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Effect of pentacaine and its derivatives on the contractile responses of smooth muscle in the guinea-pig stomach

Mai Phuong Mai [a], Viktor Bauer [a,*], Viera Nosáľová [a], Štefan Mátyás [a], Želmíra Bezáková [b]

[a] *Institute of Experimental Pharmacology, Slovak Academy of Sciences, Dúbravská cesta 9, 842 16 Bratislava, Slovak Republic*
[b] *Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic*

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Abstract

The effect of a carbanilic local anesthetic pentacaine [(±)-*trans*-2- (1-pyrrolidinyl)cyclohexyl ester of 3(*n*)-pentyloxyphenyl-carbanilic acid] and some of its derivatives {K-1905 [(±)-*trans*-2-diethylaminocyclopentyl ester of 3(*n*)-pentyloxyphenyl-carbanilic acid], K-2002 [(±)-*trans*-2-(1-pyrrolidinyl)cyclohexyl ester of 4(*n*)-pentyloxyphenyl-carbanilic acid], K-2006 [(±)-*trans*-2-(1-pyrrolidinyl)cyclopentyl ester of 4(*n*)-pentyloxyphenyl-carbanilic acid], and carbanilates P2 [(±)-*trans*-2-(1-pyrrolidinyl)cyclohexyl ester of 4-methoxy-carbonylphenyl-carbanilic acid], P3 [(±)-*trans*-2-(1-pyrrolidinyl)cyclohexyl ester of 3-methoxy-phenyl-carbanilic acid], and PeJ, the quaternized derivative of pentacaine}, as well as that of oxethazaine was studied on longitudinal antral and circular fundic smooth muscle strips of the guinea-pig stomach. All the carbanilates studied relaxed the smooth muscle, attenuated the spontaneous smooth muscle contractions and shifted the acetylcholine, histamine, and $BaCl_2$ cumulative concentration effect curves to the right, reducing their maximum. There was no direct relationship between their relaxing potency and the ability to reduce the action of different stimulants. For the effectiveness of the carbanilates studied, substitution in the lipophilic part of the molecule was more important than in the hydrophilic part and the *meta* position was more advantageous than the *para* position. Pentyloxy-derivatives (pentacaine, K-1905, K-2002 and K-2006) were more active than the methylcarbonyloxy (P2)- and methoxy (P3)-derivatives. Opening of the heterocyclic ring (K-1905) in the hydrophilic part of the molecule did not affect significantly the potency of the derivative studied, while quaternization (PeJ) significantly reduced the potency. It is suggested that the carbanilates studied may affect the smooth muscle responses via changes in the membrane fluidity and Ca^{2+} availability, and that these effects might be partly responsible also for their antiulcer activity.

Keywords: Local anesthetic; Pentacaine; Pentacaine derivative; Smooth muscle, gastric; (Guinea-pig)

1. Introduction

Gastric ulcer is frequently accompanied by smooth muscle spasms of the stomach wall. It was suggested that the inhibition of hypercontraction participates in the mechanism of gastroprotective effect of prostaglandins (Takeuchi and Nobuhara, 1985). Several agents including local anesthetics are currently employed to treat gastric ulcer by reducing acid secretion, contractility and pain (Marks, 1980; Bianchi Porro and Parente, 1988; Misiewicz, 1988). Most of the local anesthetics and spasmolytics have been suggested to act via a receptor independent mechanism (Barbezat et al., 1978).

The local anesthetics oxethazaine (Barbezat et al., 1978), pentacaine and some of its derivatives were found to be effective substances with antiulcer effects and marked gastroprotective properties (Nosáľová et al., 1987, 1995; Beneš et al., 1992; Štolc and Mai, 1993). To investigate the antispasmodic activity of these carbanilates, their effect on the guinea-pig stomach longitudinal and circular muscle's spontaneous activity, resting tension and contractions evoked by spasmogens was studied in vitro. The findings were compared with the activity of oxethazaine, a clinically used local anesthetic with antiulcer properties (Seifter et al., 1962; Pontes et al., 1975). Moreover, the present study attempted to examine the effects of pentacaine and its derivatives, as well as of oxethazaine, against stimulation of different membrane receptors and the smooth muscle cell itself.

2. Materials and methods

Guinea-pigs of both sexes, weighing 300–500 g (Dobrá Voda) were killed by cervical dislocation and exsan-

* Corresponding author. Tel.: (42-7) 373-586; Fax: (42-7) 375-928.

