

# Biophysical Effects of Adrenaline on the Smooth Muscle of the Rabbit Common Carotid Artery

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**ABSTRACT** Effects of adrenaline on the smooth muscle of the rabbit common carotid artery were studied by the partitioned chamber method. The experiments on excitation-contraction coupling were carried out in isotonic Krebs solution; the other experiments were carried out in hypertonic Krebs solution. Adrenaline ( $10^{-7}$  g/ml) caused rhythmical electrical and mechanical activity of arterial strips in isotonic Krebs solution. By addition of adrenaline ( $10^{-5}$  g/ml), the membrane was depolarized by about 10 mv and the amplitude of the electrotonic potential was decreased by 40–50% of the control in hypertonic Krebs solution. Present experimental results suggest that the depolarization of the membrane and the decrease of the amplitude of the electrotonic potential in the artery are due to the increase of Na and Cl conductance. Contraction appeared in all preparations exposed to  $10^{-8}$  g/ml adrenaline; at that concentration membrane potential and membrane resistance showed little or no change.

## INTRODUCTION

It has recently been shown that there are two different responses to the vasoconstrictor substance in the large elastic arteries of mammals. Su et al. (1964) were not able to detect any potential change with an intracellular microelectrode during contraction of the isolated pulmonary artery induced by nerve stimulation and by noradrenaline. Keatinge (1964), using the sucrose gap method, observed that the isolated common carotid artery is depolarized by the vasoconstrictor substances. Su and Bevan (1965), Keatinge (1964), and Waugh (1962) concluded from their results that contraction of arterial smooth muscle may be mediated both by electrical and by nonelectrical means. The present experiments were done in order to resolve the above problem by means of the partitioned chamber method described by Tomita (1966). Adrenaline was used as the vasoconstrictor substance. The ionic basis of the

effect of adrenaline on the arterial smooth muscle cell membrane was also studied.

#### METHODS

Rabbits weighing 1.5–2.0 kg each were stunned and bled. The common carotid artery was removed. For the study of the vascular smooth muscle of the common carotid artery, helical strips, 20 mm in length and 1 mm in width, were cut. The preparation was mounted on a rubber plate and secured in a 5 ml organ bath. The solution flowed through the bath continuously at a rate of 8 ml/min at 35°–36°C and was aerated with 97% O<sub>2</sub> and 3% CO<sub>2</sub>.

The experiments on excitation-contraction (E-C) coupling were carried out in isotonic Krebs solution. Tension was isometrically recorded simultaneously with the membrane electrical activity using a strain gauge (Nihon Kohden Ltd. Shinjuku-Ku, Tokyo, Japan). One end of the preparation was fixed on the rubber plate and the other end was tied and connected to the strain gauge.

The relative membrane resistance was measured by applying currents extracellularly, using Ag-AgCl electrodes as described by Tomita (1966). In order to measure the membrane conductance of the arterial smooth muscle, microelectrodes (20–70 MΩ) were inserted at a distance of 0.1–0.3 mm from the partition. The method has been described in detail by Mekata (1971). The composition of the bathing solutions is given in Table I.

If the tissue has cable properties and the voltage-current relation of the membrane is linear, then, according to the equation given by Hodgkin and Rushton (1946), the relation between changes in membrane resistance and changes in the amplitude of the electrotonic potential evoked by external applied current at a given distance ( $x$ ) from the partition is given by

$$\frac{V'}{\bar{V}} = \sqrt{\frac{R_m' R_i' \exp(-x/\lambda')}{R_m R_i \exp(-x/\lambda)}} \quad (1)$$

where  $R_m$  = membrane resistance,  $R_i$  = internal resistance,  $\lambda$  = space constant, and  $V$  = amplitude of electrotonic potential in one solution, and  $R_m'$ ,  $R_i'$ ,  $\lambda'$ , and  $V'$  are the same quantities in another solution. When  $x$  is considerably smaller than  $\lambda$  and  $\lambda'$ ,  $\exp(-x/\lambda')/\exp(-x/\lambda)$  converges to 1. Thus, assuming that  $x$  is smaller and the internal resistances ( $R_i$  and  $R_i'$ ) remain constant in two different solutions, equation 1 becomes

$$\left(\frac{V'}{\bar{V}}\right)^2 = \frac{R_m'}{R_m} = \frac{g_m}{g_m'} \quad (2)$$

where  $g_m$  is the membrane conductance in one solution and  $g_m'$  is the conductance in another solution. The change in the membrane conductance is given by equation 2 under such conditions (Ohashi, 1970). However, when the voltage-current relation is nonlinear, the relation between the membrane resistance and the electrotonic potential cannot be shown by simple equations.

