral gavage. The administered doses of the food additives were twofold lower than the maximum permissible levels. The animals were euthanized after 1, 4, 12, and 16 weeks of exposure by overdose of thiopental anesthesia. Following euthanasia, specimens of the submandibular salivary glands were excised and fixed in 10% neutral buffered formalin. Tissue samples were subsequently processed and embedded in paraffin according to standard histological procedures [4, 16]. Histological sections were prepared using an ARM 3600 microtome. After staining with hematoxylin and eosin, the sections were mounted in polystyrene mounting medium and examined under a light microscope. Photomicrographs were obtained using a Levenhuk D740T digital microscope equipped with a digital imaging system and software adapted for morphometric and histological analysis.

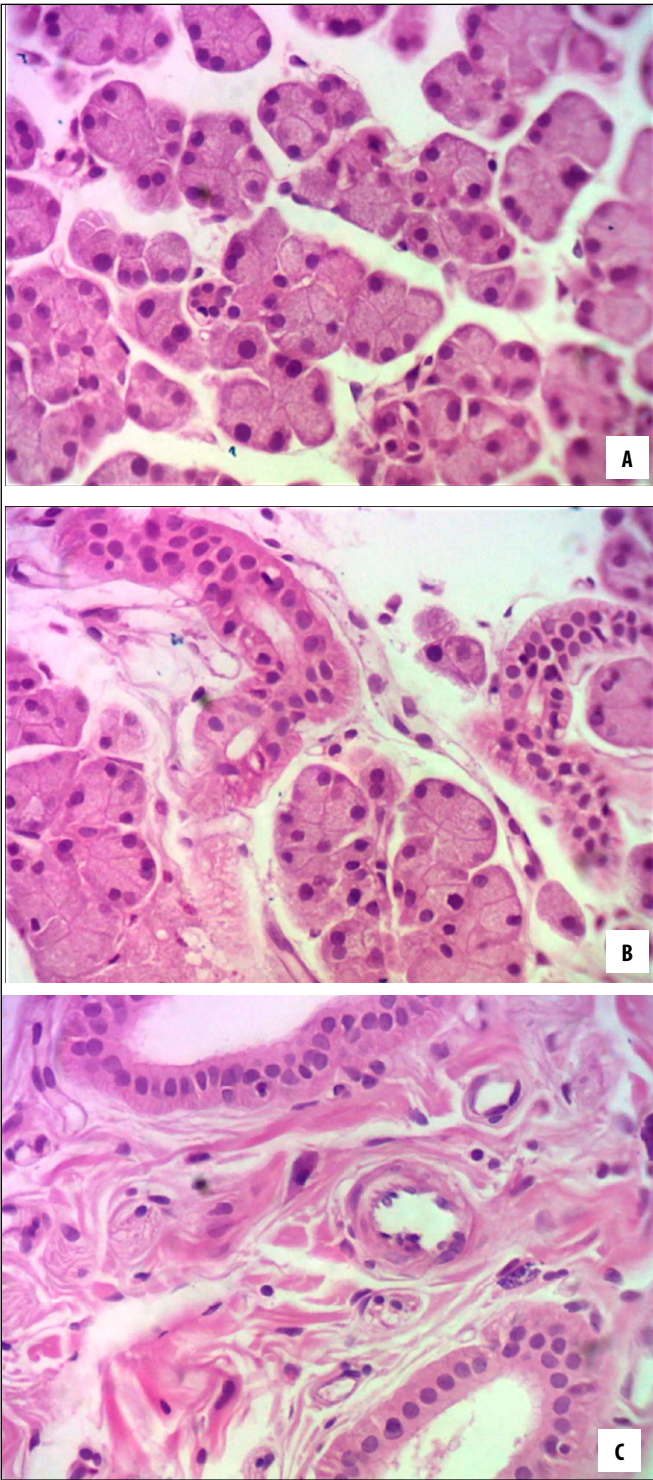


Fig. 3 A). Hydropic degeneration in glandular cells of the secretory end pieces, intercalated duct, and edema of the interstitial tissue. B). Striated ducts and signs of depletion of the exchange microvascular vessels. C). Interstitial tissue at week 4 of administration of the food additive combination. Photomicrograph. Hematoxylin and eosin staining. Magnification $\times 400$
Picture taken by the authors

