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Research Article

The Mechanism of Adrenoceptors Interfering with the Stimulating Effect of Serotonin on Colonic Contractions

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Abstract

Purpose of the Study: Study of the role of adrenoceptors in the implementation of the stimulatory effect of serotonin (as a mediator of serotonergic nerves) on the motility of the large intestine.

Materials and Methods: The experiments were carried out on rats (27) of the Wistar line under the conditions of the surgical stage of anesthesia. Electromyogram and hydrostatic pressure in the colonic cavity were recorded using a Masintosh Performa 6400/180 computer and the Chart 4.2.3 program.

Serotonin was injected into the body of intact animals and against the background of separate and joint blockade of α- and β-adrenergic receptors.

Results of the Study: In experiments on rats, it was found that preliminary simultaneous blockade of α- and β-adrenergic receptors leads to an increase in the stimulatory effect of the colon when serotonin is administered by 353%, blockade of only α-adrenergic receptors - by 331%, blockade of β-adrenergic receptors - by 265%. In intact animals, the stimulant effect of serotonin is +170%. Simultaneous and separate blockade of α- and β-adrenergic receptors without serotonin administration is accompanied by a weakening of colonic contractions by 14-19%.

Inference: Intact α- and β-adrenergic receptors interfere with the stimulatory effect of serotonin on toast motility.

Keywords: Large Intestine, Motility, Serotonin, α- and β- Adrenoceptors

Abbreviations

5HT receptors: Five Hydroxytryptamine (serotonin) Receptors; myogram: Hydrostatic Pressure in the Gastric Cavity; EMG Electromyogram

Introduction

According to experimental studies, serotonin increases intestinal peristalsis and chyme passage through it in guinea pigs [1] and rabbits [2]. Experiments on rats have shown [3] that mosapride citrate, a 5HT4 receptor agonist, is able to enhance gastric motility when injected intraperitoneally.

Other researchers [4] in experiments on anesthetized non-sensitized guinea pigs have found that intravenous administration of serotonin dose-dependently increases pulmonary resistance, i.e. serotonin causes bronchospasm.

Studies on fasting patients with the use of serotonin were performed [5], which recorded the myoelectrical activity of the gastrointestinal tract using the GASTRON-1 electrogastrointestinal inograph (Russia). This device provides reception and registration of signals from skin electrodes, as well as storage, processing and documentation of the information obtained. All patients under local anesthesia were placed an endolymphatic catheter in the inguinal lymph node on the right. With the help of the syringe pump «DSh-08» the infusion of serotonin adipinate was carried out at a dose of 10 mg once. Within 3-7 hours, patients had intestinal gases passing and the appearance of independent stools [5]. These authors believe that endolymphatic infusion of serotonin adipinate is an effective remedy in the fight against postoperative intestinal paresis. No allergic reactions or adverse reactions to the administration of the drug were noted.

However, the possible role of adrenergic receptors in the implementation of the stimulatory effect of serotonin on smooth muscle has not been studied. Knowledge of these mechanisms is important both for scientific research and for practical medicine, since serotonin is used for therapeutic purposes. It is known that intestinal paresis is a frequent and dangerous complication in elderly and elderly patients with acute intestinal obstruction.

Materials and Methods

The experiments were carried out on mature Wistar rats of both sexes, weighing 250-450 g. Studies were carried out on animals on an empty stomach (12 hours after meals) in the state of surgical anesthesia (Nembutal 60 mg/kg, intramuscularly). During the experiments, the average duration of which was 2.5 hours, anesthesia was sufficient and took place without complications. Prior to the experiment, three rats were kept in one type-4 cage. The contractile activity of the stomach was judged by changes in the hydrostatic pressure in its cavity (recorded with a catheter) and EMG of the longitudinal layer of smooth muscles of the stomach (recorded with an electrode). Signals from the catheter and electrode were sent to the BioAmp ML132 amplifier (Adinstruments, Australia), then to the Maclab 8e analog-to-digital converter (Adinstruments, Australia), connected to the Masintosh Performa 6400/180 computer, where they were recorded using the Chart 4.2.3 program.

After checking the data for normality, statistical processing of the data was carried out using the paired Student's test, taking $p < 0.05$ as the level of significance.

The effects of serotonin adipinate (0.1 mg/kg) on gastric motor activity were investigated with intra-arterial administration. The choice of injecting the drug into the artery is justified by the fact that in trial experiments we found an unexpected result - intravenous administration of various doses of serotonin (up to 20 mg/kg) did not affect gastric contractions. The use of large doses of the mediator in the experiment devalues the results obtained. Possible reflex effects of serotonin were prevented by bilateral crossing of the vagus and glossopharyngeal nerves in the neck.

