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The effect of known K^+-channel blockers on the electrical activity of bovine lymphatic smooth muscle

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Abstract. The effects of known K^+-channel blockers on the electrical properties of bovine lymphatic smooth muscle were investigated using the double sucrose-gap technique. Constant current anodal pulses elicited hyperpolarizing electrotonic potentials (EP's) which were characterised by a "sag" in the potential record. Current/voltage relationship (I/V), which were examined by measuring EP amplitude at the end of 5 s anodal pulses (< 30 μA), showed an apparent increase in conductance with increasing hyperpolarization. In the presence of caesium (10 mM), 4-aminopyridine (10 mM) or in the absence of external K^+ the sag in the EP was lost and the inward rectification characteristic of the control I/V relationship was abolished. Barium (2.5 mM) also abolished in sag in the EP although TEA (10 mM) had no effect on either EP shape or I/V relationship. Thus it would appear that lymphatic smooth muscle shows inward rectification which is slowly activating and is blocked by some of the known K^+-channel blockers or by the removal of external K^+.

Key words: Lymphatics – Smooth Muscle – K^+-channel blockers

Introduction

Lymphatic vessels are spontaneously contractile and their regular phasic contractions are known to propel lymph in the living animal and in isolated cannulated preparations (Campbell and Heath 1973; McHale and Roddie 1976, 1983). Rapid contraction of the vessel followed by a longer pause, together with the organisation of the lymphatic into valved segments, has been shown to allow the vessels to propel fluid in the manner of a number of small hearts in series (McHale and Roddie 1976). This pumping action of lymphatic vessels distinguishes them from most other organs which have smooth muscle in their walls since the latter are concerned only to produce sustained contraction or rhythmic variation in calibre.

The underlying electrical activity of lymphatic smooth muscle also reflects the function of the vessel in propelling fluid and distinguishes it from other smooth muscle types. Electrophysiological studies have shown that each spontaneous contraction of the vessel is preceded by a single action potential and that relaxation is complete before a second action potential is fired (Kirkpatrick and McHale 1977; Allen et al. 1983; Allen and McHale 1986). In most other spontaneously active smooth muscles contraction is initiated by a burst of action potentials which, in turn, may be preceded by slow membrane depolarization (slow wave). The "contraction" recorded from such preparations when isolated in an organ bath is, in reality, a partially fused tetanus resulting from the summation of individual contractions initiated by each action potential within a burst (Bolton 1979). In addition, studies using the double sucrose-gap technique have shown that when hyperpolarized by constant current pulses the electrotonic potential elicited in lymphatic smooth muscle displays a characteristic "sag" in the voltage profile which develops shortly after the onset of the pulse (Allen et al. 1986; McHale et al. 1987). Other smooth muscle preparations have also been shown to respond to hyperpolarizing currents in this way (Tomita 1966; Bülbring and Tomita 1967; Bolton 1972; Sims et al. 1985) and more recently, Benham et al. (1987) have described an inwardly rectifying current in single isolated jejunal smooth muscle cells to which sodium and potassium ions make a contribution and which is responsible for the decline in electrotonic potential amplitude with time. It was therefore the purpose of this investigation to examine the response of lymphatic smooth muscle to constant current anodal stimulation in more detail, with particular reference to the involvement of K^+ in the response.

Methods

The double sucrose-gap technique was used to record lymphatic vessel electrical activity in response to constant current (< 30 μA) anodal stimulation. Segments of lymphatic 3 cm in length and 2 mm in diameter were dissected from the mesenteries of recently slaughtered cattle. Smooth muscle cells in these vessels are arranged in a loose "basket-weave" which could be described neither as longitudinal or circular (McHale 1976) and in this respect resemble human lymphatic trunks (Boggan and Palfrey 1973). It is not surprising therefore that attempts to use either longitudinally or circularly cut strips were never successful. Nevertheless when a complete vessel was stretched lengthwise the smooth muscle cells were found to line up longitudinally and this is how the lymphatics (with their lumens collapsed) were mounted in the double sucrose gap apparatus. This consisted of a perspex trough 1 cm wide, 1 cm deep and 4 cm in length divided into four compartments by means of condom rubber partitions in which small holes had been made to allow the lymphatic to pass through. Approximately 2 mm of tissue was exposed to test solution which was pre-heated to 37° C