All animal experiments were conducted in compliance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and

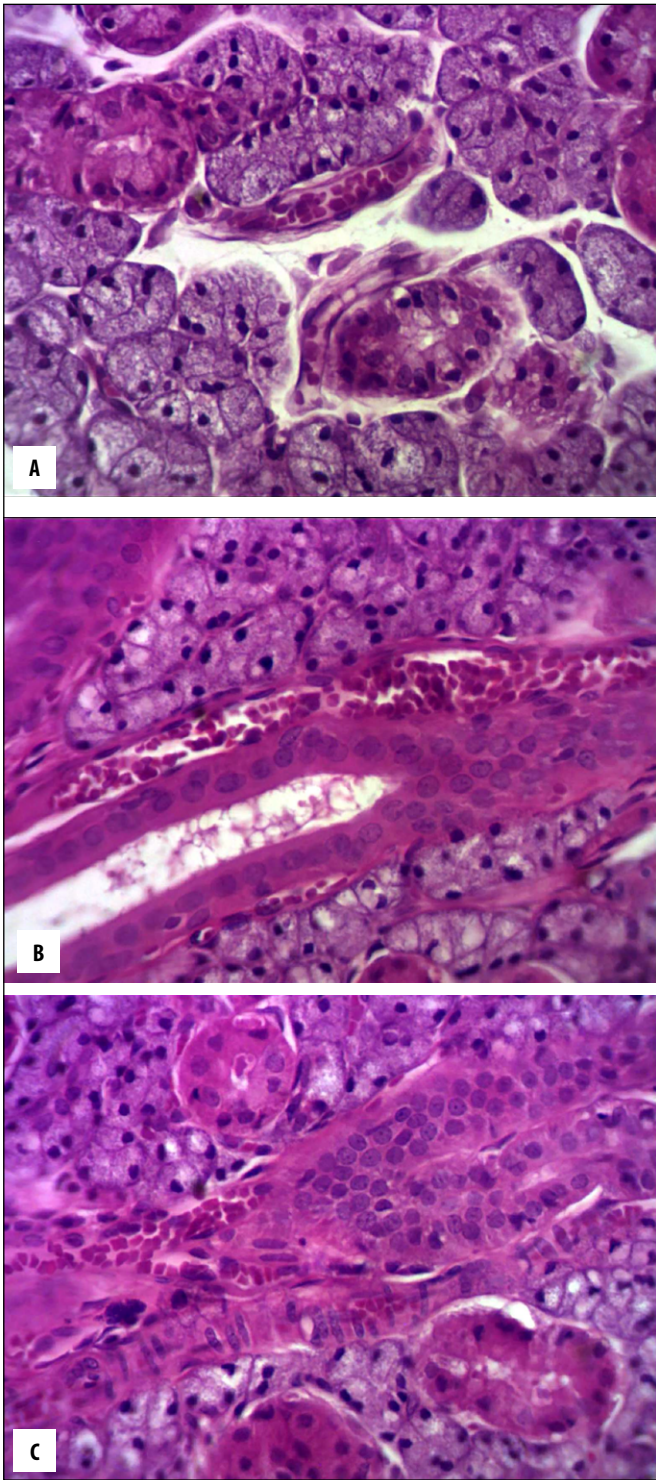


Fig. 4 A). Cytoplasmic vacuolization of the epithelial cells of the striated ducts and increased cytoplasmic basophilia of glandular cells of the secretory end pieces. B). Blood filling of the capacitance vessels. C). Spasm of the resistance vessels and vacuolization of acinar cells at week 12 of administration of the pollutant combination. Photomicrograph. Hematoxylin and eosin staining. Magnification $\times 400$
Picture taken by the authors

Other Scientific Purposes (Strasbourg, 1986), Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific