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guinated. The stomachs were excised and placed into the oxygenated (95% O_2 and 5% CO_2) Krebs solution of the following composition (mmol/l): Na^+ 136.6, K^+ 5.9, Ca^{2+} 2.5, Mg^{2+} 1.2, Cl^- 133.3, HCO_3^- 15.4, $H_2PO_4^-$ 1.2 and glucose 11.5 (pH 7.4). Circular and longitudinal muscle strips (about 1–1.5 mm in width and 15–20 mm in length) were dissected from stomach. Each strip was placed in a 20 ml organ bath. One end of the preparation was fixed at the bottom of the chamber and the other one was tied to a transducer (M100, Mikrotechna, Prague, Czech Republic). Isometric contractions were recorded with a strain gauge under constant load of 15 mN at 37°C. Tissues were equilibrated 60 min under a load of 30 mN. In the preliminary experiments, muscle strips from various stomach regions were tested. Based on the results obtained, longitudinal muscle strips from the antrum and circular muscle strips from the fundus were chosen because they best characterised the main function of those regions, i.e. propulsion of the gastric content by the antrum and adjustment to the gastric content by the fundus. Since there was no pronounced difference between the action of pentacaine in these two preparations tested, the effect of its derivatives was studied only on longitudinal antral muscle strips. The muscle strip was not separated from another layer, it was oriented according to the longitudinal axis.

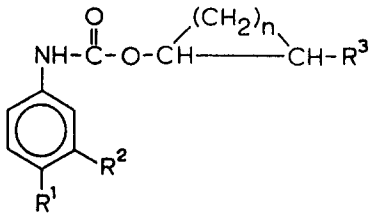
Increasing concentrations of stimulants (acetylcholine, histamine or barium chloride) were applied cumulatively to the bathing fluid. The interval between the successive concentrations of an agonist was adjusted to allow the effect of each concentration to fully develop. In each preparation the interaction between the effect of only one agonist and one antagonist was studied. Agonist applications were performed at 30–45 min intervals to avoid tachyphylaxis. This was also why the highest $BaCl_2$ concentration applied under control conditions was 4.5 mmol/l. After having recorded two reproducible cumulative concentration effect curves of the agonist, the antagonistic effect of the local anesthetic studied was assessed using one or two of its concentrations on each preparation. The application of the agonist was repeated after a 15 min pretreatment period and in the presence of the tested substance in the bathing fluid.

The following drugs were used: acetylcholine chloride (Germed), barium chloride (Riedel-De Haenag), histamine chloride (Merck), L-NAME, phentolamine, indomethacin (Sigma), oxethazaine (Wyeth), pentacaine hydrochloride [(±)-*trans*-2-(1-pyrrolidinyl)cyclohexyl ester of 3(*n*)-pentyloxyphenyl-carbanilic acid] (trapencaine INN), K-1905 [(±)-*trans*-2-diethylaminocyclopentyl ester of 3(*n*)-pentyloxyphenyl-carbanilic acid], K-2002 [(±)-*trans*-2-(1-pyrrolidinyl)cyclohexyl ester of 4(*n*)-pentyloxyphenyl-carbanilic acid], K-2006 [(±)-*trans*-2-(1-pyrrolidinyl)cyclopentyl ester of 4(*n*)-pentyloxyphenyl-carbanilic acid], and carbanilates P2 [(±)-*trans*-2-(1-pyrrolidinyl)cyclohexyl ester of 4-methoxycarbonylphenyl-carbanilic acid], P3 [(±)-*trans*-2-(1-pyrrolidinyl)cyclohexyl ester of 3-methoxy-phenyl-carbanilic acid], and PeJ, the quaternized derivative of pentacaine. The carbanilates were synthetized and prepared in the form of dihydrochloride by Beneš et al. (1992). Fresh stock solutions were prepared in distilled water, except the high concentrations of carbanilates, which were dissolved directly in Krebs solution.

The dissociation constants were determined potentiometrically and pK_a was determined as pH of the solution of the compound titrated to 50% with an alkali hydroxide. Because of poor solubility in water of the bases liberated in the course of the titration, the medium used was a mixture of water and methanol 2:3 (v/v). In calculating pK_a correction was made for the volume of methanol (Blešová et al., 1985). Table 1 summarises the chemical structure, dissociation constant and apparent distribution coefficient of the carbanilates studied.

Each experimental group consisted of at least seven

Table 1
Physico-chemical properties and chemical structure of pentacaine (Pe) and its derivatives



Drug	R^1	R^2	R^3	*n*	pK_a	log *P*
Pe	H	OC_5H_{11}	N-pyrrolidine	4	9.26	3.410
K-1905	H	OC_5H_{11}	N-diethylamine	3	8.69	3.780
K-2002	OC_5H_{11}	H	N-pyrrolidine	4	9.25	3.037
K-2006	OC_5H_{11}	H	N-pyrrolidine	3	8.61	3.190
P2	COO-CH_3	H	N-pyrrolidine	4	n.d.	1.480
P3	H	OCH_3	N-pyrrolidine	4	9.19	1.130

P, apparent distribution coefficient in octanol/phosphate buffer at pH 7.4; pK_a, dissociation constant determined potentiometrically; n.d., not determined.

preparations from different animals. The maximal tension (E_{max}), the EC_{50} and the agonist potency pD_2 ($-\log EC_{50}$) were determined from the row data of each cumulative concentration effect curve. Results are expressed as means ± S.E.M. Differences between means were assessed using Student's paired *t*-test (Delaunois, 1973).

