PHYSIOLOGY

Excitatory Effects from Stimulation of Ileac Presynaptic α-Adrenergic Receptors in Nonanesthetized Rabbits

A. N. Aleksandrov and V. I. Ovsyannikov

UDC 612.367.014.46.08

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 117, № 2, pp. 117-119, February, 1994
Original article submitted July 6, 1993

Stimulation of α-adrenergic receptors with Mezaton can either decrease or increase spike activity of the ileum. These effects of Mezaton are both abolished by preinjecting rabbits with dihydroergotoxin. If Mezaton is administered when M-cholinergic receptors are blocked, the ileac spike activity is only weakened, but when this drug is given after blockage of N-cholinergic receptors, its excitatory effect can still be observed.

Key Words: *α-adrenergic receptors; rabbit ileum; Mezaton*

The contractile apparatus of the gastrointestinal tract is known to contain excitatory α-adrenergic receptors (α-AR) in addition to inhibitory α-AR of presynaptic and postsynaptic localization [2,7], and it has recently been shown that such excitatory α-AR may occur not only in sphincter areas of the gastrointestinal tract but also in distal parts of the small intestine [2,3,5]. Their exact location, however, remains debatable. The view prevailing in the literature is that excitatory α-AR occur postsynaptically, on the membranes of smooth-muscle cells [2,3,7], although it has been claimed by some [4,6] that they may be located on cholinergic neurons of the enteral nervous system. Since this topic has been dealt with predominantly in acute or *in vitro* tests, the purpose of the present study was to see whether effects from stimulation of ileac excitatory α-AR can also be manifested in chronic tests.

MATERIALS AND METHODS

The tests were carried out on 9 male rabbits weighing 2.6-3.2 kg. Motor activity of the ileum was assessed by its spike activity, which was recorded with an EEG-16S encephalograph using looped silver electrodes implanted under the ileac serous membrane as described previously [1]; the recording was done at a rate of 7.5 mm/sec, with a time constant of 0.1. The index of spike activity was the frequency of action potential bursts, which was counted every 2 min. From the data obtained graphs were plotted that reflected variations in the recorded parameter throughout each test. The α-AR were stimulated with Mezaton (synonym: phenylephrine), which was infused into a marginal vein of the ear at a rate of 0.25 ml/min during 14 min, for a total dose of 160 mg/kg body weight. Blockers of α-AR (dihydroergotoxin in a dose of 0.2 mg/kg) and of M- and N-cholinergic receptors (atropine and benzohexonium in doses of 0.2 and 5 mg/kg, respectively) were administered intravenously in a bolus injection. Student's *t* test was used for statistical treatment of the results.

RESULTS

Mezaton infused intravenously at 160 μg/kg (n=32) when baseline ileac spike activity was high lowered this activity in 44% of tests (Fig. 1). Conversely,

Laboratory of Digestion Physiology, Department of Visceral System Physiology, Institute of Experimental Medicine, Russian Academy of Medical Sciences, St. Petersburg. (Presented B.I. Tkachenko, Member of the Russian Academy of Medical Sciences)

