

VASOACTIVE HORMONES AND MEDIATORS IN MECHANISMS
OF DEVELOPMENT OF APHTHOUS STOMATITIS

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As long ago as in 1920 I. P. Pavlov [4] drew the attention of clinicians to the appearance of aphthous lesions on the oral mucosa after operations on the stomach and intestine. On the basis of his experimental observations he postulated a reflex association between these phenomena.

In the last decade a series of experimental studies has been undertaken [3, 5], in which direct proof has been obtained of the important role of reflex mechanisms in the transmission of pathological impulses from the injured abdominal organs to the oral mucosa. The humoral components of the trigger mechanisms of these reflexes have not yet received adequate study.

The aim of this investigation was to study vasoactive hormones and mediators in the course of development of aphthous stomatitis in dogs.

EXPERIMENTAL METHOD

Experiments were carried out on 26 dogs (11 control and 15 experimental). The model of stomatitis consisted of ligation of the common bile duct [6]. Concentrations of noradrenalin (NA) and adrenalin (A), serotonin [2], histamine [8], and ascorbic acid (AA) [7] were determined at the commonest sites of aphthae in the oral mucosa (cheek, soft palate, retromolar space - RMS) and in different parts of the intestinal mucosa (duodenum, small and large intestines) of the control and experimental dogs. Weighed samples of tissue were taken 2, 6, and 12 h and also 1, 3, 7, and 10 days after ligation of the common bile duct. Aphthous lesions appeared on the oral mucosa on the 3rd day after the operation.

The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

Marked disturbances were found in relations between the vasoactive hormones and mediators in tissues of the oral and intestinal mucosa. The changes appeared as early as 2 h after the operation and were most marked with respect to the NA and serotonin concentrations. With a general tendency for the NA and serotonin levels in the mucosa to rise in all parts studied, a considerable increase in the concentration of the various hormones and mediators was observed in the oral mucosa 24 h after the operation. For instance, the NA concentration in the mucous membrane of the cheek of the experimental animals was 0.400 ± 0.027 $\mu\text{g/g}$ tissue and in the control 0.127 ± 0.037 $\mu\text{g/g}$ ($P < 0.001$), in RMS the corresponding figures were 0.710 ± 0.096 and 0.204 ± 0.073 $\mu\text{g/g}$ ($P < 0.001$), and in the soft palate 0.650 ± 0.45 and 0.330 ± 0.099 $\mu\text{g/g}$ ($P < 0.005$). The serotonin concentration in the mucous membrane of the cheek was 15.30 ± 0.83 and 7.90 ± 0.98 $\mu\text{g/g}$ ($P < 0.001$), in RMS 35.8 ± 1.0 and 25.8 ± 0.8 $\mu\text{g/g}$ ($P < 0.001$), and in the soft palate 15.7 ± 0.9 and 9.2 ± 0.6 $\mu\text{g/g}$ respectively ($P < 0.001$). The same relationship was observed in the NA and serotonin concentrations 6 and 12 after the beginning of the experiment. The most significant differences, in the direction of an increase, were observed in the serotonin concentration, which was 2-2.5 times higher than in the control in the intestinal mucosa 2 and 6 h after ligation of the bile duct: The serotonin level in the duodenum was 14.3 ± 0.9 $\mu\text{g/g}$ in the control, 24 ± 6.3 $\mu\text{g/g}$ after 2 h, and

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37.5 ± 0.8 µg/g after 6 h, in the small intestine the values were 7.4 ± 0.6, 19.0 ± 0.7, and 13.4 ± 0.9 µg/g, and in the large intestine 4.9 ± 0.4, 13.5 ± 0.8, and 9.6 ± 0.6 µg/g respectively. A sharp rise in the adrenalin level in the first hours of the experiment was observed only in the oral mucosa: In the mucous membrane of the cheek the adrenalin concentration under normal conditions was 0.086 ± 0.047 µg/g, after 2 h it was 0.55 ± 0.12 µg/g (P < 0.005), and after 6 h 0.352 ± 0.083 µg/g (P < 0.005), and in the mucous membrane of the soft palate the corresponding figures were 0.099 ± 0.013, 0.31 ± 0.084 µg/g (P < 0.005), and 0.238 ± 0.042 µg/g respectively (P < 0.005).