3. Results

3.1. Physico-chemical properties of the studied carbanilates

For an anesthetic to penetrate from the spot of application to the site of action, its solubility in lipids and water (the partition coefficient) and dissociation constant are important. As described earlier (Štolc and Mai, 1993) and shown in Table 1, pentacaine, K-1905, K-2002 and K-2006 possess much higher liposolubility than substances P2 and P3. In contrast to the liposolubility there was no pronounced difference in the degree of dissociation of carbanilates studied under our experimental conditions. Calculating according to De Jong (1977), 94.1–98.6% of the studied carbanilates was in ionized form at the pH (7.4) of our bathing fluid.

3.2. Effect of studied local anesthetics on resting tension and spontanous activity of the guinea-pig stomach

Muscle preparations of both circular fundic and longitudinal antral strips of the stomach showed spontaneous activity. Rhythmic phasic contractions were present in the antral strips and oscilations of the resting tension with occasionally superimposed phasic contractions were observed in the fundic strips. In Ca^{2+}-free solution the spontaneous activity was depressed by more than 50% ($n = 6$). Pentacaine at low concentrations (10^{-6} and 10^{-5} mol/l, $n = 10$) did not affect the resting tension and the spontanous activity of gastric antral ($n = 5$) and fundic ($n = 5$) smooth muscle strips. However, at concentrations of 10^{-4} and 10^{-3} mol/l it significantly reduced the resting tension of both antral (by 1.3 ± 0.4 mN, $n = 8$ and 6.3 ± 1.1 mN, $n = 10$, respectively) and fundic muscle strips (by 3.1 ± 0.7 mN, $n = 9$ and 4.8 ± 1.9 mN, $n = 5$,

