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THE MECHANISM OF THE CONTRACTING ACTIONS OF K, NORADRENALINE AND Ba ON THE RABBIT'S PULMONARY ARTERY STRIP IN RELATION TO Ca

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Indexing Words

rabbit pulmonary artery; K; noradrenaline; Ba; Ca influx; Ca release; contraction curve; concentration-action curve

Hiromasa ARAKI, Jiro NISHIHATA and Hiroshi MATSUMOTO. *The Mechanism of the Contracting Actions of K, Noradrenaline and Ba on the Rabbit's Pulmonary Artery Strip in Relation to Ca.* Kobe J. Med. Sci. 20, 83-95, December 1974——By the functional method of observation, it was attempted to clarify the role of Ca in the contracting mechanism of drugs in the spiral strips of rabbit's pulmonary artery. Various methods of analysis were used in order to obtain informations as detailed as possible. The analysis by means of the shape of contraction curve, and that by means of the concentration-action curve, which had not so far been widely utilized, proved considerably useful.

INTRODUCTION

There are many reports[1, 2, 4, 8, 9, 10, 11, 13, 20, 21] mentioning that the contractions by various drugs were mediated by Ca mobilization (Ca release or Ca influx) in isolated smooth muscle organs. However, evidences are not yet sufficient for the general understanding as to what similarity or particularity concerning the mode of Ca mobilization may exist among the kinds of contracting drugs and of smooth muscle organs, especially there are different views[1, 4, 6, 11, 12, 13, 14, 16, 19, 20, 22] with regard to the mechanism of Ba-induced contraction of smooth muscle organs.

In the present study, the relations between Ca and the contractions by K, noradrenaline (NA) and Ba were investigated in the strips of pulmonary artery from rabbits, by using the functional method of observing the modification in tonus of the strips.

In the present paper, the word, "contractile system of muscle", is used in the broad sense, which includes not only the contractile element of muscle (actomyosin) but also the energy metabolism required for its contraction.

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MATERIALS AND METHODS

Spiral strips (about 2 cm in length and 0.5-0.8 mm in width) were obtained from the pulmonary artery of mature rabbits (2.5-3.5 kg in weight) killed by bleeding and suspended in the bath solution (abbreviated as "BS" in the following) according to Magnus method, and the tension of the strips was isotonically recorded on a smoked drum by the lever adjusted to give about 10-fold amplification. In order to obtain the constant responses, the strips were stimulated by contracting drugs about 5 times at the interval of 30 min before initiation of the experiment. Locke solution was used as BS, which was kept at 35±1℃ and continuously bubbled by air. The BS consists of NaCl 9.0, KCl 0.42, $CaCl_2$ 0.24, glucose 1.0 and $NaHCO_3$ 0.4 g/l. The "Ca-free BS" hereinafter mentioned is the BS in which $CaCl_2$ was omitted. The solutions to be tested were dropped into the BS. The drug concentrations are shown in g/ml unless otherwise specified.

The drugs used are as follows; noradrenaline hydrochloride (Sankyo), potassium chloride (Yoneyama Yakuhinkogyo), barium chloride (Wako Chemicals), calcium chloride (Yoneyama Yakuhinkogyo), dinitrophenol (Wako Chemicals), EDTA-2Na (Yoneyama Yakuhinkogyo).

RESULTS

I. *Influence of Ca removal from BS and of exogenous Ca upon tonus*

When the BS was exchanged for the one without Ca, the tonus showed a slight relaxation, which appeared immediately and fixed in a short time (1-2 min).

In the normal BS, the preparation showed no modification in tonus by exogenous Ca (2-15 mM). But, in the preparation, in which the K (ED_{50})-induced contraction had disappeared 30-45 min later in the Ca-free BS, exogenous Ca always showed a prolonged contraction. This contraction increased with increased concentration of exogenous Ca.

II. *Action of contracting drugs K, noradrenaline and Ba*

In this experiment, the concentrations used of K (2×10^{-3}), noradrenaline (NA) (10^{-7}) and Ba (2×10^{-4}) were those corresponding to ED_{50} (shown in parentheses) unless otherwise stated.

1. *Shapes of contraction curves and various factors influencing them*

The "contraction curve" mentioned hereinafter means the curve of the development of drug-induced contraction recorded on the smoked drum.

In the normal BS, all the shapes of the contraction curves of K, NA and Ba were exponential and were without fade. The rate of rise of the curves was large in the ascending order of K, Ba and NA (Figs. 1 and 2).

