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Morphological Changes Occurring in the Gastric Mucosa of Adult Outbred White Rats under the Influence of Anti-Inflammatory Drugs

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Annotation: Anti-inflammatory drugs are widely used in medical practice; however, their effect on the gastric mucosa remains a subject of active research. This study aimed to investigate morphological changes in the gastric mucosa of adult outbred white rats under the influence of anti-inflammatory drugs. Experimental animals were administered anti-inflammatory agents, after which histological and morphometric analyses of the gastric mucosa were performed. The results revealed structural alterations in the gastric mucosa, including changes in glandular cells and mucosal integrity, indicating a drug-induced impact on gastric tissue. These findings contribute to a better understanding of the morphological effects of anti-inflammatory drugs on the stomach and may be useful for improving the safety of pharmacological therapy.

Keywords: anti-inflammatory drugs; gastric mucosa; morphological changes; glandular cells; white rats; experimental study.

INTRODUCTION.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used pharmacological agents in both clinical and experimental settings due to their effective analgesic and anti-inflammatory properties. However, a significant adverse effect of NSAIDs is their impact on the gastrointestinal tract, particularly the gastric mucosa. Experimental studies using

adult outbred white rats have extensively documented the morphological alterations induced by these drugs, providing important insights into mechanisms of NSAID-induced gastric injury.

The primary mechanism by which NSAIDs damage gastric mucosa is through inhibition of cyclooxygenase (COX) enzymes, leading to suppression of prostaglandin synthesis. Prostaglandins play a crucial role in maintaining mucosal integrity by promoting mucus and bicarbonate secretion, supporting mucosal blood flow, and regulating epithelial cell proliferation. When prostaglandin production is inhibited, the mucosal defense is impaired, rendering the tissue more susceptible to acid- and enzyme-mediated injury.

Morphological studies in rats treated with indomethacin, a classic NSAID, demonstrate that acute exposure induces early lesions in the gastric mucosa, including **vasocongestion, subepithelial edema, and superficial erosions.** With prolonged exposure, more pronounced changes such as **focal necrosis and leukocytic infiltration of the lamina propria are observed**, indicating progression from mild injury to deeper tissue damage. These changes generally manifest within hours after drug administration, evidencing a rapid onset of injury following NSAID exposure.

At the cellular level, indomethacin also alters specific populations of gastric epithelial cells. Research shows that **mucous and endocrine cell counts decrease** following NSAID administration, while parietal and chief cell morphology may remain relatively unchanged in some models. This reduction in protective mucous cells further compromises mucosal defenses and contributes to ulcer formation.

NSAID-induced mucosal injury involves not only structural disruption of superficial tissue but also **alterations in mucosal physicochemical properties**. Parenteral administration of NSAIDs such as diclofenac and indomethacin results in a significant decrease in the **hydrophobic barrier of the gastric and duodenal mucosa,** mainly due to depletion of mucus phospholipids. A weakened hydrophobic barrier facilitates acid diffusion into the epithelium, exacerbating tissue injury.

Histological studies also reveal an inflammatory component to the NSAID-induced mucosal damage. NSAIDs increase mucosal expression of inflammatory cytokines such as IL-1β and TNF-α in rats, which correlates with **inflammatory infiltration and enhanced vascular changes** in gastric tissue. These cytokines contribute to the recruitment of immune cells and can prolong or intensify tissue damage.

Another important dimension of NSAID impact is the difference in tissue response depending on the drug studied. Some NSAIDs, including selective COX-2 inhibitors, may induce less severe morphological damage compared to non-selective drugs. For instance, experimental comparison of tolmetin (a non-selective NSAID) with celecoxib (a COX-2 selective NSAID) in rats demonstrated that **COX-2 selective drugs caused less epithelial injury and reduced inflammatory cell infiltration**, suggesting a more favorable gastric safety profile. Morphometric analyses of gastric mucosa under polypharmacy with multiple anti-inflammatory agents showed that extensive use of NSAIDs leads to a **significant reduction in the thickness of the mucosal layer** and changes in the structure of the mucosal base. These structural changes are consistent with clinical observations of NSAID-induced atrophy and diminished regenerative capacity of gastric epithelium during long-term drug exposure. In addition to the direct epithelial and cellular changes, repeated or chronic NSAID administration may lead to **adaptive responses** within the gastric mucosa. Some studies have noted a partial adaptation in rats treated repeatedly with certain NSAIDs, resulting in decreased severity of deeper mucosal damage over time. This adaptation appears to depend on drug pharmacokinetics and dosing intervals.