In the vascular smooth muscle of the common carotid artery, the voltage-current relation in the hyperpolarizing direction was nonlinear in normal Krebs solution (Mekata, 1971) but linear in hypertonic Krebs solution. Therefore, in order to calculate the relative values of the membrane resistance or conductance, experiments were carried out in the hypertonic Krebs solution of about 1.7 times the normal tonicity (204 mM sucrose in Krebs solution). Hypertonic Krebs solution also suppressed the muscle movements induced by drugs or ions, which was a great advantage in the continuous recording of intracellular potentials.

TABLE I  
COMPOSITION OF SOLUTIONS

	Concentration (in millimoles per liter)										
	Na <sup>+</sup>	K <sup>+</sup>	Ca <sup>++</sup>	Mg <sup>++</sup>	Choline <sup>+</sup>	Cl <sup>-</sup>	HCO <sub>3</sub> <sup>-</sup>	H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	SO <sub>4</sub> <sup>-</sup>	Glucose	Sucrose
Modified Krebs soln	137.4	5.9	2.5	1.2	—	134.0	15.5	1.2	—	11.5	—
Hypertonic Krebs soln	137.4	5.9	2.5	1.2	—	134.0	15.5	1.2	—	11.5	204.0
Sucrose-hypertonic soln	—	5.9	2.5	1.2	—	7.4	5.5	0.4	—	11.5	478.8
Choline-hypertonic soln	—	5.9	2.5	1.2	148.2	155.6	5.5	0.4	—	11.5	204.0
SO <sub>4</sub> -hypertonic soln	137.4	5.9	3.8	1.2	—	—	15.5	1.2	68.3	11.5	268.4
11.8 mM KCl-Krebs soln	131.5	11.8	2.5	1.2	—	134.0	15.5	1.2	—	11.5	—
20.0 mM KCl-Krebs soln	123.3	20.0	2.5	1.2	—	134.0	15.5	1.2	—	11.5	—

## RESULTS

It is well known that the tissue of many visceral smooth muscles behaves as a simple cable (Tomita, 1966, 1967; Abe and Tomita, 1968; Kuriyama et al., 1970; Kuriyama and Mekata, 1971). The arterial tissue from the common carotid artery also shows a cable-like property. In this respect vascular smooth muscle resembles visceral smooth muscle (Mekata, 1971).

### *Effect of Adrenaline in Isotonic Krebs Solution*

In normal solution, the membrane potential and tension of the vascular smooth muscle were very stable and spontaneous action potentials followed by contraction were not observed. The resting membrane potential measured from artery in isotonic Krebs solution varied from -37 to -60 mv (mean  $\pm$  SD and observed number:  $-45.3 \pm 1.3$  mv,  $n = 30$ ).

When concentrations of adrenaline less than  $10^{-8}$  g/ml were applied, no changes in the membrane potential, membrane resistance, or tension were observed. All preparations contracted upon treatment with  $10^{-8}$  g/ml adrenaline. The membrane potential and the membrane resistance showed little or no change (the maximum depolarization of the membrane potential was 3 mv

[mean  $0.3 \pm 0.8$  mv,  $n = 8$ ] and the maximum decrease of the amplitude of the electrotonic potential was 5% [mean  $1.3 \pm 0.7\%$ ,  $n = 8$ ].

