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# Effects of streptomycin sulphate on $I_{CaL}$, $I_{Kr}$ and $I_{Ks}$ in guinea-pig ventricular myocytes

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**Abstract**

In single guinea pig ventricular myocytes, streptomycin sulphate (streptomycin) reduced intracellular $Ca^{2+}$ transients ($IC_{50}$ 1.9 mM) and contractility ($IC_{50}$ 1.0 mM), 2 mM streptomycin prolonged the action potential. Under switch voltage clamp, 2 mM streptomycin reduced the L-type $Ca^{2+}$ current ($I_{CaL}$) amplitude and ($Ca^{2+}$-dependent) relative inactivation at positive membrane potentials and reduced the rapid and slow components of the delayed rectifier current ($I_K$). This latter effect seemed $Ca^{2+}$-dependent, not being seen when nifedipine and BAPTA were used to reduce intracellular $Ca^{2+}$. Fifty micromolars of streptomycin had no significant effects on any parameter studied. We conclude that the negative inotropic effect of streptomycin results from blockade of $I_{CaL}$, and thus, a reduction of intracellular $Ca^{2+}$ transients, while prolongation of the action potential is more consistent with effects on $I_K$. These observations link mechanical and electrical effects of streptomycin that may be important, for example, when streptomycin is used to block stretch-activated events in cardiac muscle. 

*Keywords:* Cardiac myocyte; Streptomycin sulphate; Ion channel

## 1. Introduction

Streptomycin sulphate (streptomycin), in common with other aminoglycosidic antibiotics, decreases the contractility of cardiac muscle (e.g. Cohen et al., 1970; Slinker and Tobias, 1996; Belus and White, 2001a). The mechanism behind this negative inotropic effect has not been demonstrated, but it is associated with a reduction in the amplitude of intracellular calcium ($[Ca^{2+}]_i$) transients (Belus and White, 2001a) and may be linked to a decrease in $Ca^{2+}$ influx through the L-type $Ca^{2+}$ current ($I_{CaL}$) because streptomycin blocks these channels in skeletal muscle (Haws et al., 1996) and vascular smooth muscle (Miller and Langton, 1998).

Streptomycin has also been reported to block mechanosensitive channels (see Hamill and McBride, 1996; Pascarel et al., 1997 for reviews). In cardiac muscle, it blocks stretch-activated arrhythmias and alterations in repolarisation (Nazir et al., 1995; Salmon et al., 1997; Eckardt et al., 2000; Babuty and Lab, 2001) and stretch-induced increases in $[Ca^{2+}]_i$ (Gannier et al., 1994). The use of streptomycin in such conditions requires a detailed knowledge of its actions if observations are to be correctly interpreted; however, little is known, particularly about its actions on cardiac ion channels.

The purpose of this work, therefore, was to test the hypothesis that the negative inotropic effect of streptomycin is the result of decreased $Ca^{2+}$ influx via $I_{CaL}$ and thus, decreased $[Ca^{2+}]_i$ transients and if so, provide the first demonstration of this pathway for any aminoglycosidic antibiotic in a given cardiac preparation. Further, we wished to relate any alterations in action potential configuration to underlying ion channel activity, with the aim of aiding interpretation of the effects of streptomycin when, for example, it is used to block stretch-activated events.

## 2. Materials and methods

### 2.1. Isolation of guinea pig ventricular myocytes

Left ventricular, single guinea pig ventricular myocytes were isolated according to the method of Frampton et al. (1991). Briefly, animals (approximately 300 g) were killed by Home Office Schedule 1 methods. Hearts were removed and mounted on a Langendorff apparatus and perfused with a HEPES-based isolation solution of the following com-

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position (mM): NaCl 130; KCl 5.4; $NaH_2PO_4$ 0.4; $MgCl_2 \cdot 6H_2O$ 1.4; $CaCl_2$ 1.8; HEPES 10; glucose 10; taurine 20; creatine 10; 1% bovine serum albumin (pH 7.3). When the coronary circulation had cleared of blood, perfusion was continued with $Ca^{2+}$-free isolation solution (in which 1.8 mM $CaCl_2$ had been replaced with 0.1 mM EGTA for 5 min). This was followed by 10-min perfusion with an isolation solution containing 50 μM $Ca^{2+}$, 1 mg $ml^{-1}$ collagenase (type II; Worthington Biochemical, New Jersey) and 0.1 mg $ml^{-1}$ protease (type XIV; Sigma). The left ventricle was then separated from the rest of the heart, minced and gently shaken at 37 °C in collagenase containing isolation solution supplemented with an additional 1% bovine serum albumin. Cells were filtered from this solution at 5-min intervals and resuspended in the isolation solution containing 1.8 mM $Ca^{2+}$.