In summary, morphological changes in the gastric mucosa of adult outbred white rats under the influence of anti-inflammatory drugs involve a complex interplay of epithelial injury, inflammatory responses, compromised mucosal defenses, and alterations in tissue architecture.

These changes underscore the importance of understanding NSAID-induced gastric toxicity, as well as exploring protective strategies such as concurrent use of mucosal protectants or acid-blocking agents to mitigate adverse outcomes.

Materials and methods of research. The experiment was carried out in a vivarium on 180 five-month-old white male rats. Rats weigh 200-250 g. organized. At the beginning of the experiment, all mature rats were quarantined for 7 days; after eliminating somatic or infectious diseases, they were transferred to the usual vivarium regime with 2 meals a day. To study the effects of polypharmacy in experimental groups of animals, the following anti-inflammatory drugs were used: aspirin (a group of non-steroidal anti-inflammatory drugs - salicylic acid derivatives); paracetamol (a group of non-steroidal anti-inflammatory drugs - anilide derivatives); ibuprofen (a group of non-steroidal anti-inflammatory drugs - propionic acid derivatives); dexamethasone (synthetic glucocorticosteroid); plaquinyl sulfate (anti-inflammatory, antimalarial).

White rats were divided into 5 groups (n=250): group I - control (n=50); Group II - rats treated with 2 types of anti-inflammatory drugs: paracetamol 15 mg/kg, aspirin 5 mg/kg (n = 50); III - group - white rats treated with 3 types of anti-inflammatory drugs: paracetamol 15 mg/kg, aspirin 5 mg/kg, ibuprofen 6 mg/kg (n = 50); Group IV - white rats treated with 4 types of anti-inflammatory drugs: paracetamol 15 mg/kg, aspirin 5 mg/kg, ibuprofen 6 mg/kg, dexamethasone 0.1 mg/kg. (n = 50); Group V - white rats treated with 5 types of anti-inflammatory drugs: paracetamol 15 mg/kg, aspirin 5 mg/kg, ibuprofen 6 mg/kg, dexamethasone 0.1 mg/kg, hydroxychloroquine sulfate 6.5 mg/kg (n = 40).

Doses of this drug were calculated empirically and administered intragastrically daily as a solution for 10 days using a metal tube. From days 141 to 150 (5 months), rats were intragastrically administered 0.5 ml of distilled water (control group) and various combinations of anti-inflammatory drugs (experimental groups) for 10 days.

Results of our own research. In experimental animals, changes in the histomorphometric parameters of the main parts of the gastric mucosa were observed.

In the control group, the average number of intraepithelial lymphocytes per 100 villous epithelial cells in the cardiac section of the stomach was 10.6±0.6, in the middle section 13.8±0.3 and in the distal section 15.6±0.4. In the dynamics of the second and third groups, a clear increase in the number of intraepithelial lymphocytes was not detected, but in groups 4 and 5, intraepithelial lymphocytes increased by 21% and 34%, to a greater extent in the pyloric region of the stomach.

In the pyloric part of the stomach, the number of individual glandular tissues in the control group was 11±0.3, and in the 5th experimental group, after using 5 types of anti-inflammatory drugs, the number of glandular tissues decreased to 8.7±0.14. on average, which is comparable to the first group, 20% less. In group 4, the number of individual gland tissues decreased by 17% and amounted to 9.1±0.21. In the 3rd group, the gland tissue decreased by 13.6%, and in the 2nd group by 11.8%, respectively.

The average number of individual glandular tissues in the corporal part of the stomach of rats is 14±0.32. In the studied groups, the amount of tissue of individual glands in the body of the stomach decreased by 12.8% in 5 groups, by 7.8% in 4 groups, by 6.8% in 3 groups and by 5% in 2 groups, depending on the number of drugs used .

In the studied groups, the amount of glandular tissue in the pyloric part of the stomach also decreased by 15% in 5 groups, by 11% in 4 groups, by 9.7% in 3 groups and by 1.9% in 2 groups (Fig. 1).