0007-4888/94/0002-0115$12.50

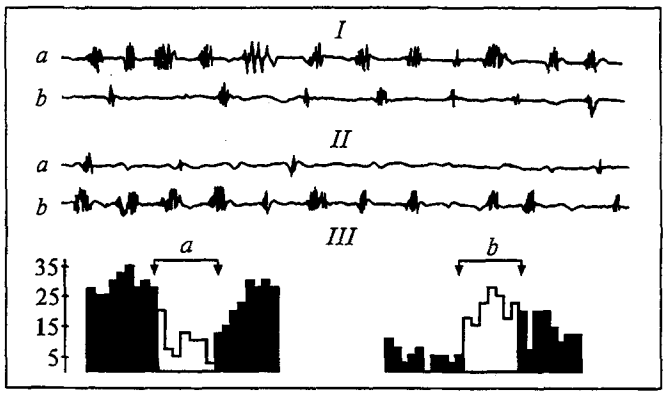

Fig. 1. Effect of Mezaton (160 μg/kg) on ileac spike activity as a function of its baseline level. Fragment *I*: response to Mezaton when baseline spike activity was high; Fragment *II*: response to Mezaton when baseline spike activity was low. *a*) baseline spike activity; *b*) response to Mezaton. Fragment *III*: alterations in the frequency of action potential bursts when Mezaton was infused in the presence of low (*a*) and high (*b*) baseline levels of spike activity. Abscissa: time (one division = 2 min); ordinate: frequency of action potential bursts (same scale for fragments *a* and *b*). Black areas: baseline spike activity; white areas: periods of Mezaton infusion. Horizontal lines with arrows indicate the start and end of infusion.

Mezaton infusion in the presence of low spike activity (in 29% of the tests) led to its rise (Fig. 1), which persisted until the end of infusion (minute 14). In 15% of the tests, Mezaton infusion caused biphasic changes in ileac spike activity; thus, the initial decrease in the frequency of action potential bursts was succeeded by its increase as the infusion was continued (Fig. 2). Finally, in 12% of the tests, the initial rise in spike activity was succeeded by its fall as the infusion was continued (Fig. 3). The mean frequency of action potential bursts was 60±6% ($p<0.05$) of its baseline value during inhibitory responses and amounted to 141±6% ($p<0.001$) of that value during activating responses. Spike activity began to change 20 to 40 sec after the start of Mezaton infusion; apparently, this was the amount of time it took for the drug infused into a marginal vein of the ear, to attain an effective concentration in the intestinal vascular bed.

In 9 tests, the effects of Mezaton on ileac spike activity were studied before and after blockade of α-AR with dihydroergotoxin (0.2 mg/kg).

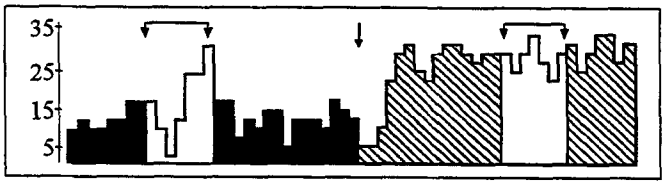

Fig. 2. Effects of Mezaton (160 μg/kg) on ileac spike activity before and after p−AR blockade with dihydroergotoxin (0.2 mg/kg). Abscissa: time (1 division = 2 min); ordinate: frequency of action potential bursts. Black areas: baseline spike activity; hatched areas: spike activity after α−AR blockade; white areas: periods of Mezaton infusion.

These tests showed no changes in spike activity under the influence of Mezaton when the α-AR were blocked (Fig. 2), which indicates that the responses to Mezaton were associated with its stimulation of α-AR.

Since both inhibitory and activating α-AR have been shown to be present in the contractile apparatus of the gastrointestinal tract, it may be thought that the Mezaton-induced weakening of ileac spike activity resulted from stimulation of inhibitory post- and/or presynaptic α-AR, and that the enhancement of this activity under the influence of Mezaton was mediated by excitatory α-AR.

In an attempt to localize the activating α-AR, two series of tests were run in which α-AR were stimulated when N- or M-cholinergic receptors were blocked.

In the control series, atropine (0.2 mg/kg) and benzohexonium (5 mg/kg) were studied for their impact on spontaneous spike activity of the ileum. The results showed that the ileac spike activity was weakened when either M-cholinergic ($n=18$) or N-cholinergic ($n=15$) receptors were blocked. The mean frequencies of action potential bursts during the first 14 min after the injection of atropine (M-receptor blocker) and benzohexonium (N-receptor blocker) were 82±13% and 25±7.7%, respectively, of their preinjection level. The infusion of Mezaton (160 μg/kg) before the blockade of these two types

