The Exciting Effects of Stimulation of Presynaptic β-Adrenoreceptors of the Ileum in Nonnarcotized Rabbits

A. N. Aleksandrov and V. I. Ovsyannikov

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It is known that catecholamines affect the inhibitory postsynaptic α- and β-adrenoreceptors (AR) and the presynaptic α-AR, thereby relaxing the intestinal smooth muscles [4,7]. There are also known to be α-AR, the stimulation of which results in a rise of the contractile activity of the bowel sphincters [6]. Recent data obtained in acute and *in vitro* experiments attest to the existence of the exciting β-AR situated on the cholinergic interneurons of the enteric nervous system [1,2,5]. The stimulation of these AR results in increased acetylcholine release and in enhanced ileum motility.

The aim of the present investigation was to study the possibility of developing exciting β-AR effects under conditions of a chronic experiment.

MATERIALS AND METHODS

Experiments were carried out on 12 male rabbits weighing 2.6-3.2 kg. The motility of the ileum was assessed by its spike activity (SA), recorded with silver loop electrodes implanted subserously according to a method described elsewhere [3]. Tracing was performed on EEσ-16s encephalograph (with a tracing rate of 7.5 mm/sec and time constant of 0.1). The frequency of the action potential bursts, measured every 2 min, was taken as the index of SA. Based on the obtained data, diagrams reflecting the changes of a recorded parameter during the whole experiment were plotted. Isoprenaline (isopropyl norepinephrine) stimulation of β-AR was performed via an infusion of the drug in the marginal vein of the ear during 14 min at a rate of 0.25 ml/min. The total dose was 100 μg/kg. Blockers of β-AR (propranolol in a dose of 1 mg/kg), and of M- and N-cholinoreceptors (atro-

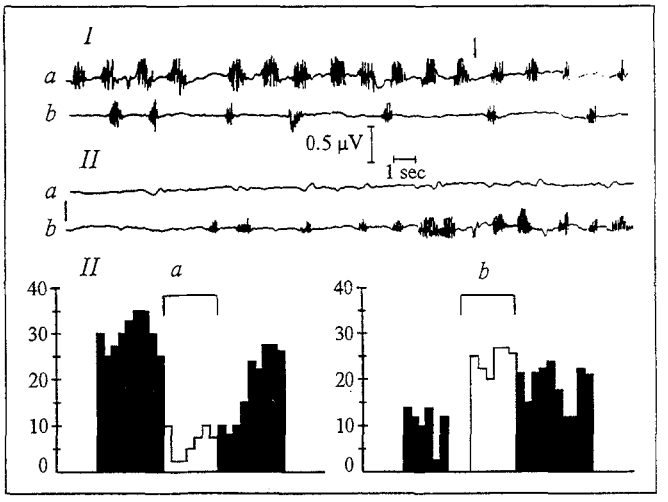

Fig. 1. Effect of isoprenaline (100 μg/kg) on ileum SA as a function of its initial level. *I*) reaction to isoprenaline for a high initial level of SA. *II*) for a low initial level of SA. *a*) background SA; *b*) reaction to isoprenaline. *III*) changes in frequency of action potential bursts for isoprenaline infusion with an initially low (*a*) and initially high (*b*) level of SA. Abscissa: time (one point = 2 min); ordinate: frequency of action potential bursts (same scale for *a* and *b*). Black plots: background SA; white plots: periods of isoprenaline infusion. A horizontal line with arrows marks the beginning and end of infusion.

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

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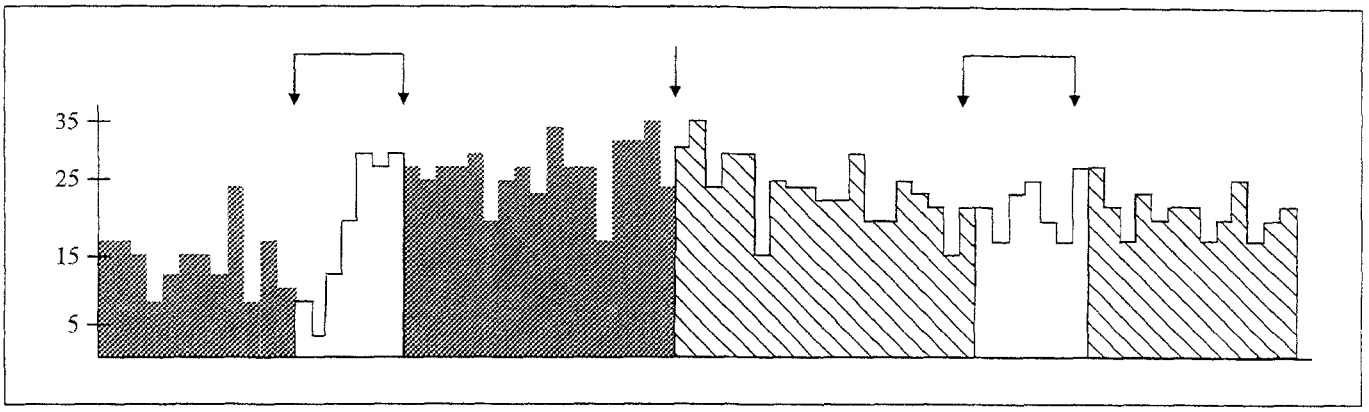

