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# The effects of local anaesthetics on the electrical and mechanical activity of the guinea-pig ureter

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**1** The effects of local anaesthetic tertiary amines (procaine, lignocaine and tetracaine) as well as neutral (benzocaine) and permanently charged (QX-314) local anaesthetics were studied on the evoked electrical and mechanical activity of the ureter smooth muscle.

**2** 'Low' concentrations of procaine and lignocaine (0.1–1 mM) at pH 7.4 increased the duration of the slow plateau component of the evoked action potentials. The amplitude of the phasic contraction was consequently increased within the first 5 min of exposure. Tetracaine 0.1 mM caused a transient increase in the duration of the plateau and amplitude of the phasic contraction within the first 1–2 min only. The stimulant action of the local anaesthetics was greatly reduced in the presence of tetraethylammonium (TEA).

**3** All the tertiary local anaesthetics caused depolarization of the membrane accompanied by an increase in the size of the electrotonic potentials. Lignocaine normally initiated the discharge of spontaneous action potentials.

**4** High concentrations of lignocaine (5 mM) and tetracaine (0.5 mM) caused complete inhibition of the evoked action potentials and phasic contractions. Procaine 5 mM predominantly inhibited the contractile responses.

**5** The permanently charged local anaesthetic QX-314 (1 mM) caused an increase in the duration and amplitude of the plateau, increasing the number of spikes and the amplitude and duration of the phasic contraction. It also depolarized the ureter smooth muscle cells increasing the size of electronic potentials.

**6** The neutral local anaesthetic benzocaine at 1 mM caused a reversible selective blockade of the plateau component of the evoked action potential and a gradual reduction in the amplitude of the phasic contraction. No change in either the membrane potential or the membrane conductance was observed.

**7** High $pH_o$ (pH 9) significantly increased while low $pH_o$ (pH 6) decreased the inhibitory action of procaine and lignocaine but did not alter the effects of benzocaine and QX-314.

**8** Benzocaine caused a relaxation of the high-K-induced contraction, preferentially blocking the tonic component, whereas QX-314 had no effect on the KCl-contracture of the ureter muscle.

**9** Two sites of action in the ureter smooth muscle cell membrane for local anaesthetics are suggested. One site interacts with local anaesthetics in a charged form, while the other one interacts with those in a lipid-soluble neutral form. The charged form of local anaesthetics has a TEA-like action, while the neutral form predominantly causes blockade of 'slow' Na/Ca channels.

## Introduction

Procaine and some other local anaesthetics have two opposite effects on smooth muscles. They stimulate smooth muscle at low concentrations and have a relaxant or inhibitory effect at higher concentrations (for review see Bolton, 1979). The present study was undertaken to elucidate the mechanisms of such complicated effects of local anaesthetics on the guinea-pig ureter smooth muscle. Under normal conditions the action potential of ureter smooth muscle evoked by just suprathreshold depolarization has an initial fast component consisting of repeated and gradually decaying spikes and a subsequent slow component, the

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so-called plateau. The action potential is accompanied by a brief contraction. It is suggested that the fast component of the action potential is due to Ca 'fast' inward current, and the plateau phase is dependent on both Na and Ca entry through the 'slow' channels (Kuriyama & Tomita, 1970; Kochemasova, 1971; Bury, 1973; Shuba, 1981). The phasic contractions are triggered by the initial spike component of the action potential, whereas the plateau is associated with the amplitude and particularly the duration of the contraction (Shuba, 1977).

Most of the clinically useful local anaesthetics are tertiary amines. These drugs are known for their ability to affect a wide range of membrane related functions. The molecular nature of the membrane site of the tertiary amine local anaesthetics action remains obscure. Local anaesthetics are capable of interacting with both membrane lipids and proteins (Koblin *et al.*, 1980; Wang *et al.*, 1983). At physiological pH tertiary amine local anaesthetics exist in both cationic protonated and neutral states in proportions given by the Henderson-Hasselbalch equation: $\log (BH^+/B) = pK_a - pH$, where $BH^+$ and B are concentrations of the protonated and neutral forms, respectively.

The neutral form which predominates at high pH is usually quite lipid soluble and can readily cross cell membranes. The cationic protonated form which predominates at neutral and low pH is largely confined to the aqueous phase and is expected to cross membranes far less readily (Strichartz, 1976; Hille, 1977).