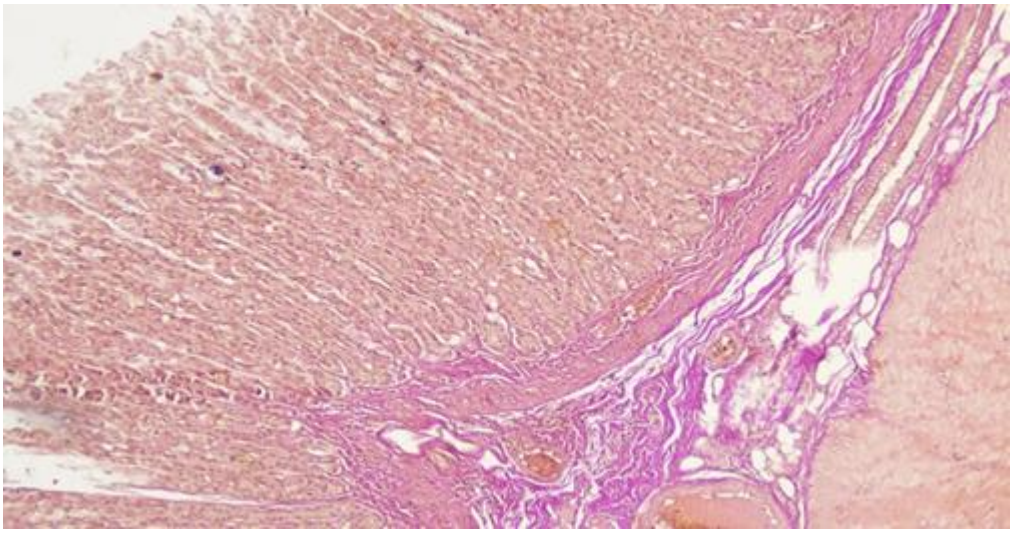

Figure 1. Average amount of glandular tissue in the control and experimental groups depending on the stomach, cm2

The experiment revealed changes in the size of glandular tissues and the distance between them during a macroscopic examination of gastric preparations in white rats. In dynamics, the distance between glandular tissues in the proximal stomach increased by 3.3% in groups 5 and 4, and in groups 3 and 2, the distance between glandular tissues did not significantly decrease (Fig. 2).

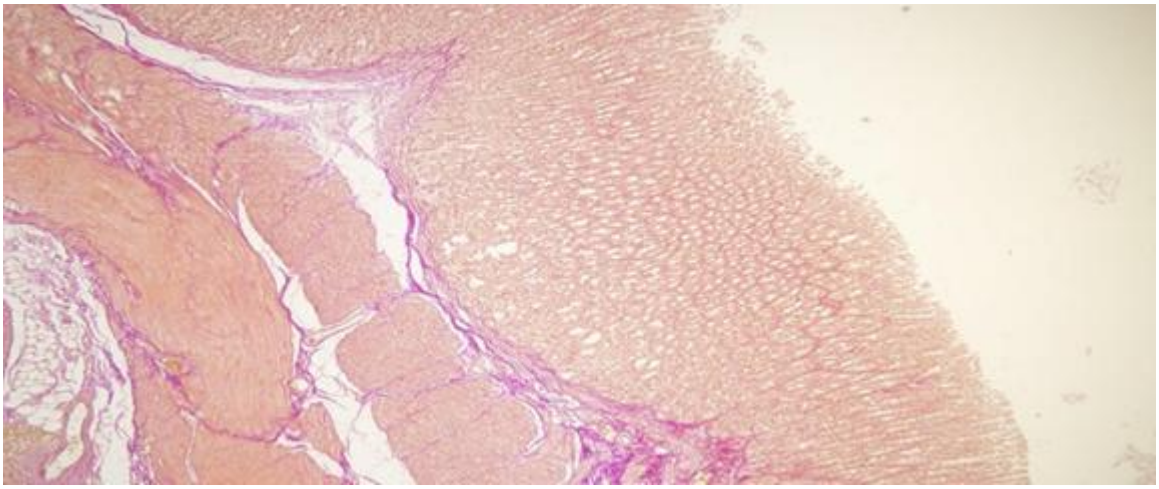

Fig. 2. Sizes of lymphoid nodes in the distal stomach in rats of the control and experimental groups, mm.