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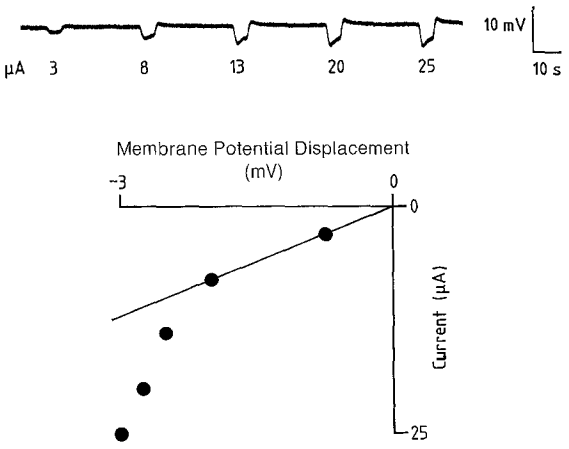

Fig. 1. In the upper record hyperpolarizing electrotonic potentials (EP's) were elicited by 5 s constant current anodal pulses applied at approximately 35 s intervals. Current strength is indicated below the record. Note the development of "sag" in the EP with increasing hyperpolarization. The current/voltage (I/V) relationship plotted in the *lower graph* was obtained by measuring the amplitude of the EP at the end of each pulse and plotting this (*abscissa*) against current strength (*ordinate*). Membrane conductance is seen to increase with increasing current strength. The *solid line* indicates the relationship which would exist in the absence of a conductance change

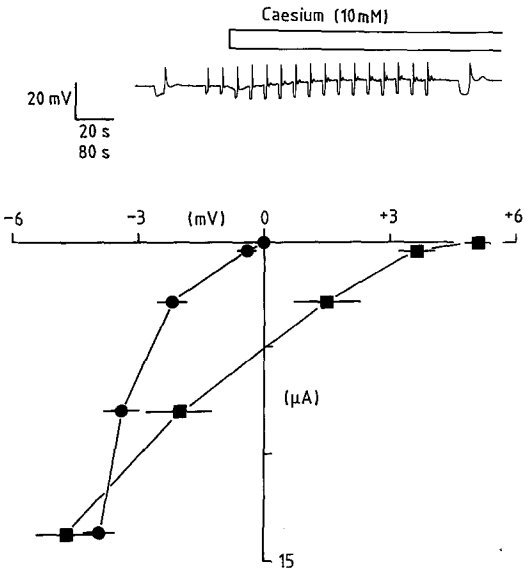

Fig. 2. The effect of caesium (10 mM) on membrane resistance and EP shape. In the *upper record* EP's were elicited every 30 s (approx.) by 5 s duration 8 μA pulses. At the beginning and end of the record paper speed was increased to allow closer examination of the EP shape. Caesium was added as indicated above the record. The *lower graph* shows the I/V relationship for the same preparation under control conditions (●) and in the presence of caesium (10 mM; ■). Each point is the mean of 6 experiments. *Horizontal bars* represent ±1 SEM

and delivered by means of a Watson Marlowe flow inducer at a rate of 5 cm^3/min, to allow a complete change of fluid every 10 s. The other compartments were perfused with deionised isotonic sucrose and K_2SO_4 solutions and their arrangement and that of the stimulating and recording electrodes was essentially similar to that of Bülbring and Tomita (1969). The compartment widths were as follows K_2SO_4, 16 mm; sucrose, 8 mm; Krebs, 2 mm; and sucrose, 16 mm. The electrodes were 2 mm rings of platinum-iridium wire and placed one at the sucrose-Krebs interface and the other 12 mm away in the sucrose compartment. The resistance of the sucrose gap in the absence of tissue was in the order of 2 MΩ. Tension was recorded by connecting one end of the segment to a Statham UC3 isometric force transducer and electrical and tension recordings were made with either a Gould Brush 2200 or Lectromed MX214 chart recorder.

Solutions used were as follows: Krebs solution (in mM) NaCl, 120; $NaHCO_3$, 25; KCl, 5.8; NaH_2PO_4, 1.2; $MgCl_2$, 1.2; $CaCl_2$, 2.5; glucose, 5.55. The solution was gassed with 5% CO_2 in O_2 and had a pH of 7.4 at 37° C. K^+ free solution was obtained by equimolar replacement of KCl with NaCl. When used, tetraethylamonium chloride (TEA), caesium chloride, 4-aminopyridine (4-AP), replaced an equimolar amount of NaCl. Barium chloride, when used, was added to the solution to give a final concentration of 2.5 mM.

