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Gold ion inhibits silver ion induced contracture and activates ryanodine receptors in skeletal muscle

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Abstract

Effects of Au^{3+} on Ag^{+}-induced contractures and Ca^{2+} release channel activity in the sarcoplasmic reticulum were studied in frog skeletal muscles. Single fibres spontaneously produced phasic and tonic contractures upon addition of 5–20 μM Ag^{+} or more than 50 μM Au^{3+}. Simultaneous application of 5 μM Ag^{+} and 20 μM Au^{3+} inhibited contractures induced by Ag^{+}. Au^{3+} applied immediately after development of Ag^{+}-induced contractures shortened the duration of the phasic contracture and markedly decreased the subsequent tonic contracture. Pretreatment of fibres with Au^{3+} inhibited the Ag^{+}-induced phasic contracture. Ca^{2+} release channels incorporated into planar lipid bilayers were activated in response to Au^{3+} at 20 to 200 μM. A close relationship was observed between Ca^{2+} release channel open probability and amplitude of the Au^{3+}-induced tonic contracture. Channel activity was inhibited by 5 μM ruthenium red. We conclude that extracellular Au^{3+} at low concentrations modifies the interaction of Ag^{+} with voltage sensors in the transverse tubules to inhibit the Ag^{+}-induced contracture and, if it enters the cell, Au^{3+} may directly activate the sarcoplasmic reticulum Ca^{2+} release channel to partially contribute to the tonic contracture.

Keywords: Ag^{+}; Au^{3+}; Skeletal muscle contraction; Ca^{2+} release channel; Single channel current

1. Introduction

Depolarization of the transverse-tubular membrane releases Ca^{2+} from the sarcoplasmic reticulum in skeletal muscle (Meissner, 1994). However, the mechanism(s) underlying signal transmission from transverse-tubule to sarcoplasmic reticulum Ca^{2+} release channels is still unknown, although a protein (dihydropyridine receptor)–protein (Ca^{2+} release channel) interaction seems to be associated with this transmission (Rios and Pizarro, 1991; Schneider, 1994). Previously, we reported that Ag^{+} induces transient contraction of intact skeletal muscle fibres followed by inhibition of excitation-contraction coupling in Ca^{2+}-free Ringer solution (Oba and Hotta, 1985), binds to critical SH groups on the dihydropyridine receptor to modify the voltage sensor (Oba and Yamaguchi, 1990; Oba et al., 1992) and elicits an inward Ca^{2+} current which is inhibited by cadmium and nifedipine (Oba et al., 1993). In the presence of extracellular Ca^{2+}, Ag^{+} produces tonic contracture after phasic contracture (Oba and Hotta, 1987). From these observations, we concluded that binding of Ag^{+} to SH groups on the dihydropyridine receptor (probably the voltage sensor) is responsible for generation of the phasic contracture. The tonic contracture may be due to Ca^{2+} influx induced by an action of Ag^{+} on dihydropyridine receptors, leading to the further release of Ca^{2+} from the sarcoplasmic reticulum. Recently, Nihonyanagi and Oba (1993) provided evidence that another heavy metal ion, Au^{3+}, contracts skeletal muscles, although much larger amounts of Au^{3+} were needed that was the case for Ag^{+}. If Ag^{+} and Au^{3+} share binding sites on the dihydropyridine receptor, the Ag^{+} contracture should be modified by a low concentration of Au^{3+} that does not cause muscle contracture.

A recent histological observation shows that Au^{3+}, but not Ag^{+}, that flowed out from implanted acupuncture needles can enter cells (Suzuki et al., 1993). If this is the case under our experimental conditions, Au^{3+} may activate the Ca^{2+} release channel and produce tonic muscle contracture. This should be reflected as an increase in the

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open probability of the Ca^{2+} release channel. To examine this possibility, we recorded single Ca^{2+} release channel current by fusing sarcoplasmic reticulum vesicles into planar lipid bilayers.