When examining the tissues of the gastric glands, it was found that there were no significant changes in the number of tissues of the gastric glands as a result of the action of anti-inflammatory drugs, that is, in the first group they amounted to 18.7 ± 0.33 pieces, in the second group 18.9 ± 0.4 pieces., in the third group 17.3±0.34 pieces, in the fourth group 17.9±0.22 pieces, in the fifth group 18.1±0.24 pieces.

Based on the results of the study, a decrease in the size of the gland tissue was determined. In the control group, the average size of glandular tissue in the proximal stomach was 2.9x3.25 mm, in group 2 - 2.8x3.15 mm, in group 3 - 2.6x3.08 mm, in group 4 it was 2.5x3.0 mm and in group 5 2.2x2.8 mm in group equally. The size of the glandular tissue in the bodily part is larger than the glandular tissue in its proximal part; in the experimental groups, the size of the glandular tissue in the bodily part of the stomach decreased as follows, that is, the average size of the glandular tissue in the first group was 3.36x4.25 mm, in the 2nd group 3.24x4.24 mm, 3rd group 3.2x4.2 mm, 4th group 3.1x4.0 mm and 5th group 3.0x3.9 mm organized.

According to the results of the examination, an increase in the distance between the glandular

tissues was detected. The distance between the glandular tissue of the gastric cardia increased by 17.2% in group 2, 21.4% in group 3, 27.3% in group 4 and 37.7% in group 5 compared with the control group. The distance between the glandular tissue in the body of the stomach increased by 2.1% in the second group, by 5% in the third, by 8.8% in the fourth and by 25.2% in the fifth group, respectively.

In the pyloric region, the distance between glandular tissues in the control group averaged 25.46 ± 0.59 mm, in the second group the distance between glandular tissues increased to 28.6 ± 0.65, in the third group 30.3 ± 0.59, in the fourth group 33.1 ± 0.57 and increased to 41.6 ± 0.93 mm in the fifth and last group.

According to the identified data, significant changes in the nodes in the glandular tissue of the stomach walls were also revealed. Compared to the number of nodes in the control group, it was found that the number of glandular tissue decreased in number and size. And the distance between the fields is much greater, which was clearly manifested in the glandular tissue of the pyloric section of the stomach. (Fig. 5).

Dimensions of glandular tissue in the body of the stomach: 0.76x0.86 mm in the first group, 0.72x0.83 mm in the second group, 0.62x0.74 mm in the third group, 0.6x0.7 mm in the fourth group, and in the fifth group 0.54x0.68 mm.

The results of the study showed that the gastric gland tissue in the first control group had an oval (61.2%), round (32.9%) and irregular (5.9%) shape. The total area of accumulation of glandular tissue was 5.06% of the total area of the stomach. The accumulation of glandular tissue of the stomach in the second group was oval (59.3%) and round (34.6%), less often rectangular and irregular in shape (6.1%), the total area of the collected lymphoid nodes was 4.03% of the total area stomach. In the third group, the collected lymphoid nodes were oval (50.5%) and round (36.0%), rectangular and irregular (13.5%), the total area of the collected lymphoid nodes was 3.69% of the total area of the stomach. In the fourth group, the collected lymphoid nodes were oval (45.2%) and round (37.5%), rectangular and irregular (17.3%), the total area of the collected lymphoid nodes was 3.28% of the total area of the stomach.

Clusters of gastric lymph nodes in the fifth group had an oval (40.3%), round (40.1%), rectangular and irregular shape (19.6%), the total area of the cluster of lymphoid nodes was 2.85% of the total area of the stomach.

CONCLUSION. The effect of polypharmacy of anti-inflammatory drugs in the experimental group of rats on the mucous membrane of the stomach wall, submucosa and glandular tissue was corrected in group 5 compared to control group 1. At the same time, in the cardiac section of the wall of the organ of group 5, the height of the mucous layer of the stomach wall is 8.4%, the mucous base - 10.5%, the gland tissue - 37.0%, the mucous layer - 7.60. % at the bottom of the stomach and 17.8% falls on the mucous membrane, and in the gland tissue by 29.7%, the height of the mucous membrane in the body of the organ by 6.52%, the base of the mucous membrane by 16.7% and in the gland tissue by 34.4%, the height of the mucous membrane in the pyloric part of the stomach by 6.2%, in the mucous membrane it was found that the base decreased by 15.9% and in the gland tissue by 32.2%.

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