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ELECTRICAL PROPERTY AND CHEMICAL SENSITIVITY OF VASCULAR SMOOTH MUSCLES IN NORMOTENSIVE AND SPONTANEOUSLY HYPERSENSITIVE RATS

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SUMMARY

1. The membrane properties and sensitivity to chemical substances of smooth muscle cells of the portal vein and pulmonary artery were studied in normotensive rats (Wister Kyoto) and spontaneously hypertensive rats (Okamoto & Aoki) by the micro-electrode method.

2. The parameters of the membrane, i.e. resting membrane potential, the maximum rate of rise of the spike, space constant of the tissue and time constant of the membrane measured from the portal vein were the same in normotensive rats (< 120 mmHg) and spontaneously hypertensive rats (> 165 mmHg). Similar results were also obtained from the pulmonary artery. Such findings indicate that the passive electrical properties of the vascular muscle membrane are not involved in the generation mechanism of hypertension.

3. In the portal vein the maximum slope of the membrane depolarization produced by tenfold increase in external K^+ concentration expressed on a logarithmic scale was the same in normal and hypertensive rats (42 and 41 mV, respectively). These observations were confirmed by the effects of application of excess K^+ on the pulmonary artery (48 mV in normal and 46 mV in hypertension). With a low concentration of K^+, the membrane was depolarized to a greater extent in the portal veins than in the pulmonary arteries of both types of rats. Although the response to K^+ differed in vascular muscles excised from the different regions, no functional difference was apparent between normotensive and hypertensive.

4. In both portal vein and pulmonary artery, the smooth muscle membrane of spontaneously hypertensive rats proved to be more sensitive to noradrenaline, i.e. depolarization of the membrane appeared with noradrenaline 10^{-9} g/ml. in hypertensive but with 10^{-8} g/ml. in normotensive rats. Depolarization block of the spike generation appeared at a lower concentration of noradrenaline in hypertensive rats. Sensitivity of the smooth muscle membrane to prostaglandin E_2 in the portal vein was also higher in hypertensive rats.

5. The present results indicate that the only difference between normal and spontaneously hypertensive rats regarding smooth muscle cell membrane of the pulmonary artery and portal vein is increased chemical sensitivity in hypertensive rats, and the passive electrical properties of the membrane probably does not contribute to the generation of hypertension.

INTRODUCTION

Bohr (1974) reviewed the function of vascular smooth muscle as related to hypertension, and found that in chronic hypertension both experimental and clinical, total peripheral resistance is elevated, and vascular reactivity to pressor agents is increased.

Folkow (1971) concluded that genetic or experimental hypertension in animals and essential hypertension in man are caused by an increase in wall thickness. Concentration–response curves of the vascular resistance to noradrenaline in hypertensive animals were much the same as the calculated concentration–response curves of a mathematical model in which it was assumed that medial thickness had increased by 30%, and the increase in wall thickness had encroached on the lumen when the smooth muscle was completely relaxed. There was no change in vascular smooth muscle reactivity which would explain the difference in vascular flow reactivity. These ideas were supported by further experiments done by Folkow, Hallbäck, Lundgren, Sivertsson & Weiss (1973), who reported that reactivity to noradrenaline of strips from aorta and portal vein from spontaneously hypertensive (s.h.) rat does not differ from that of comparable muscle from normotensive (n.) rats. The structural component of resistance contributes greatly to the overall increase in resistance in the generation of hypertension. However since the structural change is secondary to the increase in arterial pressure, such would not initiate the hypertension (Bohr 1974).

Drug actions on isolated perfused vessels of vascular beds of n. and s.h. rats have been extensively studied and data indicating that vascular reactivity is increased in hypertension (Bohr, 1974; Lais & Brody, 1975) are fairly consistent. However, it is difficult to determine how much of the increase is due to wall thickening and how much is due to hyper-reactivity of the vascular smooth muscle (Spector, Fleisch, Maling & Brodie, 1969; Bohr & Strin, 1970; Holloway, Strin & Bohr, 1972; Shibata, Kurahashi & Kuchii, 1973).

Recently, Hermsmyer (1976*a*, *b*) and Hermsmyer & Walton (1977) measured the membrane potential of vascular muscles of s.h. and n. rats, and concluded from studies on the effect of changes in external K on the membrane potential at 36 and 16 °C that the equilibrium potential for K is lower in s.h. than n. rats. The effect of the reduced K gradient on the membrane potential was compensated by an increased electrogenic component contributed by the Na pump in s.h. rats, resulting in similar membrane potentials in s.h. and n. rats. These studies were prompted by observations on ionic fluxes and ion distribution made by Jones (1973, 1974). Jones (1973) concluded that functional alterations observed in s.h. rats probably resulted from primary changes in ion transport by smooth muscle rather than from secondary effects of an altered regulatory system. The decreased selectivity to K^+ over Na^+ and the increased turnover of ions could lead to increased reactivity to noradrenaline through effects on membrane potential. Blaustein (1977) has discussed the generation of hypertension in relation to Na-Ca exchange mechanism in resistance vessels; however, no experiment was done on n. and s.h. rats.

To investigate further the nature of hypertension caused by either increased

peripheral resistance or increased reactivity, or both, it is essential to understand the passive membrane properties in both n. and s.h. rats.

The present experiments were an attempt to clarify the characteristics of passive membrane properties of the vascular smooth muscle cells in these animals. The portal vein and pulmonary artery served as the vascular tissue.

METHODS

As s.h. rats, Okamoto & Aoki strain (1963) and as n. rats, Wistar Kyoto (Okamoto & Aoki, 1963) were used. These animals were supplied by the Nippon Rat Supply Co. Ltd. The average weights of 4–5 months old s.h. and n. rats of either sex were about 180 and 250 g, respectively. The systolic blood pressures measured from the rat tail in s.h. rats ranged from 165 to 185 mmHg and that in n. rats from 110 to 120 mmHg. The rats were stunned and bled. The portal vein or pulmonary artery was excised and dissected. The connective tissue was carefully removed in Krebs solution at room temperature under a binocular microscope. The portal vein (15–20 mm in length and 1·5 mm in width) was cut along the longitudinal axis, and the pulmonary artery was cut along the helical axis in a counter-clockwise direction (1·5 mm in width and 15–20 mm in length). The vascular tissue was mounted in an organ bath 2 ml. in capacity, through which solution flowed continuously at a temperature of 35–36 °C driven by a thermostatically controlled perfusion pump. The solution was perfused at a rate of 3 ml./min.

A micro-electrode was inserted into the muscle cell from the outer surface of the portal vein and the pulmonary artery. The intracellular recordings were made with glasscapillary micro-electrodes filled with 3 M-KCl. The distance of the micro-electrode from the stimulating partition plate was measured under a binocular microscope. The arrangement for stimulating and recording was the same as in the partition stimulation method described by Abe & Tomita (1968), i.e. a piece of the vascular strip was placed in the recording chamber and one end was pulled through the opening into the stimulation chamber. Measurement of the membrane activity was started after 60–90 min perfusion in the organ bath.