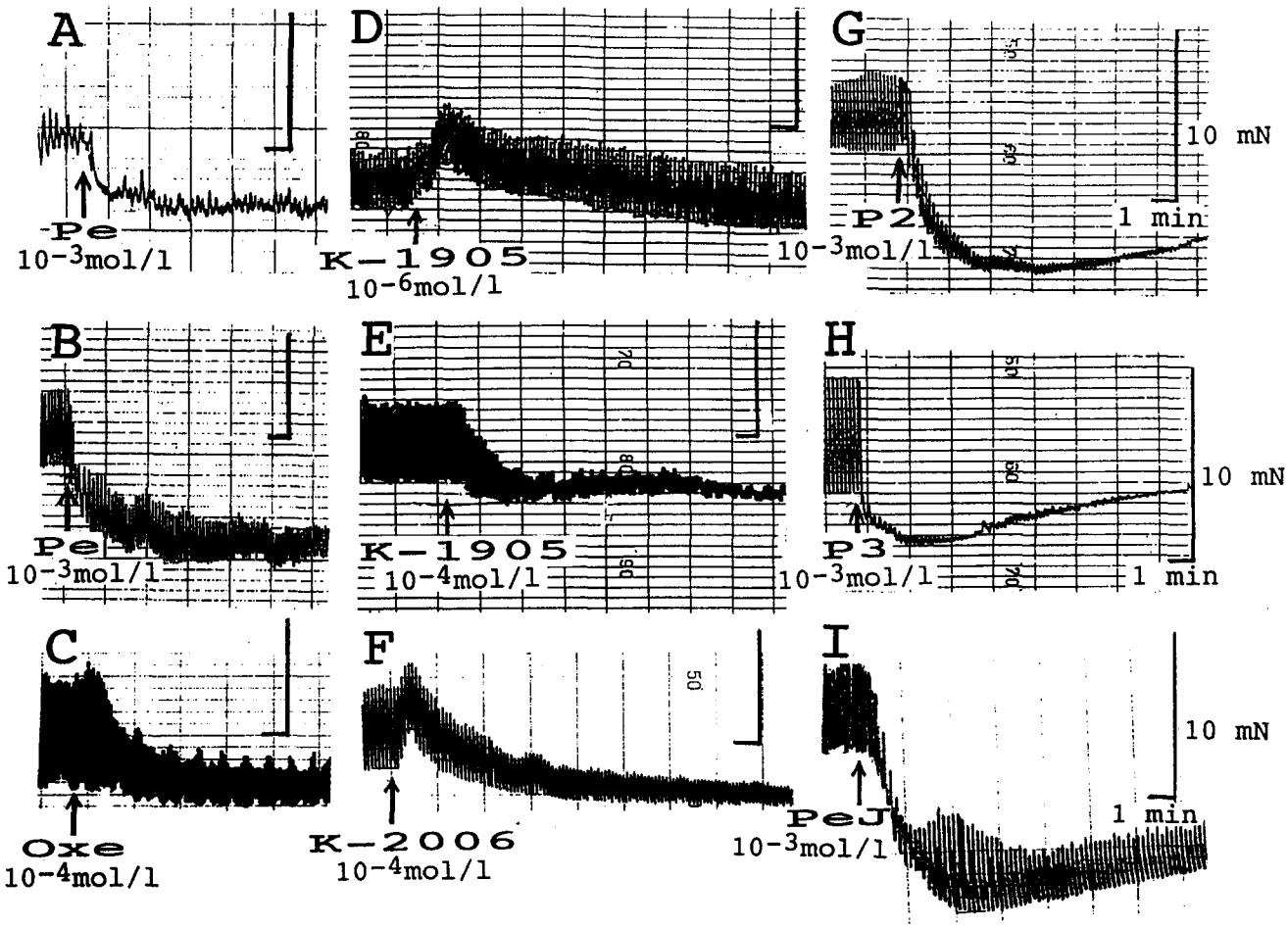


Fig. 1. Original records of the action of oxethazaine (Oxe), pentacaine (Pe) and other related carbanilates (K-1905, K-2006, P2, P3, and PeJ) on spontaneous activity and resting tension of the guinea-pig stomach fundic circular strips (A) and antral longitudinal strips (B–I).

respectively). Under Ca^{2+}-free conditions pentacaine (10^{-4} mol/l) slightly but not significantly elevated the resting tension. Spontaneous activity of antral longitudinal preparations was less sensitive to pentacaine than that of the fundic circular smooth muscle (Fig. 1A,B). In indomethacin (10^{-6} mol/l for 45 min) or in indomethacin and Ca^{2+}-free medium pretreated tissues tension gradually decreased. Pentacaine did not affect significantly the resting tension under these conditions but its effect on spontaneous activity remained unchanged.

The action of oxethazaine (10^{-6}–10^{-3}mol/l) on the basal tension and spontaneous activity of the stomach antral longitudinal smooth muscle was dose dependent and in its intensity similar to that of pentacaine (Fig. 1C). Carbanilates K-1905 (Fig. 1D), K-2002 and K-2006 (not shown) in low concentration (10^{-6} mol/l) transiently contracted the antral longitudinal muscle strips by 1.6 ± 0.3 mN, 0.7 ± 0.1 mN and 1.2 ± 0.2 mN, $n = 10$, respectively but did not affect the spontaneous activity. An increase in the concentration of K-2006 to 10^{-4} mol/l (Fig. 1F) resulted in biphasic effect on the resting tension (2.8 ± 0.9 mN initial contraction followed by relaxation of 5.3 ± 1.2 mN amplitude, $n = 6$) and in the reduction of the amplitude of spontaneous activity by 60–70%. In contrast, the compounds K-1905 (Fig. 1E) and K-2002 (not shown) in the concentration of 10^{-4} mol/l produced only a monophasic reduction in the resting tension (by 4.2 ± 0.9 mN and 2.8 ± 0.6 mN, $n = 10$, respectively) and reduced the amplitude of spontaneous activity by 80 to 90%. Carbanilates P2, P3 and PeJ in concentration of 10^{-4} mol/l only marginally reduced the resting tension of antral longitudinal smooth muscle (by 0.4 ± 0.4 mN, 1.5 ± 0.8 mN, and 2.3 ± 0.7 mN, $n = 11$, respectively). In the concentration of 10^{-3} mol/l, however, these compounds decreased the resting tension (by 4.6 ± 1.2 mN, 4.1 ± 1.0 mN, and 9.5 ± 1.7 mN, $n = 11$, respectively) and except PeJ also reduced the spontanous activity of the antral strips (Fig. 1G,H,I).

3.3. Effects of studied local anesthetics on the cumulative concentration effect curve elicited by acetylcholine

Cumulative administration of acetylcholine in a bath concentration range of 10^{-8}–10^{-3} mol/l elicited concentration dependent contraction of both circular fundic strips and longitudinal antral strips of the stomach. The fundic