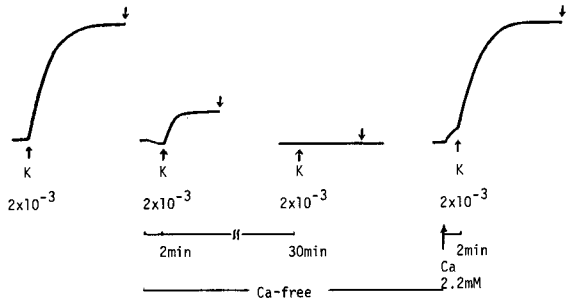

Fig. 1 Influence of Ca removal from the bath solution (BS) on the contraction curve of K.

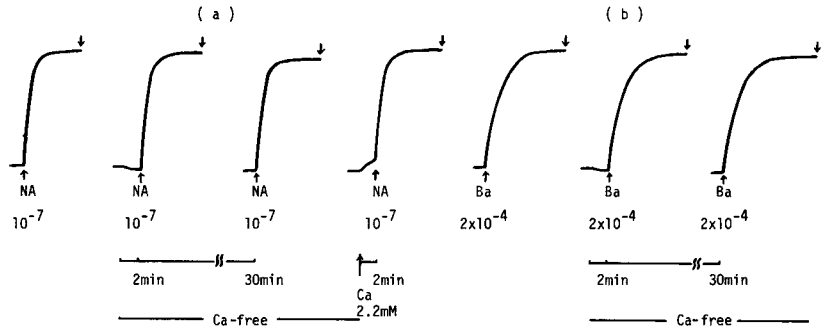

Fig. 2 Influence of Ca removal from the BS on the contraction curves of NA and Ba.

a) *Effect of Ca removal from BS*

In a short time (2-3 min) after the exchange of the normal BS for the Ca-free BS, the K-induced contraction decreased strongly in the height and slightly in the rate of rise, whereas the contraction curves of NA and Ba did not change. The K-induced contraction disappeared at 30 (7 of 10 cases) or 45 (3 of 10 cases) min after the exchange. At these times, the NA-induced contraction did not change in the rate of rise but sometimes (6 of 10 cases) decreased slightly in the height, whereas the contraction curve of Ba showed no modification. The above modifications of K- and NA-induced contractions in the Ca-free BS were completely removed in a few minutes by the re-exchange of BS to the normal (Figs. 1 and 2).

With further lapse of time after the Ca removal from BS, the rate of rise of the contraction curves gradually decreased in both cases of NA and Ba, whereas the contraction height by NA remained constant at approximately 80% of its initial height about 4 hr or more later and that by Ba did not change even 6 hr later (Fig. 3).

On the other hand, after application of EDTA (0.1-0.2 mM for 20 min and then wash), which was without effect on the contraction by exogenous Ca in the Ca-free BS, the contraction by NA disappeared, whereas that by Ba remained

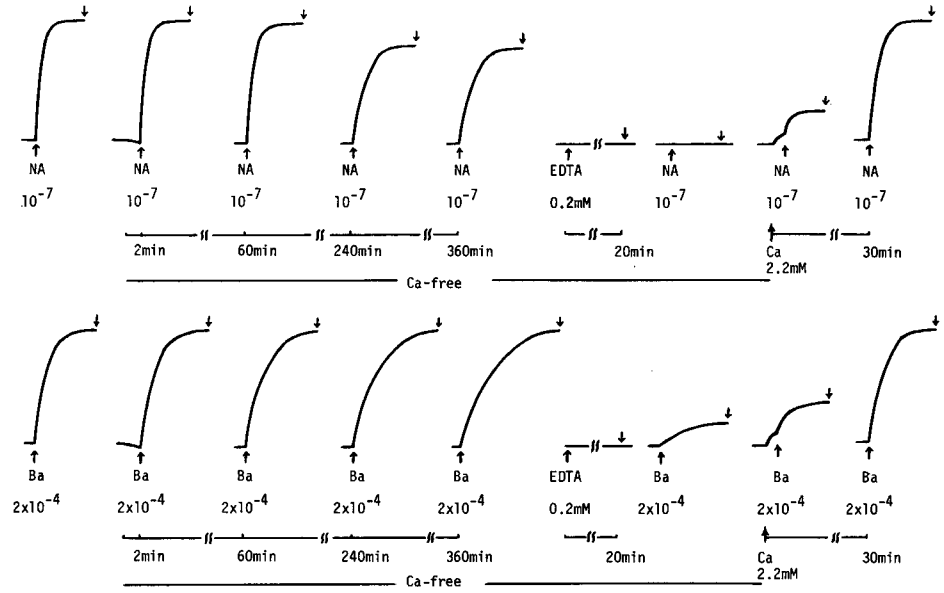

Fig. 3 Time-dependent influence of Ca removal from BS and influence of subsequent application of EDTA on the NA- and Ba-induced contractions.

constant at the magnitude of 10-20% as compared with the initial height in the normal BS (Fig. 3).

