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REGIONAL DIFFERENCES IN MOTOR RESPONSIVENES TO HYOSCINE BUTYLBROMIDE IN RABBIT ISOLATED SMALL AND LARGE INTESTINE

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Summary. *The effect of hyoscine butylbromide (scopolamine butylbromide), a competitive nonselective antagonist of acetylcholine at muscarinic receptors, on the isolated rabbit duodenum, ileum and colon was investigated. Hyoscine butylbromide (9×10^{-9}M - 9×10^{-6}M) decreased in a concentration-dependent manner the amplitude of the spontaneous pendular movements of the rabbi-isolated duodenum ($r=0.99$; $p<0.001$), ileum ($r=1$; $p<0.001$) and colon ($r=0.98$; $p<0.001$).*

Hyoscine butylbromide decreased the tone of the spontaneous pendular movements. The effect on the tone of the duodenum was not concentration-dependent. It decreased the tone of the duodenum by 20.67% ± 5.99 ($r=0.69$; $p>0.05$); ($F=1.38$; $p>0.05$) and had no significant effect on the ileal tone. However, the tone of distal colon was decreased in a concentration-dependent manner ($r=0.98$; $p<0.001$).The frequency of the pendular movements was the least sensitive to hyoscine butylbromide. The frequency of duodenal and ileal contraction did not change. However, the frequency of pendular movements of the colon was slightly, but concentration-dependently ($r=0.93$; $p<0.01$) decreased.

It is concluded that hyoscine butylbromide reduced the amplitudes of pendular movements most effectively in all parts of the intestines. The inhibitory effect on the tone was most pronounced on the colonic contractions, whereas the duodenal tone was less sensitive, and the ileal tone was unaffected. Only the frequency of the pendular movements of the rabbit colon was sensitive to the muscarinic blockade. It is suggested that hyoscine butylbromide predominantly acted on M1 muscarinic receptors.

Key words: *Pendular movements, muscarinic receptors, hyoscine butylbromide, rabbit, duodenum, ileum, colon*

Introduction

Hyoscine butylbromide (scopolamine butylbromide) is a competitive non-selective antagonist of muscarinic receptors (1). It is poorly absorbed from the gastrointestinal tract and thus has a local effect. It does not cross the blood-brain barrier and has no central effects. Its action is most evident on the smooth muscle of the gastrointestinal tract. Hyoscine butylbromide, like atropine, has an inhibitory effect on the smooth muscles and reduces the intestinal motility. Its peripheral anticholinergic effects are somewhat less obvious and of shorter duration than those of atropine (2-4).

On the basis of selective M_1, M_2, M_3 and non-selective muscarinic antagonists, it is possible to assess the muscarinic receptor subtypes involved in the regulation of gastrointestinal motility. Since the data on the involvement of the subtypes of muscarinic receptors in the regulation of pendular movements are scarce,, the aim of the present experiments was to study the muscarinic receptor subtypes in different parts of the small and large intestine of the rabbit. Therefore we investigated the effects of hyoscine butylbromide, a competitive non-selective muscarinic antagonists, on the isolated duodenum, ileum and colon.

Materials and methods

Subjects

Rabbits of either sex (2-2.5 kg; n=10) were used in this study. All experimental procedures with animals where in compliance with The European Council Directive of November 24, 1986 (86/609/EEC).

Isolated preparations from rabbit duodenum, ileum and distal colon

Rabbits were killed by cervical dislocation. The duodenum, terminal ileum and distal colon were removed and immediately rinsed in Tyrode solution (NaCl 136.9, KCl 2.68, $CaCl_2$ 1.8, $MgCl_2$ 1.05, $NaHCO_3$ 11.9, $NaH2PO_4$ 0.42 and glucose 5.55 mM l^{-1}).

Testing procedures

Segments of the rabbits duodenum, ileum and distal colon (3 cm long) were longitudinally mounted in an isolated organ bath (20 ml) with Tyrode solution gassed with 95% O_2 and 5% CO_2 at 37^0C. One end of the segment was attached to the bath bottom and the other to an isotonic frontal writing lever. The segments were suspended under 1 g tensions**.** The longitudinal muscle

movements were magnified about 10 times**.** Recordings were made on a smoked drum with a frontal isotonic lever. The tissues were allowed to equilibrate for about 45 min, during which interval the spontaneous activity and the tone developed**.** Hyoscine butylbromide was added into the organ bath at noncumulative increasing concentrations. After recording the effect of the one dose, the bath was drained, washed three times and refilled with fresh Tyrode solution. Between each two doses there was a 30-min pause. Drug-induced changes of the duodenal, ileal and colonic muscular tone were described as force variations (g) in comparison with the initial tension. The amplitude and the frequency of the spontaneous contractions were measured. The modifications of the intestinal spike amplitude and frequency were expressed as a percentage of the correspondent basal value.

Drug

The hyoscine butylbromide was used.