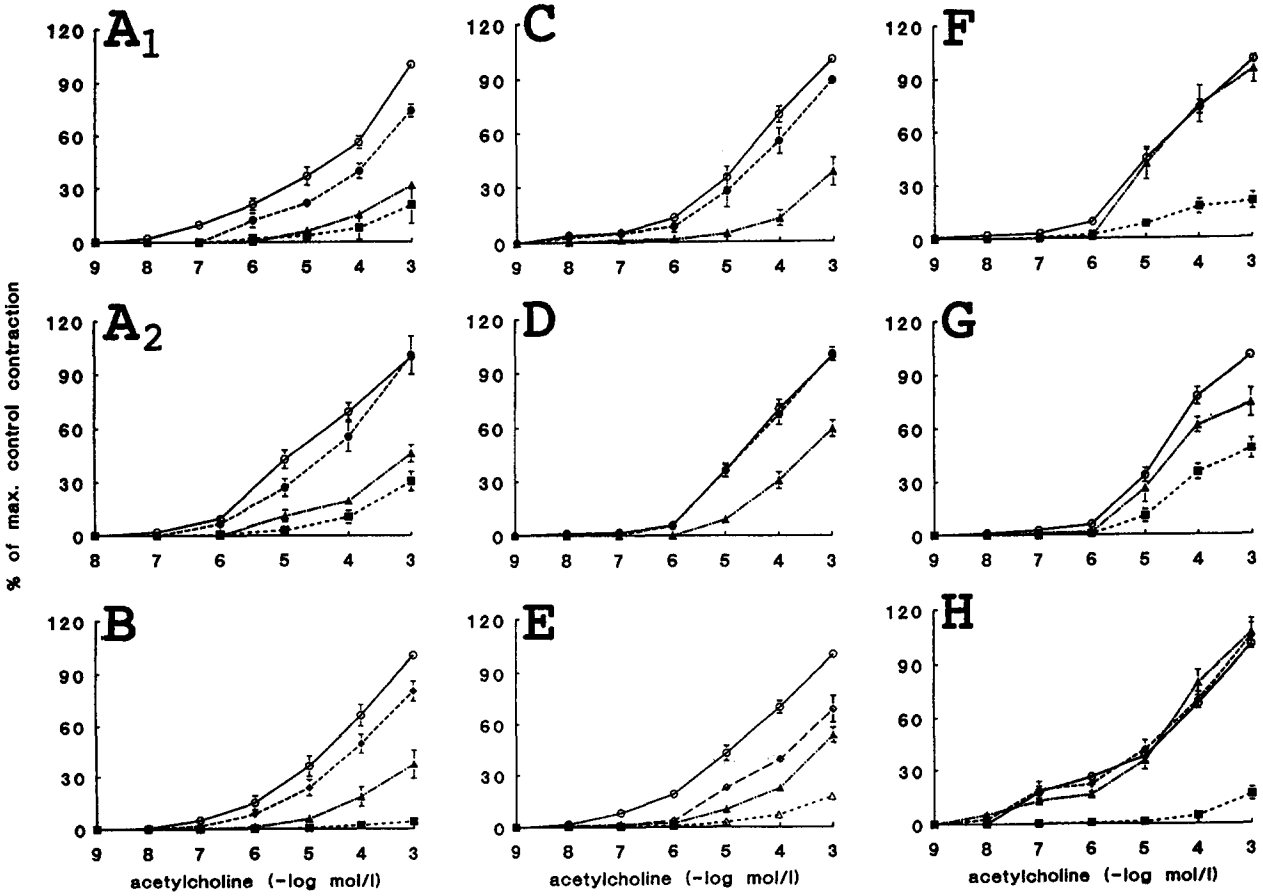


Fig. 2. Effect of pentacaine (A_1,A_2), oxethazaine (B), K-1905 (C), K-2002 (D), K-2006 (E), P2 (F), P3 (G) and PeJ (H) on cumulative concentration effect curves of acetylcholine in stomach fundic circular strips (A_1) and antral longitudinal strips (A_2, B–H). ○ Control response, ● 10^{-6}, ◆ 10^{-5}, ◇ 3.3×10^{-5}, ▲ 10^{-4}, △ 3.3×10^{-4}, ■ 10^{-3} mol/l.

and antral strips had similar susceptibility to the action of acetylcholine ($pD_2 = 4.63 \pm 0.89$, $n = 7$ and 4.68 ± 0.14, $n = 35$, respectively). Pentacaine in a concentration of 10^{-6} mol/l did not change the slope and the reached maximum of the cumulative concentration effect curve in the antral strips and reduced them significantly ($P < 0.05$) in fundic strips. In high concentrations (10^{-4} and 10^{-3} mol/l), its effect on both tissues was similar, i.e., significant ($P < 0.01$) reduction in the amplitude and slope of the acetylcholine cumulative concentration effect curve (Fig. $2A_1$,A_2). Since in the action of acetylcholine also different autacoids might participate, its interaction with pentacaine was studied in tissues pretreated with indomethacin (10^{-6} mol/l), phentolamine (10^{-6} mol/l) and L-NAME (10^{-5} mol/l) as well. The effect of pentacaine ($n = 7$) did not differ significantly from that in nontreated tissues; therefore in further experiments pretreatment by coctail of indomethacin, phentolamine and L-NAME was not used.

Since there was no pronounced difference between the actions of pentacaine in the two gastric preparations tested, the effects of the other local anesthetics was studied only on the longitudinal muscle strips of the antrum. The effect of oxethazaine in concentrations of 10^{-6}–10^{-3} mol/l on the cumulative concentration effect curve of acetylcholine was comparable to that of pentacaine (Fig. 2B). Carbanilates K-1905, K-2002 and K-2006 seem to antagonize the contraction produced by acetylcholine with a potency which was slightly lower than that of pentacaine and oxethazaine (Fig. 2C,D,E). The substances P2, P3 and PeJ were even less effective and reduced the acetylcholine cumulative concentration effect curve only in the concentration of 10^{-3} mol/l (Fig. 2F,G,H).

3.4. Effects of studied local anesthetics on the cumulative concentration effect curve elicited by histamine

Cumulative administration of histamine in concentrations of 10^{-7}–10^{-3} mol/l produced a concentration-dependent contraction of the longitudinal muscle strips of the guinea-pig stomach ($pD_2 = 5.35 \pm 0.26$, $n = 38$). In contrast, the strips of the circular fundic muscle ($n = 5$) were unaffected or only slightly stimulated by histamine. This was why in the experiments on the interaction between histamine and carbanilates only the longitudinal strips of the antrum were used. It has been shown that pentacaine (10^{-6}–10^{-4} mol/l) reduced both the maximum contraction reached and the slope of the histamine produced cumulative concentration effect curve (Fig. 3A).