This paper examines the effects of the tertiary amine local anaesthetics procaine, tetracaine and lignocaine on the electrical and mechanical activity of the ureter smooth muscle. The effects of benzocaine, a permanently neutral analogue of procaine, and a quaternary ethyl derivative of lignocaine QX-314 have also been investigated.

## Methods

The experiments were performed on isolated pieces of ureter from male white guinea-pigs weighing

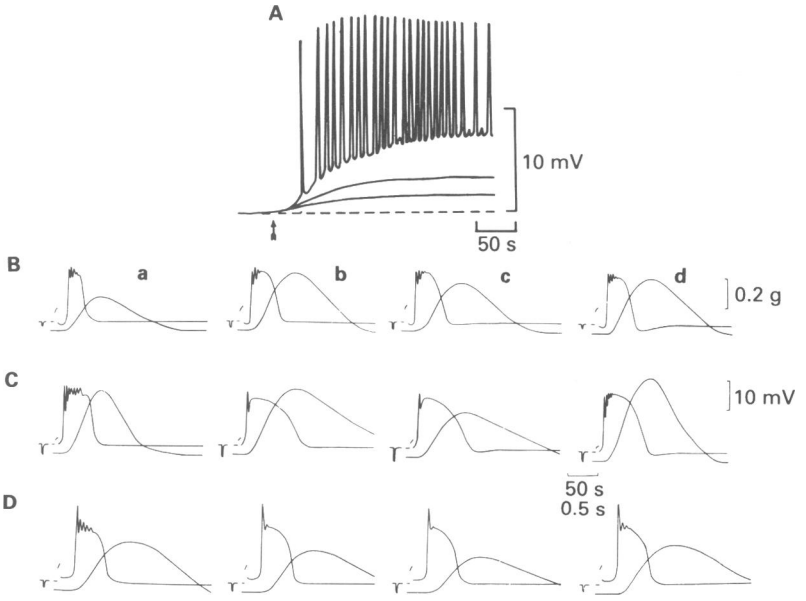


**Figure 1** Effects of local anaesthetics at 'low' concentrations on the ureter smooth muscle. (A) The changes in the resting membrane potential in Krebs solution caused by lignocaine 1 mM (top trace), procaine 1 mM (middle trace) and tetracaine 0.1 mM (bottom trace). The records are superimposed. (B, C and D) The effects of local anaesthetics at concentrations indicated on the evoked action potentials and phasic contractions. In this and subsequent figures (except Figure 6) the lower trace shows the mechanical and the upper trace the electrical response to a suprathreshold constant current pulse. Anelectrotonic potentials evoked by rectangular current pulses of 2–3 s duration were recorded on a slow time base (calibration, 50 s) and were followed by the responses to the cathodal current pulses of 20–50 ms duration on a fast base (calibration 0.5 s), (a) in normal Krebs solution; (b and c) during exposure to (B) procaine (1 mM), (C) lignocaine (1 mM) and (D) tetracaine (0.1 mM) after (b) 5 and (c) 10 min; (d) after washout with Krebs solution for 10 min. (Double sucrose-gap method). All records were taken from individual tissues.