A modified Krebs solution of the following composition was used (mM): Na^+ 137·4, K^+ 5·9, Mg^{2+} 1·2, Ca^{2+} 2·5, Cl^- 134·0, HCO_3^- 15·5, $H_2PO_4^-$ 1·2 and glucose 11·5; equilibrated with 97% O_2–3% CO_2. The pH of the solution was kept about 7·2.

Excess K^+ solution was prepared isotonically by replacing NaCl by equivalent amounts of KCl, and low K^+ solution was prepared by addition of isomolar NaCl instead of KCl at any desired concentration. Isotonic K^+ solution was prepared by replacing NaCl and $NaHCO_3$ by equivalent amounts of KCl and $KHCO_3$.

The following drugs were used at the concentrations described in the results (g/ml.); L-noradrenaline (Merck), procaine-HCl (Daiichi), phentolamine (Regitin; CIBA-Geigy), isoprenaline (Merck), propranolol (Suitomo), and prostaglandin E_2 (EG 602; Ono).

RESULTS

Passive electrical properties of the membrane

The membrane potentials measured from the smooth muscle cell of the portal vein of n. and s.h. rats were $-48{\cdot}6 \pm 1{\cdot}9$ mV S.D. ($n = 145$) and $-49{\cdot}1 \pm 1{\cdot}6$ mV, S.D. ($n = 168$), respectively. The smooth muscle cells of the portal vein in the n. and s.h. rats showed spontaneous spike generation. The amplitude of the spike often exceeded +10 mV. In the fresh tissue (up to 3–4 hr), the spikes appeared on a slow depolarization as burst discharges between the quiescent periods. However, the burst discharges tended to become continuous with further perfusion. Fig. 1 shows various patterns of spontaneous discharges recorded from the portal vein of the n. rats. The maximum rate of rise of the spike was $11{\cdot}6 \pm 2{\cdot}5$ V/sec ($n = 28$) measured

from the spikes showing overshoot potentials, and that in s.h. rats was $12{\cdot}6 \pm 2{\cdot}4$ V/sec ($n = 35$).

The membrane potentials measured from the smooth muscles cells of pulmonary arteries from n. and s.h. rats were $-50{\cdot}6 \pm 1{\cdot}8$ mV, S.D. ($n = 251$) and $-51{\cdot}2 \pm 1{\cdot}6$ mV, S.D. ($n = 196$), respectively. The cells were electrically quiescent, and depolarization of the membrane induced by excess K^+ or 10^{-6} g/ml. noradrenaline did not evoke spikes. However, application of tetraethylammonium or procaine evoked

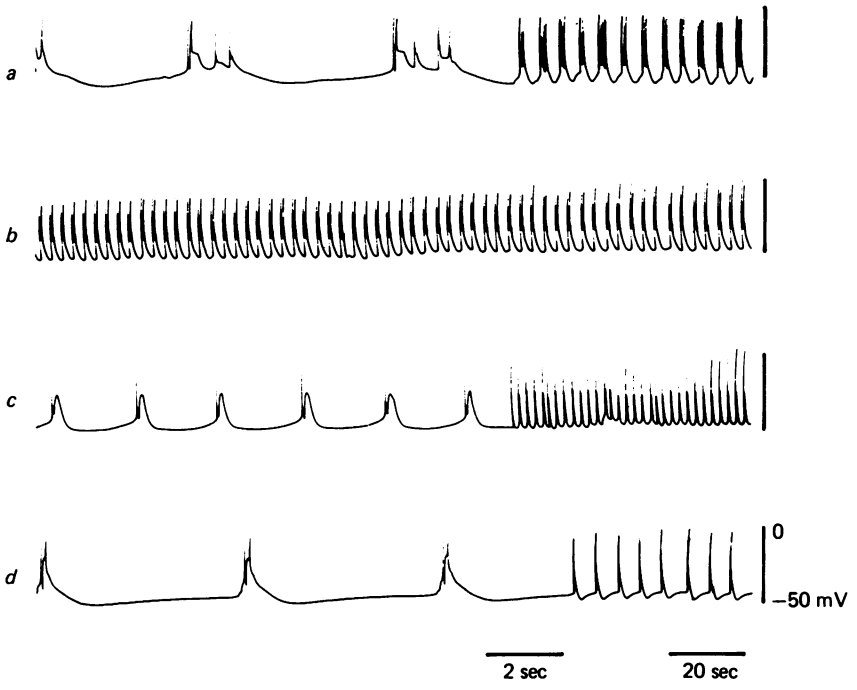

Fig. 1. Various patterns of the spike generation obtained from the smooth muscle of portal vein of normotensive rat. Two different speeds are illustrated, except in *b*.

spikes. By application of 5 mM-procaine ($1{\cdot}36 \times 10^{-2}$ g/ml.), the membrane was depolarized slightly ($-50{\cdot}1 \pm 1{\cdot}4$ mV, $n = 20$ to $-46{\cdot}3 \pm 1{\cdot}8$ mV, $n = 20$), the amplitude of the electrotonic potential was increased (1·4 times the control measured at 0·8 mm distance from the stimulation partition before and during application of procaine), the rectifying properties were suppressed and spikes generated. These actions of procaine were the same as those observed in the pulmonary artery of the rabbit (Casteels, Kitamura, Kuriyama & Suzuki, 1977*a*).

The current–voltage relationships at the steady state of electrotonic potential (pulse duration 3·0 sec) recorded from the smooth muscle cells of portal vein of n. and s.h. rats were observed at several distances from the stimulating partition. Linear relationships between the applied inward current intensities and the amplitudes of the electrotonic potential were observed.

Fig. 2 shows the relationship between the amplitude of the electrotonic potentials which were produced by a given current intensity and the distance from the partition of the smooth muscle tissues of the portal vein in n. and s.h. rats. The relationships

were linear in both tissues and indicated an exponential decay of the electrotonic potential along the tissue. The space constant (λ) was calculated as the distance at which the electroronic potential decays to 1/e. The values of the space constant in both tissues varied widely and the maximum and minimum values obtained in the present experiments are illustrated in Fig. 2. The space constants of the n. rats were 1·77 and 1·02 mm and those in the s.h. rats were 1·63 and 0·93 mm, respectively. The average value of the space constant of the portal vein of n. rats was $1{\cdot}22 \pm 0{\cdot}30$ mm ($n = 9$) and that of s.h. rats was $1{\cdot}20 \pm 0{\cdot}19$ mm ($n = 12$).