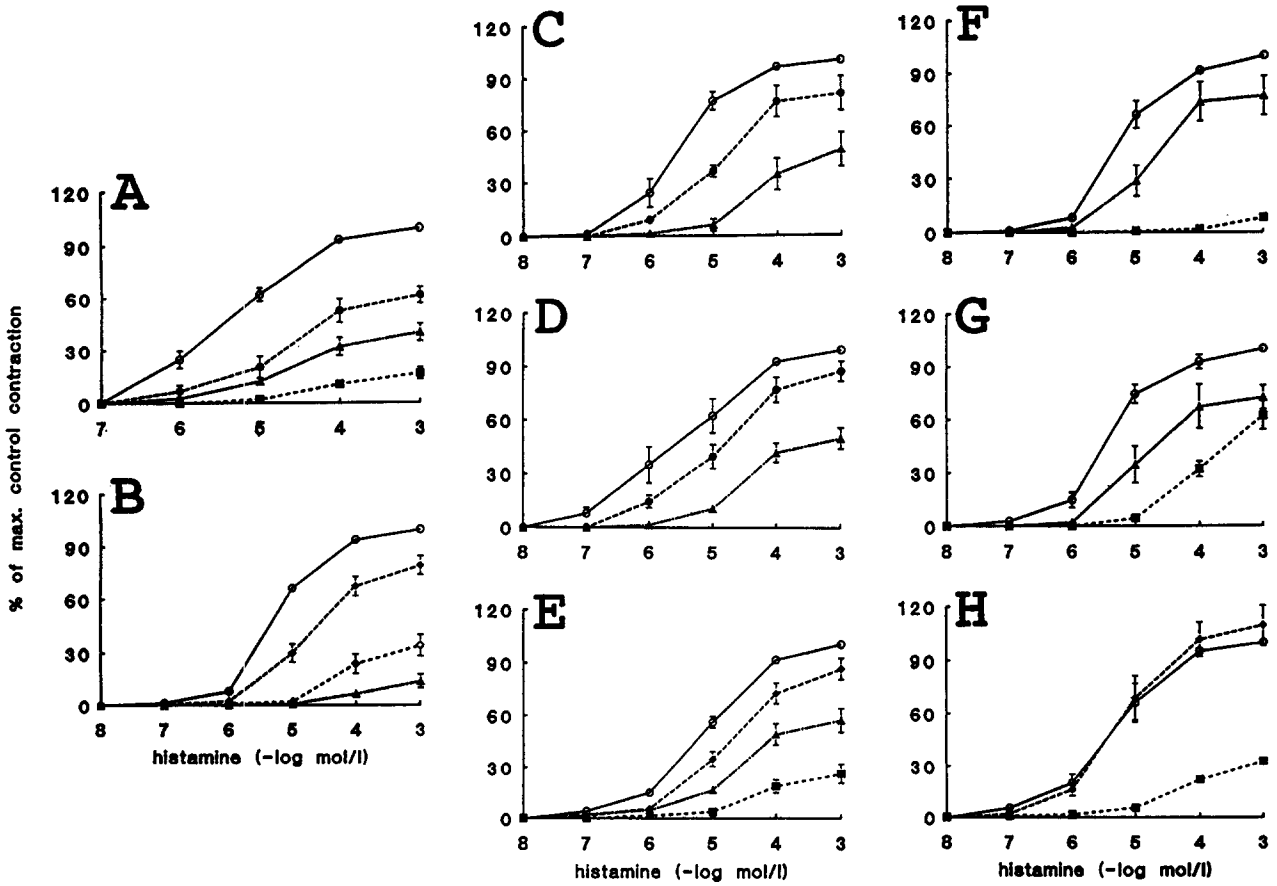


Fig. 3. Effect of pentacaine (A), oxethazaine (B), K-1905 (C), K-2002 (D), K-2006 (E), P2 (F), P3 (G) and PeJ (H) on cumulative concentration effect curves of histamine in stomach antral longitudinal strips. ○ Control response, ● 10^{-6}, ♦ 10^{-5}, ◇ 3.3×10^{-5}, ▲ 10^{-4}, ■ 10^{-3} mol/l.

Of the drugs studied, oxethazaine was the most effective in inhibiting histamine induced contractions (Fig. 3B). Its inhibitory effect was closely concentration dependent. The carbanilates K-1905 (Fig. 3C), K-2002 (Fig. 3D) and K-2006 (Fig. 3E) also reduced the amplitude and slope of the cumulative concentration effect curve produced by histamine. They were in this respect almost as effective as pentacaine. As shown in Fig. 3F,G,H, the effectiveness of the carbanilates P2, P3, and PeJ was lower than that of the former ones.