2. Materials and methods

2.1. Materials

Single muscle fibres were dissected from the toe muscle (Musculus flexor digitorum brevis) of bullfrog (*Rana catesbiana*) in ice-cold Ringer solution (115 mM NaCl, 2.5 mM KCl, 1.8 mM $CaCl_2$ and 3 mM sodium phosphate buffer, pH 7.0), as described previously (Oba et al., 1981). Single fibres were allowed to equilibrate for 20 min in Ringer solution. Before experiments were started, the Ringer solution was replaced by a Cl^--free MOPS solution (115 mM $NaNO_3$, 2.5 mM KNO_3, 10 mM 3-(*N*-morpholino)propanesulfonic acid (MOPS), 1.8 mM $Ca(NO_3)_2$, pH 7.0) to prevent AgCl formation.

Membrane fractions of sarcoplasmic reticulum enriched in terminal cisternae (heavy sarcoplasmic reticulum vesicles) were isolated from leg muscle of the bullfrog, as described previously (Koshita and Oba, 1989). Heavy sarcoplasmic reticulum vesicles were suspended in a small amount of 100 mM KCl, 20 mM Tris-maleate (pH 6.8), 20 μM $CaCl_2$ and 0.3 M sucrose for single channel current recording experiments using planar lipid bilayers. The sarcoplasmic reticulum vesicles were quickly frozen in liquid N_2 and then stored at −50°C until use. Protein concentration was determined by the biuret reaction using serum albumin as the standard.

Stock solutions for each chemical were prepared by dissolving $NaAuCl_4$ (5 mM solution, Nakarai Chem. Co., Kyoto) and caffeine (20 mM solution, Sigma Chem. Co., St. Louis, MO) in MOPS solution. $AgNO_3$ (5 mM solution, Sigma) and ruthenium red (1 mM solution, Sigma) were dissolved in ultra-pure water (18.3 MΩ/cm, Barnstead, Boston, MA).

2.2. Contraction experiments

After isometric tetanus tension was induced by supramaximal rectangular pulses with 0.2 ms duration at a frequency of 100 Hz for 1 s, the fibre was exposed to solutions containing various concentrations of Au^{3+} and/or Ag^+. To examine the inhibitory effect of Au^{3+} on Ag^+-induced contracture, Au^{3+} was applied to single fibres: (i) 5 min before; (ii) just after Ag^+ application; or (iii) at different times after development of Ag^+-induced contracture. In some experiments, 20 mM caffeine was added to the fibre at the end of the experiment to determine if the sarcoplasmic reticulum and contractile proteins were still functional after treatment with heavy metals.

2.3. Planar lipid bilayer methods and single channel data acquisition

Single channel currents were measured by incorporating sarcoplasmic reticulum vesicles into planar lipid bilayers. Lipid bilayers consisting of crude phosphatidylcholine (azolectin, Sigma, MO) in decane (30 mg/ml) were formed across a 200–300 μm hole in a polystyrene cup separating two chambers into the *cis* chamber (volume 3 ml; 250 mM choline Cl, 3 mM $CaCl_2$, 10 mM Hepes-Tris, pH 7.4) and the *trans* chamber (volume 2.2 ml; 250 mM Hepes, 53 mM $Ba(OH)_2$, pH 7.4). Sarcoplasmic reticulum vesicles were added to the *cis* chamber (a final concentration of 5 μg/ml of protein) and stirred once every 5 min until a fusion event was observed. Following visualization of step-like increases in Cl^- conductance due to the incorporation of Cl^- channels, the *cis* solution was replaced with a solution containing 125 mM Tris, 250 mM Hepes (pH 7.4), and 2 μM free Ca^{2+} to avoid further fusion of sarcoplasmic reticulum vesicles and to prevent Cl^- channel currents. Ba^{2+} was used as a current carrier. Au^{3+} and ruthenium red were added to the *cis* chamber. The *trans* chamber was held at ground potential and the *cis* chamber was clamped at 0 mV using 1.5% agar in 3 M KCl and Ag-AgCl electrodes. A single channel current amplified through a patch/whole cell clamp amplifier (CEZ-2300, Nihon Kohden, Tokyo) was displayed on an oscilloscope and filtered at 200 Hz, using a four-pole low-pass Bessel filter. Data were digitized at 1 kHz and stored on the hard disk of a NEC/PC computer. Mean open probability (Po) of channels was identified by 50% threshold analysis using QP-120J software (Nihon Kohden, Tokyo). When multiple channels are present in the bilayer, channel activity was determined by

$$(Po)_1 + 2 \times (Po)_2 + 3 \times (Po)_3 + \ldots.$$

where $(Po)_n$ is the fraction of time that n channels are open simultaneously. Channel openings are presented as upward deflections.

