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Inotropic effects of atropine on ureteral muscle

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Atropine (1–10 μg ml) produced an inotropic effect in the smooth muscle of the guinea-pig isolated ureter. This appeared to be caused by an increase in the safety factor for conduction in this muscle. Whether the effect of atropine is exerted directly on the muscle fibres or via intramural nerves is discussed.

Atropine, and other antimuscarinic drugs have been reported to have inotropic effects on a number of smooth muscles (Magnus, 1905; Cuthbert 1963a, b; Christensen & Lund, 1968; Wood, 1972). The purpose of this report is to describe the effects of atropine on another smooth muscle, the guinea-pig ureter. Comparison of the results with this tissue with those obtained using other muscles allow some conclusions about the mode of action to be made.

METHODS

Spontaneous and electrically evoked contractions of guinea-pig isolated ureters have been recorded isotonically or isometrically by conventional means. In these experiments the whole of the ureter, including part of the renal pelvis was used. In addition simultaneous recording of electrical and mechanical activity from pieces of ureter not including the renal end has been made using a sucrose-gap electrode. The methods have been fully described elsewhere (Cuthbert, 1965).

Experiments were made in Tyrode solution at 37° and gassed with air. The Tyrode solution had the following composition (mM) NaCl, 137; KCl, 2·7; $MgCl_2$, 1·05; $CaCl_2$, 1·8; NaH_2PO_4, 0·4; $NaHCO_3$, 11·9 and glucose 5·6. Concentrations of atropine are given as the sulphate.

RESULTS

The response of isolated guinea-pig ureters to electrical stimulation is dependent on frequency (Cuthbert, 1965). Fig. 1a shows the effect of atropine (10 μg/ml) on isotonic contractions in response to electrical stimuli applied at the renal end and at two frequencies (0·02 and 0·06 Hz). Atropine potentiates the response at both frequencies, the effect taking some 3 min to develop. The same effect could be demonstrated at lower concentrations of atropine (1 μg/ml), but then the effect was less pronounced and took longer to develop. A different effect of atropine is shown in Fig. 1b in which a ureter was stimulated at a frequency of 0·02 Hz. Not every stimulus was effective and then only small, local, non-propagated contractions were recorded. After addition of atropine, 10 μg/ml, all stimuli became effective, but no inotropic effect was seen since atropine increased the effective frequency of contraction, thus reducing the force of contraction.

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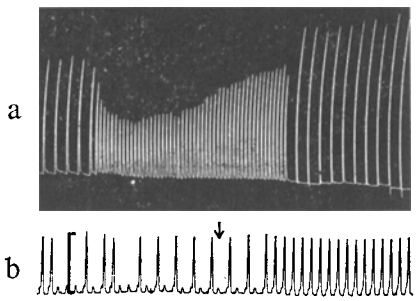

FIG. 1a. Isotonic responses of an isolated ureter to electrical stimuli applied at the renal end. Stimuli applied at a frequency of 0·02 or 0·06 Hz. Atropine (10 μg/ml) added at white dot.
b. Isometric responses of isolated ureter to electrical stimuli applied at the renal end, frequency 0·02 Hz. Calibration 0·5 g. Atropine (10 μg/ml) added at arrow.

To gain a better understanding of the effects of atropine, simultaneous recordings of the electrical and mechanical activity were made using a sucrose-gap electrode. Fig. 2 illustrates an experiment with conditions similar to those obtaining in Fig. 1b.

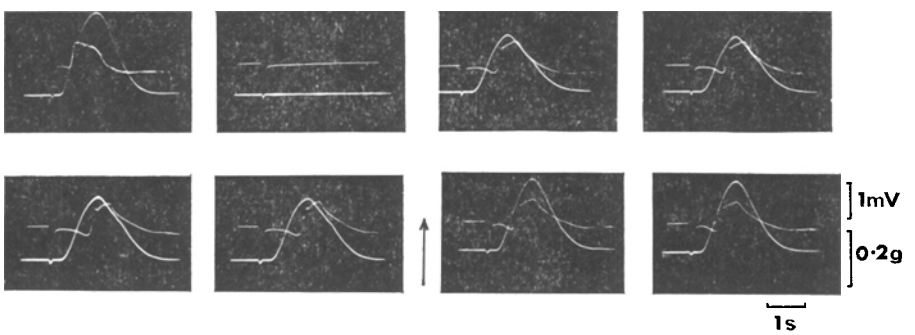

FIG. 2. Records made in sucrose gap electrode. Upper traces show potential and lower traces show tension. The ureter was stimulated at a frequency of 0·06 Hz with stimuli of either 60 or 100 ms duration. The effects of atropine (10 μg/ml) on the responses are shown to the right of the arrow.