Results

The upper record of Fig. 1 shows the change in membrane potential recorded in response to 5 s duration constant current anodal pulses of 3–25 μA applied at approximately 35 s intervals. As the current strength increased the hyperpolarizing electrotonic potential (EP) was characterised by a marked sag in the potential which developed approximately 1 s after the onset of the pulse. On cessation of the pulse the larger EP's decayed back to the resting potential with a slight depolarizing overshoot.

To examine the current/voltage (I/V) relationship of the preparation the amplitude of the EP was measured at the end of each 5 s pulse and plotted against current strength as shown in the lower graph of Fig. 1. It is clear from this relationship that when hyperpolarized by more than about 2 mV there is an apparent increase in conductance with increasing current strength. The solid line on the graph indicates the relationship which would exist in the absence of any conductance change with hyperpolarization. All preparations investigated (> 50) showed this apparent increase in membrane conductance with increasing current strength.

The effect of caesium and barium

The upper record of Fig. 2 shows the effect of caesium (10 mM) on the response to membrane hyperpolarization. In this experiment EP's were elicited by 8 μA pulses (5 s duration) delivered at approximately 30 s intervals. At the beginning and end of the record paper speed was increased to allow examination of EP shape. Under control conditions the EP showed the characteristic sag previously described. Single action potentials were fired at the end of each pulse (anode-break excitation). Upon addition of caesium (10 mM) the preparation depolarized, membrane resistance increased (as indicated by the increase in EP amplitude) and the sag in the EP was lost. Note that the effect of caesium on the amplitude and shape of the EP was evident before membrane depolarization. The amplitude or shape of the action potential was not noticeably altered by caesium.

In the lower graph of Fig. 2, I/V relationships under control conditions (circles) and in the presence of caesium

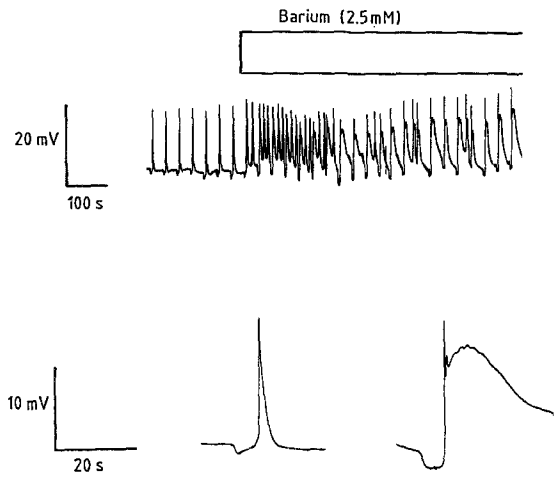

Fig. 3. Barium (2.5 mM) caused membrane depolarization, spontaneous firing of action potentials and increased membrane resistance. In addition, the action potential duration was greatly increased in the presence of barium and the sag in the EP was lost. In the *upper record* EP's were evoked by 8 μA pulses and barium was added as indicated above the record. The *lower records* (at higher gain and expanded time scale) show EP's and anode-break responses in control solution and after 15 min in Krebs containing barium (2.5 mM)

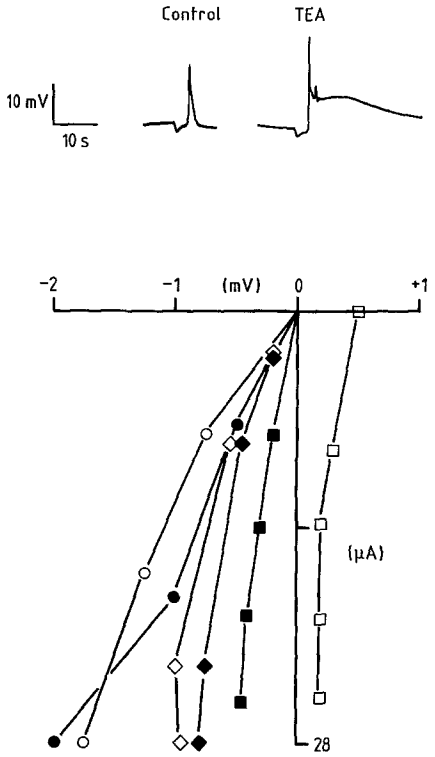

Fig. 4. The *upper records* show EP's and anode-break responses evoked by 8 μA pulses in the absence (control) and presence of TEA (10 mM). Although TEA had quite a dramatic effect on the amplitude and duration of the action potential it failed to abolish the sag in the EP · I/V curves for three experiments are shown below the original records. The control relationships are shown by the *closed symbols*. The corresponding *open symbols* show the relationship after 30 min in the presence of TEA (10 mM)

(10 mM; squares) are plotted. Each point is the mean of 6 experiments. Horizontal bars represent ± 1 SEM. It is clear that the increase in membrane conductance with increasing current strength (characteristic of the control) is largely abolished by caesium.