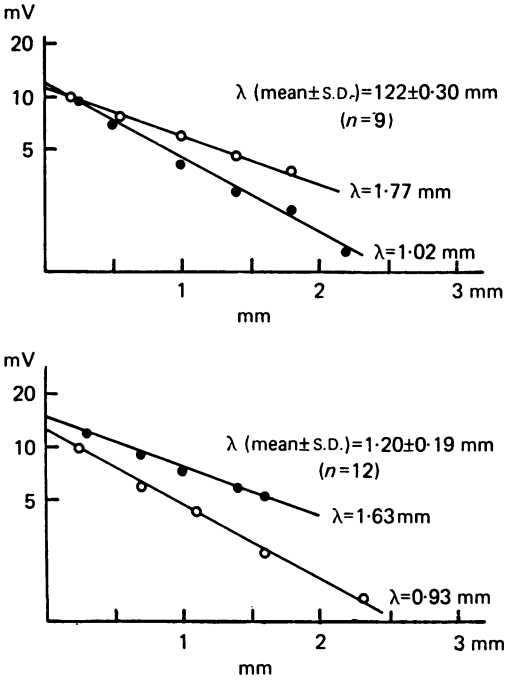

Fig. 2. Relationships between the amplitude of the electrotonic potential and distance from the stimulating partition obtained from the portal vein of n. (top) and s.h. (bottom) rat. The amplitudes of the tonic potential were expressed as a logarithmic scale. Space constant of tissue (λ) was calculated from the decay of the tonic potential at e^{-1}. The maximum and minimum values obtained in the present experiments are illustrated. The mean values of space constant measured from n. and s.h. rats are inserted in the Figure.

Fig. 3 shows the relationship between the time required to reach the half amplitude of the electrotonic potential and the distance from the stimulation partition. The above relationship should be linear when the tissue possesses cable properties and the slope is expressed by $\tau/2\lambda$ (Hodgkin & Rushton, 1946; Katz, 1948; Tomita, 1970), where τ is the time constant of the membrane. The relationships observed in the portal vein of n. and s.h. rats were roughly linear. The values of τ calculated from the slope and the space constant in n. rats was 190 ± 38 msec ($n = 7$) and that in s.h. rats was 202 ± 29 msec ($n = 6$).

Similar experimental procedures were also applied to the pulmonary artery. Fig. 4 shows the current–voltage relation of the pulmonary artery of the s.h. rats

at the steady state of the electrotonic potential (pulse duration 3·0 sec) at three different distances from the stimulation partition. In the portal vein, the outward current pulse easily generated spikes, and the accurate measurement of the electrotonic potential produced by outward current was difficult. On the other hand, in

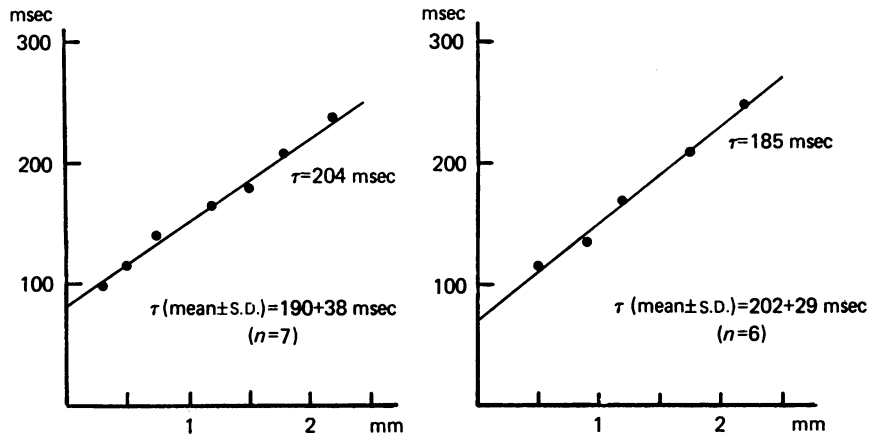

Fig. 3. Relationships between the time to reach half amplitude of the electrotonic potential and the distance from the stimulating partition of the smooth muscle cells of the portal vein of n. (left) and s.h. (right) rat. The time constant of the membrane (τ) was calculated from the equation for the slope, $\tau/2\lambda$, where λ is the space constant. The mean values are also indicated.

the pulmonary artery, the outward current produced the electrotonic potential without interference of spike generation. The outward current consistently produced a lower amplitude of the electrotonic potential than the inward current in smooth muscle membrane of the pulmonary artery at any given current intensity, i.e. the membrane showed rectifying properties. The average value of the space constant of the pulmonary artery in s.h. rats was $1{\cdot}46 \pm 0{\cdot}26$ mm ($n = 7$), and that in the n. rats was $1{\cdot}40 \pm 0{\cdot}28$ mm ($n = 8$). The time constant of the membrane was calculated from the amplitude of the electrotonic potential, distance from the stimulation partition and space constant of the tissue as calculated previously for the portal vein. The mean value of the time constant of the membrane was 259 ± 58 msec ($n = 5$) in s.h. rats and that in n. rats was 238 ± 43 msec ($n = 5$).

The results obtained on the passive membrane properties are summarized in Table 1. These properties of the smooth muscle cells of the portal vein and pulmonary artery show much the same values in n. and s.h. rats, and it is clear that there was no apparent difference in electrical properties between n. and s.h. rats.

Effects of various concentrations of K^+ on the membrane potential

Fig. 5 shows the effects of various concentrations of K^+ on membrane potential and spike activity of the portal vein of n. rats. Excess-K^+ depolarized the membrane and increased the spike generation. When K^+ concentration was increased from 5·9 to 39·2 mM, the membrane depolarized markedly and a depolarization block of the spike generation appeared (Fig. 5, d_1). With a low concentration of K^+ (3·6 and

1·5 mM), the spike frequency was markedly reduced and often slow potential changes appeared without spike generation (Fig. 5*a*). These slow potentials were not suppressed by treatment with phentolamine (10^{-6} g/ml.), thus indicating the myogenic nature of the slow depolarization. When the tissue was immersed in 1·5 mM K^+ longer than 30 min or in a concentration less than 0·6 mM-K^+, the spontaneous spike generation nearly ceased but application of an outward current pulse evoked