All experiments were performed at 18–20°C. The results are presented as means ± S.E.M. Statistical analysis was performed with Student's *t*- or paired *t*-test. Values of $P < 0.05$ were regarded as significant.

3. Results

3.1. Effects of Au^{3+} on Ag^+-induced contracture

Exposure of a single fibre to 5 μM Ag^+ spontaneously produced a transient contraction (0.50 ± 0.07 T, $n = 5$, where T represents tetanus tension) with a time lag of 6 s and a subsequent tonic contracture (0.34 ± 0.06 T) (Fig. 1A and Fig. 3A), similar to that described in our previous report (Oba and Hotta, 1987). When 20 μM Au^{3+} was added during the middle phase of the transient Ag^+-in-

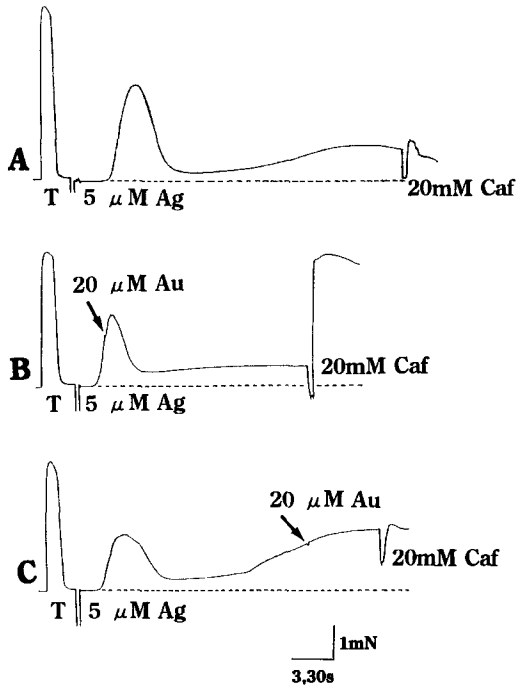

Fig. 1. Contractures induced by 5 μM Ag^+ and their inhibition by Au^{3+}. (A) Phasic and tonic contractures induced by 5 μM Ag^+. At the mid-phase of Ag^+-induced phasic (B) or tonic (C) contractures, 20 μM Au^{3+} was applied at time indicated by each arrow. Note shortening of Ag^+-induced phasic contracture and no occurrence of the tonic component in (B). Caffeine at 20 mM (20 mM Caf) was given to each fibre at the end of experiment. In (A) and (C), the fibre no longer responded to caffeine. Similar traces were observed with three separate fibres. Each broken line indicates resting tension level. Calibration: 30 s except for tetanus tension (T, 3 s) and 1 mN.

duced contracture, the duration of the phasic component decreased and the tonic contracture was markedly inhibited (Fig. 1B). Such fibres still responded to 20 mM caffeine to elicit a large contracture, suggesting that Ca^{2+} release channels in the sarcoplasmic reticulum and the contractile apparatus were still functional. Application of Au^{3+} in the middle phase of the Ag^+-induced contracture affected neither the amplitude nor the time course of tension development (Fig. 1C). Such fibres no longer responded to caffeine. Microscopically, disordered striated structures were observed in a part(s) of such fibres, indicating partial fibre injury.

When applied simultaneously with 5 μM Ag^+ to fibres, Au^{3+} at 20 μM inhibited markedly the phasic component of the Ag^+-induced contracture and completely abolished the tonic component (Fig. 2B). The time required to develop phasic tension after heavy metal application was prolonged (60.1 ± 2.3 s, $n = 5$). The fibres still responded to caffeine (Fig. 2B). Simultaneous exposure to 5 μM Au^{3+} and 5 μM Ag^+ did not affect the Ag^+-induced contracture (Fig. 2A), similar to the situation shown in Fig. 1C.

