CHARACTER OF THE RECEPTORS OF AUERBACH'S PLEXUS IN THE STOMACH AND SMALL INTESTINE

S. D. Groisman and K. B. Krasil'shchikov

UDC 612.327+612.337]-06:612.819.913-064:615.214.24

Movements of the stomach and small intestine in eight fed dogs with intact vagus nerves were recorded graphically by a balloon method. Subcutaneous injection of a mixture of benzohexonium (0.125-0.5 ml of a 2.5% solution) with atropine (0.125-0.25 ml of a 0.1% solution) or oxyphenonium (0.125-0.25 ml of a 0.1% solution) first inhibits food motor activity and then converts it to periodic. A similar effect after injection of 0.5-1.0 ml of a 0.1% solution of atropine was found in only two dogs and after injection of 1.0 ml of a 0.1% solution of oxyphenonium in only one dog. Since the preservation of periodic contractions after feeding is characteristic of vagotomized dogs, it is concluded that a "pharmacological vagotomy" was obtained in the animals studied. It was postulated that the number of muscarinic receptors on cells of Auerbach's plexus exceeds the number of nicotinic receptors.

KEY WORDS: *pharmacological vagotomy; motor activity of the stomach and small intestine; atropine; benzohexonium; oxyphenonium.*

Since intramuscular injection of 50 mg hexonium and 0.325 mg atropine in man, like vagotomy, inhibited histamine secretion of acid in the stomach, it has been suggested that this mixture of ganglion blocker and peripheral parasympatholytic produces "pharmacological vagotomy" [9]. However, since a similar effect also arises after injection of atropine alone in a larger dose, which produces a complete block of transmission not only between the vagus nerves and the intramural plexuses, but also between the intramural nerve plexuses and the effector cells, further investigations were necessary in order to show whether the functions of the intramural plexuses are preserved after injection of the vagolytic mixture. For this purpose, it was decided to use the phenomenon of preservation of periodic contractions of the gastrointestinal tract in fed vagotomized animals, observed previously by the present writers [2], and others [8]. Injection of 0.025-0.05 mg/kg atropine into such animals abolishes this phenomenon [2], showing that it depends on the normal function of Auerbach's plexus. It was to be expected that true "pharmacological vagotomy" without a complete block of the cholinergic systems would cause food contractions to change into periodic contractions in fed dogs with intact vagus nerves.

EXPERIMENTAL METHOD

Experiments were carried out on eight dogs with a fistula of the stomach and proximal part of the jejunum. Movements of the digestive tract were recorded graphically by a balloon method using an electromanometer equipped with chromium-plated bronze bellows and 6 MKhIS mechanotron tubes. Contractions were recorded on an RPCh-2 two-channel ink-recorder. The balloon in the stomach contained 15 ml air and that in the intestine 1.5 ml air. At the beginning of the experiment the dogs were fed with a mixture of bread (75 g) and meat (75 g) and 30-40 min later they were given subcutaneous injections of the following drugs: atro-

Department of Pharmacology and Experimental Pathology of the Digestive Apparatus, Institute of Physiology, T. G. Shevchenko Kiev University. (Presented by Academician of the Academy of Medical Sciences of the USSR, V. N. Chernigovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 84, No. 9, pp. 316-319, September, 1977. Original article submitted January 29, 1977.

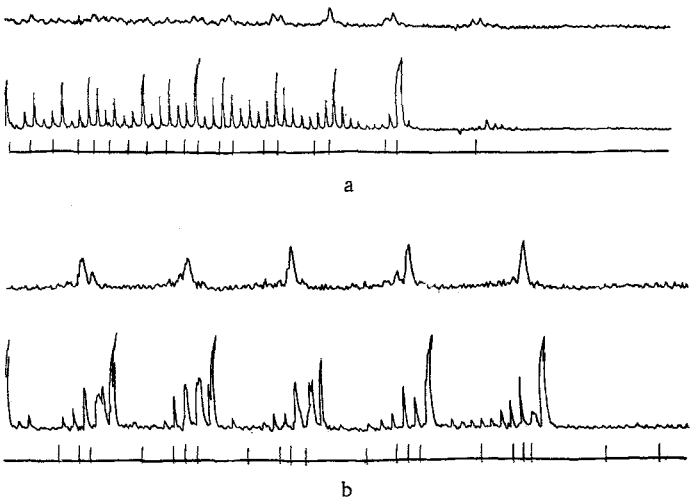

Fig. 1. Periodic contractions of stomach of fed dog No. 4 after injection of 0.5 ml of a 0.1% solution of atropine: a) first period of work 90 min after injection of atropine; b) second period of work after an interval of 80 min, during which the stomach was at rest. From top to bottom: contractions of fundal portion of stomach, contractions of pyloric portion, marker of integrator of motor activity of fundal portion of stomach.

