EFFECT OF SOME AUTONOMIC NERVOUS SYSTEM POISONS ON MITOTIC ACTIVITY OF REGENERATING EPITHELIUM OF THE GASTRIC MUCOSA

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In experiments on rats in which a standard injury was inflicted on the gastric mucous membrane, repeated injection of hexamethonium (a compound used in the treatment of peptic ulcer) sharply inhibited repair of the injured tissue.

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Drugs blocking synaptic transmission are nowadays widely used in medicine. Some of them effectively prevent the development of reflex tissue degeneration, and they have therefore been recommended for the treatment of peptic ulcer [3]. However, although the use of these compounds for prophylactic purposes can be accepted as valuable and promising, it is not yet absolutely certain what action they could have if given in the presence of an established ulcer. This state of affairs is largely due to the almost total absence of information concerning the action of these drugs on the course of regeneration.

The object of the present investigation was to determine the action of autonomic nervous system poisons on the intensity of epithelial reproduction in the regenerating gastric mucous membrane.

EXPERIMENTAL METHOD

Experiments were performed on 92 noninbred male rats weighing 200-300 g. A standard injury was inflicted on the gastric mucosa by Townsend's method [9]. A piece of mucous membrane measuring 3×6 mm was removed from the fundus of the stomach on the greater curvature at a distance of 4-5 mm from the fold at the junction with the esophagus. The base of the defect was formed by the submucosa. In the experiments of series I the following drugs were injected subcutaneously into the animals at intervals of 12 h for 5 days: atropine sulfate (10 mg/kg body weight), hexamethonium bromide (50 mg/kg), and phentolamine hydrochloride (20 mg/kg), and in the experiments of series II they received aceclidin (10 mg/kg), dimecolin (20 mg/kg), and phenylephrine (10 mg/kg). The injections began on the day after operation. Control rats received 0.9% NaCl solution. An intraperitoneal injection of colchicine (2 mg/kg) was given to all the animals 30 min before the last injection, and 4.5 h later the control and experimental rats were decapitated, all at the same time of day. The stomachs were fixed in Bouin's fluid. The material was embedded in paraffin wax, sections were cut through the zone of the defect to a thickness of 7 μ, and these were stained with hematoxylin and eosin. Reproduction of the epithelial cells on the surface of the regenerating tissues was estimated by a technique involving the use of a drawing apparatus [4]. Under a magnification of 80× of the microscope the outlines of the mucous membrane were drawn up to a width of 500 μ, counting from the edges of the defect. According to Hunt's investigations [8], the overwhelming majority of regeneration mitoses are to be found in this zone. Under high power of the microscope, the number of mitoses was counted in the surface epithelial cells of the regenerating zone within the limits of the area drawn. Knowing the weight of 1 cm^2 of the paper used for drawing, and the weight of the outlined portion, its area was determined and the mitotic index calculated (the number of mitoses per unit area of the regenerating epithelium).

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TABLE 1. Mean Mitotic Index for Regenerating Epithelium of Gastric Mucous Membrane of Control and Experimental Rats

Series of experiments	Drug	Number of animals	Mitotic index (M±m)	P
I	Control	7	61.1±5.1	
	Atropine	11	50.0±4.5	> 0.25
	Hexamethonium	9	36.3±6.9	< 0.02
	Phentolamine	11	48.2±8.6	> 0.25
II	Control	8	88.7±8.5	
	Aceclidin	7	83.1±14.3	> 0.5
	Dimecolin	8	85.5±9.6	> 0.5
	Phenylephrine	7	69.3±9.3	> 0.1

In the experiments of series III the effect of atropine and hexamethonium on epithelization of the floor of the defect was examined. The drugs were administered as described above. The animals were sacrificed 14 days after the operation.

EXPERIMENTAL RESULTS

In all sections obtained from the control and experimental rats many dividing cells were found in the zone studied, where they surrounded the site of injury with a "mitotic barrier." Metaphases blocked by colchicine were the most common finding (C mitoses). They constituted about 95% of all dividing cells. Late mitotic figures (anaphase and telophase) were always absent. These results show that administration of colchicine against the background of the action of the test drugs led to the arrest of cell division at the metaphase stage in 100% of cases. The mean values of the mitotic indices given in Table 1 therefore reflect accurately the intensity of proliferation of the regenerating epithelial cells, for these values were determined by the rate of accumulation of C mitoses and, consequently, they were entirely dependent on the frequency of mitotic divisions taking place in the tissues. The experimental results show that true inhibition of cell reproduction was observed only after injection of the ganglion-blocking drug hexamethonium bromide. In this case the inhibition of proliferation evidently was not due to ganglion blocking, for the drug dimecolin, which has a similar action, produced no such effect.

The decrease in intensity of reproduction of the cells caused by hexamethonium was evidently due to other aspects of its action. This may be associated with the ability of hexamethonium to inhibit thyroid function [2, 7], for thyroid hormone causes proliferation in many tissues [1, 5, 6].

The data concerning the antimitotic action of hexamethonium bromide given above are confirmed by the results of the experiments of series III, in which administration of this drug interfered substantially with regeneration of the damaged gastric mucosa. Complete epithelization of the floor of the defect occurred in only 1 of the 9 animals receiving hexamethonium. In the control group of rats (7 animals) and in the group of (8) animals receiving atrophine, the region of the defect was always completely covered by newly formed glandular epithelium.

The results thus indicate that certain poisons acting on the autonomic nervous systems and used in clinical practice for the treatment of peptic ulcer may actually inhibit the course of regeneration.

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