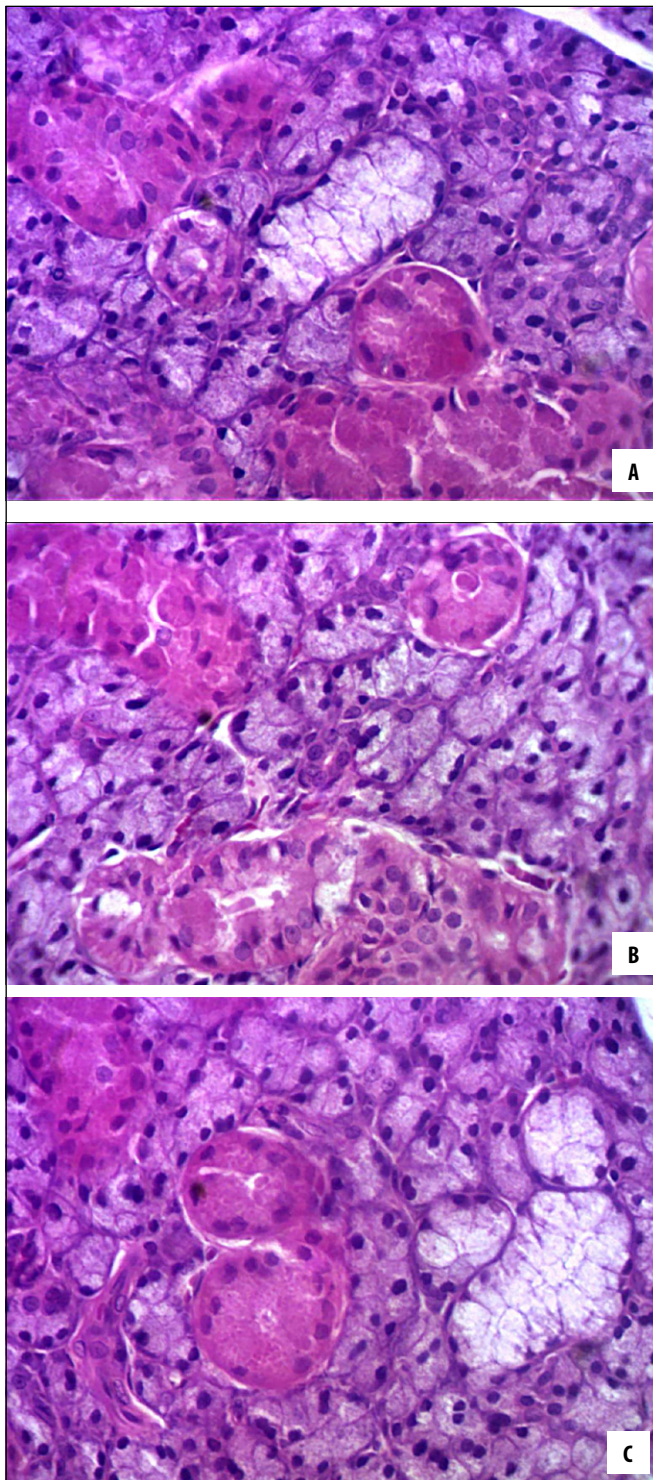


Fig. 5 A). Mucinization of the cells of the secretory end pieces and the appearance of vacuole-like dilatations in the basal portions of the striated ducts. B). Desquamation of the epithelial cells of the striated ducts. C). Degenerative changes in the ductal epithelium of the intercalated ducts of the rat submandibular salivary glands at week 16 of the experiment. Photomicrograph. Hematoxylin and eosin staining. Magnification $\times 400$
Picture taken by the authors

purposes, and Order No. 249 of the Ministry of Education and Science, Youth and Sports of Ukraine dated March 1, 2012, "On Approval of the Procedure for Con-

ducting Experiments and Scientific Studies on Animals by Scientific Institutions." The study also adhered to the recommendations of the First National Congress on Bioethics (2001) and was approved by the Biomedical Ethics Commission of Poltava State Medical University (Minutes No. 220, October 25, 2023).