Isolated cells were placed in an experimental chamber on the stage of an inverted microscope (Diaphot, Nikon, Japan). The chamber was continuously superfused with a HEPES-based physiological solution containing (mM): NaCl 113; KCl 5; $MgSO_4 \cdot 7H_2O$ 1; $NaH_2PO_4$ 1; $CH_3COONa$ 20; $CaCl_2$ 2; HEPES 5; glucose 10; insulin 5 units $l^{-1}$; pH was adjusted to 7.3 with NaOH. Aliquots of stock streptomycin (Sigma) solution were added to this solution. All experiments were performed at 37 °C. Effects of streptomycin were measured at steady state, approximately 1 min after exposure and after wash.

### 2.2. Measurement of cell length and $[Ca^{2+}]_i$

Cells were field-stimulated by external platinum electrodes at a frequency of 0.5 Hz, cell length and $[Ca^{2+}]_i$ were measured simultaneously. Myocytes were illuminated with red light (>610 nm) to generate an image of the cell detected by a camera mounted on the microscope and displayed on a monitor. This image was measured using an edge detection system (Crescent Electronics, Utah) and the percentage change in cell length following stimulation was our index of contractility. Cells were loaded with the $Ca^{2+}$-sensitive fluorescent indicator fura-2 AM (acetoxymethyl ester form of fura-2) (Molecular Probes, OR) by incubation in 1.8 mM $Ca^{2+}$ isolation solution containing 3–5 μM fura-2 AM for 10 min at 22–24 °C. The ratio of fluorescence emitted at 510 nm in response to alternate excitations with light of 340 and 380 nm (340:380 ratio) was used as our index of $[Ca^{2+}]_i$.

### 2.3. Measurement of action potentials and membrane currents

Action potentials were measured using sharp microelectrodes containing 600 mM KCl (resistance of 30–60 MΩ) in conjunction with an Axopatch 2B amplifier (Axon Instruments). High chloride content of microelectrodes can cause 'blebbing' of the myocyte sarcolemma; however, we saw no

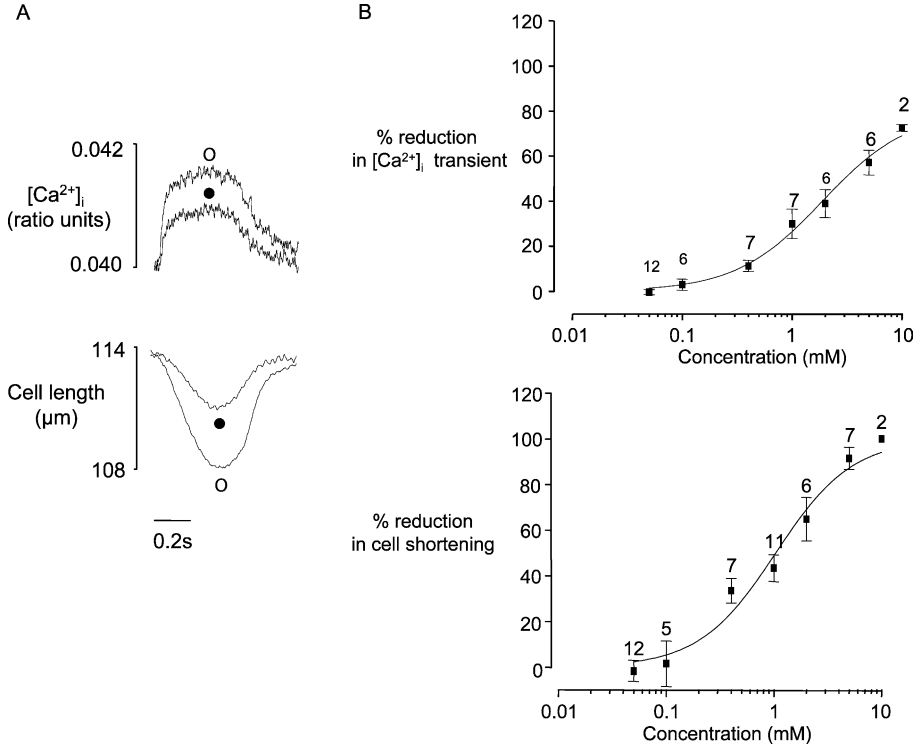
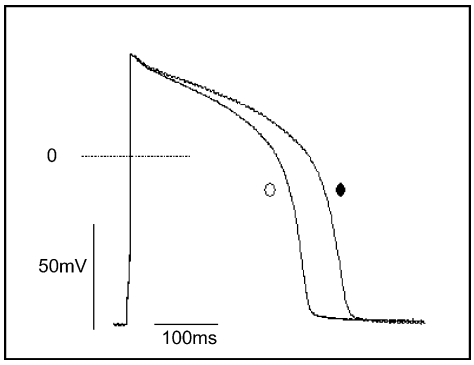