The NA- and Ba-induced contractions inhibited by treatment with EDTA in the Ca-free BS were completely recovered in about 30 min by application of the normal BS and were partially recovered (up to 50% for NA and 70% for Ba) by the transient treatment with exogenous Ca (Ca uptake) (2.2 mM Ca for 20 min and then wash). The K-induced contraction, which had disappeared in the Ca-free BS was not (5 of 7 cases) or slightly (2 of 7 cases) recovered by Ca uptake. Examples of K- and NA-induced contractions are shown in Fig. 4.

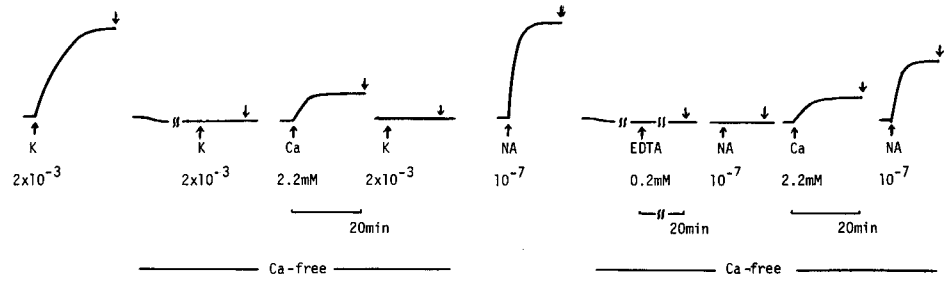

Fig. 4 Effect of Ca uptake (2.2 mM for 20 min and then wash) on the disappearance of the contraction by K (in the Ca-free BS) and that by NA (after application of EDTA in the Ca-free BS).

b) *Effect of metabolic inhibition*

This experiment was carried out in the 1/20 Ca-BS, in which the influence of metabolic inhibition on the contraction curves appeared more clearly than that in the normal BS. The discontinuation of aeration to BS (anoxia) and the treatment with dinitrophenol (DNP) were used for the metabolic inhibition.

i) *Effect of anoxia*

No influence was produced by anoxia on the tonus. In the case of NA, a slight fade occurred in the contraction curve at 30 min after anoxia, and the fade increased with a concomitant slight decrease of contraction height at 90 min after (5 cases). On the other hand, the contraction curves of K and Ba were not influenced by anoxia. The influence of anoxia on the NA-induced contraction was completely removed in 15-30 min by re-aeration to BS (5 cases) (Fig. 5).

ii) *Effect of dinitrophenol*

DNP was applied by the pretreatment (20 min) method. By DNP 10^{-5}, no influence was produced on the contractions by K and Ba (5 cases), whereas a slight fade came out in the contraction by NA. This fade was removed reversibly by washing out DNP (5 cases) (Fig. 6). All of the contraction heights by K, NA and Ba were reduced by DNP 2×10^{-5}. These reductions were removed reversibly, but the fade in the contraction by NA remained at 60 min after washout of DNP.

III. *Analysis of the effect of Ca in BS on the drug-induced contractions by means of the concentration-action curve*

The concentration-action (C-A) curves of the contractions induced by K, NA and Ba were constructed by the cumulative dose method.

1. *Effect of Ca removal from BS on C-A curve*

In a short time (2-3 min) after the Ca removal from BS, the log C-A curve of K was shifted to the right at low but not at high concentrations as compared with that in normal BS. In 1 hr after the Ca removal when the K (ED_{50})-induced contraction disappeared, the log C-A curve of K was shifted remarkably to the right and downward. This shift got larger gradually but the curve did not disappear even after a long lapse of time (2 hr). The log C-A curve of NA was not changed in a short time after the Ca removal. When 4 hr elapsed at which the NA (ED_{50})-induced contraction remained constant, the log C-A curve of NA was shifted slightly to the right and downward, and this shift grew much larger after application of EDTA (0.1-0.2 mM for 20 min and then wash), which did not affect the contraction by exogenous Ca (2.2 mM). On the other hand, the log C-A curve of Ba remained unchanged in a short time after the Ca removal and showed just a slight shift to