AI STATEMENT

The author states that no AI tools were used in writing this article.

FRAMEWORK

The paper has been written within the research scientific work "Restructuring of the organs of the immune, respiratory and excretory systems under the effect of various exogenous factors (monosodium glutamate, sodium nitrite, Ponceau 4R, ethanol, methacrylate)", State Registration No 0121U108234.

RESULTS

In the control group, the submandibular salivary gland exhibited a typical lobular architecture. The parenchyma consisted of densely arranged secretory end pieces and a well-developed system of intra- and interlobular excretory ducts. The stroma was moderately developed and represented by delicate layers of loose fibrous connective tissue and interlobular septa.

The secretory end pieces were compactly arranged and composed predominantly of pyramidal seromucous cells. The basal portions of the cells exhibited basophilic staining, whereas the apical regions displayed a more eosinophilic and granular appearance. The nuclei of the glandular cells were round, normochromatic, and characterized by distinct contours. Intercellular spaces were not enlarged, and the basement membranes remained intact (Fig. 1a).

The intercalated ducts possessed narrow, well-defined lumina and were lined by simple cuboidal epithelium. Epithelial cells were arranged regularly, and their nuclei were round and predominantly centrally located, indicating preservation of the transport function of the ductal system (Fig. 1a).

The striated ducts were larger in caliber, with wide lumina and tall columnar epithelium. Pronounced eosinophilia of the cytoplasm and preservation of basal striations indicated functional activity and participation in the modification of primary saliva. The surrounding interstitial tissue was moderately developed, and the blood vessels showed no signs of stasis (Fig. 1b).

The microcirculatory bed consisted of arterioles, capillaries, and venules without evidence of vascular stasis

or erythrocyte aggregation (Fig. 1c). The interlobular connective tissue contained orderly arranged collagen fibers, fibroblasts, and fibrocytes, while the parenchyma-to-stroma ratio remained preserved (Fig. 1d).

After one week of administration of the food additive combination, the acinar organization of the gland remained generally preserved; however, the secretory end pieces were arranged less compactly. Optically clear spaces appeared between acini and around ducts and blood vessels, indicating the accumulation of tissue fluid within the interstitium. Some glandular cells exhibited hyperchromatic nuclei, uneven cytoplasmic staining, and occasional vacuolated areas. Acinar lumina varied in size, suggesting disturbances in the secretory cycle and impaired outflow of secretory products.

At this stage, the intercalated ducts displayed a small diameter and narrow slit-like lumina. Clear periductal spaces corresponding to stromal edema were observed and could potentially interfere with the transport of primary saliva (Fig. 2a). In the striated ducts, irregular nuclear distribution, heterogeneous eosinophilia of the cytoplasm, and partial loss of basal striations indicated early functional stress of the ductal epithelium (Fig. 2b).

Alterations in the microcirculatory bed during the first week were predominantly hemodynamic in nature. Arterioles exhibited narrowed or irregular lumina, while endothelial cells protruded into the vascular lumen. Venules were dilated and irregularly shaped (Fig. 2d). Capillaries showed indistinct contours due to edema, and areas of reduced blood filling were observed within their lumina (Fig. 2c). The interstitial tissue was expanded, with fibrous structures separated by accumulated fluid, whereas interlobular ducts demonstrated dilated lumina containing pale secretory material (Fig. 2d).

After four weeks of exposure to the food additive combination, the predominant histological feature was further expansion of the interstitial compartment. Wide optically clear spaces were observed between secretory end pieces, ducts, and blood vessels, indicating edema and disruption of the compact arrangement of the glandular parenchyma. In some secretory cells, the cytoplasm remained moderately eosinophilic, whereas in others it appeared paler, granular, and finely vacuolated, consistent with hydropic degeneration. Acinar lumina were visualized irregularly and varied considerably in size.