Fig. 1. Effects of streptomycin on $[Ca^{2+}]_i$ transients and cell shortening in guinea pig ventricular myocytes. (A) Experimental records of $[Ca^{2+}]_i$ transients (upper traces) and cell shortening (lower traces) in the absence (○) and presence (●) of 1 mM streptomycin. (B) Concentration–inhibition curves for the effect of streptomycin on $[Ca^{2+}]_i$ transients (upper panel) and cell shortening (lower panel). Data were fitted to a Hill equation, $n_H$ which is the slope of the relationship and $IC_{50}$ which is the concentration of the drug at half-maximal inhibition are given in the text and the number of observations are given in the figure.

Table 1
Effect of 2 mM streptomycin on action potential characteristics of guinea pig ventricular myocytes




| | Control | Streptomycin |
|---|---|---|
| Membrane potential (mV) | − 77.9 ± 1.1 | − 79.0 ± 1.3 |
| Peak amplitude (mV) | 128.0 ± 1.8 | 126.6 ± 1.4 |
| APD20 (ms) | 134.5 ± 18.2 | 160.1 ± 18.2[a] |
| APD50 (ms) | 262.5 ± 21.3 | 296.9 ± 19.5[a] |
| APD90 (ms) | 309.1 ± 21.3 | 337.1 ± 19.2[a] |
| Number of cells | 15 | 15 |

Streptomycin significantly prolonged the action potential duration at 20% (APD20), 50% and 90% repolarisations but had no significant effect on resting membrane potential or action potential amplitude, mean ± S.E.M. Experimental records of APD in the absence (○) and presence (●) of streptomycin are shown inset.

[a] $P < 0.05$.

evidence of this in our experiments. Action potentials were elicited at a stimulation frequency of 0.5 Hz by 2-ms current pulses at just above the threshold amplitude. Membrane currents were measured using switch voltage clamp with a microelectrode resistance <30 MΩ, and a switching frequency of 3 kHz, an oscilloscope was used to check the settling characteristics of the microelectrode. Voltage clamp protocols to measure $I_{CaL}$ and the rapid ($I_{Kr}$) and slow ($I_{Ks}$) components of the delayed rectifier ($I_K$) are detailed in Results. Membrane currents were not normalised to cell size as all comparisons were between control and streptomycin and were paired in each cell.

### 2.4. Statistical analysis

Data were expressed as mean ± S.E.M. of $n$ (=number of cells) observations. Statistical significance was set at 0.05 and was tested using either Student's paired or unpaired $t$-test as appropriate or repeated measures analysis of variance (ANOVA) when analysing current–voltage relationships.

## 3. Results

### 3.1. Effects of 50 μM streptomycin

The effect of exposure to 50 μM streptomycin on all the parameters described below was tested in order to detect a potential subthreshold concentration. For brevity, these data are not presented in full. We found that 50 μM streptomycin had no effect ($P>0.05$) upon cell shortening ($n=12$), $[Ca^{2+}]_i$ transients ($n=12$), action potential duration ($n=6$), $I_{CaL}$ ($n=11$), $I_{Kr}$ ($n=9$) or $I_{Ks}$ ($n=6$).

