GENERAL PATHOLOGY AND PATHOPHYSIOLOGY

Microcirculatory Disturbances in Gastric Mucosa during Ulcer Disease and Effects of Serotonin on Their Dynamics

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Experiments on rat model of stress-induced gastric ulcers revealed marked circulatory disturbances in ulcerated gastric mucosa associated with arteriolar spasm and venous congestion and leading to perivascular edema, diapedesis of erythrocytes, and microhemorrhages. These changes were most pronounced on day 1 after ulcer modeling and progressively decreased during healing (day 14-21). On day 3, arterial hyperemia developed against the background of venous congestion, which was probably related to progressive repair. Serotonin adipinate administered after ulcer modeling accelerated the development of arterial hyperemia (day 1) and reduced venous congestion and extravascular changes. Pretreatment with serotonin was even more effective in attenuating venous congestion and extravascular changes.

Key Words: *experimental gastric ulcer; microcirculation; serotonin adipinate*

Disturbances in the peripheral circulation and microcirculation in gastric and duodenal mucosa play a role in the pathogenesis of ulcer disease [1,7,9]. However, the state of the vascular bed is usually studied by single gastric biopsy, while the dynamics of changes accompanying ulcer disease received little attention. Biomicroscopy of the bulbar conjunctiva generally used to study the dynamics of terminal circulation does not reflect the state of the vascular bed in the ulcerated area [2,8]. Most published data are descriptive and do not provide quantitative information.

The effects of biogenic amines on the endothelium and smooth muscles of the vascular wall play an important role in the pathogenesis of peripheral circulatory and microcirculatory disturbances. The metabolism of serotonin and histamine is impaired in various pathological states, including ulcer disease [11]. It was shown that serotonin adipinate (SA) produces positive effects under conditions of tissue hypoxia, microcirculatory disturbances, and smooth muscle dysfunction observed after surgery and in some diseases characterized by relative serotonin insufficiency, including smooth muscle insufficiency [10,11].

Here we studied vascular changes in the gastric mucosa during experimental ulcer disease and the effects of serotonin on their dynamics.

MATERIALS AND METHODS

Experiments were performed on 84 male albino WAG/Sto rats weighing 180-200 g. Gastric ulcer in group 1 rats was induced by 24-h fixation in the supine position. Group 2 rats with stress-induced ulcers received 4 mg/kg SA 2 times a day for 6 days. Group 3 rats were pretreated with the same dose of SA before stress. Six intact rats served as the control.

The animals were decapitated on days 1, 3, 7, 14, and 21. Samples of ulcerated gastric tissue were fixed in 10% neutral formalin and embedded into paraffin. The preparations were stained with hematoxylin and

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eosin by routine methods. Vascular changes in the ulcer area were examined, diameters of arterioles (D_A) and venules (D_V) were measured, and the arteriole/venule ratio (AVR) was calculated.

RESULTS

In control rats, the mean D_A, D_V, and AVR were 11.73 μ, 25.09 μ, and 0.47, respectively. Intravascular changes (erythrocyte aggregation and microthromboses) were revealed in group 1 rats on day 1 after stress. Perivascular edema, diapedesis of erythrocytes, and focal or diffuse hemorrhages were found in the surrounding tissue. D_A decreased and D_V increased, which indicated spasm of arterioles and dilatation of venules. AVR in the ulcer area decreased. On day 3, intra- and extravascular changes were less pronounced. Dilation of arterioles developed against the background of venous plethora. AVR increased compared to day 1 post-stress and even surpassed the control. On day 7, circulatory disturbances decreased, but arterial and venous hyperemia was retained. On days 14-21, circulatory disturbances were not found; D_A, D_V, and AVR did not differ from the control (Fig. 1, *a*).

SA administered after stress attenuated circulatory disturbances. On day 1, D_A in group 2 rats 2.7- and 1.6-fold surpassed that in untreated rats and controls, respectively. Hence, arterial hyperemia in these rats developed on the 1st day of ulcer disease (instead of 3 days in untreated animals). On days 3, 7, and 14, venules were less dilated. AVR did not differ from the control on days 3 and 7, but was lower than in untreated rats on day 3. Perivascular edema, diapedesis of erythrocytes, and the area of hemorrhages decreased (Fig. 1, *b*).

Pretreatment with SA attenuated stress-induced circulatory disturbances. Arterial hyperemia developed on day 1 after stress, venous congestion was less pronounced, and AVR was maximum. On day 3, all parameters did not differ from the control. Perivascular edema, diapedesis of erythrocytes, and the area of hemorrhages were lower than in group 1 and 2 rats (Fig. 1, *c*).