The minimum concentration of Au^{3+} required to develop spontaneous tension was about 50 μM, as shown in

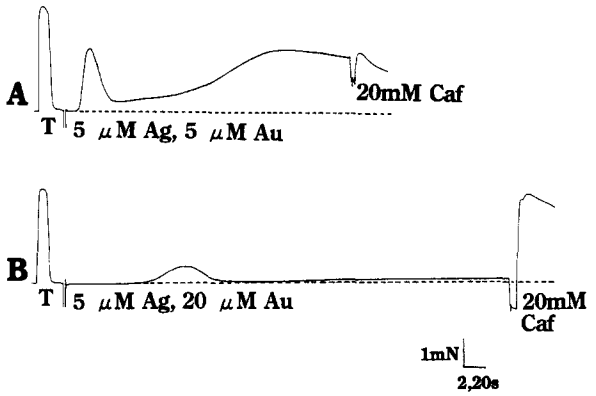

Fig. 2. Effects of Au^{3+} applied simultaneously with Ag^+ on 5 μM Ag^+-induced contracture. (A) No inhibition of Ag^+-induced contracture by 5 μM Au^{3+}. (B) Marked inhibition of the phasic component of Ag^+-induced contracture and no occurrence of the tonic component in the presence of 20 μM Au^{3+}. Caffeine (20 mM) contracture was checked at the end of each experiment. Each experiment was carried out with two separate fibres. Broken lines indicate resting tension levels. Calibration: 20 s except for tetanus tension (2 s) and 1 mN.

Fig. 3B (a low level of tension was observed) and *D* (no tension here), consistent with our previous paper (Nihonyanagi and Oba, 1993). Pretreatment of fibres with 50 μM Au^{3+} for 5 min markedly inhibited the phasic component of the 5 μM Ag^+-induced contracture (Fig.

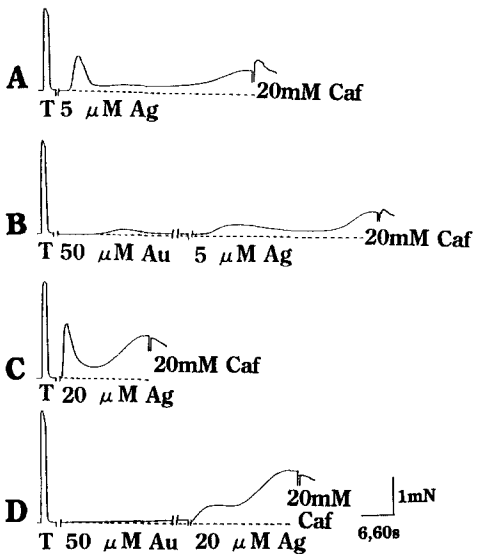

Fig. 3. Effects of Au^{3+} pretreatment on Ag^+-induced contracture. (A) Control contracture produced by 5 μM Ag^+. (B) Inhibition of 5 μM Ag^+-induced phasic contracture by 50 μM Au^{3+} pretreatment. (C) Control contracture elicited by 20 μM Ag^+. (D) Inhibition of 20 μM Ag^+-induced phasic contracture by 50 μM Au^{3+} pretreatment. Fibres were treated with Au^{3+} for 5 min before exposure to Ag^+. Au^{3+} pretreatment did not affect the tonic contractures induced by Ag^+. Note that 50 μM Au^{3+} produced a very small contracture in (B), but not in (D), indicating that this concentration of Au^{3+} is near the mechanical threshold. These fibres responded little or not at all to 20 mM caffeine given at the peak of each tonic contracture. Each experiment was done with 4 separate fibres. Broken lines indicate resting tension levels. Calibration: 60 s except for tetanus tension (6 s) and 1 mN.

3B) (0.50 ± 0.07 T in control without Au^{3+} pretreatment to 0.03 ± 0.02 T, $n = 5$, $P < 0.01$). However, the tonic contracture was not affected by pretreatment with Au^{3+} (0.34 ± 0.06 T in control vs. 0.30 ± 0.02 T in Au^{3+}-treated, $P > 0.05$). An increase in Ag^+ concentration from 5 μM to 20 μM increased tension amplitude (0.64 ± 0.11 T, $n = 5$, in phasic tension and 0.41 ± 0.05 T in tonic tension), as clearly shown in Fig. 3C. The phasic tension transient produced by a high concentration of Ag^+ was also inhibited by pretreatment with 50 μM Au^{3+} (0.17 ± 0.06 T, $n = 5$, $P < 0.01$), although tonic tension was not affected (0.50 ± 0.03 T, $n = 5$, $P > 0.05$) (Fig. 3D).