The epithelial cells of the intercalated ducts retained their simple epithelial arrangement; however, some nuclei exhibited increased staining intensity. Due to marked expansion of the interstitium, the lumina of certain intercalated ducts were poorly visualized, potentially impairing the drainage of primary saliva (Fig. 3a). In the striated ducts, nuclei appeared intensely

basophilic, occasionally clustered, and irregularly distributed. The cytoplasm was heterogeneous, and basal striations were indistinct, indicating impairment of epithelial functional activity.

Capillaries were located within markedly expanded interstitial spaces. Owing to tissue edema, vascular contours appeared indistinct, and erythrocytes were not readily identified within the lumina (Fig. 3b). The interstitial tissue was substantially expanded, with collagen fibers separated by edematous fluid. The presence of fibroblasts, fibrocytes, occasional immunocompetent cells, and mast cells suggested activation of compensatory-reparative processes and progression toward chronic tissue remodeling. Interlobular ducts exhibited wide lumina containing pale secretory masses or amorphous material (Fig. 3c).

At week 12 of prolonged administration of the combination of monosodium glutamate, sodium nitrite, and Ponceau 4R, the condition of the glandular cells was heterogeneous. In some cells, the cytoplasm remained moderately eosinophilic, whereas in others it appeared pale, granular, and vacuolated, consistent with moderate hydropic degeneration. In certain secretory end pieces, increased cytoplasmic basophilia was observed, reflecting compensatory activation of the protein-synthesizing apparatus. The coexistence of enhanced basophilia, cytoplasmic vacuolization, and clearing indicated the simultaneous presence of compensatory and degenerative alterations within the acinar compartment (Fig. 4a–c).

The epithelial cells of the striated ducts at week 12 remained relatively compactly arranged, although their distribution was uneven. Their cytoplasm was eosinophilic, heterogeneous, and vacuolated, while the basal striations were poorly discernible, indicating reduced efficiency of ion transport and secretory modification. The ductal lumina exhibited irregular contours and contained pale secretory material. The apical surface of the epithelium was uneven and demonstrated focal signs of desquamation (Figs. 4a, 4c).

At this stage, the interlobular ducts exhibited relatively wide lumina lined by tall columnar or pseudostratified epithelium characterized by variable cell height and irregular nuclear arrangement. The lumina contained pale amorphous or secretory material, suggesting alterations in the composition of the secretion and partial impairment of its drainage against the background of edematously altered stromal tissue (Fig. 4b).

Arterioles at week 12 were characterized by relatively thick walls and narrowed lumina, consistent with vascular spasm. These changes indicated impaired regulation of vascular tone, restricted blood supply to the glandular parenchyma, and consequently reduced oxygenation

and trophic support of the secretory epithelium. Perivascular edema was observed around the arterioles (Fig. 4c). In contrast, venules exhibited wider lumina and thinner walls, and their lumina were filled with densely packed erythrocytes. Venular congestion indicated impaired venous outflow and localized blood stasis, which, together with arteriolar spasm, reflected microcirculatory imbalance within the gland (Figs. 4b, 4c).

By week 16 of administration of the food additive combination, further alterations in the tinctorial properties of the cytoplasm were observed within the secretory end pieces. A substantial proportion of cells displayed pale, weakly stained, foamy, or vacuolated cytoplasm, indicative of mucinous transformation of the secretory apparatus and accumulation of mucous glycoprotein-rich secretory material. The nuclei were predominantly located in the basal portions of the cells, occasionally displaced toward the periphery, and exhibited intense basophilia or hyperchromasia. Their irregular distribution suggested disruption of acinar cell polarity. Acinar lumina varied considerably in appearance, ranging from barely discernible to markedly dilated and irregularly shaped structures containing pale material, indicating disturbances of the secretory cycle and impaired secretion outflow (Fig. 5a).

Pronounced destructive alterations were observed in the striated ducts at week 16. The lumina of some ducts were mildly dilated or poorly defined, and the epithelial cells were arranged irregularly. While a portion of the epithelial cells remained attached to the basement membrane, individual epithelial cells and cellular fragments were detected within the ductal lumina, indicating epithelial desquamation. The apical surface appeared irregular and focally loosened, whereas the cytoplasm was heterogeneous and contained vacuole-like areas adjacent to the basal surface (Fig. 5a). Basal striations were weakly expressed or indistinct (Fig. 5b).

