THE MECHANISM OF RESERPINE ULCERS OF THE STOMACH

I. S. Zavodskaya and B. R. Khodzhaev

Division of Pharmacology (Head – Active Member of the Academy of Medical Sciences, USSR, Professor S. V. Anichkov), Institute of Experimental Medicine, Academy of Medical Sciences, USSR)
(Presented by Active Member of the Academy of Medical Sciences, USSR, S. V. Anichkov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 57, No. 2, pp. 78-80, February, 1964
Original article submitted January 10, 1963

It is known that large doses of reserpine cause the formation of gastric ulcers in animals, which, according to their morphological picture, are suggestive of the destructive changes in the gastric mucosa of patients suffering from ulcerative disease. Its administration, in large doses, to such patients sometimes leads to severe complications; it is possible to note the appearance of bleeding, hemorrhages, and sometimes also ulcerations of the mucosa which lead to perforation of the stomach wall.

The majority of authors connect all these changes with the increase in the acidity and digestive strength of the gastric juice under the influence of reserpine.

In the opinion of certain authors [3], a central component participates in the mechanism for the formation of reserpine ulcers, since ligation of the vagi below the diaphragm, stropinization of the animals, and preliminary injection of gangliolytics in very large doses, prevent the development of these ulcers.

A number of authors explain the formation of these ulcers by intervention of reserpine in the metabolism of serotonin. As is well known, serotonin and its precursor, when applied in large doses, are capable of causing destructive changes in the stomach wall [6, 7].

This investigation was undertaken with the purpose of studying the development of experimental gastric ulcers caused by reserpine, and of elucidating the mechanism of their formation.

EXPERIMENTAL METHOD

The experiments were carried out on rats of the same weight. The animals were kept under a definite feeding regimen. One day prior to the experiment, they were deprived of food and water. Reserpine was injected intraperitoneally, in doses of 10 mg/kg.

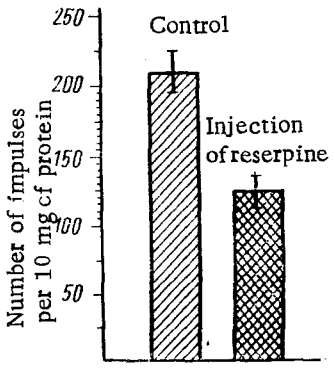
EXPERIMENTAL RESULTS

Gastric ulcers and hemorrhages arose as early as 12-18 h after injection of the alkaloid. Judging from the nature of the course, the rapidity of the emergence, the localization, and the histological picture, the lesions were quite similar to the destructive changes in the gastric wall caused by histamine, and to neurogenic dystrophies [1].

However, in contrast to the neurogenic lesions, the destructive changes in the mucosa caused by reserpine were not prevented either by denervation or the injection of substances that interrupt the reflex arc at its various links.

In our experiments, reserpine caused the development of destructive changes in the mucosa to the same degree in the control animals as in the experiment involving preliminary (by 2 weeks) transection of the vagus nerves below the diaphragm.

Atropinization of the animals also proved to be ineffective. The injection of relatively large doses of atropine (1 mg/kg), paralyzing normal secretion, did not prevent the development of reserpine ulcers. While the number of destructive changes that occurred per single animal in the control group, subsequent to the injection of reserpine, was equal to 4.5, in the experimental group of animals, preliminarily atropinized, the figure, subsequent to injection of the same dose of reserpine, was equal to 5.



Incorporation of S^{35} in the protein of the gastric mucosa.

We then investigated a whole series of compounds that interrupt the reflex arc at its various links (barbiturates, central cholinolytics, gangliolytics). The results of these experiments showed that blocking the central link in the reflex arc by the use of phenobarbital in a dose of 100 mg/kg, and diasil in a dose of 3 mg/kg, did not prevent the development of experimental gastric ulcers caused by reserpine. The number of destructive changes occurring per single animal, with preliminary injection of hexonium, was 4.4, and in the animals of the control group (injected only with reserpine) – 6.8. At the same time, the barbiturates, central cholinolytics, and gangliolytics prevented, to a large degree, the development of reflex dystrophies.

The obtained data testify that the central component in the development of reserpine ulcers is not a leading one.

In order to elucidate the immediate nature of the emerging lesions in the stomach wall, experiments were performed to study the influence of reserpine on protein metabolism in the gastric wall, based on determination of protein resynthesis. Protein resynthesis in the mucosa of the stomach wall was appraised by the rate of incorporation of radioactive methionine (S^{35}).