3.2. Activation of single calcium release channel of sarcoplasmic reticulum by Au^{3+}

Au^{3+} may enter muscle cells (Suzuki et al., 1993) to act on sarcoplasmic reticulum membranes and to release Ca^{2+} from the internal Ca^{2+} stores, resulting in a sustained contracture. Thus, it is of interest to examine if there is a close relationship between tonic tension amplitude and Po of the Ca^{2+} release channel in response to Au^{3+}. To study this possibility, we recorded single Ca^{2+} release channel currents from sarcoplasmic reticulum vesicles incorporated into planar lipid bilayers. The channels observed have been proven to be sarcoplasmic reticulum ryanodine receptor/Ca^{2+} release channels, as evaluated by their conductance of 101.5 ± 2.1 pS ($n = 4$), activation upon 2–100 μM Ca^{2+} and 2 mM ATP applied from the *cis* (cytoplasmic) side and by their blockage by 1 mM Ca^{2+}, 5 mM Mg^{2+} and 2–5 μM ruthenium red applied from the *cis* side (data not shown). Furthermore, when treated with 10 μM ryanodine, the channels were rapidly locked into an open state configuration and unitary conductance was reduced to 43.7 ± 4.9 pS ($n = 4$) (data not shown).

The effects of Au^{3+} concentration on channel activity are summarized in Fig. 4. A typical example is shown in A of this figure. In this case, at least two channels were fused to bilayers. The amplitude of the single channel current in the presence of Au^{3+} was the same as that in control without Au^{3+}, indicating that Au^{3+} did not affect the unitary conductance of the channel. The Ca^{2+} channel activity observed after application of 20 μM Au^{3+} to the *cis* solution containing 2 μM Ca^{2+} (Po = 0.088 ± 0.007, $n = 6$) was comparable to that of control (Po = 0.068 ± 0.009, $n = 6$). An increase in Au^{3+} concentration to 50 μM tripled the Po (0.237 ± 0.047, $n = 5$), although it was not significantly different from that of control or 20 μM Au^{3+}-groups ($P > 0.05$) due to large channel-to-channel variations. A further increase in Au^{3+} to a final concentration of 200 μM markedly increased channel activity to Po = 0.534 ± 0.064 ($n = 4$) ($P < 0.05$ from 50 μM Au^{3+}-group). The open lifetime distribution was best fitted by two exponentials. Time constants of the mean open lifetime after application of 200 μM Au^{3+} were significantly prolonged from $\tau_1 = 6.8 \pm 0.6$ ms and $\tau_2 = 18.6 \pm 0.7$ ms in control to $\tau_1 = 12.4 \pm 2.8$ ms and $\tau_2 = 46.5 \pm 5.8$ ms. Closed time constants were little affected by application of Au^{3+}. These results indicate that the action of Au^{3+} on a single (or at most two) Ca^{2+} release channel is to increase Po and to prolong the mean open time. Exposure of the Au^{3+}-activated channels to 5 μM ruthenium red resulted in a rapid closure of gates, followed by an almost closed state 5 min later (Fig. 4).