Research Results

The possible role of α-adrenergic receptors in the implementation of the stimulatory effects of serotonin was investigated in experiments on 8 rats with doxazosin blockade of these receptors (1 mg/kg subcutaneously). (Figure 1, Table 1)

The amplitude of slow EMG waves practically did not change over the results of the entire series.

After 10 minutes, rats were injected with intra-arterial serotonin (0.1 mg/kg) under conditions of blockade of α-adrenoceptors. In all animals, a powerful increase in intestinal contractions was observed (see Table 1 and Figure 1). The amplitude of slow EMG waves in this experiment also increased from 0.24 ± 0.09 to 0.71 ± 0.05 mV (+196%, $p < 0.01$).

The results of this series of experiments indicate that intact α-adrenergic receptors interfere with the action of serotonin.

Adrenergic blocker	Background before the introduction of blockers	Result on the introduction of blockers	Background before serotonin administration	Result of serotonin administration
Doxazosin is a α-adrenergic blocker	8,1 ± 0,25	7,0 ± 0,3 (-14%), p < 0,05	7,0 ± 0,2	30,2 ± 2,0 (+331%)*, p < 0,001
Propranolol is a β-adrenergic blocker	8,1 ± 2,0	6,9 ± 0,1 (-15%), p < 0,05	6,9 ± 1,0	25,2 ± 1,0 (+265%), p < 0,01
Proxodolol is a α- and β-adrenergic blocker	7,5 ± 0,2	6,1 ± 0,1 (-19%), p < 0,05	7,5 ± 0,2	34,0 ± 3,6 (+353%), p < 0,001

Table 1: Increase in hydrostatic pressure (mm Hg and %) in the colonic cavity in rats for the introduction of serotonin into the body under various conditions.

*The increase in colonic contraction to rats administered serotonin prior to adrenergic receptor blockade is + 170%.

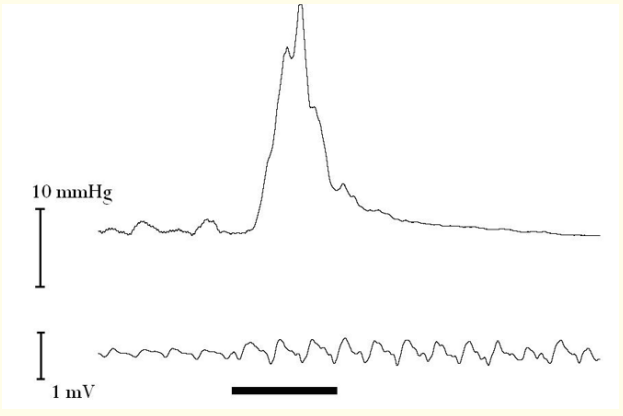

Figure 1: Increased contractions of the colon during the administration of serotonin under the action of α-adrenergic blockers doxazosin: at the top - myogram; at the bottom - EMG; a thick horizontal line at the bottom - the mark of serotonin administration (30s).

In the second series of experiments, the role of β-adrenergic receptors in the development of stimulatory reactions to serotonin was studied.

The experiments were carried out on 7 rats with the β-adrenoceptors turned off by propranolol (1 mg/kg, subcutaneously). At the same time, it was found that propranolol also reduced the contractile tone of the intestine (see Table 1), but increased its peristalsis. The amplitude of slow EMG waves increased from 0.23 ± 0.05 to 0.36 ± 0.06 mV (+56%, $p < 0.02$).

After 10 minutes after the administration of propranolol, 7 intestinal reactions in 7 rats to the administration of serotonin were investigated. In all animals, a sharp increase in intestinal contractions was observed (see Table 1 and Figure 2). The amplitude of slow EMG waves increased slightly according to the results of the entire series of experiments, although in this experiment it was expressed quite well.

At the last stage, experiments were carried out with simultaneous blockade of α and β adrenergic receptors with proxodolol.

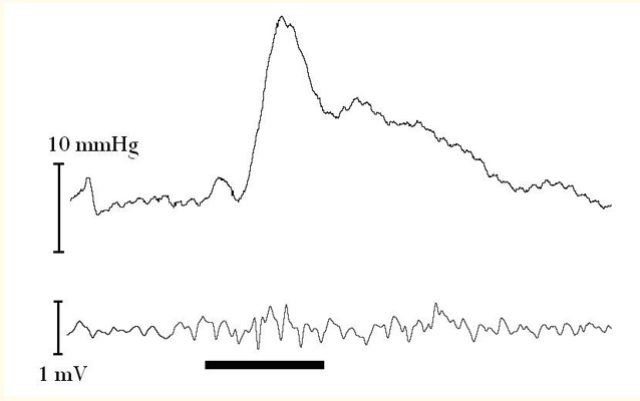

Figure 2: Increased contractions of the colon after the administration of serotonin against the background of the action of the β-blocker propranolol: at the top is the myogram; at the bottom is the EMG; the thick horizontal line at the bottom is the mark of serotonin injection (30s).