Changes in the adrenalin level in the intestinal mucosa were less marked.

The histamine concentration in the oral and intestinal mucosa was reduced in the first hours of the experiment (2, 6, and 12 h), especially so in the mouth: Its level in RMS in the control was 6.7 ± 1.1 µg/g, falling after 2 h to 5.0 ± 0.8 µg/g (P > 0.05), after 6 h to 3.2 ± 0.8 µg/g (P < 0.01), and after 12 h to 3.5 ± 0.6 µg/g (P < 0.01), and in the soft palate the corresponding values were 8.2 ± 1.2 and 6.5 ± 1.1 µg/g (P > 0.1), 5.1 ± 0.9 µg/g (P < 0.02), and 5.2 ± 0.78 µg/g (P < 0.02).

Changes in the relations between the various mediators in the later periods of the experiment (after 3, 7, and 10 days) deserve special attention, when aphthous lesions began to appear on the oral mucosa, to develop, and then to regress.

Starting from the first day after ligation of the common bile duct the NA and serotonin concentrations fell a little although they still remained higher than normal. The histamine level rose under these circumstances, especially at the sites of the aphthous lesions: After 1 day the histamine level in the mucous membrane of the cheek was 9.1 ± 0.4 µg/g (P < 0.05), after 3 days it was 8.3 ± 0.4 µg/g (P < 0.01), after 7 days 7.9 ± 0.7 µg/g (P < 0.02), and after 10 days 5.3 ± 0.8 µg/g (P < 0.005) compared with a normal value of 4.8 ± 0.9 µg/g. Similar relations also were found in other parts of the oral mucosa (RMS, soft palate).

On the 10th day of the experiment, during the period of healing of the aphthae, the normal concentrations, both absolute and relative, of the vasoactive hormones and mediators in the oral and intestinal mucosa were restored.

The study of AA in the oral and intestinal mucosa of dogs with induced stomatitis showed that the changes observed in the ratio between the vasoactive hormones and mediators were aggravated by a fall in the tissue saturation with AA. It is particularly important to note that the decrease in the AA level in the oral mucosa preceded and coincided with the development of aphthae. The most significant decrease in this parameter was observed in the oral mucosa 7 days after the operation: The AA concentration in the mucous membrane of the cheek was 0.150 ± 0.020 µg/g compared with a normal value of 0.396 ± 0.01 µg/g (P < 0.001), in RMS the corresponding values were 0.178 ± 0.067 and 0.373 ± 0.024 µg/g (P < 0.02), and in the soft palate 0.166 ± 0.031 and 0.360 ± 0.015 µg/g (P < 0.001). A sharp fall in the parameters was observed compared with those in areas symmetrically opposite to the aphthae.

Disturbances in relations between the vasoactive hormones and mediators revealed in these experiments, accompanied by a marked fall in the tissue AA saturation, reflect the dynamics of development of the aphthae lesions accurately.

A pathological trophic reflex from the damaged liver to the oral mucosa, leading to the formation of aphthous lesions, is thus realized against the background of a lower tissue concentration of AA and predominantly spastic reactions of the blood vessels, as is shown by the considerable accumulation of NA and serotonin during the first hours of the experiment. The increase in histamine concentration in the later stages of the experiment reflects a hyperemic reaction and the development of inflammatory changes.

LITERATURE CITED

1. O. M. Avakyan, The Sympathicoadrenal System [in Russian], Leningrad (1977).
2. I. V. Komissarova, Lab. Delo, No. 1, 4 (1975).
3. V. S. Kulikova, A. G. Veretinskaya, N. Ya. Kosorukova, et al., Stomatologiya, No. 4, 14 (1983).
4. I. P. Pavlov, Collected Works [in Russian], Vol. 1, Moscow-Leningrad (1951), p. 577.
5. V. G. Chemisov, "Mechanisms of pathogenetic connections of experimental stomatitis with disturbances in activity of the liver," Author's Abstract of Candidate's Dissertation, Moscow (1979).

6. V. G. Chemisov, Tr. Tsent. Nauchn.-Issled. Inst. Stomatol., 5, 87 (1975).
7. J. H. Roe and K. A. Kuether, J. Biol. Chem., 147, 399 (1943).
8. A. Shore and A. Parkhurst, J. Pharmacol. Exp. Ther., 127, 182 (1959).