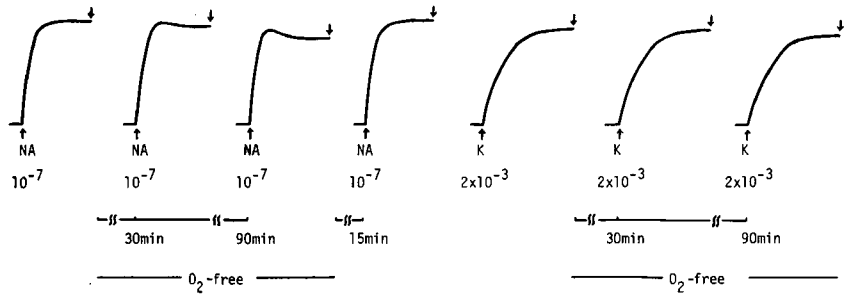

Fig. 5 Influence of anoxia (discontinuation of aeration to the BS) on the contraction curves of NA and K.

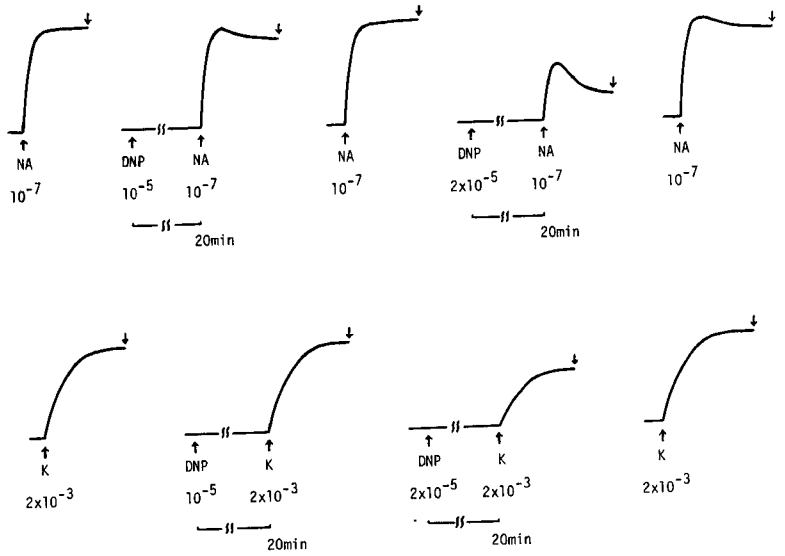

Fig. 6 Influence of dinitrophenol (DNP) on the contraction curves of NA and K.

the right at low concentrations of Ba at 4 hr after. With subsequent application of EDTA, this shift increased at low concentrations of Ba, while the contractions by high concentrations of Ba were still unchanged. Examples are shown in Fig. 7.

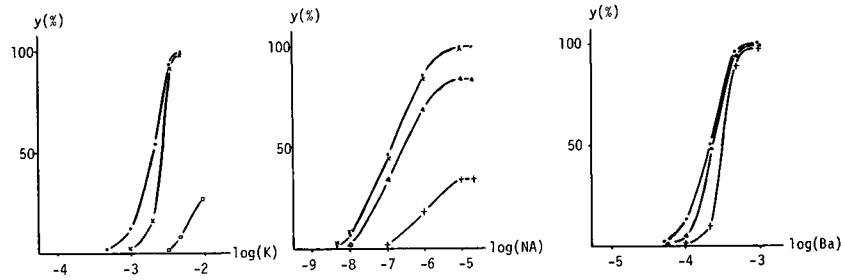

Fig. 7 Influence of Ca-free BS on the concentration-action curves of K, NA and Ba. —•—: in normal BS, —×—, —□—, —△—: at 2-3 min, 1 hr, 4 hr, respectively after exchange of the normal BS for the Ca-free BS. —+—: after application of EDTA (0.1 mM for 20 min and then wash).

2. *Effect of Ca decrease in BS*

This effect was investigated at 30 min after the exchange of BS for the Ca-reduced BS.

In the 1/40 Ca-BS, the log C-A curves of K, NA and Ba showed no difference as compared with those in the normal BS. In the 1/80 Ca-BS, the log C-A curve of K was shifted to the right and downward, and that of NA showed a rightward shift only at low concentrations, while that of Ba showed no shift (Fig. 8).