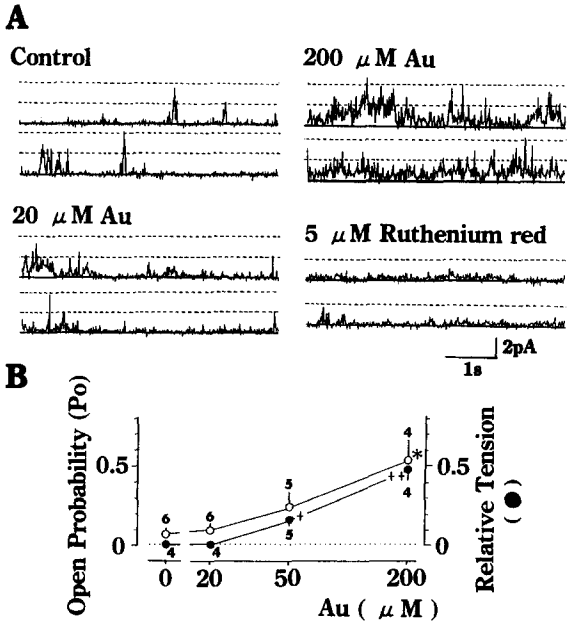

Fig. 4. Activation of the Ca^{2+} release channel by Au^{3+}. (A) Channel activity in control (nPo = 0.071), 20 μM Au^{3+}-treated (nPo = 0.088) 200 μM Au^{3+}-treated (nPo = 0.699) and 5 μM ruthenium red-applied (nPo = 0.002) conditions. Single channel currents were recorded on the same channels at a holding potential of 0 mV. Each broken and solid line indicates the open and closed channel levels, respectively. Drugs were cumulatively applied to the *cis* side of the channels. At least two Ca^{2+} release channels were incorporated into planar bilayers. (B) The close relationship between channel open probability (Po) (○) and relative tonic tension amplitude (●) is apparent when both are plotted as a function of Au^{3+} concentration (μM). Numbers given at each response indicate experiments done. * $P < 0.05$ from control or 50 μM Au^{3+}-group. + $P < 0.05$ from control; ++ $P < 0.01$ from control or 50 μM Au^{3+}-group. Calibration: 1 s and 2 pA.

The relative amplitudes of tonic tension induced by addition of various concentrations of Au^{3+} to single fibres are compared with Po in Fig. 4B. A parallel relationship between both events is shown here. The minimum concentration of Au^{3+} required for tension development and channel activation was near 50 μM, at which concentration the fibre initiated a small tonic contracture (0.15 ± 0.01 T, $n = 5$, $P < 0.05$ from control) with a long delay (130 ± 15 s) and Po was increased to 0.237 ($n = 5$) from Po = 0.068 in control. An increase in the concentration of Au^{3+} to 200 μM tripled the tonic tension amplitude (0.48 ± 0.04 T, $n = 4$, $P < 0.01$ from control or 50 μM Au^{3+}-groups) and decreased the delay (77 ± 16 s).

4. Discussion

The main findings in the present study are that extracellularly applied Au^{3+} modified the Ag^{+}-induced contracture in a manner dependent on dose and on the timing of its application to fibres and that Au^{3+} directly activated sarcoplasmic reticulum Ca^{2+} release channels incorporated into planar lipid bilayers. Au^{3+} at concentrations lower than 50 μM does not produce muscle contracture (Nihonyanagi and Oba, 1993). Even after exposure to an extremely high concentration of Au^{3+} (200 μM), fibres developed only a small phasic contracture (22% of the tetanus tension). In contrast, Ag^{+} at concentrations lower than 0.5 μM elicited a small phasic contracture. Tension was increased upon Ag^{+} addition in a dose-dependent manner and reached a maximum level at about 10 μM (61% of the tetanus tension) (Oba and Hotta, 1985; Oba et al., 1995). Our previous studies have shown that the muscle contracture induced by either Ag^{+} or Au^{3+} was prevented by oxidation of sulfhydryl groups in transverse-tubular Ca^{2+} channels (Nihonyanagi and Oba, 1993; Oba and Yamaguchi, 1990; Oba et al., 1992). Given the present observation that Ag^{+} contracture was markedly inhibited by applying 20 μM Au^{3+} concomitantly with 5 μM Ag^{+} (Fig. 2B), both heavy metals probably share the same binding sites. When applied immediately after the Ag^{+}-induced tension developed, Au^{3+} shortened the Ag^{+}-induced phasic tension and blocked tonic tension development (Fig. 1B). This result suggests that Au^{3+} could bind rapidly to its binding sites even in the presence of Ag^{+}. However, large amounts of Au^{3+} were required for induction of a phasic contracture comparable to that of Ag^{+}. Therefore, Au^{3+} may have a binding affinity that is lower than that of Ag^{+} to L-type Ca^{2+} channels naturally present in transverse-tubular membranes, although both heavy metals could bind to the sulfhydryl groups of cysteine in a cuvette with similar affinity (Nihonyanagi and Oba, 1993). Further biochemical experiments on the binding of heavy metals to transverse-tubular Ca^{2+} channels could provide support for this possibility.