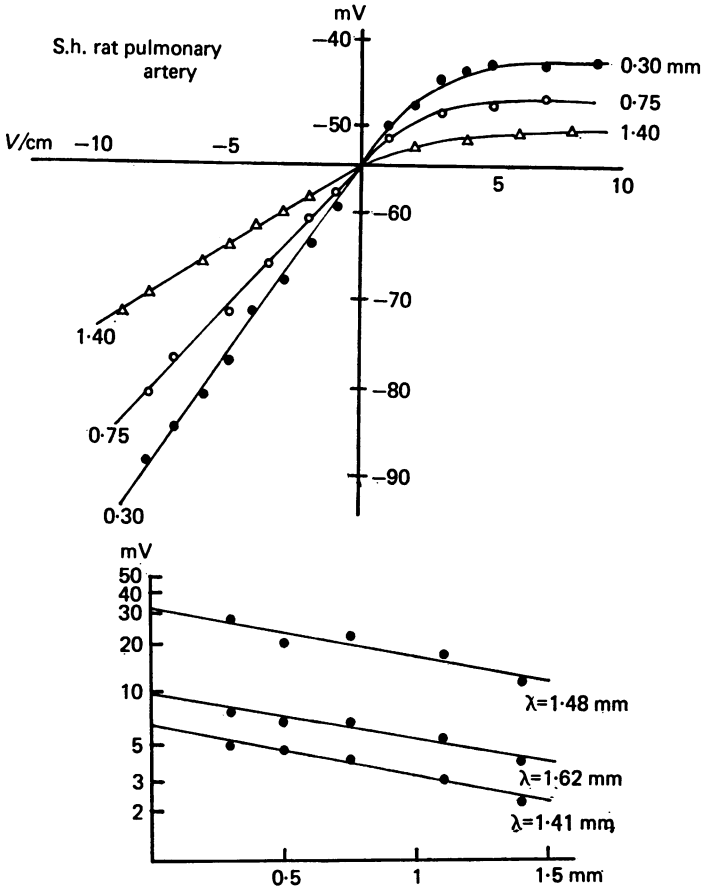

Fig. 4. Relationship between the applied current pulse (inward and outward pulse) and the amplitude of the electrotonic potential in the pulmonary artery of s.h. rats measured at three different distances from the stimulating partition (0·30, 0·75 and 1·40 mm, respectively), and the relationship between the amplitude of the electrotonic potential expressed on a logarithmic scale and the distance from the stimulating partition. The inserted space constant (λ) was calculated from the decay of the electrotonic potential at e^{-1}.

the spike without any remarkable suppression of the spike amplitude. Similar electrical properties of the membrane were also observed in smooth muscle cells of the portal vein of s.h. rats. Figs. 6 and 7 show the effects of various concentrations of K^+ on membrane potential of the portal vein in n. and s.h. rats and those of the pulmonary artery in n. and s.h. rats, respectively.

When the relationship between the external K^+ concentration expressed on a logarithmic scale and the changes in the membrane potential was observed, a linear relation was observed in solutions containing more than 20·3 mM-K^+, and the maximum slope of membrane depolarization produced by a tenfold change of K^+ concentration was 42 mV in the portal vein of n. rats, and 41 mV in s.h. rats. The above slope in the pulmonary artery of n. rats was 48 mV, and in s.h. rats, it was 46 mV. These values were much lower than the value expected from the Nernst equation for the K electrode (61 mV). The n. and s.h. rats showed nearly the same maximum slope of K-induced depolarization in both portal vein and pulmonary artery. When the effects of K^+ on the membrane potential were compared between the pulmonary artery and portal vein, these two tissues showed two different

TABLE 1. Various membrane characteristics of vascular smooth muscle membrane in normotensive and spontaneously hypertensive rats

	Portal vein		Pulmonary artery	
	N. rats	S.h. rats	N. rats	S.h. rats
Membrane potential (mV)	−48·6 ± 1·9	−49·1 ± 1·6	−50·1 ± 1·8	−51·2 ± 1·6
Spontaneous activity	+	+	−	−
Evoked potential in Krebs solution	+	+	−	−
The maximum reat of rise of spike (V/sec)	11·6 ± 2·5	12·6 ± 2·4	−	−
Space constant (mm)	1·22 ± 0·30	1·20 ± 0·19	1·40 ± 0·28	1·46 ± 0·26
Time constant of the membrane (msec)	190 ± 38	202 ± 29	238 ± 43	259 ± 59
Maximum slope of K-induced depolarization (mV)	42	41	48	46
Low K^+ (0·6 mM)-induced potential change (mV)	−48·1 ± 0·2* to −42·9 ± 0·3*	−47·5 ± 0·3* to −41·9 ± 0·3*	−49·2 ± 0·2* to −52·5 ± 0·1*	−50·6 ± 0·1* to −52·8 ± 0·1*
Depolarization induced				
By 10^{-9} g/ml. noradrenaline ($P < 0·05$) (mV)	—	−50·1 ± 1·8 to −47·1 ± 2·1	—	−50·6 ± 2·3 to −47·8 ± 1·7
By 10^{-8} g/ml. noradrenaline ($P < 0·05$) (mV)	−49·8 ± 2·5 to −47·2 ± 2·2	to −44·1 ± 2·5 ($P < 0·01$)	−49·5 ± 1·8 to −47·2 ± 1·9	to −44·2 ± 1·6 ($P < 0·01$)

* S.E., other values are S.D.

features, i.e. the maximum slope of the membrane depolarization produced by excess K^+ was steeper in the pulmonary artery than that in the portal vein, and, on the other hand, in low K^+ the membrane was markedly depolarized in the portal vein in comparison with a small hyperpolarization seen in the pulmonary artery. The results are summarized in Table 1.

Effects of catecholamines and prostaglandin E_2 on the membrane

When the effects of noradrenaline and isoprenaline on the membrane activity of smooth muscle cells of the portal vein of NR were observed, noradrenaline

(5×10^{-8} g/ml.) depolarized the membrane and increased the spike frequency, and isoprenaline (10^{-8} g/ml.) suppressed the spike frequency without any remarkable change in the membrane potential. These effects of noradrenaline and isoprenaline were blocked by treatment with phentolamine (10^{-7} g/ml.) and propranolol (10^{-7} g/ml.), respectively. Fig. 8*A* shows the relationship between membrane depolarization and applied noradrenaline in the portal veins of n. rats and s.h. rats. In n. rats, a

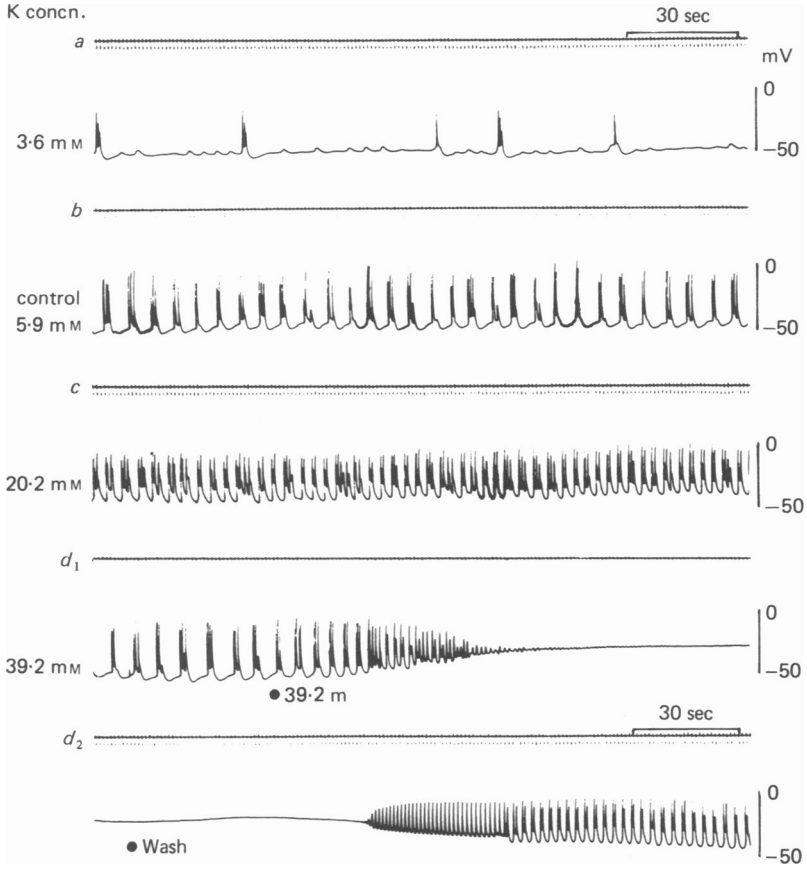

Fig. 5. Effects of various concentrations of K^+ on the membrane activity of smooth muscle cells of the portal vein of n. rat. *a*, 3·6 mM-K^+. *b*, 5·9 mM-K^+ (control). *c*, 20·2 mM-K^+. d_1–*d* , continuous record, 39·2 mM-K^+ added between dots.