Strong contraction, depolarization of the membrane by 4–7 mv, and large reduction of the amplitude of the electrotonic potential to about 40% of the control ( $38.7 \pm 2.8\%$ ,  $n = 6$ ) were obtained by applying  $10^{-7}$  g/ml of adrenaline. Depolarization induced by adrenaline ( $10^{-7}$  g/ml) was accompanied by oscillatory potentials (amplitude,  $5.0 \pm 2.0$  mv; frequency,  $8.0 \pm 2.0$  cycle/min;  $n = 6$ ) which corresponded with phasic contractions of the arterial strip (Fig. 1). It has been shown by Mekata (1971) that an action potential cannot

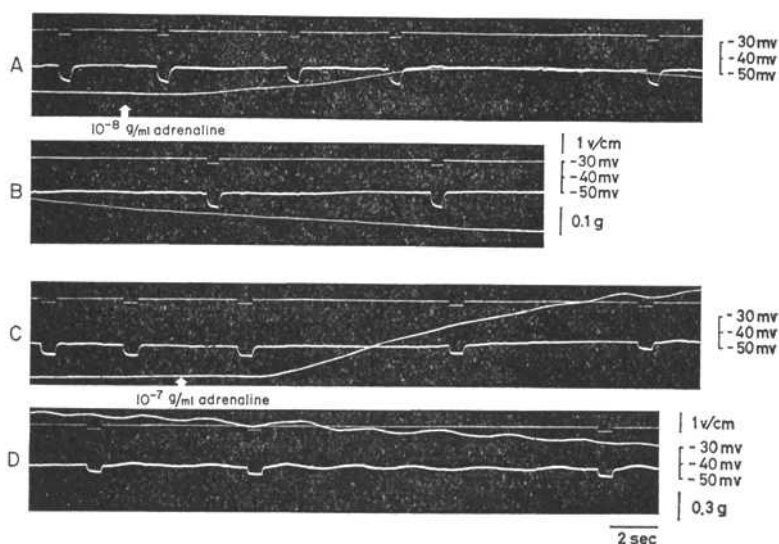


FIGURE 1. Electrical and mechanical responses to adrenaline ( $10^{-8}$  g/ml, A and B,  $10^{-7}$  g/ml, C and D). The left end in Fig. 1 A and C shows control responses in normal Krebs solution. Adrenaline ( $10^{-8}$  and  $10^{-7}$  g/ml) was applied at the arrows in (A) and (C), respectively. Current was applied by external electrodes. (A) and (B), (C) and (D) are continuous. (A) (B) and (C) (D) were recorded from different preparations. Upper trace: current intensity; middle trace: intracellular potential and electrotonic potential evoked by extracellular current application; lower trace: tension. Note tension development without any electrical changes after application of adrenaline ( $10^{-8}$  g/ml) at (A).

be triggered by strongly depolarizing current pulses delivered with an extracellular plate electrode in isotonic Krebs solution. In the present experiments outward current pulses applied extracellularly could not trigger action potentials in the presence of adrenaline ( $10^{-7}$  g/ml in isotonic Krebs solution or  $10^{-6}$  g/ml in hypertonic Krebs solution).

#### *Effects of High Potassium in Isotonic Krebs Solution*

The membrane potential, the membrane resistance, and the tension development were measured in the presence of different external potassium concentra-

tions (ranging from 5.9 to 20.0 mM). The threshold concentration of external potassium needed to produce contraction was 12.8 mM. No tension developments were observed in the presence of an external potassium concentration below 12.8 mM.

Membrane potential and membrane resistance were measured in solutions containing 11.8 mM and 20.0 mM KCl. These concentrations of the external potassium were used because no contraction occurred in the former solution and considerable contraction was produced in the latter.

When the external potassium concentration was increased to 11.8 mM, the membrane was depolarized about 6 mv ( $6.1 \pm 2.1$  mv,  $n = 11$ ) and the amplitude of the electrotonic potential was slightly decreased, by about 5% compared with the control ( $4.8 \pm 2.0\%$ ,  $n = 6$ ). In the presence of 20.0 mM external potassium, depolarization ( $14.0 \pm 3.0$  mv,  $n = 7$ ) and decrease of the amplitude of the electrotonic potential ( $10.1 \pm 1.9\%$ ,  $n = 7$ ) were observed. Action potentials could not be evoked by applying further cathodal current externally even when the preparation was soaked in the solutions containing  $K^+$  in concentrations of 11.8 or 20.0 mM (Fig. 2).