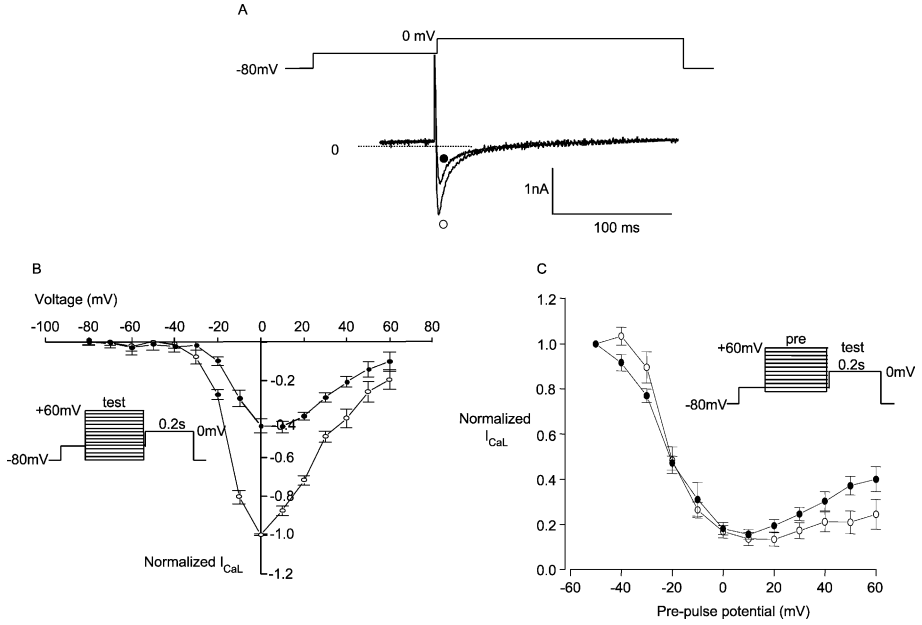



Fig. 2. Effect of streptomycin on $I_{CaL}$ in guinea pig ventricular myocytes. $I_{CaL}$ before (○) and during (●) exposure to 2 mM streptomycin. (A) Representative traces of $I_{CaL}$. (B) Current activation–voltage relationship, mean ± S.E.M. for $n=9$. Streptomycin caused a significant reduction in $I_{CaL}$ ($P<0.05$). (C) Current inactivation–voltage relationship, mean ± S.E.M. for $n=9$. Streptomycin caused a significantly less inactivation of $I_{CaL}$ following positive potential pre-pulses ($P<0.05$). Insets show voltage protocols.

### 3.2. Effects on cell shortening and $[Ca^{2+}]_i$ transients

Streptomycin caused a reduction in both contractility (cell shortening) and $[Ca^{2+}]_i$ transients (Fig. 1A). These effects were seen within 30 s of exposure and were fully reversible upon wash. The reduction in these two parameters was concentration dependent (Fig. 1B). These relationships were fitted to the Hill equation,

$$\%\text{inhibition} = \max[A]^{n_H}/IC_{50}^{n_H} + [A]^{n_H}$$

where max was the maximal percentage inhibition (100 for cell shortening and 80 for $[Ca^{2+}]_i$ transients, [A] was the