Fig. 2. Changes in ileum SA effected by isoprenaline (100 μg/kg) before and after blockade of β−AR by propranolol (1 mg/kg). Shaded plots: SA after blockade of β−AR. For other symbols see Fig. 1.

pine and benzohexonium in doses of 0.2 and 5 mg/kg, respectively) were injected i.v. in boluses. The results were processed statistically using the Student *t* test.

RESULTS

The experiments showed that the i.v. injection of isoprenaline in a dose of 100 μg/kg (n=28) resulted in a decrease of SA in 18% of experiments under conditions of a high initial level of SA (Fig. 1, *Ib*, *IIIa*). In 50% of the cases isoprenaline caused a two-phase change of ileum SA: a decrease of the frequency of action potential bursts which was superseded by its enhancement against the background of isoprenaline infusion (Figs. 2 and 3, *IIa*). Reactions of the same type appeared when administration of the drug was combined with a pronounced SA. On the other hand, in 22% of cases with a low initial level of SA the stimulation of β-AR resulted in its enhancement (Fig.1, *IIc*, *IIIb*), which lasted as long as the isoprenaline infusion (14 min). In 10% of the cases an initial boost of SA against the background of isoprenaline infusion gave way to its attenuation (Fig. 3, *IIb*). The mean frequency of action potential bursts in a period of inhibitory reactions was 62±6%, and in a period of stimulatory reactions 154±6% of the initial level. Changes of SA appeared 20-40 sec after the beginning of infusion. Clearly, this time was needed for the isoprenaline injected in the marginal vein of the ear to reach the bowel circulatory bed and for its concentration to become effective.

Twelve experiments dealt with the changes of ileum SA induced by isoprenaline before and after the blockade of β-AR by propranolol (1 mg/kg). The changes of SA noted in the control were not found under blockade of β-AR (Fig. 2), testifying to a connection between the changes found and stimulation of the β-AR.

On the basis of what is now known about the existence of inhibitory and excitatory β-AR in the bowel contractile apparatus, we may deduce that the weakening of ileum SA induced by isoprenaline may be related to stimulation of the inhibitory β-AR, while the enhancement of SA by this drug is mediated by the excitatory β-AR.

Two series of experiments where the stimulation of β-AR was under N- and M-cholinoreceptor blockade were performed to pinpoint the inhibitory and excitatory β-AR .

The effects of atropine (0.2 mg/kg) and benzohexonium (5 mg/kg) on the spontaneous ileum SA were studied in the control series. The findings showed that the blockade both of the M- (n=18) and of the N-cholinoreceptors (n=15) resulted in a weakening of ileum SA (Fig. 3, *Ia*, *b*). The frequency of action potential bursts in the first 14 min after administration of the drug was 82±13% and 25±7.7% of the initial level, respectively, for the series with M- and N-cholinoreceptor blockade. Isoprenaline (100 μg/kg) infusion before the cholinoreceptor blockade resulted in two-phase reactions of the ileum, which were defined as an alternating waning and waxing of SA (Fig.3, *IIa*, *b*). An infusion of isoprenaline (100 μg/kg) during 14 min after administration of atropine or benzohexonium under conditions of both M- (n=11) and N-cholinoreceptor (n=15) blockade resulted only in a weakening of ileum SA (Fig. 3, *IIa*, *b*). The frequency of action potential bursts was 27.5±5.7% and 6.9±2.6% of the initial level, respectively, for the blockade of M- and N-cholinoreceptors, which is significantly lower than the values of this index in the control series, in which the effects of atropine and benzohexonium on the spontaneous ileum SA were studied.