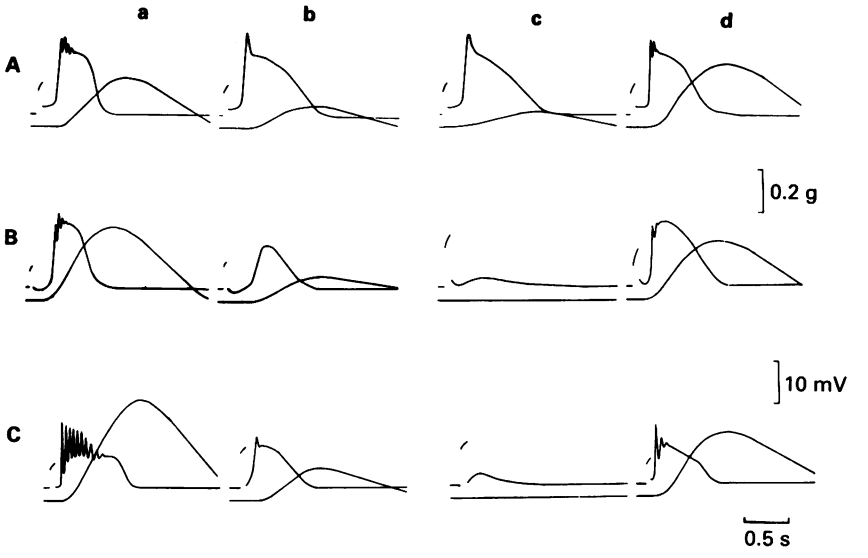


**Figure 2** Effects of (A) procaine, (B) lignocaine and (C) tetracaine at 'high' concentrations. (a) Control in normal solution. (A, b and c) After exposure to procaine (5 mM) for (b) 5 and (c) 10 min. (B, C, b and c) After exposure to (B) lignocaine (5 mM) and (C) tetracaine (0.5 mM) for (b) 2 and (c) 5 min. (d) After washout with normal Krebs solution for 10 min.

250–300 g. Simultaneous electrical and mechanical records were obtained using a double sucrose gap method (Bülbring & Tomita, 1969). Action potentials were evoked by just suprathreshold depolarizing current pulses (in the order of $10^{-7}$A) of short duration (20–50 ms) to avoid the possible influence of prolonged depolarization on the shape and amplitude of the action potentials. Anelectrotonic potentials were evoked by rectangular current pulses of the order of $10^{-7}$A and 2–3 s duration.

Tension alone was recorded using the continuous superfusion technique described in detail by Brading & Sneddon (1980). Four tissue pieces of about 1 cm length could be studied simultaneously by the use of four chambers and contractions were recorded on a 12 channel loop oscilloscope.

A modified Krebs solution used in the majority of the experiments was of the following composition (mM): $Na^+$ 120.3, $K^+$ 5.9, Tris 16.6, $Ca^{2+}$ 2.5, $Mg^{2+}$ 1.2, $Cl^-$ 150.2, glucose 11.5, equilibrated with 100% $O_2$, pH 7.4. When the pH of the modified Krebs solution was altered, this was done by altering either the Tris/HCl or Tris/maleic acid ratio.

Table 1 gives values of $pK_a$ and partition coefficients of local anaesthetics (Hille, 1977) and the ratio of charged and neutral forms at various pH, calculated from the Hendersson-Hasselbalch equation. Partition coefficient for the permanent cation QX-314 has not been measured, but would be expected to be extremely low (Hille, 1977).

The experimental values were expressed as means ± s.e.mean and the statistical significance was assessed by Student's $t$ test, $P<0.05$ being taken as significant.

Drugs used were: TEA (tetraethylammonium chloride, B.D.H., U.K.), procaine hydrochloride (Sigma), tetracaine hydrochloride (Sigma), lignocaine (lidocaine, Egyt, Hungary), benzocaine (Pharmprom, U.S.S.R.), QX-314 iodide (2-triethylamino-N-[2,6-dimethylphenyl] acetamide); kindly provided by Dr A.F. Brading of the Department of Pharmacology, Oxford University).

## Results

### *Effects of tertiary local anaesthetics in normal Krebs solution*

Procaine and lignocaine, both at 1 mM, and tetracaine 0.1 mM caused depolarization of the ureter smooth muscle (by, respectively, 4.1 ± 0.6 mV, 6.4 ± 0.4 mV and 2.3 ± 0.2 mV; $n = 9$) and increased the size of the electrotonic potential (to, respectively, 141 ± 4.6%, 151 ± 8.1% and 120 ± 4.5% of normal; $n = 9$). Normally, lignocaine initiated the discharge of spontaneous action potentials (Figure 1A). Local anaesthetics strongly affected the parameter of the action potential itself (Figure 1B–D). In all experiments, procaine and lignocaine (0.1–1 mM) increased the duration of the

plateau component, although the number of spikes was usually reduced. At the same time the amplitude and duration of the phasic contraction was increased. All these changes occurred within the first 5 min of exposure. Similar effects of tetracaine (0.1 mM) were observed within the first 1–2 min of action. However, during the continuous exposure of the ureter to local anaesthetics the stimulant action gradually decreased. The changes in the action potential and phasic contraction after 10 min of exposure to tertiary local anaesthetics are illustrated in Figure 1c. Also, lignocaine decreased the relaxation rate by 2–3 times. Removal of local anaesthetics from the bathing fluid caused the recovery of the resting membrane potential (not shown) and membrane conductance, although the action potential remained somewhat prolonged (Figure 1d).

Lignocaine 5 mM ($n = 5$) and tetracaine 0.5 mM ($n = 7$) caused a complete blockade of both the action potential and phasic contraction, while procaine 5 mM preferentially inhibited the phasic contraction (Figure 2).

