Urological Research 3, 155-158 (1975)

The Influence of Potassium on the Electrical and Mechanical Activity of the Guinea Pig Ureter

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Received: May 16, 1975; and in revised form: September 15, 1975

Summary. Increase of the external K^+ concentration depolarises the ureteral muscle membrane and induces, after a transient period of increased spontaneous activity, a tonic contraction. Tetraethylammonium, in concentrations normally required for ganglion blocking activity, does not influence the ureteral activity, but in higher doses it prolonges the duration of the action potential several times and increases the intraluminal pressure. Ouabain has only an inhibitory effect on the guinea pig ureter.

Key words: Ouabain, Tetraethylammonium, Potassium, Ureteral action potentials.

The membrane stability of a smooth muscle cell can be disturbed in two ways: either by a sudden short depolarisation, accompanying an action potential and inducing a phasic contraction, or by a sustained steady depolarisation, which does not necessarily result in the development of tension within the wall (tonic contraction). In this paper the influence of changes in extracellular potassium concentrations on the action potential and the tension of the ureteric muscle and the relationship between the latter and the resting membrane potential are examined. It is known (7) that in the absence of the pacemaker region in the pelvis the guinea pig ureter does not show spontaneous activity. This preparation is therefore particularly suited for this investigation.

It has been shown clinically that variations of serum K^+ levels may influence ureteric contractility (6). The present study may provide an explanation for this observation.

Material and Methods

The ureters of 20 guinea pigs were investigated using the methods described in a previous paper (7). Ureteric segments, 30 to 50 mm in length were mounted in an organ bath, 5 ml in volume, through which solution flowed continuously. Into one end of the ureter a hollow glass tube was inserted, which was connected to a pressure transducer via a short plastic catheter. The other end was tied by silk thread to the hook of a strain gange for isometric tension recording.

The intracellular electrical activity is picked up by mean of glass-micropipettes filled with 3 M KCl, and suspended in a Ag-agarbridge, which can be moved by a micrometer screw for penetration into the cell. The bioelectrical signals are displayed on an oscilloscope via a high impedance input amplifier. Furthermore one or two pairs of external macroelectrodes could be slid under the ureter. Every minute the preparations were stimulated by rectangular electrical pulses of 50 msec. at 3 to 10 Volts applied to electrodes placed at one end of the ureter.

Krebs solutions of the following compositions were used (mM): NaCl 137; KCl 5,9; CaCl 2,5; $NaHCO_3$ 15,5; $MgCl_2$ 1,2; NaH_2PO_4 1,2 and glucose 11,5. The influence of potassium was investigated by two methods:

a) by the stepwise replacement of the NaCl in the Krebs solution with equimolar KCl, so that the concentration of extracellular K^+ increased, or vice versa to produce decreasing K^+ concentrations.

b) by studying the effect of Tetraethylam-

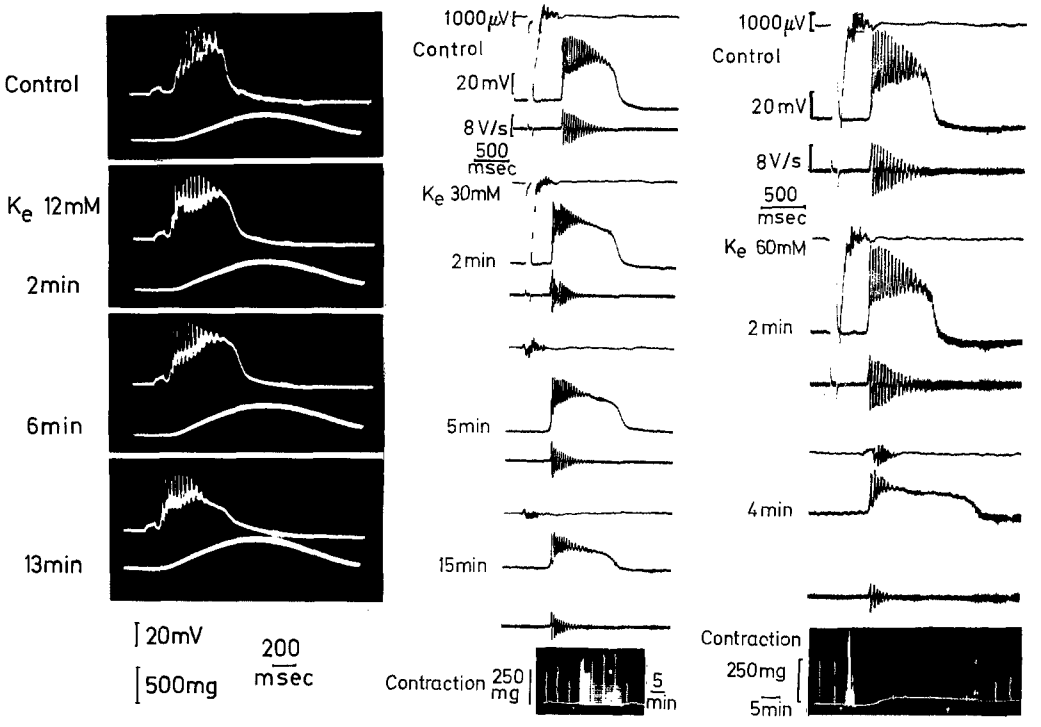

Fig. 1. Influence of 12 mM, 30 mM and 60 mM (K^+) on the intracellular action potential, its rate of rise and the contraction amplitude of the guinea pig ureter

monium (TEA) which is supposed to selectively block K^+ permeability or the K^+ channel (5), and of ouabain, which inhibits the K^+ uptake and decreases the intracellular K^+ concentration in the guinea pig ureter (10).