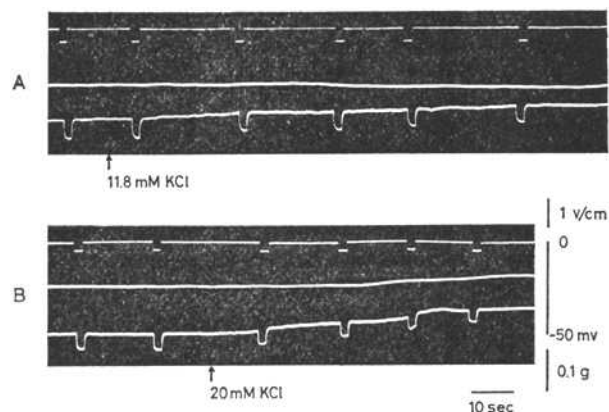


FIGURE 2. Effect of high  $K^+$  on electrical and mechanical responses of the artery. Bath solution was changed from normal Krebs solution to high KCl solution at each arrow (A, 11.8 mM KCl; B, 20.0 mM KCl). In order to measure changes in membrane resistance by high  $K^+$ , current was applied externally. Upper trace: current intensity; middle trace: tension; lower trace: intracellular potential and electrotonic potential evoked by extracellular stimulation. Note no tension development in spite of depolarization by 5 mv with 11.8 mM KCl in (A).

#### *Effect of Adrenaline in Hypertonic Krebs Solution*

Fig. 3 A shows the effects of adrenaline ( $10^{-7}$  and  $10^{-5}$  g/ml) on the membrane activity of arterial smooth muscle in hypertonic Krebs solution. As shown in Fig. 3 A,  $10^{-7}$  g/ml of adrenaline produced no membrane activity.

When the concentration of adrenaline was increased to  $10^{-6}$  g/ml, membrane potential was decreased by 2–5 mv, oscillatory potentials were produced in 7 out of 12 preparations, and the amplitude of the electrotonic potential was decreased by 23% of the control value.

When  $10^{-5}$  g/ml of adrenaline was applied, membrane potential was decreased by 5–15 mv, oscillatory potentials were produced in all preparations ( $n = 8$ ), and decrease of the amplitude of the electrotonic potential by 43% of the control value was observed.

Average changes in the amplitudes of the electrotonic potential and in the membrane conductances in terms of the square of the ratio  $V'/V$  are shown in Table II. Action potentials were recorded 1–2 min after application of adrena-

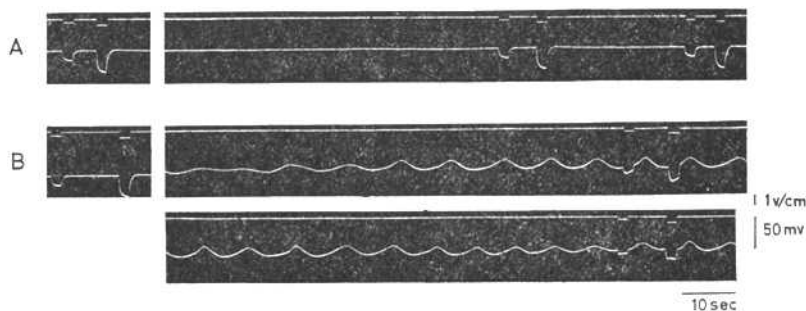


FIGURE 3. Effects of adrenaline,  $10^{-7}$  g/ml (A) and  $10^{-5}$  g/ml (B), on the smooth muscle of the common carotid artery in hypertonic solution. Left: control; right: responses of the arterial muscle 2 min after application of adrenaline ( $10^{-7}$  g/ml, A) and 1 min after application of adrenaline ( $10^{-5}$  g/ml, B). Resistance was measured by two current pulses applied extracellularly. Upper trace: current intensity; lower trace: intracellular potential and electrotonic potential evoked by extracellular current application.

line ( $10^{-6}$  and  $10^{-5}$  g/ml). The mean values of the amplitude and frequency of the action potential were  $8 \pm 3$  mv and  $9.0 \pm 2.1$  cycle/min for  $10^{-6}$  g/ml ( $n = 7$ ) and  $17 \pm 6$  mv and  $5.5 \pm 1.2$  cycle/min for  $10^{-5}$  g/ml ( $n = 12$ ) adrenaline.