Statistics

Concentration response curves were constructed using linear regression according to the method of least squares. A coefficient of correlation (r) of linear regression was used to determine the existence of concentration-response relationship. The results were considered statistically significant when $p<0.05$. The mean inhibitory concentrations ID50, that is, the concentration required to reduce by 50% the components of the pendular movements (tone, amplitudes and frequency) of the isolated segments were determined and its 95% confidence limits were calculated.

Results

Spontaneous activity

Pendular movements of rabbit isolated duodenum were characterized by regular contractions which amplitude was 48.73 ± 2.54 mm and frequency 11.24 ± 2.31 c/min.

Basal ileal phasic contractions were the stable amplitude (51.32 ± 2.91 mm) and frequency 10.42 ± 1.32 c/min.

In basal conditions, colon preparations exhibited the spontaneous tone and phasic activity with irregular frequency about 5.35 ± 0.55 c/min and amplitude about 44.83 ± 3.75 mm.

The effect of hyoscine butylbromide on amplitudes, tone and frequency on the various parts of the intestine

Amplitudes

Hyoscine butylbromide (9×10^{-9} M-9×10^{-6} M) decreased, in a concentration-dependent manner, the amplitudes of the spontaneous pendular movements of the rabbit-isolated duodenum ($r=0.99$; $p<0.001$), ileum ($r=1$; $p<0.001$) and colon ($r=0.98$; $p<0.001$) (Fig. 1). The maximal reduction of the duodenal amplitude was 60.0 ± 7.69%, ileal 86.33 ± 4.97% and colonic 82.0 ± 9.52.

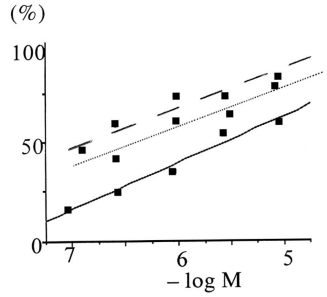

Fig. 1. Concentration-response relation of hyoscine butylbromide on the amplitude of pendular movements of rabbit duodenum (——), ileum (…....) and colon (– – –). The inhibitory responses are expressed as percentage of the control contractions. Each point is the mean ± SE from 7-10 experiments. Ordinate: % reduction; abscissa: concentration of hyoscine butylbromide in mol log. scale.

Tone

Hyoscine butylbromide decreased the tone of the spontaneous pendular movements. The tone of duodenum reduced by 20.67±5.99 % ($r=0.69$; $p>0.05$); ($F=1.38$; $p>0.05$) and the effect was not concentration-dependent. Hyoscine butylbromide at same concentrations did not affect the ileal tone. However, the tone of the distal colon was decreased in a concentration dependent manner ($r=0.98$; $p<0.001$) (Fig. 2): the maximal relaxation was 85.97 ± 17.91%.

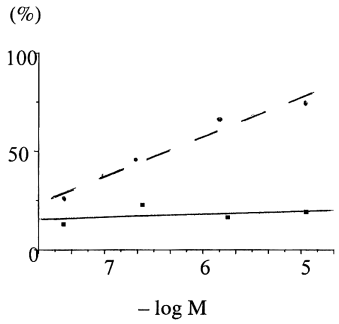

Fig. 2. Concentration-response relation of hyoscine butylbromide on the tone of rabbit duodenum (——) and colon (– – –). Each point is the mean ± SE from 7-10 experiments. Ordinate: % reduction; abscissa: concentration of hyoscine butylbromide in mol log. scale.

Frequency

The frequency of the pendular movements was the least sensitive to hyoscine butylbromide. The frequency of duodenal and ileal contraction did not change. However, the frequency of pendular movements of the colon was concentration-dependently decreased ($r=0.93$; $p<0.01$) (Fig. 3). The maximal reduction of the colonic frequency was 60.42±7.87%.

The IC50 values for hyoscine butylbromide are given in Table 1.

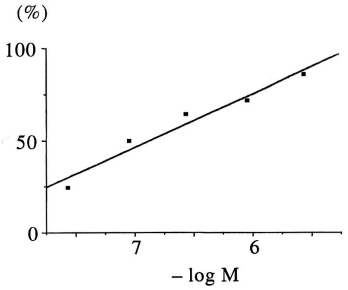

Fig. 3. Concentration-response relation of hyoscine butylbromide on the frequency of pendular movements of rabbit colon The inhibitory responses are expressed as percentage of the control frequency. Each point is the mean ± SE from 8 experiments. Ordinate: % reduction; abscissa: concentration of hyoscine butylbromide in mol log. scale.

Table 1. IC50 values for hyoscine butylbromide

	Amplitude	Tone	Frequency
Duodenum	2.7×10^{-6} M		
Ileum	2.8×10^{-7} M		
Colon	1.1×10^{-7} M	1.1×10^{-7}M	4×10^{-7}M

Discussion

The role of various muscarinic receptor subtypes (M_1, M_2, M_3) in the motor control and migrating myoelectric complex of different parts of the intestine has already been pointed out (5,6). The inhibitory effect of the nonselective muscarinic antagonist atropine on pendullar movements of rabbit duodenum, ileum and colon has previously been shown (7). In these experiments, the effects of hyoscine butylbromide on the basal tone, amplitudes and frequency of the pendular movements of the rabbit isolated duodenum, ileum and colon were investigated. Our present experiments demonstrate that the nonselective muscarinic antagonist hyoscine butylbromide reduced the spontaneous motor activity of rabbit duodenum, ileum and distal colon in a concentration dependent manner. In addition, these results confirm the previous findings that the cholinergic system subserves the spontaneous movements of the intestine (5). The sensitivity of different parts of the bowel, as well as the sensitivity of the amplitudes, tones and frequency to the blockers of muscarinic receptors was variable. However, marked differences were obtained in the inhibitory potencies of the antimuscarinic drugs.