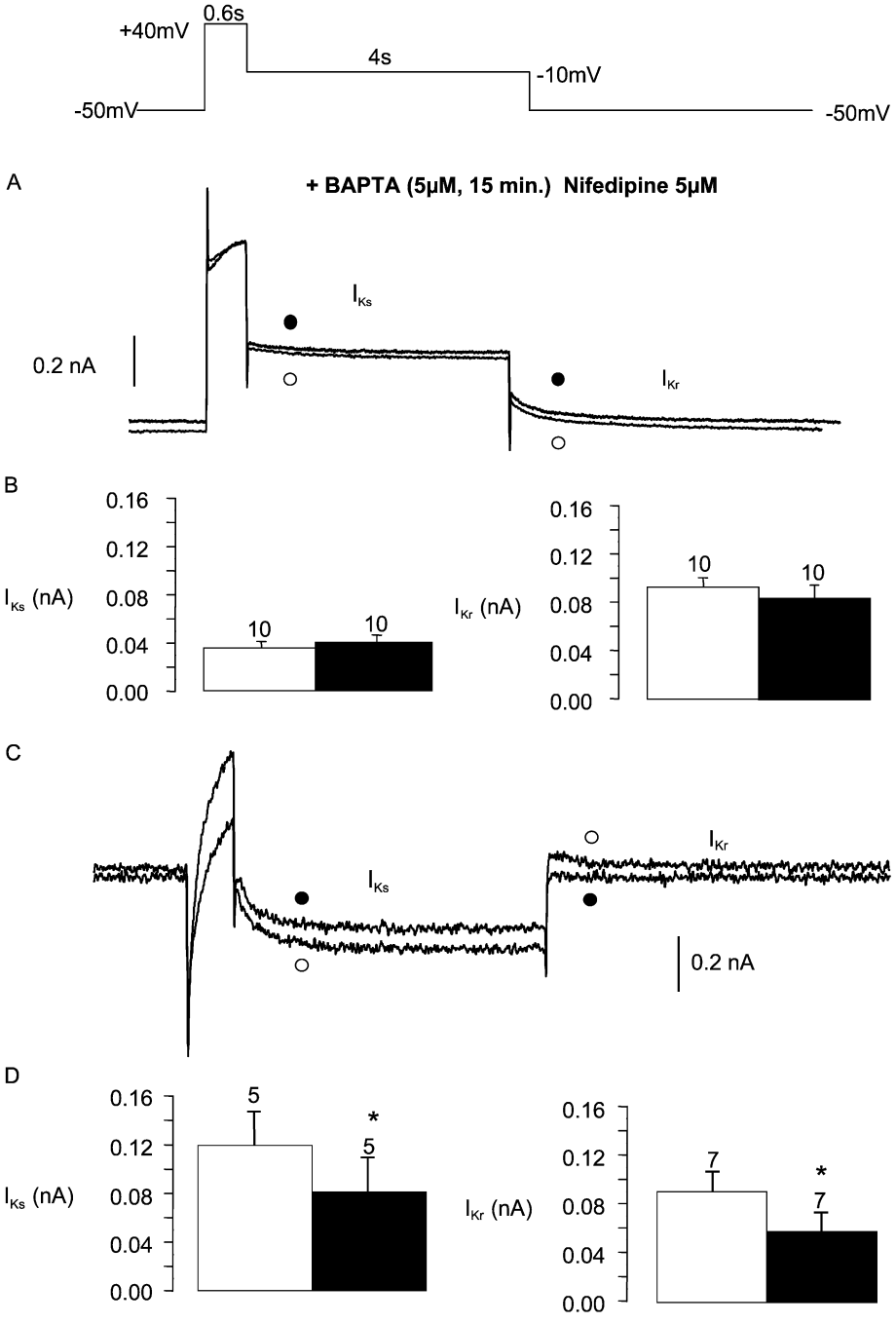



Fig. 3. Effects of streptomycin on the slow ($I_{Ks}$) and rapid ($I_{Kr}$) components of the delayed rectifier in guinea pig ventricular myocytes. (A) Representative traces of $I_{Kr}$ and $I_{Ks}$ tail currents before (○) and after (●) exposure to 2 mM streptomycin in the presence of BAPTA-AM (5 μM, 15 min) and 5 μM nifedipine. (B) Mean ± S.E.M. currents for $n = 10$. Streptomycin had no significant effect on the currents. (C) Representative traces of $I_{Kr}$ and $I_{Ks}$ tail currents before and after exposure to 2 mM streptomycin in the absence of BAPTA-AM and nifedipine. (D) Mean ± S.E.M. currents for $n = 5-7$ cells. Streptomycin significantly reduced both currents ( $^*P < 0.05$). $I_{Kr}$ and $I_{Ks}$ were measured as decaying tail currents. Inset shows voltage protocol.

antibiotic concentration, $n_H$ was the slope of the relationship and $IC_{50}$ was the concentration of the drug at half-maximal inhibition. The $IC_{50}$ was $1.04 \pm 0.15$ mM for cell shortening and $1.89 \pm 0.14$ mM for $[Ca^{2+}]_i$ transients. The $n_H$ was $0.97 \pm 0.11$ mM for cell shortening and $1.10 \pm 0.09$ mM for $[Ca^{2+}]_i$ transients. The $n_H$ values for contractility and $[Ca^{2+}]_i$ were not significantly different, the $IC_{50}$ for contractility was significantly lower than that for $[Ca^{2+}]_i$ ($P < 0.05$).

Exposure to streptomycin at concentrations close to the $IC_{50}$ of the negative inotropic effect (1 mM) had no significant effect upon the time course of shortening or the $[Ca^{2+}]_i$ transient, assessed for each parameter as the time at peak and time taken to fall from peak to half peak levels ($P > 0.05$).

### 3.3. Effects on action potential duration

The effect of streptomycin on action potentials was tested, as this represents the overall effect of an agent upon electrical activity and gives a general indication of the underlying ionic currents affected. Exposure to 2 mM streptomycin (a concentration close to the $IC_{50}$ for shortening and $[Ca^{2+}]_i$) caused a significant prolongation of the action potential duration at 20%, 50% and 90% of repolarisation. There was no significant effect upon the amplitude of the action potential or the resting membrane potential (Table 1).

### 3.4. Effects upon $I_{CaL}$

Even though action potential prolongation is not usually consistent with a block of $I_{CaL}$ (see Discussion), a reduction in $[Ca^{2+}]_i$ transients might be caused by a block of $I_{CaL}$. Cells were voltage-clamped at a membrane potential of $-80$ mV, step-depolarised to $-40$ mV for 100 ms to inactivate sodium current, then step-depolarised to 0 mV for 200 ms to evoke $I_{CaL}$ at a stimulation frequency of 0.5 Hz. Exposure to 2 mM streptomycin reduced $I_{CaL}$ from $1.02 \pm 0.1$ nA by $50 \pm 7\%$ ($P < 0.05$, $n = 10$) with no significant effect on the time to peak of the current ($6.05 \pm 0.39$ ms, $P > 0.05$) (Fig.