Exposure of single fibres to either Ag^{+} or Au^{3+} elicited tonic contracture in the presence of external Ca^{2+} (Oba and Hotta, 1987; Nihonyanagi and Oba, 1993; Fig. 1 in this experiment). Our previous results that Ag^{+} did not produce tonic contracture in the absence of external Ca^{2+} (Oba and Hotta, 1985) and that Ag^{+}-induced tonic contracture was inhibited by Ca^{2+} channel blockers, diltiazem, nifedipine and Cd^{2+} (Oba and Hotta, 1987; Oba et al., 1993) strongly suggest that the tonic contracture is due to the influx of external Ca^{2+}. However, the tonic contracture induced by Au^{3+} also required external Ca^{2+}, because the tonic contracture was inhibited by reducing external Ca^{2+} and induced by reapplying Ca^{2+} to such fibres (Nihonyanagi and Oba, 1993). These findings suggest that Au^{3+} acts on the L-type Ca^{2+} channel of the surface and/or transverse tubular membrane to increase Ca^{2+} permeability and to produce tonic contracture, as does Ag^{+}. However, Suzuki et al. (1993) have reported that Au^{3+} can enter cells. If this is the case under our experimental conditions, Au^{3+} may release Ca^{2+} from the sarcoplasmic reticulum to contract the muscle fiber. Fig. 4 shows that Au^{3+} at more than 20 μM directly activated Ca^{2+} release channels in the sarcoplasmic reticulum incorporated into planar lipid bilayers. In addition, we found a parallel relationship between relative amplitudes of tonic contracture and Po induced by addition of various concentrations of Au^{3+}. These findings suggest the possibility that the Au^{3+}-induced contracture may be partially attributable to Au^{3+} influx from the extracellular space. Abramson et al. (1983) found that various heavy metals such as Cu^{2+}, Hg^{2+}, Ag^{+}, Cd^{2+} and Zn^{2+} caused the release of Ca^{2+} from sarcoplasmic reticulum vesicles. We observed similar results on applying Ag^{+} and Hg^{2+} to mechanically skinned fibres (Aoki et al., 1985, 1986). However, we have no evidence that Au^{3+} can enter muscle cells in sufficient quantities to activate the Ca^{2+} release channels under our experimental conditions. Biochemical data on Au^{3+} influx are required to clarify the relationship between tonic tension and Po.

Ca^{2+} release channels incorporated into planar lipid bilayers were activated by applying Au^{3+} (more than 20 μM) in a dose-dependent manner (Fig. 4). The Po of channels tripled in response to 50 μM Au^{3+} and was increased 10-fold by application of 200 μM Au^{3+}. We found that the open time constants for the control channel were τ_1 (open level 1) = 6.8 ms and τ_2 (open level 2) = 18.6 ms and those for the 200 μM Au^{3+}-treated group were $\tau_1 = 12.4$ ms and $\tau_2 = 46.5$ ms. The mean open times after 200 μM Au^{3+} application were prolonged 2- to 3-fold compared to control. However, the unit current amplitude was not affected by Au^{3+}. Therefore, Au^{3+} probably modifies Ca^{2+} release channel gating and changes the conformation of the channel from a short open state to a long open state without affecting the physical pathway of the conducting pore. Closure of Au^{3+}-activated channels by ruthenium red (Fig. 4A) indicates that Au^{3+} seems to act through the Ca^{2+}-induced Ca^{2+} release mechanism, because ruthenium red is a specific inhibitor of the Ca^{2+}-induced Ca^{2+} release channel (Meissner, 1994; Ohnishi, 1979; Palade et al., 1989; Smith et al., 1985).

The present finding that Au^{3+} acts directly on the sarcoplasmic reticulum to open the Ca^{2+} release channel is the first report to our knowledge. We do not know the molecular mechanism(s) by which Au^{3+} opens the gate of the Ca^{2+} release channel. Accumulating evidence strongly suggests the possibility that Ag^{+} releases Ca^{2+} from the sarcoplasmic reticulum by modifying the gating mechanism (Abramson et al., 1983; Kawasaki and Kasai, 1989; Moutin et al., 1989; Nagasaki and Fleischer, 1989; Oba et al., 1989; Salama and Abramson, 1984). A recent study by Salama et al. (1992) provides evidence that oxidation and reduction of sulfhydryl groups on the Ca^{2+} release channel

may open and close the gate, respectively. As Au^{3+} seems to share the binding sites with Ag^{+} at the level of the sarcoplasmic reticulum membranes, the conformational changes of the Ca^{2+} release channel caused by binding of Au^{3+} to sulfhydryl groups would probably lead to opening of Ca^{2+} release channel.

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