Hyoscine butylbromide reduced most effectively the amplitudes of pendular movements in all parts of the the intestine. On the basis of the IC50 values, there was a significant difference between the potencies of hyoscine butylbromide and atropine. Hyoscine reduced the amplitude of duodenal contractions 15 times less than atropine. On the other hand, hyoscine butylbromide was more effective in reducing the basal tone (14 times) as well as the frequency (8 times) of the pendular movements of the isolated colon strips than atropine (7).

The inhibitory effect of hyoscine butylbromide was most pronounced on the colonic contractions, whereas the duodenal tone was less sensitive, and ileal tone was unaffected. It is possible that the effect on the tone of the small and large bowel depends on the preexisting parasympathetic tone, or that other mediators of the enteric nervous system like 5HT, SP, VIP and other peptides regulate the tone of the longitudinal muscle of different parts of the bowel. Also, there are some differences between hyoscine butylbromide and atropine on the tone of the small and large bowel. Atropine strongly reduces the tone of the duodenum (7), while the effect of hyoscine butylbromide is weaker and not concentration-dependent.

On the other hand, the effect of hyoscine butylbromide is similar to the effect of the selective antagonist of M_1 muscarinic receptors, pirenzepine (9,10). Furthermore, on the basis of our previous study (10), the effects of hyoscine butylbromide and pirenzepine on pendular movements of the distal colon were almost identical. However, pirenzepine at nanomolar concentrations had a stimulatory effect. Our present results also showed that hyoscine butylbromide was as potent M_1 muscarinic receptors antagonists as pirenzepine (10,11). These results show that the cholinergic system predominantly regulates the tone of the large bowel trough muscarinic receptors, while noncholinergic pathways probably regulate the tone of the duodenum and ileum.

The differences in the effects of muscarinic antagonists on different parts of the bowel showed that the pendular movements were subserved by cholinergic mechanisms. Muscarinic receptors were unevenly distributed to various parts of the digestive tract.

Hyoscine butylbromide inhibited the pendular movements and it has been used successfully for its antispasmodic action on the gastrointestinal tract, especially, the distal parts of the bowel. The effects of hyoscine butylbromide on the duodenum and colon were much more like pirenzepine than atropine. It is suggested that hyoscine butylbromide predominantly acted on M1 muscarinic receptors.

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REGIONALNE RAZLIKE U MOTORNOJ AKTIVNOSTI IZOLOVANIH SEGMENATA TANKOG I DEBELOG CREVA KUNIĆA IZAZVANE HIOSCIN BUTILBROMIDOM

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Kratak sadržaj: *Ispitivan je uticaj buskopana (hioscin butilbromida), neselektivnog blokatora muskarinskih receptora, na motornu aktivnost izolovanih segmenata duodenuma, ileuma i kolona kunića.*

Hioscin butilbromid (scopolamin butilbromid, buskopan) (9×10^{-9}M - 9×10^{-6}M) koncentracijski zavisno smanjuje amplitudu pendularnih pokreta izolovanog duodenuma (r=0,99; p<0,001), ileuma (r=1; p<0,001) i kolona (r=0,98; p<0,001) kunića. Hioscin butilbromid ne deluje podjednako na tonus tankog i debelog creva. On smanjuje tonus duodenuma prosečno za 20,67% ± 5,99 (r=0,.69; p>0,05); (F=1,38; p>0,05). Efekat nije koncentracijski zavisan. U istim koncentracijama nema uticaja na tonus ileuma, a koncentracijski zavisno snižava tonus distalnog kolona kunića (r=0,98; p<0,001). Najslabiji efekat ispoljava na frekvenciju pendularnih pokreta. Ne menja frekvenciju duodenuma i ileuma, a neznatno, ali koncentracijski zavisno, smanjuje frekvenciju pendularnih pokreta kolona (r=0,93; p<0,01).

Možemo zaključiti da hioscin butilbromid najsnažnije redukuje amplitudu pendularnih pokreta celog digestivnog kanala. Slabije deluje na tonus gornjih partija creva, a snažno smanjuje tonus kolona. Najslabiji uticaj ispoljava na frekvenciju pendularnih pokreta. Na osnovu naših nalaza možemo pretpostaviti da efekte ostvaruje pretežno preko muskarinskih M_1 receptora.

Ključne reči: *Pendularni pokreti, muscarinski receptori, hioscin butilbromid, kunić, duodenum, ileum, kolon*