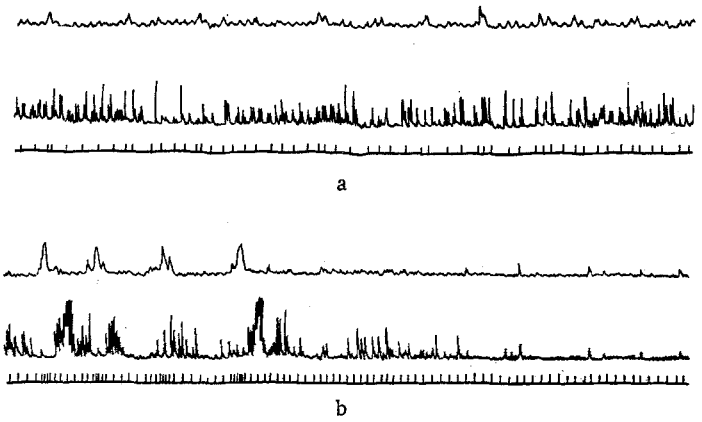

Fig. 2. Development of periodic contractions of stomach and small intestine in a fed dog after "pharmacological vagotomy." a) Preliminary food contraction; b) periodic contractions arising 7 min after subcutaneous injection of 0.25 ml of a 2.5% solution of benzohexonium and 0.25 ml of a 0.1% solution of atropine into dog No. 2. From top to bottom: contractions of fundal portion of stomach, contractions of jejunum, marker of integrator of motor activity of fundal portions of stomach.

pine (0.25, 05, or 1.0 ml of a 0.1% solution), benzohexonium (0.25, 0.5, 1.0, or 3.0 ml of a 2.5% solution), oxyphenonium (0.5 or 1.0 ml of a 0.1% solution), benzohexonium (0.125 or 0.25 ml of a 2.5% solution) with atropine (0.125 or 0.25 ml of a 0.1% solution), and benzohexonium (0.125 or 0.5 ml of a 2.5% solution) with oxyphenonium (0.125 or 0.25 ml of a 0.1% solution). Movements of the stomach and small intestine were recorded for the next 4-6 h. Since dogs of about equal weight (15-17 kg) were chosen for the experiments, it was unnecessary to calculate the dose of the drugs per kilogram body weight in every case.

EXPERIMENTAL RESULTS AND DISCUSSION

Injection of atropine, oxyphenonium, or benzohexonium separately into all the dogs temporarily inhibited contractions of the stomach and small intestine; the duration of this inhibition depended on the dose injected. If the duration of the inhibitory effect of 1 ml of a 0.1% solution of atropine was taken as 1, the duration of the inhibitory effect of 1 ml of a 0.1% solution of oxyphenonium was $^1/_3$, and that of 1 ml of a 2.5% solution of benzohexonium was $^1/_{10}$ to $^1/_{20}$. Isolated injection of any dose of benzohexonium never caused the conversion of food contractions into periodic contractions. Injection of oxyphenonium (1 ml of a 0.1% solution) first inhibited motor activity for 30–40 min and then caused the appearance of periodic contractions in only one of the eight dogs, but in only two of the five experiments. Atropine gave a similar effect in two dogs in doses of 0.5 and 1.0 ml of the 0.1% solution (30% of the experiments). In these cases the first period of work after the phase of inhibition was characterized by increased amplitude of Anichkov's type A contractions (Fig. 1a). This was followed by a period of rest of the ordinary duration (60–80 min), after which contractions of the next period of work with normal amplitude appeared (Fig. 1b).

Food contractions were converted most effectively into periodic contractions by a mixture of atropine or oxyphenonium with benzohexonium. This phenomenon was observed in six of eight dogs. After injection of a mixture of 0.125 ml 0.1% atropine and 0.125 ml of 2.5% benzohexonium periodic contractions were observed in 40% of the experiments. Doubling the dose of the drugs led to an increase in this index to 70%, or in some dogs to 100%. The same effects were found in experiments in which a mixture of benzohexonium and oxyphenonium was given. Characteristically, in the two dogs in which the mixture of ganglion blocker and peripheral parasympatholytic did not cause periodic contraction to appear, this effect developed after injection of atropine alone.

After injection of the mixtures, the onset of periodic contractions also was preceded by a period of inhibition of contractions of the stomach and small intestine. However, with small doses of these drugs in the mixtures it was possible to obtain conversion of food contractions into periodic contractions after a latent period of between 0.5 and 10 min (Fig. 2) Under these circumstances either a period of work with type A contractions of the usual amplitude appeared immediately or prolonged adynamia developed in the digestive tract, the duration of which was close to that of the resting period, and this was followed by a period of work. The ensuing periodic phenomena generally corresponded in their indices to the same phenomena in fasting dogs, both as regards the character of contractions during the period of work and as regards the duration of the periods of work and rest in the stomach and small intestine. Periodic contractions evoked in the fed dogs were recorded for 4–5 h, i.e., a period which corresponded to the duration of action of benzohexonium and atropine [3, 5]. It must be pointed out that with an increase in the number of experiments carried out on each of the dogs, induction of periodic contractions was facilitated.