Arterial smooth muscle soaked in hypertonic Krebs solution had a low sensitivity to adrenaline electrically compared with the responses of arterial smooth muscle to adrenaline in normal Krebs solution. However, there are no qualitative differences between the effects of adrenaline, i.e. the increase of membrane conductance, the depolarization of the membrane, and the generation of oscillatory potentials were observed in both isotonic and hypertonic Krebs solution.

#### *Effects of Ionic Changes and Adrenaline in Hypertonic Krebs Solution*

The depolarization of the membrane and the decrease of membrane resistance caused by adrenaline is probably due to changes in the cell membrane perme-

ability. Therefore, the effect of ionic changes on the response of the membrane to adrenaline ( $10^{-5}$  g/ml) was studied in hypertonic Krebs solution.

(A) SULFATE Sulfate substitution for chloride caused a small increase in the amplitude of the electrotonic potential ( $10.3 \pm 2.5\%$ ,  $n = 3$ ), but the membrane potential was not changed. Both the reduction of the membrane resistance and the depolarization of the membrane by adrenaline were suppressed and the spontaneous discharge was decreased in this solution (Fig. 4).

(B) SUCROSE When sodium chloride was replaced by sucrose, a transient hyperpolarization of 10–30 mv was observed initially; thereafter the membrane potential returned to its initial level in hypertonic Krebs solution. After the return to the initial level, oscillatory potentials were produced. The amplitude and the frequency of these oscillatory potentials were 10–15 mv and 6–10 cycle/min ( $n = 3$ ), respectively. Oscillatory potentials in this solution continued for 5–10 min and finally ceased.

TABLE II  
EFFECT OF ADRENALINE ON MEMBRANE POTENTIAL AND MEMBRANE CONDUCTANCE IN HYPERTONIC KREBS SOLUTION

Concentration of adrenaline, g/ml	0	$10^{-8}$	$10^{-7}$	$10^{-6}$	$10^{-5}$
Membrane potential, mv	$49.1 \pm 0.8$ (17)*	$49.4 \pm 0.9$ (12)	$48.4 \pm 1.3$ (8)	$45.5 \pm 1.4$ (9)	$39.0 \pm 1.1$ (12)
$V'/V$ , %	100	$96.3 \pm 1.4$ (14)	$93.0 \pm 2.3$ (12)	$77.0 \pm 4.4$ (11)	$57.3 \pm 4.9$ (12)
$g'/g$ , %	100	107.9	115.6	168.7	304.6

\* Numbers in parentheses are the numbers of experiments ( $n$ ).

The effect of adrenaline on the membrane potential and membrane resistance was strongly depressed in this solution. However, this depressing effect was not complete. Adrenaline produced a small depolarization and decrease in membrane resistance in some preparations (Fig. 5).

(C) CHOLINE Sodium chloride was replaced by choline chloride. In this solution atropine ( $10^{-5}$  g/ml) was added to eliminate the acetylcholine-like effect of choline. Responses similar to those seen in sucrose-hypertonic Krebs solution were observed, i.e. initial transient hyperpolarization (10–15 mv), generation of oscillatory potentials after return to the potential level of the control, and increase of the amplitude of the electrotonic potential. However, these changes were generally distinguishable from those in sucrose solution (i.e., magnitude of the transient hyperpolarization and the period of the generation of the action potential).

When adrenaline was applied in this solution, the membrane was slightly depolarized and the amplitude of the electrotonic potential was decreased by 5–15% of the control. Average changes in the membrane potential, the ampli-

tude of the electrotonic potential evoked by ionic changes in the external solution, and the calculated membrane conductance are shown in Table III.

*Effects of  $Mn^{++}$  and Tetrodotoxin on Adrenaline-Induced Action Potentials in Hypertonic Krebs Solution*

In order to investigate whether the generation of the oscillatory potential is related to sodium or calcium inward current, the effects of Mn ion and tetrodotoxin on adrenaline-induced oscillatory potentials were examined.