The preparation was stimulated at a frequency of 0·06 Hz using two different pulse durations, 60 and 100 ms. With the shorter pulses only alternate stimuli elicited a response, while after atropine each stimulus was effective (top row). There was no inotropic effect for the reasons given previously and also it will be noted that delay between the stimulus and response was increased. When stimuli of 100 ms duration were applied every stimulus was effective (bottom row). Addition of atropine (10 μg/ml) increased the contractile force developed by the ureter to each stimulus and also decreased the delay between stimulus and response. In other experiments the inotropic response to electrical stimuli was accompanied by an increase in the duration of the action potentials. Atropine also increased the duration of action potentials arising spontaneously in ureters. Fig. 3 shows how atropine (1 μg/ml) increased the duration of spontaneous action potentials by 30% at half-maximal amplitude. In this experiment the reference side of the electrode was perfused with Ringer solution rather than isotonic KCl. The action potentials were conducted through the sucrose gap and appear biphasic. The reason for this is that since the ureter is a hollow

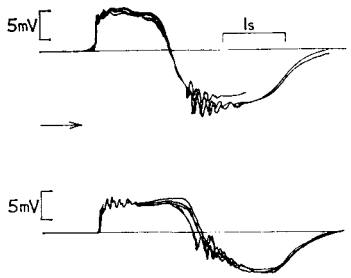

FIG. 3. Superimposed spontaneous action potentials in an isolated ureter. The lower record illustrates activity 10 min after exposure to atropine, 1 μg/ml.

organ the lumen is probably not ion-free where it passes through the non-ionic sucrose solution.

Experiments were performed in which the experimental tissue was bathed in modified Ringer-solutions. Fig. 4 illustrates an experiment in which all but 5% of the NaCl

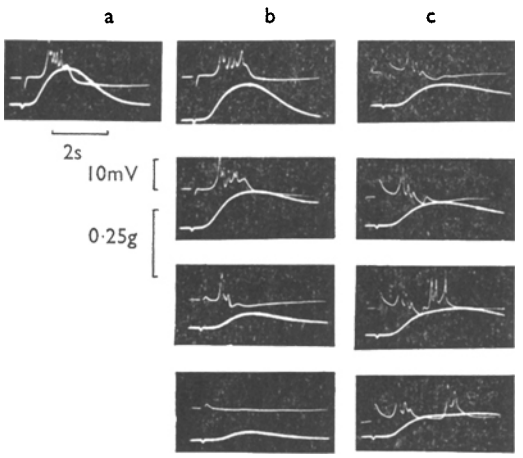

FIG. 4. Electrical and mechanical activity of a ureter in response to electrical stimuli of 60 ms duration at a frequency of 0·02 Hz. (a) control, (b) responses obtained in low sodium Ringer over a period of 20 min, (c) responses obtained in low sodium Ringer containing 10 μg/ml atropine. The responses were obtained after 15 to 25 min exposure to atropine.

was replaced by sucrose, while the concentrations of other cations remained constant. Action potentials and tension responses disappeared over a period of about 20 min. First the plateau was lost, leaving only spike activity and finally this too disappeared. The tension responses obtained at this stage were small and not conducted. When atropine (10 μg/ml) was added to the low sodium solution, spontaneous activity and intermittent responses to electrical stimuli reappeared after a delay of 15 min. The electrical responses were essentially spikes arising from small plateaux, and were accompanied by tension responses.

DISCUSSION

The results suggest atropine increases the safety factor for conduction in isolated guinea-pig ureters. Thus previously ineffective stimuli become effective, action

potentials at a given frequency are increased in duration and latency is decreased. Thus once activity is initiated it spreads to a greater proportion of the smooth muscle fibres and an inotropic effect results.

Wood (1972) and Christensen & Lund (1968) have reported similar effects for the circular intestinal muscle of cats and for the oesophagus, ileum and transverse colon of opossum respectively. Both these reports, like this one, describe the effects of atropine at high concentrations (10^{-5}–10^{-4} g/litre). A common feature of these reports, and of the earlier ones on chick amnion (Cuthbert 1963a, b), is that atropine facilitates conduction so that spontaneous activity is increased, electrical activity spreads further from its source and the tension responses to electrical or mechanical stimuli are potentiated. While Christensen & Lund (1968) ascribe the effect to a direct action on the smooth muscle cells, Wood (1972) claims the effects result from the blockade of cholinergic enteric neurons. His main evidence for this is that stimulation by atropine diminishes when preparations are stored in the cold. The great similarity of the effects of atropine in a variety of different smooth muscles together with the fact that the chick amnion is never innervated makes an explanation based on a direct effect on muscle cells seem the most plausible.

There is little evidence to indicate what the direct effect of atropine might be. The action potentials in ureters consist usually of a plateau and superimposed spikes. Kuriyama (1970) has summarized the evidence which suggests that in ureters the current during the spikes is carried by calcium and that the plateau is due to sodium entry. Here we have seen that atropine increases both the plateau and in low sodium solutions the spike components. It would seem very unlikely that intramural nerves could function in low sodium solutions since the action potential spike in nerves is sodium dependent. From these considerations it appears that atropine may increase the inflow of both sodium and calcium in muscle during electrical activity and that the inotropic effect may result from an increased safety factor for conduction and increased calcium influx.

REFERENCES

CHRISTENSEN, J. & LUND, G. F. (1968). *J. Pharmac. exp. Ther.*, **163**, 287–289.

CUTHBERT, A. W. (1963a). *J. Physiol.*, **168**, 20–21P.

CUTHBERT, A. W. (1963b). *Brit. J. Pharmac. Chemother.*, **21**, 285–294.

CUTHBERT, A. W. (1965). *J. Physiol.*, **180**, 225–238.

KURIYAMA, H. (1970). In *Smooth Muscle*, pp. 366–395. Editors: Bülbring, E., Brading, A., Jones, A. and Tomita, T. London: Arnold.

MAGNUS, R. (1905). *Pflüg. Archiv Ges. Physiol.*, **108**, 1–71.

WOOD, J. D. (1972). *Am. J. Physiol.*, **222**, 118–125.