3.5. Effects of studied local anesthetics on the cumulative concentration effect curve elicited by barium chloride

Cumulative administration of the musculotropic agent $BaCl_2$ in the concentration range of 0.15–4.5 mmol/l contracted both the circular fundic and longitudinal antral strips ($pD_2 = 3.2 \pm 0.15$, $n = 7$ and 3.04 ± 0.35, $n = 35$, respectively). Pentacaine in concentrations of 10^{-6} and 10^{-4} mol/l shifted the $BaCl_2$ cumulative concentration effect curve to the right and reduced the maximum of the contraction amplitude reached to a higher extent in the longitudinal (Fig. $4A_2$) than in the circular muscle strips (Fig. $4A_1$). The intensity of K-1905 (Fig. 4C), K-2002 (Fig. 4D), K-2006 (Fig. 4E) action did not differ significantly from that of pentacaine on the longitudinal muscle strips. Oxethazaine (Fig. 4B) was in this respect the most effective drug studied. Even in the concentration of 10^{-6} mol/l, it shifted the $BaCl_2$ cumulative concentration effect curve significantly to the right without changing its slope. In the concentration of 10^{-4} mol/l oxethazaine reduced also the maximum of $BaCl_2$ produced cumulative concentration effect curve.

The substances P2 (Fig. 4F) and P3 (Fig. 4G) affected the barium chloride cumulative concentration effect curve significantly only in the concentration of 10^{-4} mol/l. In a 10-times higher concentration, however, they prevented its action completely.

4. Discussion

The results presented showed minimal differences between oxethazaine and pentacaine and in high concentrations also between them and the highly liposoluble carbanilates K-1905, K-2002 and K-2006 in reducing the resting

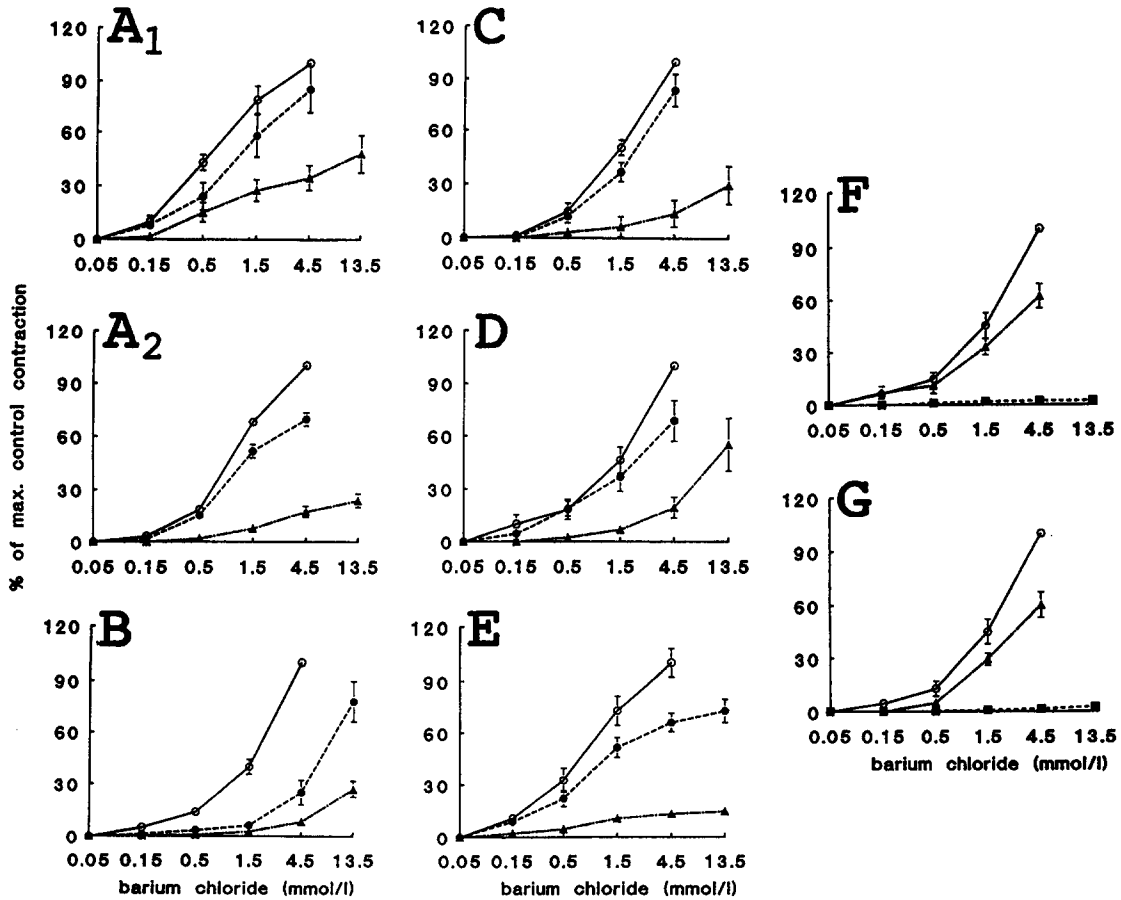


Fig. 4. Effect of pentacaine (A_1,A_2), oxethazaine (B), K-1905 (C), K-2002 (D), K-2006 (E), P2 (F) and P3 (G) on cumulative concentration effect curves of barium chloride in stomach fundic circular strips (A_1) and antral longitudinal strips (A_2, B–G). ○ Control response, ● 10^{-6}, ▲ 10^{-4}, ■ 10^{-3} mol/l.