The results with procaine and lignocaine and to a lesser extent with tetracaine clearly show a dual action of tertiary local anaesthetics on the ureter smooth muscle. The stimulant action is likely to be due to a decrease in potassium conductance, while the inhibitory action is presumably associated with the blockade of both 'fast' and 'slow' Ca and Na/Ca channels, respectively, responsible for the generation of the action potential. We considered that the dual effect of tertiary local anaesthetics on the ureter muscle might be related to different effects of the charged and neutral forms. To test this, we studied the effect of permanently charged QX-314 and neutral benzocaine, and also the effects of tertiary local anaesthetics at various pH values.

The experiments with QX-314 showed that this local anaesthetic had an excitatory action at all concentrations studied (up to 5 mM), significantly prolonging the plateau component and increasing the amplitude and number of spikes. The amplitude and duration of the phasic contraction were also increased (Figure 3A). Like tertiary local anaesthetics, QX-314 caused depolarization of the membrane accompanied by an increase in size of the electrotonic potential. Unlike QX-314, benzocaine was inhibitory at all concentrations up to 1 mM (the highest concentration possible due to its poor solubility). Benzocaine caused a selective blockade of the plateau component and significant suppression of the phasic contraction. The amplitude of the first spike was actually increased by benzocaine (Figure 3B) but it did not affect the membrane potential and membrane resistance. The effect of benzocaine was remarkably quick and easily reversible and reminiscent of that of papaverine (Brading *et al.*, 1983).

Thus, the results with benzocaine and QX-314 strongly suggest the existence of two separate sites of action for local anaesthetics on the ureter smooth muscle. In the charged form local anaesthetics block K-conductivity from the outer surface of the cell membrane, while in the neutral form they predominantly block potential-operated Na/Ca channels. One might expect the potency of tertiary local anaesthetics to depend on pH, so the effects of tertiary local anaesthetics on the ureter muscle were studied at different pH.

*Effects of tertiary local anaesthetics at different pH*

Preliminary experiments showed that at pH 9 the amplitude of both components of the action potential was reduced, while at pH 6 the opposite effect was observed. Despite these changes in the action potential, the amplitude of the phasic contraction both at pH 6 and pH 9 was actually the same as that at pH 7.4. Further alkalinization and acidification had more pronounced effects on both the electrical and mechanical activity of the ureter muscle. The effects of tertiary local anaesthetics on the ureter muscle were tested at pH 9 and pH 6 in five experiments with each anaesth-

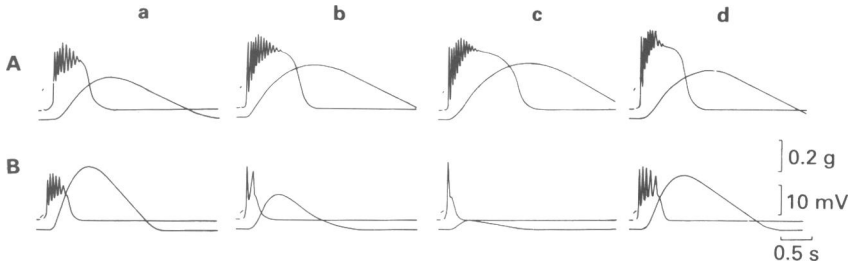


**Figure 3** The effects of (A) QX-314 and (B) benzocaine. (a) Control in normal solution. (A, b and c) During exposure to QX-314 (1 mM) for (b) 5 and (c) 10 min. (B, b and c) During exposure to benzocaine (1 mM) for (b) 2 and (c) 5 min. (d) After washout with normal Krebs solution for 10 min.

etic studied. The experiments with all tertiary local anaesthetics at pH 9 demonstrated an increase in their inhibitory action on the action potential and phasic contraction. The effect of lignocaine 1 mM on the ureter muscle at pH 6 and pH 9 obtained from the same tissue is illustrated in Figure 4A. At pH 6 lignocaine prolonged, while at pH 9 it shortened, the duration of the action potential, reducing the amplitude and number of spikes. Similar results have been obtained when studying the effects of pH on the actions of procaine and tetracaine. Unlike tertiary local anaesthetics, the effect of benzocaine did not depend upon pH (Figure 4B).