The upper record of Fig. 3 illustrates the effect of barium (2.5 mM). During the control period the preparation was hyperpolarized at 35 s (approx) intervals with 8 μA, 5 s pulses. Action potentials were fired at the end of each EP as before. Addition of barium caused depolarization, increased membrane resistance and induced spontaneous action potential firing. After approximately 3 min spontaneous firing of action potentials was reduced although anode-break excitation was evident and spontaneous fluctuations in membrane potential still occurred. Closer examination of the EP and anode-break response (Fig. 3, lower records) shows that barium abolishes the sag in the EP and dramatically increases the action potential duration. It was not possible to accurately determine I/V relationships in the presence of barium because of continual fluctuation in membrane potential and the occurrence of spontaneous action potentials.

The effect of TEA and 4-aminopyridine (4-AP)

Like barium, TEA (10 mM) dramatically increased action potential duration although it failed to abolish the sag in the EP or in any way alter the response to anodal stimulation. The upper records of Fig. 4 show EP's and anode-break responses evoked by 8 μA pulses in the absence (control) and presence of TEA (10 mM). Although TEA increased both action potential height and duration it failed to abolish the sag in the EP · I/V curves for three experiments are shown below the original records. The control relationships are shown by the closed symbols. The corresponding open symbols show the relationship in the presence of TEA (10 mM).

In contrast to the effect of TEA, 4-AP (10 mM) abolished the sag in the EP but had little effect on action potential duration or amplitude. The upper record of Fig. 5 again shows EP's and anode break responses to constant current (22 μA) anodal pulses. In the presence of the drug the sag in the EP, characteristic of the control response, is lost although the anode-break response is not markedly altered. Again, I/V curves for the control (circles) and in the presence of 4-AP (10 mM; squares) are shown below the original records. Each point is the mean of five experiments. Horizontal and vertical bars represent ± 1 SEM.

The effect of zero K^+ solution

External caesium is known to block only inward K^+ currents in other preparations (Hagiwara et al. 1976; Gay and Stanfield 1977; Adelman and French 1978). The finding that caesium (and the other known K^+ channel blockers barium and 4-AP) is capable of preventing the delayed increase in conductance during hyperpolarization suggests that this is due to delayed activation of an inward K^+ current. Further support for this hypothesis comes from the experiments illustrated in Figs. 6 and 7 in which the effect of K^+-free solution was examined. In Fig. 6, EP's were evoked by 5 s pulses delivered at approximately 30 s intervals. Upon the introduction of K^+-free solution the preparation depolarized, membrane resistance increased and the sag in the EP was lost. The gap in the record represents a 20 min

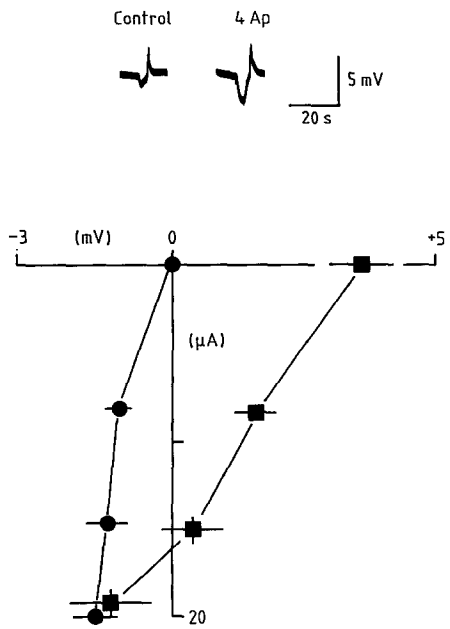

Fig. 5. The *upper records* shown EP's and anode-break responses evoked by 22 μA pulses in the absence (control) and presence of 4-aminopyridine (4-AP; 10 mM). I/V relationships under control conditions (●) and after 20 min in the presence of 4-AP (■) are plotted below the original records. Each point is the mean of five experiments. *Horizontal* and *vertical bars* represent ± 1 SEM. If not shown, *error bars* were smaller than the symbol