tension. The latter compounds, however, exhibited a concentration dependent biphasic effect on resting tension and they suppressed the stomach muscle spontaneous activity more intensively than the previous ones. Methoxy derivatives (P2, P3) and the quaternary derivative (PeJ) reduced the resting tension to the same extent only in concentrations higher by at least one order of magnitude compared to the other compounds. The transient elevation of the resting tension elicited by K-1905, K-2002 and K-2006 might have resulted, as described for other local anesthetics, from their direct contractile effect in low concentrations (Downes and Loehning, 1977). The uncharged form of local anesthetics should enter the cell rapidly and release Ca^{2+} from internal stores before the charged form inside the cell increases to the point where internal Ca^{2+} release is blocked (Bianchi and Bolton, 1967; Bianchi and Strobel, 1968). The carbanilates studied are supposed to penetrate slowly to their site of ation. They were mainly in ionized form at pH of the bathing fluid in our experiments. As suggested previously (Bauer et al., 1986) they may cause transient contraction since they reach the threshold of K^+ channels earlier than that of other channels. Procaine and some other local anesthetics were reported to block not only K^+ channels but also Ca^{2+} and other cation channels. This nonselective blockade of the cation influx, suggested also in the case of the carbanilates (Bezeková and Bauer, 1986), might prevent membrane depolarization, thus resulting in reduced Ca^{2+} influx and smooth muscle relaxation.

$BaCl_2$ and the receptor agonists acetylcholine and histamine exert an excitatory contractile effect on longitudinal muscle strips of the antrum. While acetylcholine and $BaCl_2$ were effective in circular muscle strips of the fundus, histamine was ineffective in this tissue. Acetylcholine reacting with M-receptors (Bauer and Kadlec, 1970; Bolton, 1979a,b) and histamine with H_1-receptors of the smooth muscle membrane (Anderson and Nilsson, 1977; Ishii and Kato, 1987) enhance the influx of extracellular Ca^{2+} and act at least to some extent on the same intracellular Ca^{2+} store (Shibata et al., 1978; Bolton, 1979a,b; Kuriyama et al., 1982; Bauer et al., 1991). $BaCl_2$ was shown to substitute for Ca^{2+} in the contractile process (Ebashi and Endo, 1968) and may cause membrane depolarization due to suppression of K^+ conductance (Benham et al., 1985) independently of receptor activation. The ability of the drugs studied to antagonize the effect of different spasmogens and to reduce the maximum contraction reached suggests that their action is independent of a specific membrane-receptor-mediated action. The shift of the acetylcholine, histamine and $BaCl_2$ cumulative concentration effect curve to the right and reduction of the slope and maximum of cumulative concentration effect curve are indicative of their noncompetitive type of action. A similar effect had been described also for other local anesthetics in different smooth muscles (Feinstein and Paimre, 1969; Weinstock and Weiss, 1979). Antagonism of the effects of acetylcholine, histamine and $BaCl_2$ by the local anesthetics studied could result from the change of the fluidity of the smooth muscle membrane, as demonstrated in the action of different carbanilates (Ondriaš et al., 1984, 1987), thereby making it more difficult for the stimulants to open Ca^{2+} channels, as suggested for the mechanism of procaine action in the rat stomach fundus (Weinstock and Weiss, 1979).

All the carbanilates studied were shown to possess local anesthetic property (Štolc and Mai, 1993). There was no correlation between the ability of the drugs studied to inhibit nerve conductivity and their relaxing potency observed in the present experiments. It is thus unlikely that the relaxation induced by the carbanilates studied would be directly coupled with their local anesthetic property and effects on the intramural nerves.

Our results are indicative of a higher activity of the pentyloxy-derivatives (pentacaine, K-1905, K-2002 and K-2006) than of the methylcarbonyloxy (P2)- and methoxy (P3)-derivatives. Moreover, substitution in the *meta* position (pentacaine and K-1905) may be responsible for a higher effectivity against receptor-mediated action than substitution in the para position. Opening of the heterocyclic ring (K-1905) in the hydrophilic part of the molecule did not affect significantly the potency of the derivative studied, while quaternization (PeJ) significantly reduced the potency. Substitution in the lipophilic part of the molecule was found to be much more important for the spasmolytic property of the drugs studied than that in the hydrophilic part of the molecule. It is suggested that the carbanilates studied may affect the smooth muscle responses via changes in the membrane fluidity and Ca^{2+} availability.

Both the recently described local anesthetic action of the carbanilates studied (Štolc and Mai, 1993) and their spasmolytic properties shown in the present experiments may participate in the multifactorial mechanisms of their antiulcer effect (Nosáľová et al., 1995).

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