3-(β-AMINOETHYL)-5-AMINO-1,2,4-TRIAZOL, A HISTAMINE-LIKE STIMULANT OF GASTRIC SECRETION

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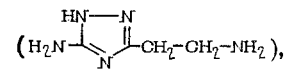
The compound 3-(β-aminoethyl)-5-amino-1,2,4-triazol, or IÉM-759, acts chiefly on H_2-histamine receptors of the dog stomach. Its action on the H_1-histamine receptors of the intestine, blood vessels, and bronchi is many times weaker than that of histamine. Unlike the preparation histalog (betazol), IÉM-759 is also active if given by mouth; it can accordingly be used in clinical gastroenterology in order to investigate gastric secretion.

KEY WORDS: gastric secretion; histamine-like substances; histamine receptors.

Histamine causes the liberation of gastric juice, but the shock and allergic reactions associated with the use of this substance greatly limit its employment for testing gastric secretory function.

Recently histamine analogues, acting predominantly on the H_2-histamine receptors as stimulants or blockers, have been synthesized [2]. The pyrazole analogue of histamine, histalog (betazol), has become extensively used in medical practice in the West [4, 6]. The substance 3-(β-aminoethyl)-1,2,4-triazol differs only a little from histamine in its action on H_1- and H_2-receptors [3, 5].

An analogue of this compound, 3-(β-aminoethyl)-5-amino-1,2,4-triazol hydrochloride, or IÉM-759



has been obtained in the laboratory of chemical synthesis, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, and its properties are described in this paper.

EXPERIMENTAL METHOD

The activity of IÉM-759 with respect to H_1- and H_2-histamine receptors was compared by various methods. Its action on gastric secretion was tested on four dogs with a gastric fistula. The substances were injected intramuscularly or given by mouth at intervals, with doubling of the dose every 40 min. Administration ceased after secretion had reached its maximum. The volume and titratable acidity of the gastric juice were measured. Affinity for the H_1-receptors of the smooth muscle was investigated on an isolated segment of guinea pig ileum by plotting dose vs response curves. Mathematical analysis of the data was carried out by computer in accordance with a predetermined program. The effect of the compound on arterial pressure was tested in acute experiments on cats by intravenous injection. The response of the arterial vessels was investigated on the isolated rabbit ear [1]. The toxicity of the substances (LD_{50}) was determined in guinea pigs by intravenous injection.

In all the experiments the action of IÉM-759 was compared with that of histamine dichloride, 3-(β-aminoethyl)-1,2,4-triazol (IÉM-760) and histalog (Lilley, USA).

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TABLE 1. Histamine-Like Action of IÉM-759 Compared with Other Compounds

Compound	Gastric secretion (H_2-receptors)	Contractions of isolated segments of guinea pig intestine (H_1-receptors)	Hypotensive action	Contraction of peripheral vessels of rabbit ear	Bronchospasm with 50% mortality among guinea pigs
Histamine	1	1	1	1	1
IÉM-760	0.32	0.03	0.94	0.66	–
IÉM-759	0.06	0.006	0.63	0.33	0.051
Histalog	0.016	0.0031	0.18	0.33	0.002

EXPERIMENTAL RESULTS

Compound IÉM-759 has a powerful stimulant action on gastric secretion in dogs. The minimal dose causing the appearance of secretion on intramuscular injection was 0.01 mg/kg and the maximal dose 0.16 mg/kg. The hourly production of hydrochloric acid at the maximum was 15.3 ± 2.1 meq/h. By their affinity (PD_2) for H_2-histamine receptors of the stomach the substances were arranged as follows: histamine 5.90, IÉM-760 5.40, IÉM-759 4.73, and histalog 4.13. After oral administration of IÉM-759 in a dose of 0.5 mg/kg, a secretory response occurred with maximal production of hydrochloric acid of 12 ± 2 meq/h. Histamine in the same dose, and also histalog in a dose of 5 mg/kg, when given by mouth had no effect.

By the strength of its action on H_1-histamine receptors of the isolated guinea pig intestine IÉM-759 differed only slightly from histalog and was many times weaker than histamine and IÉM-760. By their affinity for H_1-receptors the compounds were arranged as follows: histamine 6.73, IÉM-760 5.22, IÉM-759 4.51, and histalog 4.23.

Intravenous injection of the test substances into anesthetized cats in a standard dose of 7.5 μg/kg lowered the arterial pressure by different degrees: histamine by 45 mm, IÉM-760 by 30 mm, IÉM-759 by 20 mm, and histalog by 10 mm. The compounds reduced the volume of perfusion fluid flowing through the vessels of the rabbit's ear by 50% for IÉM-759 and histalog in a concentration of $3 \cdot 10^{-5}$ M, for IÉM-760 in a concentration of $1 \cdot 10^{-5}$ M, and for histamine in a concentration of $1.5 \cdot 10^{-5}$ M.

The dose causing bronchospasm and death of 50% of the guinea pigs (LD_{50}) was 6.2 mg/kg for IÉM-759, 0.37 mg/kg for histamine, and 180 mg/kg for histalog.

IÉM-759 thus acts predominantly on H_2-histamine receptors (Table 1).

Unlike histalog, IÉM-759 can be given by mouth. This property indicates that the compound can be used in clinical gastroenterology for testing gastric secretion.

LITERATURE CITED

1. S. A. Pisemskii, Russk. Vrach, 11, No. 8, 264 (1912).
2. J. W. Black, W. A. Duncan, C. J. Durant, et al., Nature, 236, 365 (1972).
3. A. C. Ivy and K. W. Liepins, Am. J. Physiol., 198, 614 (1960).
4. J. B. Kirsner, Ann. New York Acad. Sci., 140, 882 (1967).
5. T. M. Lin, R. Alphin, F. Henderson, et al., J. Pharmacol. Exp. Ther., 134, 88 (1961).
6. C. E. Rosiere and M. J. Grossman, Science, 113, 651 (1951).