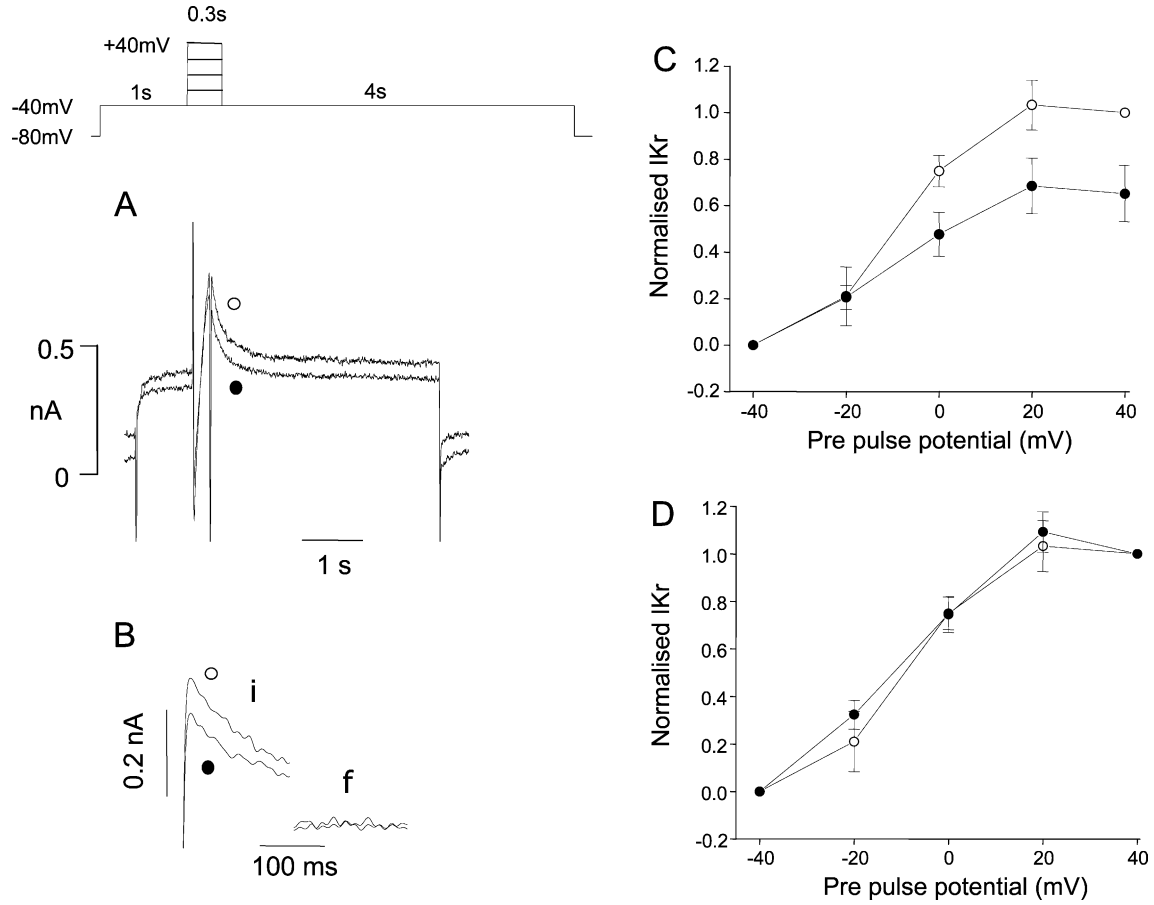



Fig. 4. Effects of streptomycin on $I_{Kr}$ in guinea pig ventricular myocytes. (A) Experimental records, showing decay of $I_{Kr}$ tail current in the absence (○) and presence (●) of 2 mM streptomycin. (B) $I_{Kr}$ tail currents from A during the initial (i) and final (f) 200 ms of the 4-s pulse to $-40$ mV, differences in resting current have been removed to draw attention to the reduction in the amplitude of $I_{Kr}$ in the presence of 2 mM streptomycin. (C) Current–voltage relationships for $I_{Kr}$ measured as tail currents at $-40$ mV before and after exposure to 2 mM streptomycin, $I_{Kr}$ normalised to that following a depolarising pulse to $+40$ mV in the absence of streptomycin (maximum, mean control current (1.0) = $0.15 \pm 0.03$ nA). Streptomycin significantly reduced $I_{Kr}$ evoked by pre-pulses to 0 and $+40$ mV ($P < 0.05$). (D) $I_{Kr}$ normalised to current in the presence or absence of streptomycin. Streptomycin did not alter the shape of the current–voltage relationship, (maximum, mean current (1.0) = $0.15 \pm 0.03$ nA in the absence and $0.098 \pm 0.02$ nA in the presence of streptomycin) mean ± S.E.M. for $n = 8$. Inset shows voltage protocol.

2A). A double-pulse protocol was then used to record the activation and inactivation current–voltage curves of $I_{CaL}$ (see inset Fig. 2). Streptomycin reduced the amplitude of $I_{CaL}$ activated by depolarisations between −30 and +60 mV but did not alter the characteristic bell shape of the curve (Fig. 2B). The inactivation curve showed the voltage and $Ca^{2+}$-dependent inactivation that is characteristic of $I_{CaL}$. However, in the presence of streptomycin, there was less ($P<0.05$) relative inactivation in response to pre-pulses between +20 and +60 mV (where inactivation is thought to be $Ca^{2+}$-dependent, see Discussion) (Fig. 2C).