In previous investigations, we showed that S^{35} is centralized and renewed chiefly in the mucosa of the stomach. The concentration of S^{35} rises most intensely in the course of the first hours, when the processes of accumulation prevail over the processes of excretion of S^{35} from the gastric mucosa. Thus, in appraising the protein resynthesis in the tissue of the gastric mucosa, the most interesting data is obtained in those first few hours. Therefore, S^{35} was injected in an amount equal to 8000 impulses per minute per gram of tissue of the animal, one hour after the injection of the reserpine; after one hour, the animal was sacrificed and the specific radioactivity was determined in the tissue of the stomach wall.

The results of the investigation showed that reserpine significantly slows the resynthesis of proteins in the tissues of the stomach wall, as determined by the rate of incorporation of sulfur-tagged methionine into the proteins.

In control pigs, one hour after the injection of S^{35}, we measured an average of 196 impulses per minute from 10 mg of protein removed from the gastric wall; in the pigs injected with reserpine, the number of impulses per 10 mg of protein was decreased to an average of 117 impulses per minute (mean data of 12 control and 12 experimental animals) (see figure). It is interesting to note that inhibition of protein resynthesis in the mucosa subsequent to injection of reserpine, both in the experiments with reflex dystrophies and dystrophies caused by histamine, preceded the morphological changes. Apparently, reserpine interferes in the histometabolic processes of the gastric mucosal tissue itself, and disrupts protein resynthesis, which appears to be the reason for its dystrophic lesions.

In order to elucidate the nature of reserpine interference in the tissue metabolism of the gastric wall, experiments were set up with the antiaminoxidase substance – ipraside. These experiments showed that a 1% solution of ipraside, injected in a dose of 0.5 ml (into a rat), prevented the development of dystrophic lesions in the stomach wall caused by reserpine. While in the control experiments, with the injection of reserpine, the number of destructive changes occurring per single animal was equal to 7.1, with preliminary injection of ipraside it was equal to 0.2.

The antagonism between reserpine and ipraside in the central nervous system is explained by the opposing influence of the two preparations on the metabolite processes of serotonin: reserpine potentiates the egress of serotonin from the tissues, and ipraside, on the other hand, induces its accumulation [4, 8]. This permitted postulating that the dystrophic changes in the stomach wall, caused by reserpine, are related to interference by the latter in the balance of serotonin within the tissues.

However, the results of our experiments with determining the concentration of serotonin in the actual tissue of the gastric wall [2] showed that neither reserpine nor ipraside lead to significant changes in the serotonin concentration within the gastric wall tissue of rats. These data are in accord with the investigations [5] in which it was established that the use of reserpine does not change the level of serotonin in the mucosa of the stomach wall of animals. Obviously, the formation of reserpine ulcers and the antagonism between reserpine and ipraside in their action on dystrophic processes within the stomach wall are not connected with serotonin balance.

Thus, destructive changes in the stomach wall, leading to dystrophy of the mucosa, are caused by the direct interference of reserpine in the biochemical processes that occur in the wall of the stomach and determine the trophic state.

SUMMARY

A dose of 10 mg/kg of reserpine caused destructive changes in the wall of the stomach, consisting of hemorrhages, erosions, and ulcers. Denervation and blocking (by means of pharmacological substances) of various links in the reflex arc failed to prevent the development of dystrophic alterations in the stomach wall subsequent to reserpine injection; however, the antiaminoxidase agent, ipraside, was effective in preventing the development of reserpine ulcers. The formation of reserpine ulcers, and the antagonism between the reserpine and ipraside action on dystrophic processes within the wall of the stomach was not connected with serotonin balance. Reserpine delayed the rate of radioactive methionine incorporation into the proteins of the stomach wall, and disturbed protein resynthesis, causing the dystrophic lesions.

LITERATURE CITED

1. I. S. Zavodskaya, Gangliolytics and Blockaders of the Neuro-Muscular Synapses [in Russian], Leningrad (1958), p. 96.
2. A. H. Amin, T. B. B. Crawford, and J. H. Gaddum, J. Physiol. (London) (1954) 126, p. 596.
3. I. G. Blackmann, D. S. Campion, and F. N. Fastier, Brit. J. Pharmacol. (1959), 14, p. 112.
4. B. B. Brodie, A. Pletscher, and P. A. Shore, Science (1955), 122, p. 968.
5. S. Emas, Biochem. Pharmacol. (1961), 8, p. 169.
6. B. J. Haverback and D. F. Bogdanski, Proc. Soc. exp. Biol. (N. Y.) (1957), 95, p. 92.
7. C. Hedinger, F. Veraguth, and F. Veraguth, Schweiz. med. Wschr. (1957), 87, p. 1175.
8. S. Udenfriend, H. Weissbach, and D. F. Bogdanski, J. Pharmacol. exp. Ther. (1957), 120, p. 255.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