significant depolarization was not seen at a noradrenaline concentration of less than 10^{-8} g/ml., whereas in s.h. rats, 10^{-9} g/ml. already depolarized the membrane. Thus the smooth muscle cells of the portal vein of s.h. rats are apparently more sensitive to noradrenaline than are these cells from n. rats. Increased concentration of noradrenaline further depolarized the membrane in both n. and s.h. rats, although depolarization in the latter was consistently higher than that in n. rats at any given concentration. Fig. 8*B* shows the effects of noradrenaline on smooth muscle cells of the pulmonary artery of n. and s.h. rats. A lower concentration of noradrenaline produced a response in the s.h. rats cells. These results are summarized in Table 1.

When the effects of various concentrations of noradrenaline on the spike activity of the portal vein of n. and s.h. rats were observed, depolarization block of the spike generation appeared on treatment with noradrenaline 10^{-7} g/ml. in n. rats, and the depolarization block appeared with application of noradrenaline 10^{-8} g/ml. in s.h. rats.

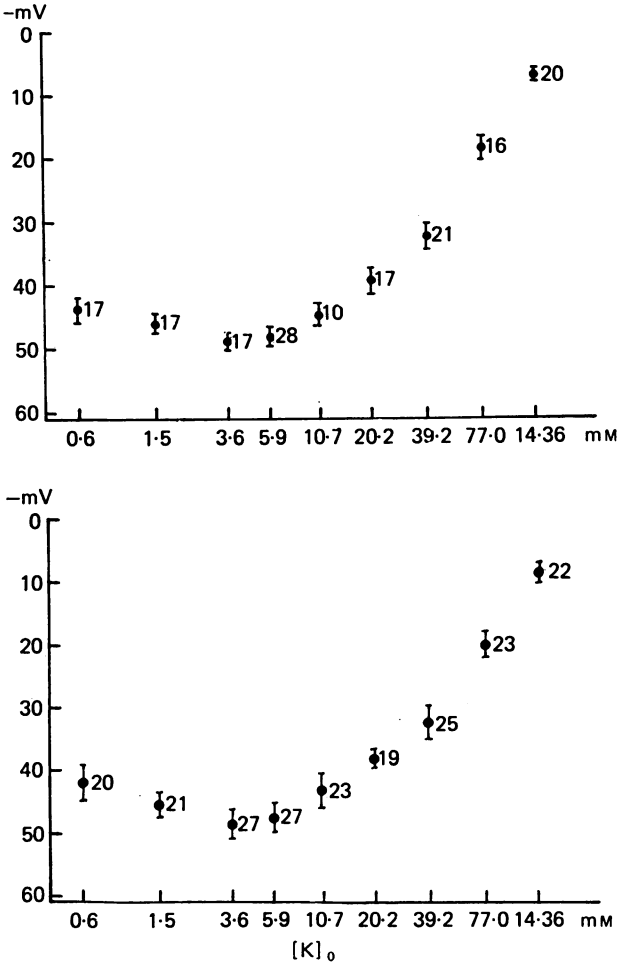

Fig. 6. Relationships between various concentrations of K^+ and the membrane potential measured from smooth muscle cells of the portal vein of n. (top) and s.h. (bottom) rat. Inserted numbers indicate the number of cells measured. Bars indicate 2 × S.E.

Effects of PGE_2 on the membrane potential and membrane activity of the portal vein were examined in both n. and s.h. rats. In n. rats, application of PGE_2 10^{-6} g/ml. depolarized the membrane from $-50{\cdot}1 \pm 1{\cdot}5$ mV, S.D. (n = 28) to $-46{\cdot}3 \pm 2{\cdot}4$ mV, S.D. (n = 28), and in s.h. rats the membrane was further depolarized from $-50{\cdot}7 \pm 1{\cdot}9$ mV, S.D. (n 21) to $-42{\cdot}3 \pm 2{\cdot}4$ mV, S.D. (n = 25). Fig. 9*A* and *B* shows the effects of various concentrations of PGE_2 (10^{-9}–10^{-6} g/ml.) on the membrane activity of the portal vein in n. and s.h. rats, respectively. The results indicate that the

smooth muscle membrane of the portal vein in s.h. rats has increased sensitivity to PGE_2. These responses of smooth muscle cells of the portal vein of n. and s.h. rats differed from observations in the guinea-pig and rabbit since PGE_2 depolarized the tissues of these animals but hyperpolarized the rat tissue (Kitamura, Suzuki & Kuriyama, 1976).

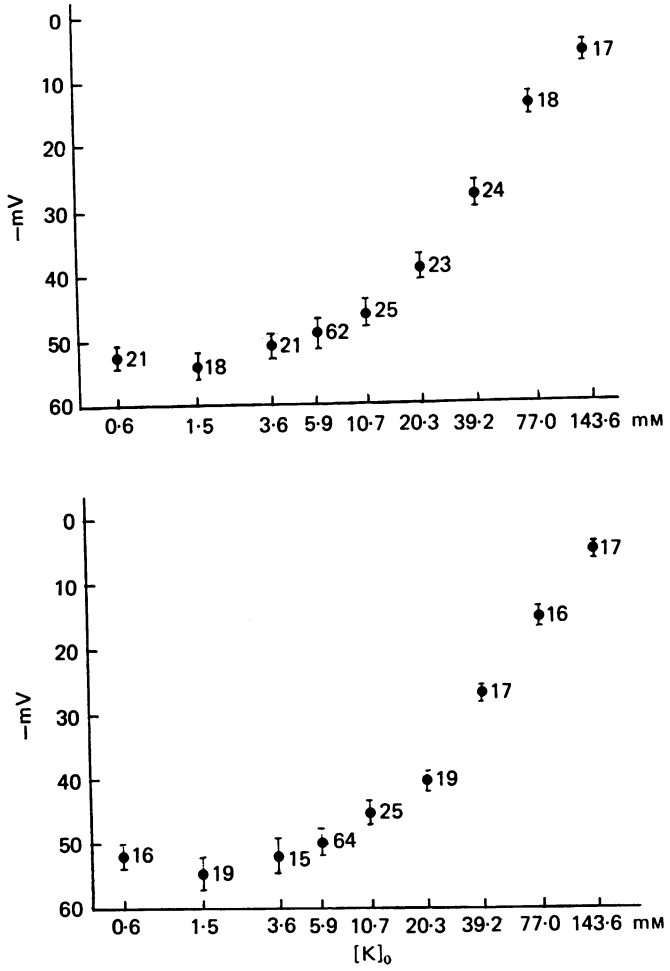

Fig. 7. Relationships between various concentrations of K^+ and the membrane potential measured from smooth muscle cells of the pulmonary artery of n. (top) and s.h. (bottom) rats. Explanation as in Fig. 6.