In previous studies it was suggested that the stimulant action of procaine is due to a decrease in K-conductance (see Bolton, 1979). Our indirect data confirm this suggestion. To test this assumption further, the effects of local anaesthetics on the ureter smooth muscle in the presence of TEA, a potassium-channel blocker, were studied.

*Effect of local anaesthetics in the presence of TEA*

TEA significantly weakened the stimulant action of local anaesthetics on the ureter smooth muscle. The effect of 1 mM procaine in the presence of TEA on the action potential and phasic contraction is illustrated in Figure 5A. The traces show that procaine shortened the duration of the plateau component reducing the amplitude of the phasic contraction. Using the superfusion technique, the dose-response curves for the effects of local anaesthetics on the amplitude of the evoked phasic contractions both in normal Krebs and in Krebs with TEA have been obtained. As illustrated in Figure 5B the dose-response curves obtained in the presence of TEA for both procaine and lignocaine were reduced and shifted to the left. The stimulant action of these local anaesthetics normally observed in Krebs solution was lost in the presence of TEA and the inhibitory action was unmasked. The dose-response curves for both tetracaine and benzocaine obtained in Krebs with TEA were practically the same as in normal Krebs solution (Figure 5B, C and D).

*Effect of local anaesthetics on KCl-induced contractions*

In our previous paper we showed that procaine blocked KCl-induced contractions of the ureter smooth muscle in a dose-dependent manner (Aickin *et*

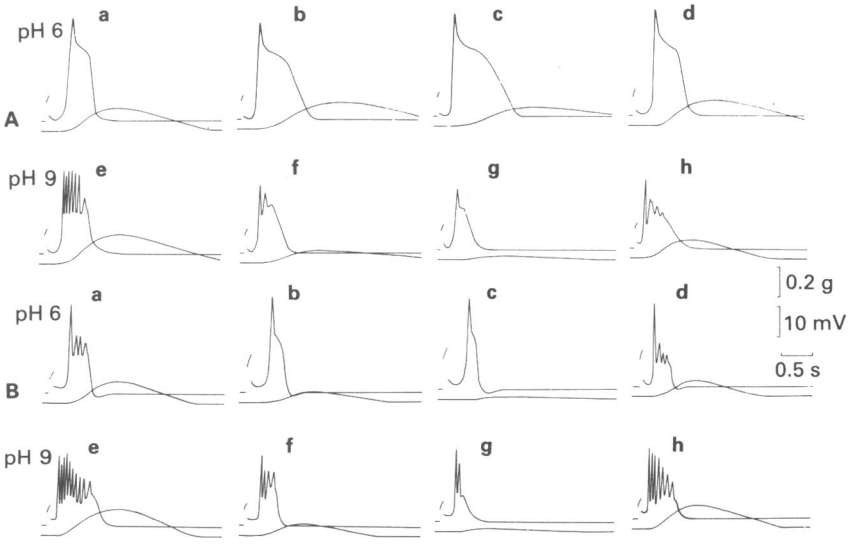


**Figure 4** The effects of lignocaine and benzocaine at various pH. (A) Responses in Krebs solution at pH 6; (A, b and c) during exposure to lignocaine (1 mM) for (b) 5 and (c) 10 min and (A, d) after washout with Krebs solution at pH 6 for 10 min. (A, e) Responses in Krebs solution at pH 9; (A, f and g) during exposure to lignocaine (1 mM) for (f) 5 and (g) 10 min and (A, h) after washout with Krebs solution at pH 9 for 10 min. These recordings were taken from the same tissue. (B, a) Responses in Krebs solution at pH 6; (B, b and c) during exposure to benzocaine (1 mM) for (b) 2 and (c) 5 min and (B, d) after washout with Krebs solution at pH 6 for 10 min. (B, e) Responses in Krebs solution at pH 9; (B, f and g) during exposure to benzocaine (1 mM) for (f) 2 and (g) 5 min and (B, h) during washout with Krebs solution for 10 min. The recordings were taken from the same tissues. Note the dependence of the inhibitory action of lidocaine on the pH and the pH independence of the inhibitory action of benzocaine.