The intercalated ducts at week 16 exhibited narrow, occasionally slit-like lumina associated with reactive epithelial remodeling, stromal edema, and mechanical compression by altered acinar structures. The epithelial lining appeared less organized, with indistinct intercellular boundaries and intensely basophilic, hyperchromatic nuclei. The cytoplasm was weakly eosinophilic and focally pale, indicating reactive-degenerative alterations. As remodeling of the secretory end pieces progressed, the secretion became more viscous and enriched with carbohydrate-containing components, thereby increasing the functional load on the intercalated ducts and reducing the flow of primary saliva available for subsequent modification within the ductal system (Fig. 5c).

DISCUSSION

The present findings demonstrate that prolonged administration of a combination of food additives, including monosodium glutamate, sodium nitrite, and Ponceau 4R, induces progressive remodeling of the lobular architecture of the rat submandibular salivary gland. This process is characterized by the development of vascular reactions during the early stages of the experiment and persistent degenerative and destructive alterations of both the secretory and ductal epithelium at later stages. These morphological changes appear to reflect impairment of the two principal functional components of salivary gland activity, namely the production of primary saliva by the secretory end pieces and its subsequent modification within the ductal system.

In the control group, the structural organization of the submandibular salivary glands ensured a normal relationship between the parenchyma, ductal system, stroma, and microvasculature. The secretory end pieces were compactly arranged and composed of seromucous glandular cells exhibiting preserved basophilia in the basal cytoplasmic regions and characteristic granularity in the apical portions, indicating adequate protein-synthesizing and secretory activity. The narrow acinar lumina, without evidence of secretory retention, reflected the coordinated balance between saliva production and drainage. The intercalated ducts were lined by simple cuboidal epithelium with well-defined narrow lumina, consistent with their transport function and role in the initial conveyance of secretory products. The striated ducts displayed preserved tall columnar epithelium, eosinophilic cytoplasm, and distinct basal striations. The interstitium was moderately developed and showed no signs of edema, vascular stasis, or inflammatory cell infiltration, while the interlobular ducts maintained normal histological architecture.

After one week of administration of the food additive combination, early reactive and hemodynamic alterations predominated. These changes resulted in the development of initial interstitial edema caused by increased permeability of the microvascular network. Alterations in the glandular cells of the secretory end pieces reflected an early phase of functional stress, during which a proportion of cells retained secretory activity, whereas others exhibited signs of disturbed intracellular water-electrolyte homeostasis. Compression of the intercalated ducts by the edematous stroma, together with initial reactive epithelial changes, likely impaired saliva drainage from the secretory end pieces. Concurrently, the striated ducts demonstrated early disruption of basal striations, structures essential for active ion transport. Expansion of the interstitial tissue, arteriolar spasm, perivascular edema, and reduced

capillary perfusion collectively compromised trophic support to both acinar and ductal epithelium. These alterations may have contributed to tissue hypoxia and the subsequent development of dystrophic changes. Similar observations have been reported in previous studies investigating the effects of exogenous factors on the submandibular salivary glands [16]. Furthermore, monosodium glutamate has been associated with oxidative stress, histopathological alterations of the submandibular gland, and increased apoptotic activity, including enhanced caspase-3 expression in both acinar and ductal cells [10].

After four weeks of exposure, the observed alterations in the secretory end pieces were consistent with the development of hydropic degeneration and disruption of the secretory cycle. Impaired coordination between saliva production and outflow may lead to a reduction in salivary volume, alterations in protein composition, and increased viscosity of saliva. Early reactive changes within the ductal epithelium progressed toward more persistent functional disturbances. The interstitial tissue exhibited features indicative of a transition from isolated edema to stromal remodeling, characterized by increased numbers of fibroblasts, fibrocytes, and immunocompetent cells. The presence of mast cells within the interlobular connective tissue is of particular pathogenetic significance, as their degranulation may enhance vascular permeability, thereby sustaining edema and promoting a nonspecific inflammatory response. These findings are consistent with previous reports demonstrating the pro-inflammatory and oxidative effects of sodium nitrite on the histological structure of the submandibular salivary gland, including elevated malondialdehyde levels and suppression of antioxidant defense mechanisms. Notably, antioxidant administration has been shown to partially mitigate these alterations [12].