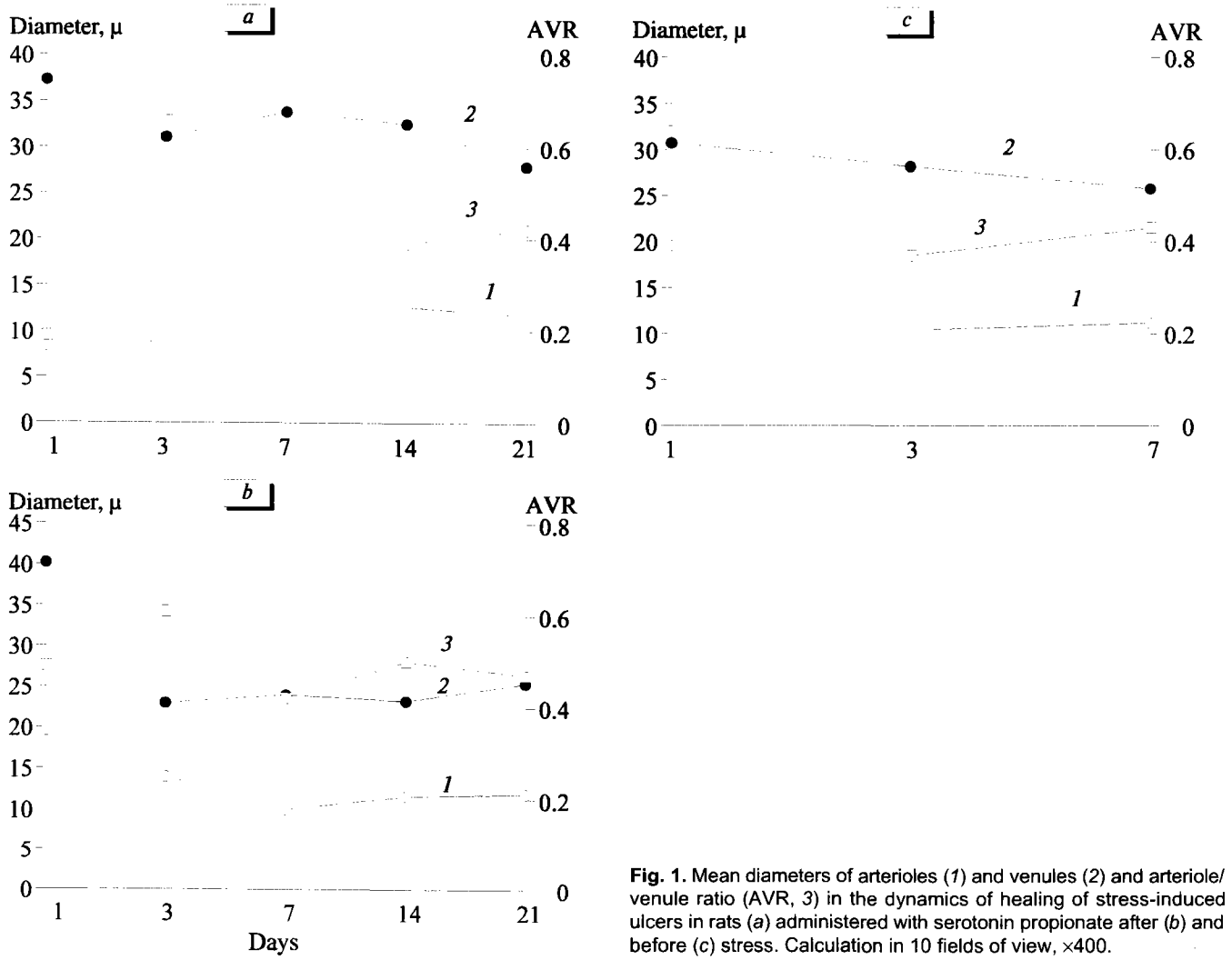

Fig. 1. Mean diameters of arterioles (*1*) and venules (*2*) and arteriole/venule ratio (AVR, *3*) in the dynamics of healing of stress-induced ulcers in rats (*a*) administered with serotonin propionate after (*b*) and before (*c*) stress. Calculation in 10 fields of view, ×400.

Thus, we revealed marked vascular changes in the ulcerated gastric mucosa (arteriolar spasm, venous congestion, and AVR shift), which lead to perivascular edema, diapedesis of erythrocytes, and microhemorrhages. These changes were most pronounced on day 1 after stress and progressively decreased with ulcer healing (day 14-21). On day 3, arterial hyperemia developed against the background of venous congestion, which was probably related to progressive reparative processes. Administration of SA after stress accelerated the development of arterial hyperemia (day 1) and attenuated venous congestion (day 3) and extravascular disturbances. Pretreatment with SA more effectively reduced venous congestion (day 1) and extravascular changes.

These disturbances in the peripheral circulation and microcirculation play an important role in the pathogenesis of ulcer disease. They are observed during inflammation and impaired neurohormonal regulation of the vascular tone and lead to tissue hypoxia and acidosis. These changes promote the release and activation of inflammatory mediators (histamine, serotonin, and kinins), lysosomal enzymes, reactive oxygen species, nitric oxide, and lytic complement complex (C5b-C9) [5,6]. Damages to epitheliocyte membranes enhance reverse diffusion of H^+ into the mucosa. Destruction of glandular cell membranes leads to HCl-induced activation of pepsinogen in the submucosal layer. Higher incidence of ulcers in the antral portion of the stomach and duodenal bulb can be explained by poor development of the capillary bed in these regions, numerous terminal arteries and arteriovenous shunts, high density of nerve endings, and thick muscle layer requiring greater amounts of oxygen for adequate propulsive capacities of the pylorus and duodenum [4].

Mast cells in rats are the main source of serotonin and histamine, which are released simultaneously. Histamine is a vasodilator, while serotonin can also act as a vasoconstrictor (depending on a dose and tissue) [3].

Protective effects of SA administered after stress are probably related to vasodilation [11,12]. In addition, pretreatment with SA before stress can produce tachyphylaxis of vessels to vasoconstrictive effects of endogenous serotonin [3,10,11]. In both cases, rapid restoration of circulation promotes reparative processes contributing to rapid ulcer healing [12]. Exogenous serotonin produces not only direct, but also indirect effects on vessels. This substance is involved in the mediator cascade and interaction between mediators and, therefore, counteracts the effects of vasoconstrictors.

In humans, blood basophils also serve as the source of histamine, while serotonin is formed only in platelets. Therefore, circulatory disturbances during ulcer disease and other inflammatory processes accompanied by ischemia, venous congestion, stasis, and thrombosis cause even more severe serotonin insufficiency in humans [3].

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