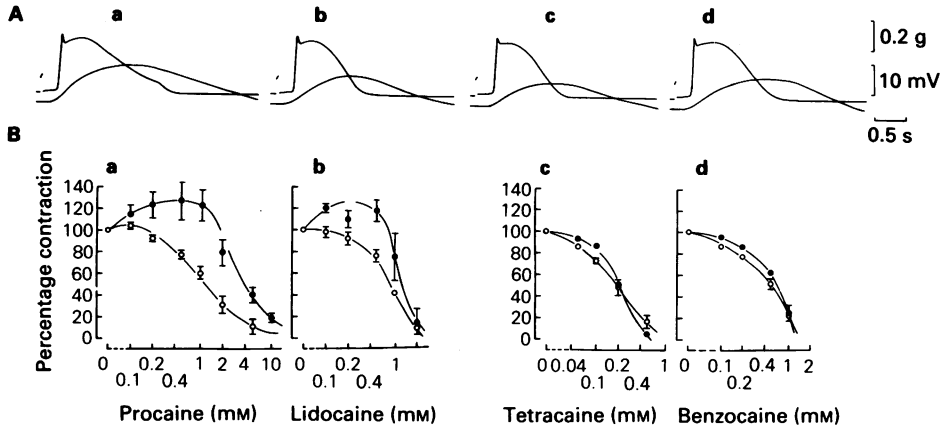


**Figure 5** Effects of local anaesthetics on the ureter smooth muscle in the presence of tetraethylammonium (TEA) at pH 7.4. (A, a) The action potential and phasic contraction in the presence of TEA (5 mM); (A, b and c) during exposure to procaine (1 mM) for (b) 5 and (c) 10 min; (A, d) after washout with Krebs for 10 min in the continuous presence of TEA. (B) Dose-response curves for the effects of (a) procaine, (b) lignocaine, (c) tetracaine and (d) benzocaine, on the amplitude of the evoked phasic contractions (tension recording) in Krebs solution (●) and in the continuous presence of 5 mM TEA (○). The amplitude of the phasic contraction before the administration of local anaesthetics was taken as 100%. The concentration of local anaesthetic was increased in an ascending order, and the readings were taken 5 min after the administration of each dose. Each point is the mean of four tissues, with vertical lines representing s.e.mean when it is larger than the symbol. Note that TEA masks the stimulant action of procaine and lignocaine.

*al.*, 1984). It was of interest to know which form of the local anaesthetic is active against high-K-induced contractions. Hence, the effects of QX-314 (1–5 mM) and benzocaine (1 mM) as two extremes, on the KCl-induced contraction of the ureter muscle were studied. Six experiments were performed with QX-314 and benzocaine. The results demonstrated that QX-314 did not affect the tonic component of the K-induced contraction but increased the amplitude of the phasic contractions associated with action potentials, while benzocaine caused a preferential blockade of the tonic component (Figure 6).

## Discussion

The effects of the tertiary local anaesthetics procaine, lignocaine and tetracaine on the electrical and mechanical activity of the ureter smooth muscle are strongly dependent on pH. At low pH, when the cationic protonated form predominates, the stimulant action of these anaesthetics is more distinct than it is at neutral and high pH. Only a stimulant action of the permanently charged quaternary ethyl derivative of lidocaine, QX-314, was observed in the guinea-pig ureter. The reaction of charged drugs with their site of action brings about depolarization of the membrane, a decrease in membrane conductance, a prolongation of the plateau of action potentials, and an increase in the amplitude of contraction. This stimulant action of local anaesthetics probably results from a TEA-like action decreasing potassium permeability by blocking not only potassium channels, which are open at the resting membrane potential, but also those channels responsible for the repolarizing phase of the action potential (for review see Bolton, 1979).

The lipid soluble free amine form of the local anaesthetics and the neutral derivative of procaine, benzocaine, suppressed predominantly the plateau component of the action potential and mechanical response. The neutral form of tertiary anaesthetics predominate at neutral and high pH (see Table 1).

We suggest the existence of two sites of action for local anaesthetics in the cell membrane of smooth muscle. One is located presumably at the external surface of the membrane. It reacts with the charged form of the local anaesthetics. The other site interacts with the lipid soluble neutral forms. We speculate that externally applied local anaesthetics must cross a hydrophobic barrier to reach this site. It is suggested that the inhibitory action of the lipid soluble neutral form of the drug on the ureter smooth muscle results from its preferential blockade of the 'slow' Na/Ca channels responsible for the generation of the plateau component of the action potential.