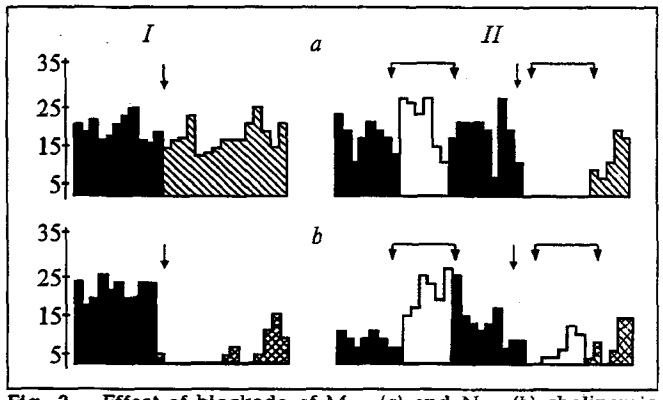

Fig. 3. Effect of blockade of M− (*a*) and N− (*b*) cholinergic receptors on changes in ileac spike activity induced by Mezaton (160 μg/kg).. Fragment *I*: frequency of action potential bursts before and after blockade of M−cholinergic receptors (*a*) with atropine (0.2 mg/kg) and of N−cholinergic receptors (*b*) with benzohexonium (5 mg/kg). Fragment *II*: change in spike activity in response to Mezaton infusion before and after blockade of M−cholinergic receptors with atropine (*a*) and of N−cholinergic receptors with benzohexonium (*b*). Abscissa: time (one division = 2 min); ordinate: frequency of action potential bursts (same scale for fragments *I* and *II*). Black areas: baseline spike activity; hatched areas: spike activity after blockade of M−cholinergic receptors (*a*) and N−cholinergic receptors (*b*); white areas: periods of Mezaton infusion. Vertical arrows indicate the times of atropine and benzohexonium injection. Horizontal lines with arrows indicate the start and end of Mezaton infusion.

of cholinergic receptors resulted in elevated ileac spike activity, whereas its infusion during the first 14 min after the atropine injection (n=11) led only to a decrease in the frequency of action potential bursts to 37.4±11% of its initial value, which is lower than the percentage obtained in the control tests (p<0.05). Mezaton infusion (160 μg/kg) at a time when N-cholinergic receptors were blocked led, in 9 tests out of 12, to a significant (p<0.001) fall in the frequency of action potential bursts (to 1.2±0.8% of the baseline level). In the remaining 3 tests, however, the spike activity increased (Fig. 3); the frequency of action potential bursts was lowered to only 45±10% of its baseline level, i.e., the frequency was higher than in the control tests in which benzohexonium was studied for its effect on spontaneous spike activity.

The observed weakening of ileac spike activity during Mezaton infusion under conditions where the cholinergic circuit of ileac smooth-muscle regulation was not operating indicates that this effect is mediated by inhibitory α-AR located directly on smooth muscle. The finding that Mezaton could still enhance spike activity when N-cholinergic receptors were blocked indicates that this effect could result from stimulation of excitatory α-AR located both on smooth-muscle cells and on cholinergic motor neurons. Furthermore, the failure of Mezaton to stimulate spike activity when M-cholinergic receptors were blocked suggests that excitatory α-AR are located presynaptically.

The results of this study thus permit the conclusion that effects from stimulation of excitatory ileac α-AR can be manifested in chronic tests, and that these receptors may be located presynaptically, on cholinergic motor neurons of the enteral nervous system.

REFERENCES

1. V. N. Ustinov and V. I. Kotel'nikova, *Fiziol. Zh. SSSR*, **56**, № 3, 426-433 (1970).
2. V. Bauer and H. Kuriyama, *Brit. J. Pharmacol.*, **76**, № 4, 603-611 (1982).
3. K. J. Broadley and P. F. Grassby, *Naunyn-Schmiedeberg's Arch. Pharmak.*, **331**, № 2, 316-323 (1985).
4. J. Christensen and E. E. Daniel, *J. Pharmacol. Exp. Ther.*, **159**, № 2, 243-249 (1968).
5. D. A. Fox and P. Bass, *Ibid.*, **239**, № 1, 9-14 (1986).
6. J. Gonella, J. P. Niel, and G. Roman, *J. Physiol. (London)*, **287**, 177-190 (1979).
7. P.-E. Pahlin, *Acta Physiol. Scand.*, Suppl. **426** (1975).