The fact that "pharmacological vagotomy" is best reproduced by means of a mixture of the ganglion blocker benzohexonium with atropine or oxyphenonium suggests that both nicotinic (n) and muscarinic (m) receptors are present on the neurons of Auerbach's plexus. This suggestion is not contradicted by the observations showing that in some dogs "vagotomy" can be reproduced by the action of atropine or oxyphenomium alone, for both these substances not only have the properties of a peripheral cholinolytic, but they can also block n-cholinergic receptors [4]. There is evidence in the literature of the presence of not only n, but also of m receptors on autonomic ganglia, although these observations were made on the cervical sympathetic ganglia of rats [7, 10]. Since benzohexonium alone, a powerful ganglion blocker and comparatively weak peripheral cholinolytic [3, 5], unlike oxyphenonium and atropine, which have the reverse properties, never produced "vagotomy" this suggests that there are more m- than n-cholinergic receptors on the ganglia of Auerbach's plexus. On the other hand, effector cells of the alimentary tract contain only m receptors [6]. During the action of average doses of m and n blockers or of substances possessing both properties, it is thus possible to block conduction of the vagus nerves to the intramural plexuses while leaving the activity of those plexuses intact. With the development of periodic contractions of the alimentary tract in response to injection of atropine or oxyphenonium alone, the initial phase of general inhibition of gastric and intestinal contractions was caused by the blocking of conduction between Auerbach's plexus and the smooth muscles. Later, a block arises between Auerbach's plexus and the smooth muscles, while the disturbance of conduction between the vagus nerves and ganglia of Auerbach's plexus still continues for a long time. The

gradual increase in amplitude of the type A contractions during consecutive periods of work is evidently attributable to recovery of communication between Auerbach's plexus and the smooth muscles. On the other hand, average doses of m and n cholinoblockers in mixtures of the ganglion blocker with oxyphenonium and atropine enable a conduction block to be obtained from the vagus nerves to the intramural plexuses while retaining normal conduction between the latter and the effector cells.

In the light of these findings it is possible to choose vagolytic mixtures which would protect the digestive tract and, in particular, the stomach against the action of increased tone of the vagus nerves while preserving normal functional activity of Auerbach's plexus [1].

LITERATURE CITED

1. G. I. Burchinskii, V. E. Kushnir, S. D. Groisman, et al., in: Current Problems in Gastroenterology [in Russian], No. 8, Moscow (1975), pp. 255-262.
2. S. D. Groisman, in: The Physiology and Pathology of Digestion (Proceedings of a Scientific Conference of Physiologists, Pathophysiologists, and Clinicians of the Ukraine and Moldavia) [in Russian], Kishinev (1972), pp. 22-23.
3. P. P. Denisenko, Gangliolytics [in Russian], Leningrad (1959).
4. S. G. Kuznetsov and S. N. Golikov, Synthetic Atropine-Like Substances [in Russian], Leningrad (1962).
5. D. A. Kharkevich, Ganglionic Drugs [in Russian], Moscow (1964).
6. E. E. Daniel, in: Handbook of Physiology. Alimentary Canal, Vol. 4 (ed. by C. F. Code), Washington (1968), pp. 2267-2327.
7. J. C. Eccles, The Physiology of Synapses, Springer-Verlag, Berlin–New York (1964).
8. K. F. Marik and C. F. Code, Physiologist, 15, 208 (1972).
9. J. McArthur, H. I. Tankel, and A. W. Kay, Gut, 1, 230 (1960).
10. U. Trendelenburg, J. Pharmacol. Exp. Ther., 154, 426 (1966).

EFFECT OF FUROSEMIDE AND ETHACRYNIC ACID ON SODIUM TRANSPORT AND POTASSIUM SECRETION

E. I. Shakhmatova and Yu. V. Natochin

UDC 615.254.1.015.42:612.467.1.015.31:546.33

Like strophanthin K, ethacrynic acid increases the sodium concentration and reduces the potassium concentration in frog urinary bladder tissue, with the result that potassium secretion is reduced; furosemide does not change these concentrations. The results point to differences in the intracellular action of furosemide and ethacrynic acid.

KEY WORDS: *furosemide; ethacrynic acid; sodium transport, potassium secretion; frog urinary bladder.*

Inhibition of the reabsorption of chlorine ions is now ascribed an important role in the mechanism of action of the most effective modern diuretics (furosemide and ethacrynic acid) [6]. Meanwhile, previous investigations showed that these substances inhibit sodium transport [3, 8]. Both these diuretics increase the potassium excretion by the kidney [2]; this could depend both on their direct effect on one component of the system secreting this

Laboratory of Evolution of the Kidney and Water–Salt Metabolism, I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Academy of Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR V. N. Chernigovskii.)

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 84, No. 9, pp. 319-321, September, 1977. Original article submitted March 10, 1977.