### 3.5. Effects upon $I_{Kr}$ and $I_{Ks}$

Action potential prolongation is consistent with a blockade of repolarising current, and the major repolarising current in guinea pig ventricular myocytes is the delayed rectifier channel $I_K$. The effects of streptomycin on the rapid and slow components of $I_K$ were tested using electrophysiological separation of the currents with a voltage clamp protocol (Carmeliet, 1992; Heath and Terrar, 1996) shown in the inset of Fig. 3, at a stimulation frequency of 0.1 Hz. Depolarisation to +40 mV activates both $I_{Kr}$ and $I_{Ks}$, repolarisation to −10 mV reveals $I_{Ks}$ as a deactivating tail current, while subsequent repolarisation to −50 mV reveals deactivating $I_{Kr}$. Initial experiments were performed in the presence of 5 μM nifedipine following 15-min exposure to 5 μM 1,2-bis-(*O*-aminophenox)ethane-*N*,*N*,*N*,*N*,-tetraacetic acid, acetoxymethyl ester (BAPTA-AM) in order to block $Ca^{2+}$ currents and $Ca^{2+}$-activated currents that might interfere with the measurement of $I_K$. Under these conditions, 2 mM streptomycin has no effect upon the amplitude of $I_{Kr}$ and $I_{Ks}$ (Fig. 3A and B). However, in many cells, it was difficult to record both $I_{Kr}$ and $I_{Ks}$. It is known that $I_K$ is sensitive to levels of $[Ca^{2+}]_i$ and buffering of $[Ca^{2+}]_i$ can interfere with the measurement of $I_K$ (see Discussion). We therefore repeated our experiments in the absence of nifedipine and BAPTA. Under these conditions, 2 mM streptomycin caused a significant reduction in both $I_{Kr}$ and $I_{Ks}$ ($P<0.05$) (Fig. 3C and D).

We further tested the effects of streptomycin on $I_{Kr}$ using a voltage protocol that requires only short depolarisation and allows the recording of the current–voltage relationship for $I_{Kr}$ deactivating at −40 mV (Sanguineti and Jurkiewicz, 1990; Heath and Terrar, 1996, inset Fig. 4). Streptomycin reduced $I_{Kr}$ (Fig. 4A and B, mean results are shown in Fig. 4C) but did not alter the shape of the current–voltage relationship (Fig. 4D).

## 4. Discussion

### 4.1. Mechanism for the negative inotropic effect of streptomycin

Our study is the first to demonstrate that the negative inotropic effect of streptomycin is associated with reduced influx of $Ca^{2+}$ via $I_{CaL}$ and decreased $[Ca^{2+}]_i$ transients. In addition, this is the first demonstration of this pathway for any aminoglycosidic antibiotic under a single set of experimental conditions. It seems likely that reduced $Ca^{2+}$ influx leads to decreased $Ca^{2+}$ loading of sarcoplasmic reticulum (SR) and/or trigger for SR $Ca^{2+}$ release and thus, to a reduced $[Ca^{2+}]_i$ transient and as a result, a reduced contraction (see Bers, 2001). This conclusion is strengthened by the similar responses of the three parameters to streptomycin ($I_{CaL}$ 40–50% block at 2 mM, depending on the voltage protocol, $[Ca^{2+}]_i$ $IC_{50}$ 2 mM, contractility $IC_{50}$, 1 mM). The proposed mechanism seems likely to be general for the action of aminoglycosidic antibiotics as our observations for streptomycin are consistent with the fall in contraction (Adams, 1975, rat atrial muscle), $[Ca^{2+}]_i$ transients (Belus and White, 2001a, rat ventricular myocytes) and slow inward current (Hino et al., 1982, guinea pig papillary muscle) reported for gentamicin. In addition to its role in altering contractility, the fall in $[Ca^{2+}]_i$ also seems to play an important role in the electrical responses to streptomycin (see below).

### 4.2. Streptomycin and $I_{CaL}$

Little previous information on the effect of aminoglycosidic antibiotics on cardiac ion channels is available, except for the block of gentamicin on net inward and outward currents recorded from multicellular cardiac preparations (Hino et al., 1982). Our observation that streptomycin blocks $I_{CaL}$ is in agreement with findings from vascular smooth muscle (Miller and Langton, 1998) and skeletal muscle (Haws et al., 1996), the latter suggested blockade was via an open channel-type block. The activation current–voltage relationship was not affected by streptomycin but there was less inactivation in response to positive membrane potential pre-pulses. Inactivation at positive potentials is thought to be largely due to a $Ca^{2+}$-dependent mechanism (Lee et al., 1985) and in the presence of streptomycin, may occur in response to the fall in $[Ca^{2+}]_i$ transients. This suggests that the relative blockade of $I_{CaL}$ during the action potential plateau of guinea pigs will be less than that seen in response to voltage clamp pulses that elicit maximum $I_{CaL}$ (e.g. to 0 mV).