DISCUSSION

Our results indicate that smooth muscle cells of pulmonary artery and portal vein of the rat do have cable-like properties. The passive electrical properties of smooth muscle cells of the pulmonary artery and portal vein observed in n. and s.h. rats were much the same. The space constant of the pulmonary artery observed in n. and s.h. rats was nearly the same as that observed in pulmonary artery of the rabbit (λ = 1·46 mm in n. rats; λ = 1·48 mm in rabbit) but that in the portal

vein of n. rats was much longer than that observed in guinea-pig and rabbit (λ = 1·2 mm in n. rats; λ = 0·52 mm in guinea-pig and λ = 0·79 mm in rabbit). Smooth muscles of the pulmonary artery in n. and s.h. rats were electrically quiescent. Tetraethylammonium and procaine depolarized the membrane, increased the membrane resistance, suppressed the rectifying property of the membrane and generated a graded response to outward current pulses. The mechanism underlying

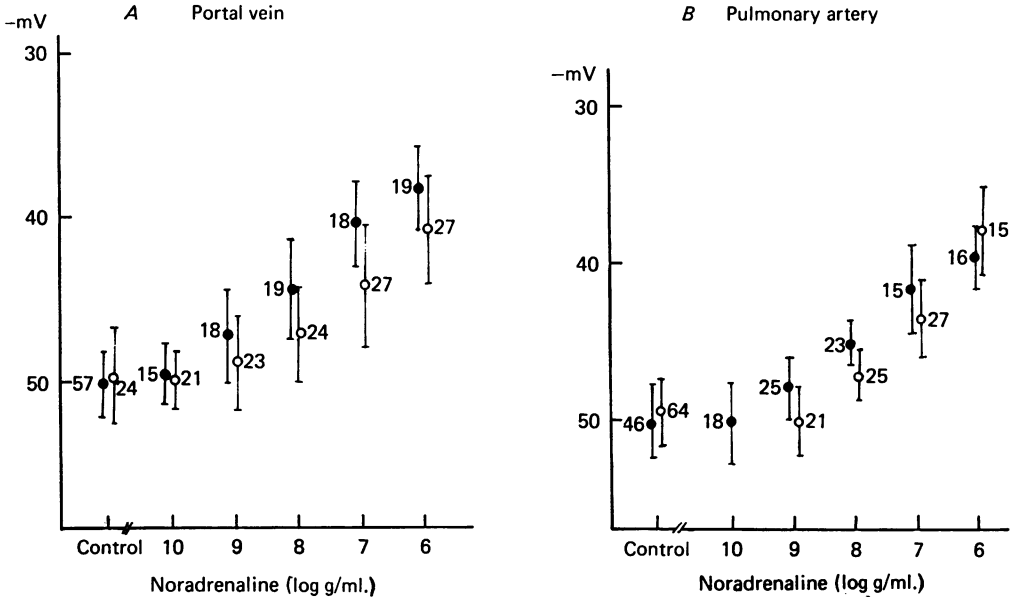

Fig. 8. *A*, relationship between the membrane depolarization and concentration of noradrenaline observed in smooth muscle cells of the portal vein of n. (○) and s.h. (●) rats. Inserted numbers indicate the number of cells measured. Horizontal bars indicate 2 × S.D. In n. rats, noradrenaline 10^{-8} g/ml. causes significant depolarization of the membrane (Student's t test, $P < 0·05$) and in s.h. rats, noradrenaline 10^{-9} g/ml. depolarizes the membrane ($P < 0·05$). *B*, relations between the membrane depolarization and concentrations of noradrenaline recorded from the smooth muscle cells of pulmonary artery of n. (○) and s.h. (●) rats. In s.h. rats, a significant depolarization ($P < 0·05$) was caused by noradrenaline 10^{-9} g/ml. ($P < 0·01$ in 10^{-8} g/ml.), whereas in n. rats, a significant depolarization ($P < 0·05$) was only seen at noradrenaline 10^{-8} g/ml. ($P < 0·01$ in 10^{-7} g/ml.). Inserted numbers indicate the number of cells measured.

the generation of membrane response is likely to be the same as that discussed in relation to K- and Ca-permeability by Ito, Kuriyama & Sakamoto (1970) for the guinea-pig alimentary canal and by Casteels *et al.* (1977*a*) for the rabbit pulmonary artery.

Hermsmyer (1976*a*, *b*) and Hermsmyer & Walton (1977) reported that the caudal artery excised from s.h. and n. rats showed nearly the same membrane potential at 36 °C but the cells from s.h. rats always showed a less negative membrane potential than those from n. rats at 16 °C. The caudal artery undergoes a large depolarization when K^+ is removed from the solution, and a transient hyperpolarization that exceeds the calculated K equilibrium potential appears when K^+ is reapplied.

The amplitude of the hyperpolarization was greater for vascular muscle of s.h. than n. rats. This author postulated that there was an apparently lower intracellular K^+ and a more active electrogenic ion transport in the s.h. rats vascular muscle cell, and such would result in an unaltered membrane potential at body temperature in the physiological range of K^+ concentration. Therefore, if similar