Results

1. Alterations of the extracellular K^+ concentration

If the extracellular K^+ concentration is decreased to 2,5 and 0 mM the excitability or the ureter becomes reduced: chronaxie, rheobase and conduction time increase, the mechanical responses disappear and conduction blocks occur. The action potential, which normally consists of a series of 5 to 10 fast oscillations superimposed on a depolarisation plateau of about 500 msec., undergoes marked changes: its rising phase often shows inflections and notches; its total duration is shortened; the number and frequency of the oscillations are decreased and they occur at a higher depolarisation plateau.

Increase of (K^+) to 20 mM at first prolongs the action potential (Fig. 1); the number and frequency of spikes is increased and they start at a lower depolarisation level. The conduction velocity is greatly increased and the threshold

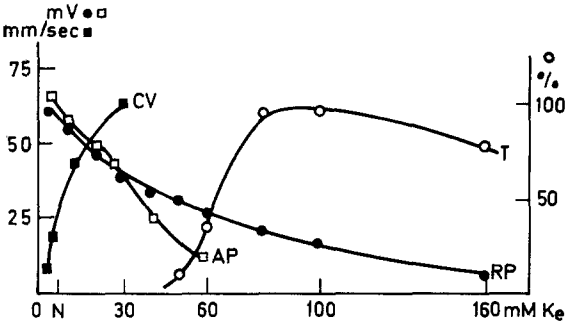

Fig. 2. Diagram showing the alterations of the resting membrane potential (RP), the action potential (AP), the conduction velocity (CV) and the amplitude of the contracture (T) (100 % = 500 mg.) of the guinea pig ureter at various concentrations of (K^+) (linear scale)

for electrical stimulation is decreased. At higher K^+ concentrations the amplitude and duration of the action potentials gradually decrease while the membrane resting potential diminishes further. The mean values of five determinations are shown in Fig. 2.

From about 10 mM (K^+) spontaneous phasic contractions accompanied by action potentials may occur, but they only occur regularly above 20 mM (K^+) and during the first 15 minutes after changing the solution. At 80 mM (K^+) no

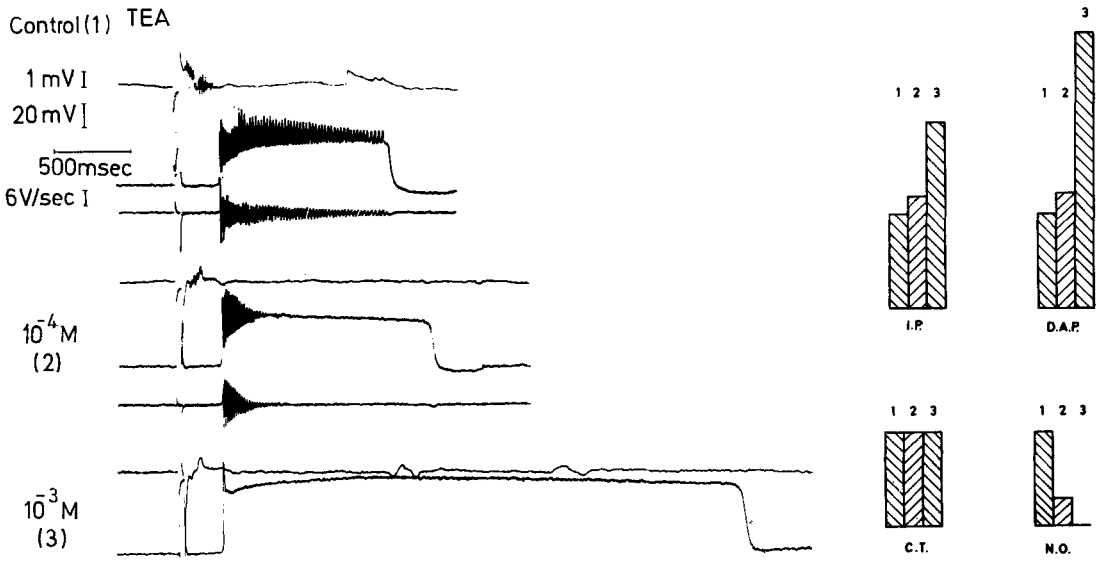

Fig. 3. Influence of TEA 10^{-4}M (2) and 10^{-3}M (3) on the extracellular and intracellular action potential and its differential in the guinea pig ureter. Symbols of diagram: I. P. intraluminal pressure; D. A. P.: duration of the action potential; C. T.: conduction time; N. O.: number of oscillations. The values are calculated in percentages from the means and S. D. of 10 values (1 = normal = 100%)