It turned out that proxodolol also inhibits the contractile activity of the large intestine (see Table 1), the amplitude of slow EMG waves practically did not change.

The introduction of serotonin into the body 10 minutes after the injection of proxodolol caused a pronounced increase in intestinal contractions (see Table 1 and Figure 3.), the amplitude of slow EMG waves for the entire series also increased significantly - from 0.23 ± 0.04 to 0.72 ± 0.03 mV (+213%, $p < 0.01$).

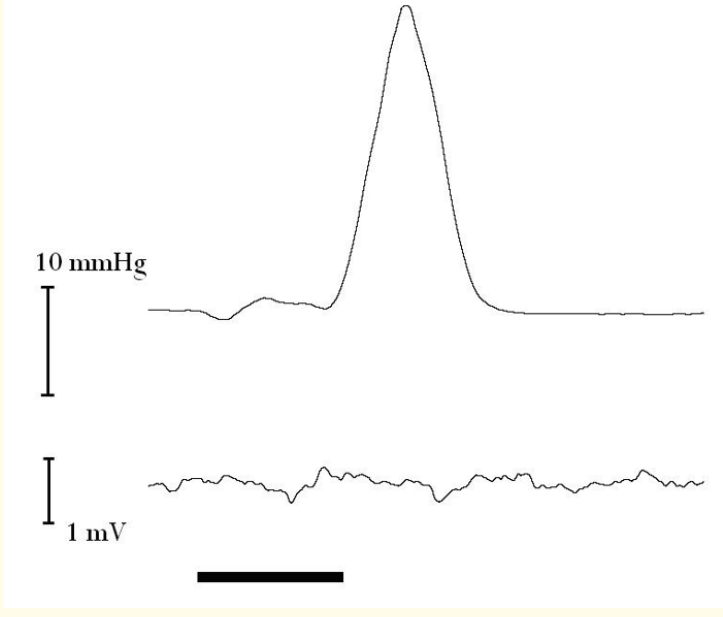

Figure 3: Increased contractions of the colon after the administration of serotonin against the background of the action of α- and β-adrenergic blockers - proxodolol: at the top-myogram; at the bottom-EMG; a thick horizontal line at the bottom - the mark of serotonin injection (30s).

The duration of stimulatory reactions after the administration of serotonin against the background of the action of a α-blocker was 87 + 3 s, β blockers 85 + 3 s, α - and β blockers 75 + 1 s. Reactions began 8-10 s after the administration of serotonin in all cases.

Discussion of the Results

Thus, we have established that the blockade of α and β adrenergic receptors, separately or together, leads to an increase in the stimulating effects of the colon on the introduction of serotonin into the body. This means that intact adrenoceptors interfere with the action of serotonin.

The question arises: what is the mechanism for the implementation of the discovered phenomenon? It is clear that serotonin injected into the body activates not only the 5HT receptors of serotonergic neurons and smooth muscles, but also the presynaptic 5HT receptors of sympathetic nerve fibers. Activation of these presynaptic 5HT receptors leads to the release of the inhibitory mediator norepinephrine, which weakens the stimulating effect of serotonin on smooth muscles. The presence of presynaptic 5HT receptors, including those on sympathetic endings, has been shown by other authors [6-8].

Why is the stimulatory effect of serotonin more powerful under the conditions of blockade of α-adrenoceptors than in the case of blockade of β-adrenoceptors? We believe that there are more α than β adrenergic receptors in the large intestine. Therefore, the release of norepinephrine from the sympathetic endings under the influence of serotonin in intact α-adrenoceptors causes a greater obstacle to the stimulatory effect of serotonin.

In our experiments, we also recorded a weakening of the contractions of the large intestine after the blockade of the sympathetic nervous system, which indicates the presence of a stimulatory tone of the sympathetic nerve for the large intestine. Similar results were observed by other authors [9]. However, it is known that the sympathetic (adrenergic) nervous system inhibits the contractions of the gastrointestinal tract [10-13]. Therefore, the blockade of the sympathetic nervous system should be accompanied not by an inhibitory, but by a stimulatory effect. This contradiction is not yet understood, it needs to be studied in further research.

It should also be noted that in a number of experiments, when serotonin was administered, EMG practically did not change with a very strong contraction of the intestine (see Figure 3). This indicates a more reliable method of myography in comparison with EMG.

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