At the later stages of the experiment, combined exposure to monosodium glutamate, sodium nitrite, and Ponceau 4R resulted in the coexistence of compensatory and degenerative responses. At week 12, a subset of glandular cells demonstrated activation of the protein-synthesizing apparatus, which may represent a compensatory response to prolonged exposure to food additives. Simultaneously, other cells exhibited cytoplasmic clearing, granularity, and vacuolization, characteristic of hydropic degeneration. These findings indicate heterogeneity in the functional state of the acinar apparatus, reflecting the coexistence of adaptive and decompensatory phases. Such alterations may contribute to changes in the ratio of protein and mucous components of saliva, thereby reducing its protective properties. Changes observed in the striated

ducts suggested decreased efficiency of sodium and chloride reabsorption, as well as impaired secretion of potassium and bicarbonate ions, ultimately affecting the electrolyte composition and buffering capacity of saliva. Occasional epithelial desquamation indicated the onset of destructive remodeling within the ductal system. Vascular alterations were consistent with microcirculatory dysfunction and corresponded to findings reported in previous studies [17]. Arteriolar spasm restricted blood supply to the glandular parenchyma, whereas venular congestion reflected impaired venous drainage. Together with perivascular edema, these changes created conditions conducive to chronic hypoxia and impaired trophic support of the secretory epithelium. Therefore, the combined action of the investigated food additives appears to induce vascular spasm, venous stasis, interstitial edema, oxidative stress, and disturbances of tissue metabolism.

By week 16, the observed histological alterations corresponded to chronic dystrophic remodeling of the submandibular salivary gland. Such changes may result in modification of salivary composition, increased viscosity, reduced lubrication of the oral mucosa, and diminished cleansing and antimicrobial functions of saliva. Narrowing of the intercalated ducts, together with reactive-degenerative epithelial alterations, likely reduced the flow of secretory products into subsequent segments of the ductal system. The striated ducts exhibited pronounced destructive changes that may impede secretory transport and diminish the capacity of the ductal epithelium to perform ion-dependent modification of saliva.

CONCLUSIONS

Prolonged administration of a combination of food additives, including monosodium glutamate, sodium nitrite, and Ponceau 4R, induces stage-dependent morphological alterations in the submandibular salivary glands of rats. During the early stages of exposure, vascular-stromal disturbances and functional stress of the epithelial components predominate, resulting in the development of persistent interstitial edema, hydropic degeneration, and ductal dysfunction. At later stages of the experiment, compensatory activation of a subset of glandular cells coexists with progressive degenerative changes and microcirculatory imbalance. By the end of the study, these alterations manifest as chronic dystrophic remodeling, mucinous transformation of the secretory end pieces, desquamation of the ductal epithelium, and disruption of the structural integrity of the ductal system.

The observed morphological alterations indicate that the combined action of the investigated food additives

adversely affects both the secretory function of the gland and the duct-dependent modification of saliva. These changes may contribute to reduced salivary output, alterations in the protein-mucous and electrolyte composition of saliva, increased salivary viscosity, impaired buffering capacity, and diminished protective properties of the oral fluid.

The principal pathogenetic mechanisms underlying the detected tissue remodeling appear to include microcirculatory disturbances, increased vascular

permeability, interstitial edema, oxidative tissue injury, and prolonged functional stress of both the secretory and ductal epithelium, ultimately leading to the development of dystrophic and destructive changes. Functionally, these alterations result in decreased secretory activity of the gland, impaired transport and modification of saliva, changes in its electrolyte and protein-mucous composition, increased viscosity of the secretion, and attenuation of the protective functions of oral fluid.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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