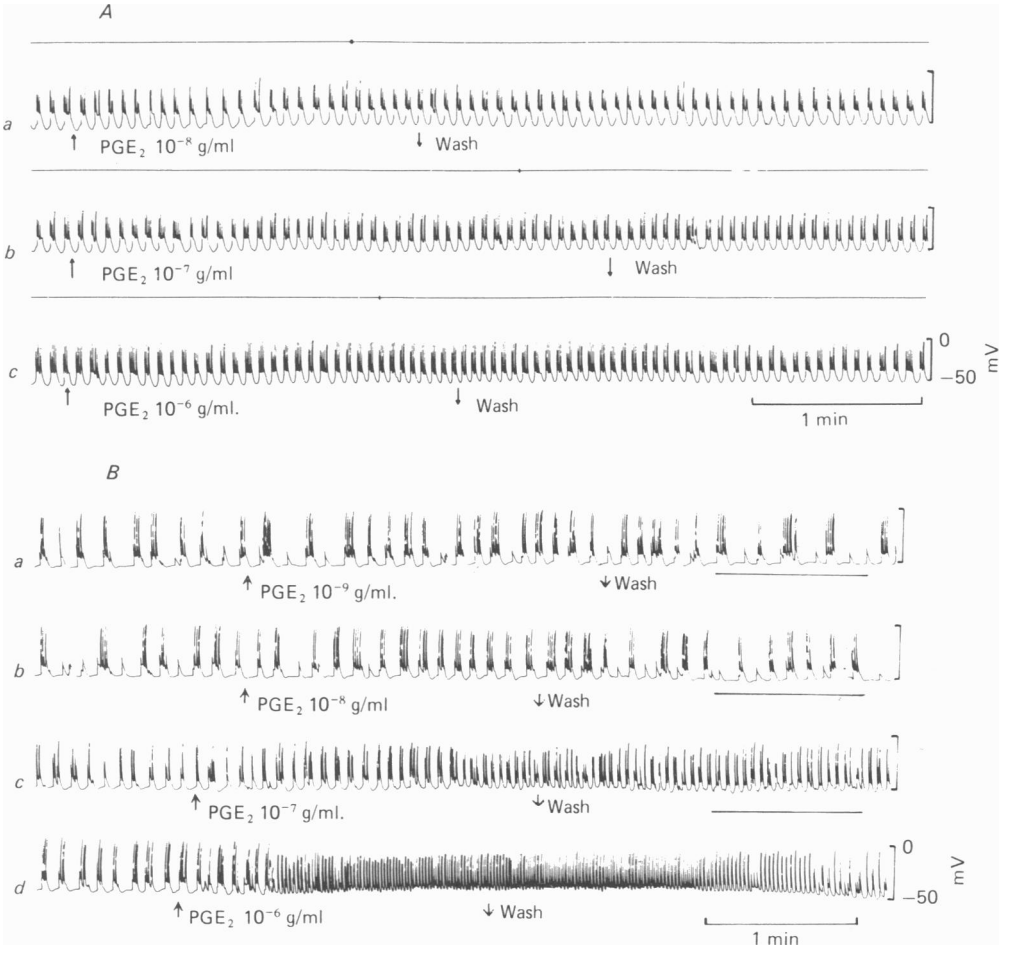

Fig. 9. *A*, effects of prostaglandin E_2 (PGE_2) on the membrane activity recorded from the smooth muscle cells of the portal vein of n. rats. Concentrations of PGE_2 varied from 10^{-8} to 10^{-6} g/ml. ↓ and ↑ indicate the application and removal of PGE_2, respectively. *B*, effects of PGE_2 on the membrane activity recorded from the smooth muscle cells of the portal vein of s.h. rats. Concentrations of PGE_2 varied from 10^{-9} to 10^{-6} g/ml.

values of the membrane potential in n. and s.h. rats were observed, the membrane resistance should differ between n. and s.h. rats. In fact, Jones (1974) reported that the rate of K^+ efflux increases consistently, which presumably reflects a reduced membrane resistance. However, in the present experiments, the space constants of the pulmonary artery and portal vein obtained from n. and s.h. rats were the same.

In the portal vein and pulmonary artery, the responses of smooth muscle cells to external K^+ were nearly the same in both n. and s.h. rats, and the maximum slope of the membrane depolarization produced by tenfold increase in external K^+ concentration was steeper in the pulmonary artery than that observed in the portal vein. However, these values were lower than that observed in the caudal artery as measured by Hermsmyer (1976*a*). When portal vein tissues was exposed low K^+ solution, the membrane was depolarized and transient hyperpolarization was produced when K^+ was reapplied. The grade of transient hyperpolarization observed in the portal vein was consistently larger than that observed in the pulmonary artery. These observations confirmed the results obtained from the same lines of the experiments made on the pulmonary artery, portal vein and mesenteric artery of the rabbit and guinea-pig, i.e. the resistance vessel and portal vein showed higher electrogenic Na-pump activity than that observed in the elastic artery (Kuriyama, Oshima & Sakamoto, 1971; Kuriyama & Suzuki, 1978). However, in response to low K^+ solution, the smooth muscle membrane of pulmonary artery and portal vein was the same in n. and s.h. rats. Presumably the caudal artery possesses a specific ability to maintain the membrane potential as is the case in the brain vascular system.

In the pulmonary artery, depolarization of the membrane by noradrenaline is not essential to produce contraction (Su, Bevan & Ursillo, 1964; Somlyo & Somlyo, 1970; Casteels *et al.* 1977*b*). Therefore, depolarization of the membrane produced by a relatively high concentration of noradrenaline may not be an accurate indicator of the vasoconstriction in response to a physiological concentration of noradrenaline. In the pulmonary artery and portal vein of s.h. rats however, the depolarization of the membrane was induced by a lower concentration of noradrenaline. Increased sensitivity of the smooth cell membrane of SHR was also observed by treatment with PGE_2. PGE_2 hyperpolarized and PGF_2 depolarized the membrane of pulmonary artery and portal vein of the guinea-pig and rabbit (Kitamura *et al.* 1976). In the rat, however, PGE_2 depolarized and increased the excitability of the membrane. The nature of these discrepancies is not clear but the species difference has to be considered.

The mechanism of generation of hypertension in s.h. rats cannot be explained solely on the basis of an increased sensitivity of the muscle cell to chemical transmitters, because many differences between n. and s.h. rats have been elucidated by various experimental procedures. For example, (i) sympathetic discharge rate in s.h. rats is higher than that in n. rats (Okamoto, Nosaka, Yamori & Matsumoto, 1967; Iriuchijima, 1973), (ii) the pontobulbar portion in the brain plays an important role to inducing the hypertension (Okamoto *et al.* 1967), (iii) enzymic activities of catecholamine synthesis in sympathetic ganglia, blood vessels and brain are higher in s.h. rats (Ooshima, 1973; Nagatsu, Kato, Numata, Ikuta, Kuzuya, Umezawa, Matsuzaki & Takeuchi, 1975; Grobecker, Rizen, Weise, Saavedra & Kopin, 1975; Nakamura & Nakamura, 1977), (iv) Ca-accumulating ability of the microsomal fraction of s.h. rats vascular smooth muscle differs from that in n. rats (Webb & Bhalla, 1976; Wei, Janis & Daniel, 1976, 1977), (v) La^{3+}, Mn^{2+} and Sr^{2+} produce contraction of vascular muscle in s.h. but not in n. rats (Shibata *et al.* 1973; Bohr, 1974).

In the present experiments, the passive membrane property and the response to external K^+ of the smooth muscle membrane in the pulmonary artery and portal vein was the same in n. and s.h. rats, thus indicating that the hypertension induced in s.h. rats might be partly due to an increased sensitivity of the smooth muscle to vasocontracting substances and also by the various other factors excluding the changes in the passive electrical property of the membrane.

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REFERENCES

ABE, Y. & TOMITA, T. (1968). Cable properties of smooth muscle. *J. Physiol.* **196**, 87–100.

BLAUSTEIN, M. P. (1977). Sodium ions, calcium ions, blood pressure regulation, and hypertension: a reassessment and a hypothesis. *Am. J. Physiol.* **232**, c165–173.

BOHR, D. F. (1974). Reactivity of vascular smooth muscle from normal and hypertensive rats: effects of several cations. *Fedn Proc.* **33**, 127–132.