The response of the ureter to applications of high-K solutions is essentially similar to that in other mammalian smooth muscles. A depolarization occurs at

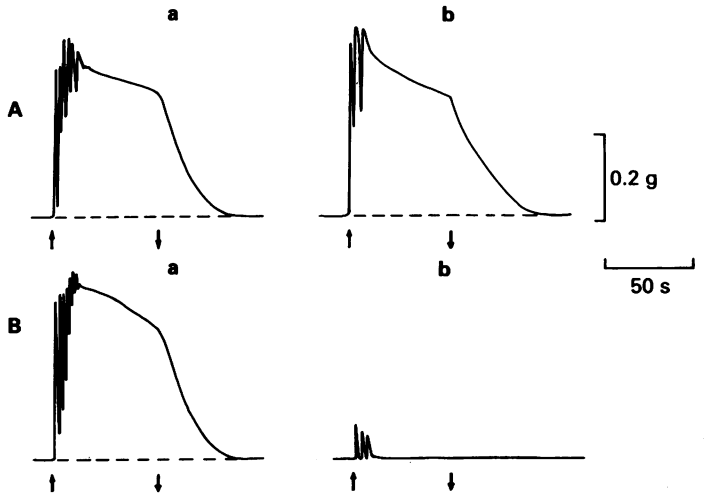


**Figure 6** The effects of QX-314 and benzocaine on the high-K response. (A and B, a) High-K-induced contraction of the ureter smooth muscle (first arrow indicates the removal of NaCl, all NaCl is replaced by KCl). (b) K-induced contraction obtained after 10 min of exposure to (A) QX-314 (1 mM) and (B) benzocaine (1 mM). Note the complete absence of an inhibitory action of QX-314 on the high-K-induced response and a suppressive action of benzocaine on the tonic component of the contraction.

the onset of which the action potentials and contraction appear; the latter consists of an initial phasic and subsequent tonic component. The contraction can be totally suppressed by using Ca-free solutions and Ca-antagonist drugs, suggesting that it is due to Ca entry through voltage-sensitive Ca channels. Washizu (1967) and Sunano (1976) have shown that verapamil and D-600 are able to suppress K contractures of the ureter. The phasic component of the contraction is blocked at lower $Mn^{2+}$ concentrations than the tonic component. Verapamil and nifedipine suppress more effectively the tonic rather than the phasic component of the high-K-induced contraction (Kochemasova & Shuba, 1979; Brading & Sneddon, 1981; Aicken *et al.*, 1984). This suggests that there may be two types of voltage-sensitive Ca channel, the 'fast' rapidly inactivating type responsible for the spike upstroke and phasic contraction, and 'slow' channels responsible for the entry of $Ca^{2+}$ during tonic tension (Kochemasova & Shuba, 1979; Brading *et al.*, 1983). The marked suppressive effect of benzocaine on the tonic component of the high-K-induced contraction suggests that neutral local anaesthetics preferentially block the 'slow' calcium channels. According to our unpublished observations, the Ca antagonist, diltiazem, more effectively blocks the 'slow' calcium channels, responsible for the tonic component of the K-contraction, than the 'slow' Ca/Na channels responsible for the generation of the plateau component of the action potential. The effects of benzocaine on the electrical and mechanical activity of the guinea-pig ureter are somewhat similar to those of papaverine (Brading *et al.*, 1983).

**Table 1** Values for $pK_a$ and partition coefficients, and proportions of cationic and neutral forms of local anaesthetics at different pH

| *Drug* | $pK_a$ | *F* | $BH^+/B$ *pH6* | *pH 7.4* | *pH 9* |
|---|---|---|---|---|---|
| Benzocaine | 2.6 | 41 | 0.000 | 0.000 | 0.000 |
| Procaine | 8.9 | 45 | 794 | 31.62 | 0.8 |
| Lignocaine | 7.9 | 225 | 80 | 3.2 | 0.08 |
| Tetracaine | 8.5 | 273 | 316 | 12.6 | 0.3 |

F = oleyl alcohol: water partition coefficient for the free amine forms

Procaine and tetracaine are known to block the release of Ca from the intracellular store in striated, smooth and cardiac muscle (Almers & Best, 1976; Endo, 1977; Chapman & Leoty, 1981; Itoh *et al.*, 1981). An inhibitory action of local anaesthetics on the ureter smooth muscle contractility through this mechanism seems unlikely since lignocaine, which lacks an ability to suppress Ca release from the intracellular stores (for review see Kuriyama, 1981), has a stronger inhibitory action on the contraction of

ureter smooth muscle than procaine. Tetracaine proved to have the most potent inhibitory action on the ureter smooth muscle, while its stimulant action was the weakest.

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