### 4.3. Streptomycin $I_{Kr}$ and $I_{Ks}$

In the presence of nifedipine and BAPTA (used to block potentially contaminating currents), streptomycin had no effect upon $I_{Kr}$ and $I_{Ks}$, though in some cells, it was difficult to elicit these currents. It is known that $I_K$ is sensitive to levels of $[Ca^{2+}]_i$ (Tohse, 1990) and it has been reported that the use of $Ca^{2+}$ buffers to reduce $[Ca^{2+}]_i$ can influence the measurement of $I_{Kr}$ (Heath and Terrar, 2000) because of the $Ca^{2+}$-dependent nature of the channels. In the absence of nifedipine and BAPTA, streptomycin reduced $I_{Kr}$ and $I_{Ks}$ tail currents (an effect inconsistent with the presence and

block of contaminating currents). Our observations suggest that in addition to any direct effect of streptomycin on these $K^+$ channels, the fall in $[Ca^{2+}]_i$ caused by streptomycin acts to decrease $I_{Kr}$ and $I_{Ks}$ via the channels' $Ca^{2+}$-dependent mechanism.

### 4.4. Effect of streptomycin on action potential duration

We have previously reported that streptomycin and gentamicin had no consistent effect upon APD in rat ventricular myocytes (Belus and White, 2001a) while here, we report a consistent lengthening of the action potential duration in guinea pig myocytes. We suggest that the different response in action potential duration to streptomycin is the result of the modulation of several ion channels and $Ca^{2+}$ handling (as demonstrated here) in two species with quite different action potential waveforms and balances of underlying currents.

In the presence of streptomycin, a fall in $I_{CaL}$ and inward $Na^+$:$Ca^{2+}$ exchange current (as a consequence of decreased $[Ca^{2+}]_i$ transients) would normally be expected to shorten the action potential duration; however, we saw a consistent prolongation. The reduction in the repolarising $I_{Kr}$ and $I_{Ks}$ that we report may be sufficient to account for the longer action potential duration. In addition, it is known that action potential duration is negatively related to extracellular calcium ($[Ca^{2+}]_o$) (see Leitch and Brown, 1996; Janvier and Boyett, 1996). Within certain ranges, as $[Ca^{2+}]_o$ falls, action potential duration prolongs while $I_{CaL}$ $[Ca^{2+}]_i$ and contractility all fall, i.e. the same effects as we see upon exposure to 2 mM streptomycin. Furthermore, it has been proposed that aminoglycosidic antibiotics may 'imitate' the effect of decreased $[Ca^{2+}]_o$ by partial displacement of $Ca^{2+}$ from the outer leaflet of the sarcolemma (Hino et al., 1982; Lullmann and Schwarz, 1985; Suarez-Kurtz and Reuben, 1987).

However, such surface charge screening would be expected to shift the current–voltage relationship of $I_{CaL}$, but we saw no evidence of this. Neither was the single channel block of $I_{CaL}$ in skeletal muscle consistent with a charge screening effect (Haws et al., 1996).

### 4.5. Use of streptomycin as a blocker of stretch-dependent mechanisms

Our study strengthens the argument that streptomycin may be a suitable agent to block stretch-activated events in the heart. Under the conditions of our experiments, the threshold of effects on contractility, $[Ca^{2+}]_i$ and electrical activity was greater than 50 μM, while stretch-activated effects in guinea pig ventricular cells have been blocked at 40 μM (Gannier et al., 1994; Belus and White, 2001b). Our data may also be useful in judging appropriate concentrations for inclusion in short-term cell storage media. Concentrations around 100 mg/l (170 μM) would be expected to affect contractility and $[Ca^{2+}]_i$ but the effects of acute streptomycin seem readily reversible. Therapeutic concentrations (1 g/day) seem below our threshold of acute effects. It is important to note, however, that the effects of antibiotics are dependent upon experimental conditions such as $[Ca^{2+}]_o$ and species (e.g. Belus and White, 2001a).

### 4.6. Conclusion

We have described the effects of streptomycin on the contractile and electrical activity of guinea pig ventricular myocytes. Our observations suggest that the negative inotropic effect of streptomycin in cardiac muscle occurs as a result of reduced $Ca^{2+}$ influx through $I_{CaL}$ and decreased $[Ca^{2+}]_i$ transients. Streptomycin modifies the electrical activity of guinea pig ventricular myocytes, prolonging the ventricular action potential duration. This effect may be explained at least in part by our observed fall in repolarising $I_{Kr}$ and $I_{Ks}$ currents, an effect that seems to be $Ca^{2+}$-dependent and related to the fall in $[Ca^{2+}]_i$.

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