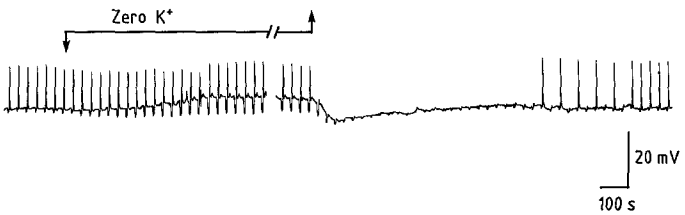

Fig. 6. The effect of K^+-free solution (isosmotic replacement with Na^+) on membrane potential, membrane resistance and EP shape. In the experiment illustrated EP's were elicited at 30 s (approx.) intervals. K^+-free solution was perfused during the period indicated above the record. The gap in the record represents a 15 min period

period. Reintroduction of K^+ caused membrane hyperpolarization to a level beyond the control value, a dramatic reduction in EP amplitude and loss of the anode-break response. Both membrane potential and resistance returned to their control levels within 15 min. Similar effects of zero K^+ solution on membrane potential have been reported for other smooth muscle preparations (taenia coli: Tomita and Yamamoto 1971; Casteels et al. 1971; Bülbring and Tomita 1977; myometrium: Bülbring and Surszewski 1974; portal vein: Kuriyama et al. 1971; ileum: Bolton 1973) and suggests an inhibition of an electrogenic sodium pump by removing K^+ and its activation upon K^+ readmission.

The effect of zero K^+ solution on EP shape is more obvious in the records of Fig. 7. The upper record of this figure shows the response to a 20 μA anodal pulse in normal Krebs solution (control) and after 15 min in K^+-free solution. It is clear that in the absence of external K^+ membrane resistance is increased and the sag in the EP is lost. The I/V

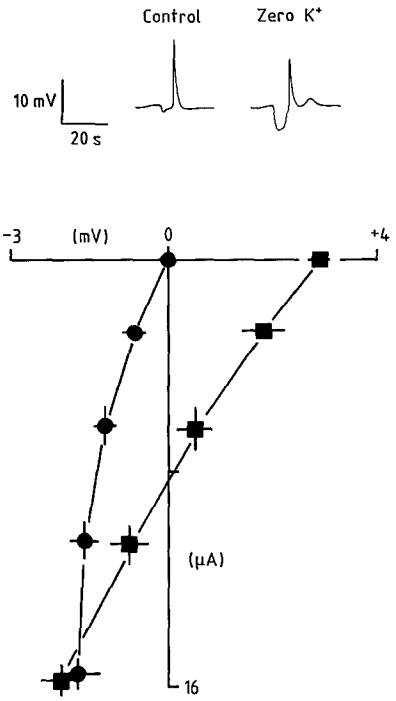

Fig. 7. The *upper record* shows the EP's (and anode-break responses) evoked by 5 s duration 20 μA pulses in control solution and 15 min after removal of external K^+. I/V relationships under control conditions (*circles*) and in zero K^+ solution (■) are plotted below the record. *Points* are the mean of 5 experiments. *Horizontal* and *vertical bars* represent ± 1 SEM. If not shown, *error bars* were smaller than the symbols

relationships plotted below the records of Fig. 7 confirm that zero K^+ solution largely abolishes the hyperpolarizing conductance change characteristic of the control. The control relationship is shown by the circles, the relationship in zero K^+ solution by the squares. Each point is the mean of five experiments. Vertical and horizontal bars ± 1 SEM.

The effect of high K^+ solution

It might be argued that in the absence of membrane potential control, such as in this study, the abolition of rectification by the K^+-channel blockers caesium, barium and 4-AP and also by zero K^+ solution was a consequence of the associated depolarization. However, the depolarization was slow to develop, membrane resistance was increased and the sag in the EP was consistently abolished before any significant change in membrane potential had occurred (e.g. Figs. 2 and 6). Further, depolarization effected by high K^+ solution (20 mM K^+, Fig. 8) was associated with a fall in membrane resistance and little obvious change in EP shape. Similarly, depolarization effected by ouabain (10^{-5} M, Allen et al. 1986) is also without effect on EP shape.