It may be assumed that the weakening of ileum SA for isoprenaline administration under conditions of M- and N-cholinoreceptor blockade is

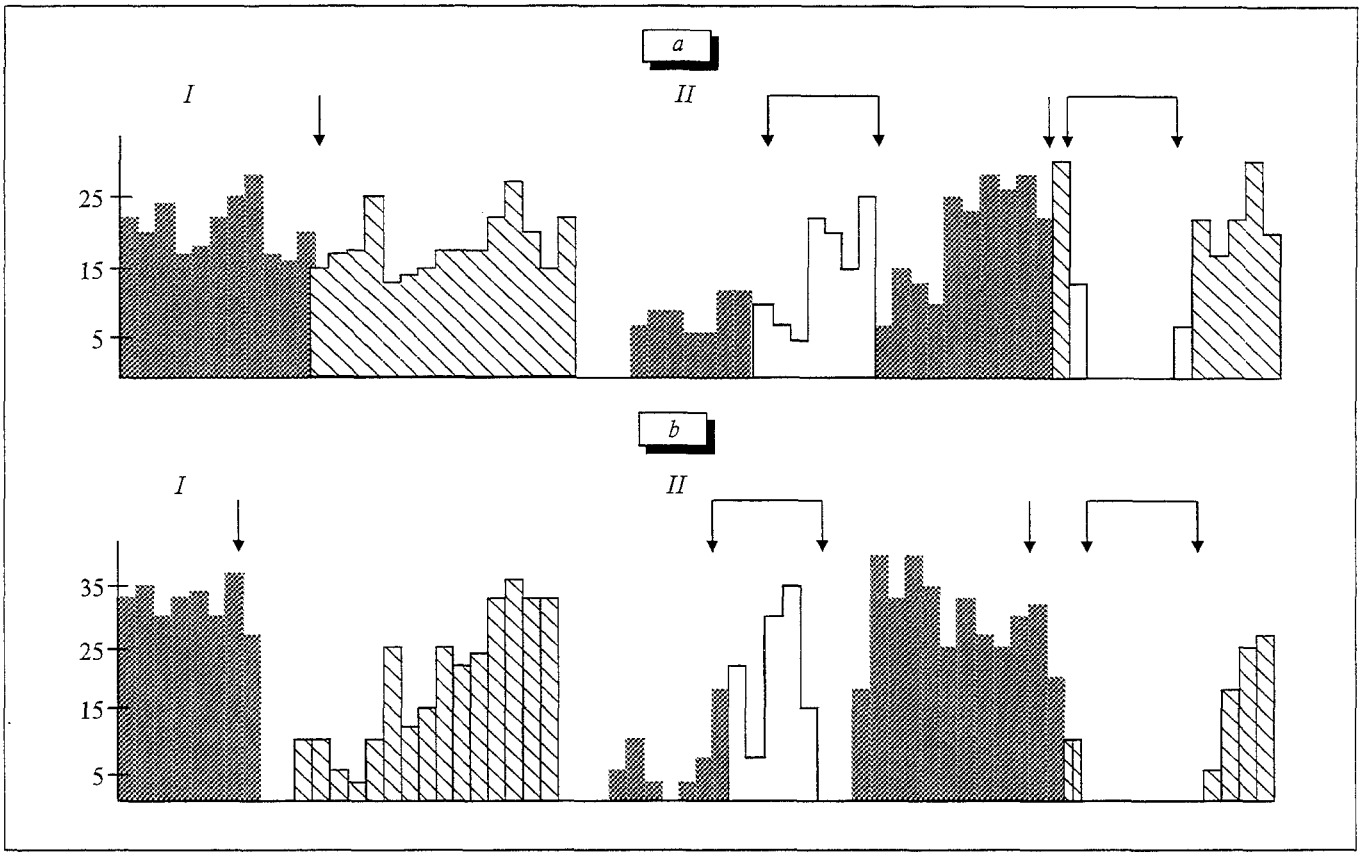

Fig. 3. Effect of M− (*a*) and N−cholinoreceptor (*b*) blockade on changes of ileum SA induced by isoprenaline (100 μg/kg) *I*) frequency of action potential bursts before and after blockade of M−cholinoreceptors (*a*) by atropine (0.2 mg/kg) and N−cholinoreceptors (*b*) by benzohexonium (5 mg/kg). *II*) changes of SA in response to isoprenaline infusion before and after blockade of M−cholinoreceptors by atropine (*a*) and N−cholinoreceptors by benzohexonium (*b*). Scales for fragments *I* and *II* are the same. The shaded plots signify SA after the blockade of M− (*a*) and N−cholinoreceptors (*b*). The single arrow shows the moment of atropine or benzohexonium administration. A horizontal line with arrows marks the beginning and end of isoprenaline infusion. For other symbols see Fig. 1.

mediated by the inhibitory β-AR situated directly on the ileum smooth muscles. The abolition of the exciting effects of isoprenaline for blockade of the M- and N-cholinoreceptors testifies that the increase of ileum SA for stimulation of β-AR is mediated by the excitatory β-AR situated on the cholinergic interneurons of the enteric nervous system. Thus, the findings obtained in the chronic experiment corroborate the previous conclusion, based on the results of acute experiments [1,2], about the existence of excitatory AR of the indicated type in the gastrointestinal tract.

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