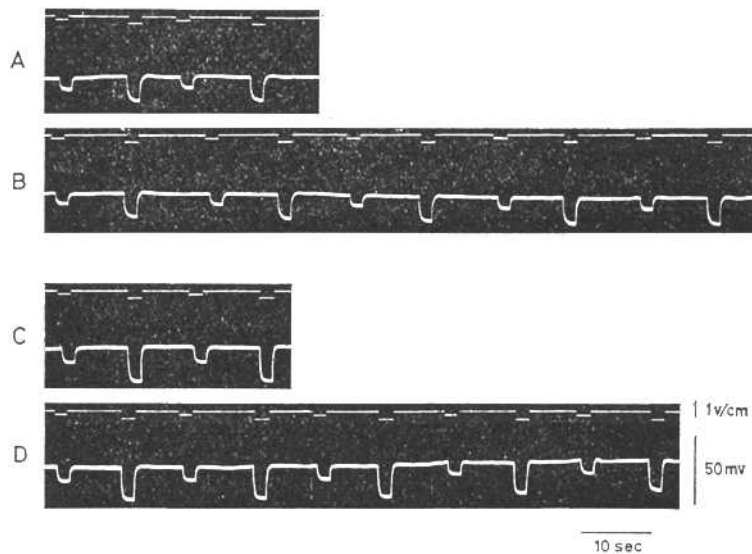


FIGURE 4. Effects of sulfate and modification of effect of adrenaline ( $10^{-5}$  g/ml) in  $SO_4$ -hypertonic Krebs solution. (A), responses of the artery in hypertonic Krebs solution. (B), in  $SO_4$ -Krebs solution. (C), 3 min after application of  $SO_4$ -Krebs solution. (D), responses to adrenaline ( $10^{-5}$  g/ml) in  $SO_4$ -Krebs solution. Two different intensities of current pulses were applied extracellularly. (A) and (B), (C) and (D) are continuous. Upper trace: current intensity; lower trace: intracellular potential and electrotonic potential evoked by extracellular current application.

Tetrodotoxin ( $10^{-5}$  g/ml) had no effect on the shape and frequency of the adrenaline-induced oscillatory potential, membrane potential, membrane resistance, or tension. In four experiments, arterial strips were left in the hypertonic solution containing adrenaline ( $10^{-5}$  g/ml) until they became electrically active, and tetrodotoxin ( $10^{-5}$  g/ml) was then added. The activity continued without any detectable change. Two other arterial strips were exposed for 5 min to tetrodotoxin ( $10^{-5}$  g/ml); adrenaline ( $10^{-5}$  g/ml) induced depolarization and oscillatory potentials.

Mn ion (1 mM) depressed the amplitude and frequency of the adrenaline-



induced oscillatory potential. However, even 5 min after application of Mn ion (1 mM), the oscillatory potential was not abolished completely. When the concentration of Mn ion was increased to 2 mM, the electrical activity produced by adreanline ceased immediately (Fig. 6).

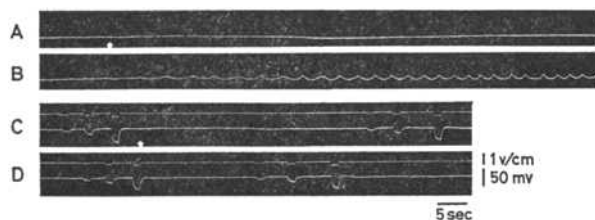


FIGURE 5. Effects of Na-free solution (substituted with sucrose) and modification of the effect of adrenaline ( $10^{-5}$  g/ml) in Na-free solution. Hypertonic Krebs solution was replaced by hypertonic Na-free solution at the arrow in (A). Adrenaline ( $10^{-5}$  g/ml) was applied at the arrow in (C). (A) and (B), (C) and (D) are continuous. 5 min elapsed between (B) and (C). Three different current pulses were applied extracellularly. Upper trace: current intensity; lower trace: intracellular potential and electrotonic potential evoked by extracellular current application.