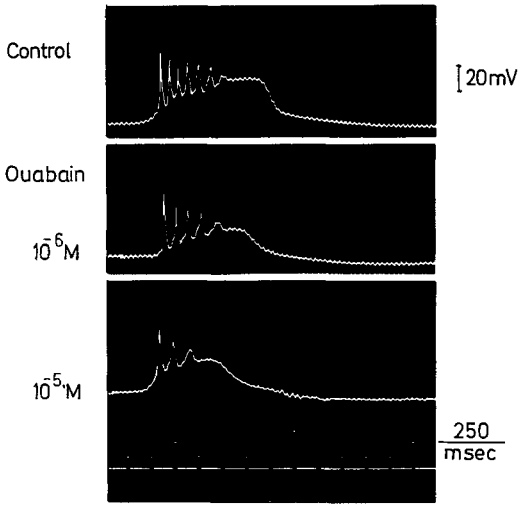

Fig. 4. Changes of the intracellular action potential of the guinea pig ureter during exposure to ouabain

more phasic responses are detected. The amplitude of the phasic contractions is initially high (related to the prolonged action potentials), but decreases thereafter (with decreasing amplitude of the action potential).

Above 40 mM (K^+) a tonic contraction appears, which reaches a maximum between 80 and 100 mM (K^+). At still higher K^+ levels a slight decrease is observed. The contraction diminishes gradually with time with a half time of about 10 minutes.

2. Influence of TEA (5×10^{-3} M)

TEA does not modify the resting potential but the action potential is markedly changed (Fig. 3). The spikes disappear completely while the plateau is prolonged up to 5 seconds duration. The overshoot of the initial spike increases with a reversed potential exceeding 20 mV but the rate of rise remains constant. The tension development is increased and prolonged in a similar manner to the plateau phase. The conduction velocity remains unchanged.

3. Ouabain (10^{-6} to 10^{-5} M)

During exposure to ouabain the membrane depolarises by 5 to 10 mV. The plateau component of the action potential (Fig. 4) is lower and the action potential itself rapidly becomes shortened. Later, the spikes also disappear. On return to normal Krebs solution the spikes return more rapidly than the plateau. At 10^{-6} M the spontaneous activity is decreased and at 10^{-5} M it is completely abolished and the excitability is reduced. However ouabain augments the K^+ induced contracture and extends it beyond the 40 mM (K^+) level.

Discussion

The effect of high (K^+) medium on the guinea pig ureter confirms the results of Bennett and Burnstock (1) who studied the action of isotonic

potassium sulphate with the sucrose-gap method. They found a marked depolarisation of 56 mV, transiently increased spontaneous activity and a decrease in the amplitude of the action potential. The increased excitability of the whole preparation is manifested by the facilitated conduction, the decreased spike interval, and the decreased threshold for contractions.

The plateau of the action potential, observed in some tissues (heart, myelinated nerve) has been attributed to asynchronous changes in the K^+ conductance versus Na^+ conductance. Washizu (9) suggested that inhibition of increased potassium conductance could explain the prolonged ureteric action potential produced by procaine. By blocking the K^+ channel TEA reduces or delays the onset of increased K^+ conductance after the onset of the increased inward currents of the action potential and in this way the depolarization is prolonged. In contrast the plateau is decreased and shortened by ouabain. Tetraethylammonium chloride (TEA) is known to be a potent ganglion blocking drug which normally stabilises the ganglion by hyperpolarisation. This effect however is obtained at much lower concentrations than the concentrations used in our experiments which are, for instance, 100 times higher than the concentrations used by Bentley and Sabine (2) with the vas deferens. It may be concluded that the prolonged depolarisation of the ureteric smooth muscle cell described in this paper is probably a direct effect, not mediated by ganglion cells which are probably absent in the wall of the proximal ureteric segments.

A tonic contraction accompanied by sustained depolarisation of the membrane in a high (K^+) medium is described for many smooth muscles. In the guinea pig ureter this phenomenon, as well as the relation to external calcium concentration, has already been described by Chapman and Holman (4). These authors however found that the tension did not reach a plateau in K^+ concentrations of up to 130 mM, while in our experiments a maximum was achieved at 80 to 100 mM (K^+).

We have confirmed the observation of Washizu (8) that ouabain has no stimulating but only an inhibiting action on the guinea pig ureter. The cat ureter however seems to exhibit a biphasic response (12).

The importance of the extracellular K^+ concentration for the conduction of ureteric peristalsis has been demonstrated in vivo. Boyarsky et al. (3) demonstrated that the variation in ureteric frequency produced by intravenous infusion of KCl could be predicted from the alteration in the ratio of intracellular to extracellular (K^+). Samellas and Le Veen (6) found that ureteric peristalsis was inhibited completely when the serum potassium was reduced to 2 meq./l. by exchange resin and the ureter became refractory to external stimuli. The dependence of serum potassium concentration on renal function should be remembered.

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