Discussion

This investigation has demonstrated that in response to constant current anodal stimulation lymphatic smooth muscle shows a delayed increase in membrane conductance. This is reflected in the shape of the EP which exhibits a characteristic sag in the voltage profile. The sag is virtually eliminated

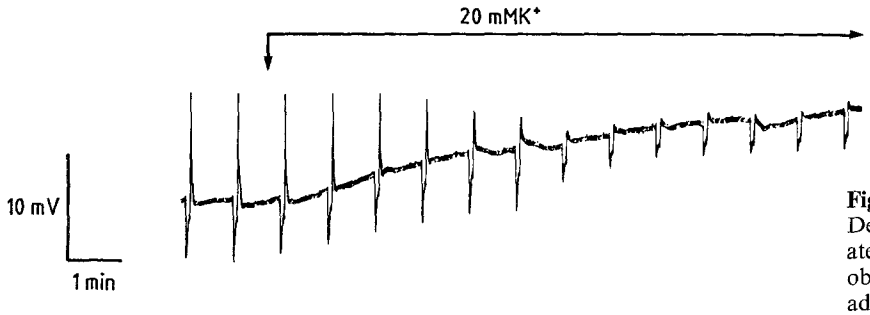

Fig. 8
Depolarization by 20 mM K^+ solution was associated with a fall in membrane resistance but little obvious change in EP shape. High K^+ solution was added as indicated above the record

by the known K^+ channel blockers caesium (10 mM), barium (2.5 mM) and 4 AP (10 mM) and is also lost in the absence of external K^+. These observations suggest that the sag is due to activation of a time-dependent inward rectifying current carried by K^+ ions. However TEA failed to alter the response to anodal stimulation although it had a dramatic effect on both action potential amplitude and duration. TEA is also known to be ineffective in blocking inward rectification in olfactory cortex neurons and the smooth muscle of the rabbit jejunum (Constanti and Galvan 1983; Benham et al. 1987).

Inward-going (or anomalous) rectification was first described by Katz (1949) as a property of skeletal muscle fibres which allows K^+ to move in more easily than out across the membrane. The rectification is anomalous since it is in a direction opposite to that predicted by the Goldman-Hodgkin-Katz equation (Goldman 1943; Hodgkin and Katz 1949) and it accounts for the increase in membrane conductance which is observed with increasing membrane hyperpolarization (Katz 1949; Adrian 1969). Time dependent activation of the rectifying conductance has been described (Hestrin 1981; Leech and Stanfield 1981) and a similar inward rectifying conductance has been identified in the egg cell membrane of starfish (Hagiwara and Takahashi 1974; Hagiwara et al. 1976) and a tunicate (Ohmori 1978).

Although we have no measure of the membrane currents underlying rectification in lymphatic smooth muscle it seems likely that this is similar to the anomalous rectifier previously described. Like the rectifier in lymphatics the anomalous rectifier in both starfish egg cells and in frog skeletal muscle is blocked by caesium and barium (Hagiwara et al. 1978; Standen and Stanfield 1978; Gay and Stanfield 1977; Hagiwara et al. 1976) and is sensitive to changes in external K^+ concentration (Hagiwara and Yoshii 1979; Hestrin 1981; Leech and Stanfield 1981). However, other explanations that might explain the sag in the EP cannot be ruled out. For example, it is possible that hyperpolarization deactivates an outward current which is normally maintained at the resting potential such as the "M" current described in bullfrog sympathetic neurons (Adams et al. 1982a, b) and gastric smooth muscle cells of the toad (Sims et al. 1985). The M current is known to be sensitive to barium but such an explanation for rectification in lymphatic smooth muscle would be difficult to reconcile with its dependence on external K^+. Further, it is possible that a slowly activating inward rectifying current of the type described in cardiac muscle (I_f. Di Francesco 1981a, b, 1982, 1984) and hippocampal pyramidal cells (I_q. Adams and Halliwell 1982; Halliwell and Adams 1982) may contribute to the rectification described in this study although these currents, while blocked by caesium, are unaffected by barium.

It is difficult to draw any definite conclusions about the properties of the membrane current(s) responsible for rectification in lymphatic smooth muscle from the current clamp data we have described. All we can safely conclude is that lymphatic smooth muscle shows a marked degree of inward rectification and that this is slowly activating and is blocked by some of the known K^+ channel blockers or by the removal of external K^+. Further characterisation and quantification will only be possible using voltage-clamp of potential, which has not as yet been applied to lymphatic smooth muscle. It is possible that in lymphatics, as suggested for other tissues, the inward rectification may be activated by hyperpolarization which follows repetitive activity thus limiting the consequent depression of excitability.

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