BOHR, D. F. & STRIN, M. (1970). Regulation of vascular smooth muscle contraction: Changes in experimental hypertension. *Circulation Res.* **27**, 83–90.

CASTEELS, R., KITAMURA, K., KURIYAMA, H. & SUZUKI, H. (1977*a*). The membrane properties of the smooth muscle cells of the rabbit main pulmonary artery. *J. Physiol.* **271**, 41–61.

CASTEELS, R., KITAMURA, K., KURIYAMA, H. & SUZUKI, H. (1977*b*). Excitation-contraction coupling in the smooth muscle cells of the rabbit main pulmonary artery. *J. Physiol.* **271**, 63–79.

FOLKOW, B. (1971). The haemodynamic consequences of adaptive structural changes of the resistance vessels in hypertension. *Clin. Sci.* **41**, 1–12.

FOLKOW, B., HÄLLBACK, H., LUNDGREN, Y., SIVERTSSON, R. & WEISS, L. (1973). Importance of adaptive changes in vascular design for establishment of primary hypertension, studied in man and in spontaneously hypertensive rats. *Circulation Res.* **32**, suppl. 1, 2–13.

GROBECKER, H., RIZEN, M. F., WEISE, V., SAAVEDRA, J. M. & KOPIN, I. J. (1975). Sympathoadrenal medullary activity in young spontaneously hypertensive rats. *Nature, Lond.* **258**, 267–268.

HERMSMYER, K. (1976*a*). Cellular basis for increased sensitivity of vascular smooth muscle in spontaneously hypertensive rat. *Circulation Res.* **38**, 53–57.

HERMSMYER, K. (1976*b*). Electrogenesis of increased norepinephrine sensitivitiy of arterial vascular muscle in hypertension. *Circulation Res.* **38**, 362–367.

HERMSMYER, K. & WALTON, S. (1977). Specificity of altered electrogenesis of membrane potential in hypertension. *Circulation Res.* **40**, 153–162.

HODGKIN, A. L. & RUSHTON, W. A. H. (1946). The electrical constants of a crustacean nerve fibre. *Proc. R. Soc.* B **133**, 444–479.

HOLLOWAY, E. T., STRIN, M. D. & BOHR, D. F. (1972). Calcium dependence of vascular smooth muscle from normotensive and hypertensive rats. In *Hypertension*, ed. GENEST, J. & KOIW, E. Berlin/Heidelberg: Springer-Verlag.

ITO, Y., KURIYAMA, H. & SAKAMOTO, Y. (1970). Effects of tetraethylammonium chloride on the membrane activity of guinea-pig stomach smooth muscle. *J. Physiol.* **211**, 445–460.

IRIUCHIJIMA, J. (1973). Sympathetic discharge rate in spontaneously hypertensive rats. *Jap. Heart J.* **14**, 350–356.

JONES, A. W. (1973). Altered ion transport in vascular smooth muscle from spontaneously hypertensive rats. *Circulation Res.* **33**, 563–572.

JONES, A. W. (1974). Altered ion transport in large and small arteries from spontaneously hypertensive rats and the influence of calcium. *Circulation Res.* **34/35**, 117–122.

KATZ, B. (1948). The electrical properties of the muscle fibre membrane. *Proc. R. Soc.* B **135**, 506–534.

KITAMURA, K., SUZUKI, H. & KURIYAMA, H. (1976). Prostaglandin action on the main pulmonary artery and portal vein of the rabbit. *Jap. J. Physiol.* **26**, 681–692.

KURIYAMA, H., OHSHIMA, K. & SAKAMOTO, Y. (1971). The membrane properties of the smooth muscle of the guinea-pig portal vein in isotonic and hypertonic solutions. *J. Physiol.* **217**, 179–199.

KURIYAMA, H. & SUZUKI, H. (1978). The effects of acetylcholine on the membrane and contractile properties of smooth muscle cells of the rabbit superior mesenteric artery. *Br. J. Pharmac.* (in the Press).

LAIS, L. T. & BRODY, M. J. (1975). Mechanism of vascular hyperresponsiveness in the spontaneously hypertensive rat. *Circulation Res.* **36/37**, 216–222.

NAGATSU, T., KATO, T., NUMATA, Y., IKUTA, K., KUZUYA, H., UMEZAWA, H., MASUZAKI, M. & TAKEUCHI, T. (1975). Dopamine β-hydroxylase and tyrosine hydroxylase activities in spontaneously hypertensive rats after NaCl administration. *Experientia* **31**, 767–768.

NAKAMURA, K. & NAKAMURA, K. (1977). Selective activation of sympathetic ganglia in young spontaneously hypertensive rats. *Nature, Lond.* **266**, 265–267.

OKAMOTO, K. & AOKI, K. (1963). Development of a strain of spontaneous hypertensive rats. *Jap. circ. J.* **27**, 282–293.

OKAMOTO, K., NOSAKA, S., YAMORI, Y. & MATSUMOTO, M. (1967). Participation of neural factor in the pathogenesis of hypertension in the spontaneously hypertensive rats. *Jap. heart. J.* **8**, 168–180.

OOSHIMA, A. (1973). Enzymological studies of arteries in spontaneously hypertensive rats. *Jap. circ. J.* **37**, 497–508.

SHIBATA, S., KURAHASHI, K. & KUCHII, A. (1973). A possible etiology of contractility impairment of vascular smooth muscle from spontaneously hypertensive rat. *J. Pharmac. exp. Ther.* **185**, 406–417.

SOMLYO, A. V. & SOMLYO, A. P. (1970). Vascular smooth muscle. II. Pharmacology of normal and hypertensive vessels. *Pharmac. Rev.* **22**, 249–353.

SPECTOR, S., FLEISH, J. H., MALING, H. N. & BRODIE, B. B. (1969). Vascular smooth muscle reactivity in normotensive and hypertensive rats. *Science, N.Y.* **166**, 1300–1301.

SU, C., BEVAN, J. A. & URSILLO, R. C. (1964). Electrical quiescence of pulmonary artery smooth muscle during sympathomimetic stimulation. *Circulation Res.* **15**, 20–27.

TOMITA, T. (1970). Electrical properties of mammalian smooth muscle. In *Smooth Muscle*, ed. BÜLBRING, E., BRADING, A., JOMES, A. & TOMITA, T., pp. 197–243. London: E. Arnold.

WEBB, C. R. & BHALLA, R. C. (1976). Altered calcium sequestration by subcellular fractions of vascular smooth muscle from spontaneously hypertensive rats. *J. mol. & cell. Cardiol.* **8**, 651–661.

WEI, J.-W., JANIS, R. A. & DANIEL, E. E. (1976). Calcium accumulation and enzymatic activities of subcellular fractions from aortas and ventricles of genetically hypertensive rats. *Circulation Res.* **39**, 133–140.

WEI, J.-W., JANIS, R. A. & DANIEL, E. E. (1977). Relationship between blood pressure of spontaneously hypertensive rats and alterations in membrane properties of mesenteric artery. *Circulation Res.* **40**, 299–305.