TABLE III  
EFFECT OF ADRENALINE ( $10^{-5}$  g/ml) ON MEMBRANE POTENTIAL AND MEMBRANE CONDUCTANCE OF ARTERIAL SMOOTH MUSCLE IN  $\text{SO}_4$ -, CHOLINE-, AND SUCROSE-HYPERTONIC KREBS SOLUTIONS

		$\text{SO}_4$ soln	Choline soln	Sucrose soln
Membrane potential, mv	Control	$50.2 \pm 3.5$ (5)*	$49.8 \pm 2.0$ (5)	$49.3 \pm 1.4$ (3)
	After application of adrenaline	$44.2 \pm 2.7$ (5)	$49.2 \pm 2.2$ (5)	$48.7 \pm 1.4$ (3)
$V'/V$ , %		$70.0 \pm 5.4$ (5)	$89.0 \pm 2.5$ (5)	$96.3 \pm 6.4$ (3)
$g'/g$ , %		204.1	126.2	107.8

\* Numbers in parentheses are the numbers of experiments ( $n$ ).

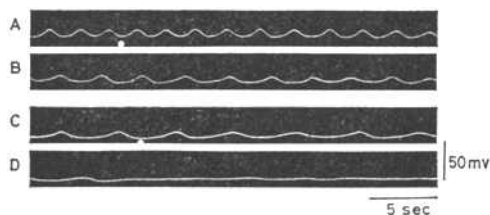


FIGURE 6. Effect of  $\text{MnCl}_2$  on adrenaline ( $10^{-5}$  g/ml)-induced action potential. Electrical responses of the artery at 5 min after application of adrenaline ( $10^{-5}$  g/ml) is shown in left part of (A).  $\text{MnCl}_2$ , 1 or 2 mM, was applied at the arrows in (A) or (B), respectively. (A) and (B), (C) and (D) are continuous. 5 min elapsed between (B) and (C).

## DISCUSSION

Contraction of visceral smooth muscle produced by drugs is generally followed by some depolarization and/or increase of spike activity. In the rabbit pulmonary artery both noradrenaline and sympathetic nerve stimulation caused a constriction without any electrical changes in the membrane (Su et al., 1964). However, a sustained depolarization of the sheep carotid artery following exposure to noradrenaline and adrenaline was recorded by Keatinge (1964). There are differences in the drug concentration used, the kind of the artery and animal, and even in the recording method used by various investigators. It is difficult to record small changes in the transmembrane potential by the sucrose gap method.

In the present experiments, low concentrations of adrenaline ( $10^{-8}$  g/ml) caused marked contraction and little depolarization in isotonic Krebs solution. Small depolarizations do not seem to induce contraction of the artery, since, even when the membrane of the arterial smooth muscle was depolarized by 4–8 mv with 11.8 mM KCl, contraction did not occur.

The results indicate that low concentrations of adrenaline can cause contraction of the arterial strip with little or no change in the electrical properties. The oscillatory potential of arterial smooth muscle was generated by adrenaline ( $10^{-7}$  g/ml) in isotonic Krebs solution and phasic contraction corresponding to the oscillatory potentials was produced. From these results, it is concluded that, with low concentrations of adrenaline, contraction occurs without either depolarization or oscillatory potential changes, whereas at higher concentrations electrical changes are observed.

It has often been reported that depolarized vascular smooth muscles, obtained from the common carotid artery of the rabbit, contract under the influence of drugs without any changes in electrical responses. A similar observation was reported in normal solutions by Su et al. (1964). The present results confirm the observation that contraction of the vascular smooth muscle caused by low concentrations of adrenaline was produced without any change of electrical potential.

Oscillatory potentials could be produced by adrenaline in the presence of tetrodotoxin but they were blocked by Mn ion. Oscillatory potentials could also be produced in sodium-free solution. These results were similar to those obtained in intestinal smooth muscle (Nonomura et al., 1966; Kuriyama et al., 1966, 1967). These observations suggest the idea that the oscillatory potential produced by adrenaline may be due to the entry of Ca ion.

The depolarization of the smooth muscle of the common carotid artery caused by adrenaline is probably due to a change in cell membrane permeability. The mechanism of action of adrenaline on the arterial smooth muscle is thought to differ from that of taenia coli in which Bülbring and Tomita

(1969) demonstrated that adrenaline caused an increase in  $G_K$  and  $G_{Cl}$ . It is concluded from the present experiments that the effect of adrenaline on arterial smooth muscle is to increase  $G_{Na}$  and  $G_{Cl}$  with little effect on  $G_K$ . These different findings for conductance in the two muscles are in accordance with the fact that adrenaline inhibits the taenia coli and excites the carotid artery.

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