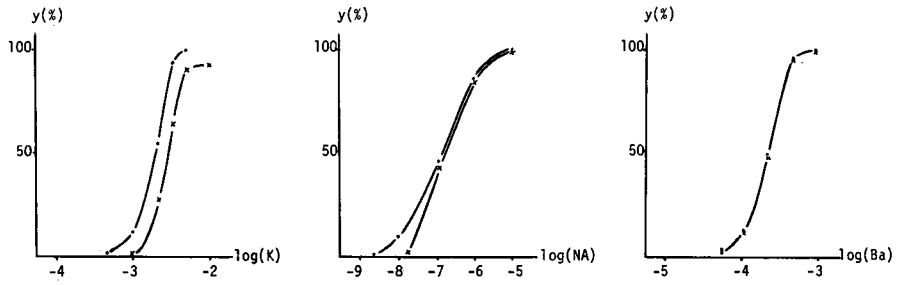

Fig. 8 Influence of low Ca (1/80 Ca) BS on the concentration-action curves of K, NA and Ba. —•—: in normal BS, —×—: in 1/80 Ca BS.

3. *Effect of Ca increase in BS*

The log C-A curves of K, NA and Ba at 30 min after addition of 7.8 mM Ca to the normal BS were compared with those in the normal BS. The log C-A curves of NA and Ba were shifted to the right at low concentrations, but not at

high concentrations. On the other hand, the log C-A curve of K was shifted to the right and upward, showing an intersection with the control curve. Examples are shown in Fig. 9.

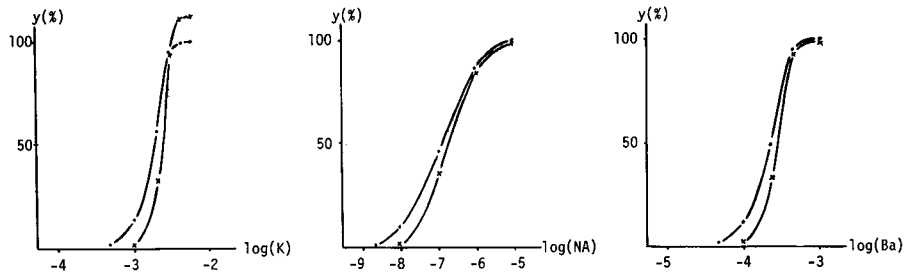

Fig. 9 Influence of high Ca (10 mM Ca) BS on the concentration-action curves of K, NA and Ba. —•—: in normal BS, —×—: in 10 mM Ca BS.

DISCUSSION

1. *Significance of Ca in BS for tonus and the action of exogenous Ca*

With the exchange of the normal BS for the Ca-free BS, the tonus of pulmonary artery strips from rabbits showed a slight decrease, which appeared immediately and fixed in a short time. This suggests that Ca influx rather than Ca release plays the main role to maintain the normal tonus. Unlike the other strips (rabbit ileum,[1] rat jejunum[13] and rat ileum[20]) used in our laboratory, this strip showed no transient contraction immediately after the exchange of BS for the Ca-free BS. It is considered that in the case of this strip the Ca to be released into cells by the Ca removal from BS (Hurwitz et al.[8]) is negligibly small.

The Ca added to BS (exogenous Ca) exerted no action on the tonus in the normal BS, but it produced a prolonged contraction when the K (ED_{50})-induced contraction disappeared at 30-45 min after the exchange of BS for the Ca-free BS. This contraction is presumably caused by the easy occurrence of Ca influx due to depolarization of muscle cell membrane in the Ca- free BS[3, 5] and also due to the decreased stability of the membrane deprived of Ca from the store site.

2. *Shape of the contraction curves of contracting drugs and its significance*

In the pulmonary artery strips from rabbits, the shapes of the contraction curves of K, NA and Ba were exponential and did not show such an apparent differentiation between the phasic and the tonic components as seen in rabbit ileum.[1] The rate of rise of the contraction curves was in the order of NA$>$ Ba$>$K. With regard to the contraction curves of K, NA and Ba (of ED_{50}, respectively), the findings have been obtained as follows; 1) Metabolic inhibition (anoxia and DNP) of a certain extent caused a slight fade on the NA-induced contraction but exerted

no influence on the contraction curves of K and Ba. 2) In a short time (within 3 min) after the Ca removal from BS, the shapes of the contraction curves of NA and Ba did not change, whereas the K-induced contraction decreased strongly in the height and slightly in the rate of rise. At 30-45 min after the Ca removal, the K-induced contraction disappeared, the NA-induced contraction decreased sometimes in the height, and the shape of Ba-induced contraction curve did not change. With a lapse of time thereafter, the rate of rise in the contraction curves of NA and Ba gradually decreased, while the contraction by NA remained constant at about 80% of its initial height 4 hr or more after the Ca removal and that by Ba was not changed even at 6 hr after. It is considered that the decrease in the rate of rise, even when it is not accompanied by the decrease in the contraction height, suggests the decrease in the Ca store of the membrane. 3) After the application of EDTA (0.1-0.2 mM for 20 min and then wash), which had no influence on the contraction by exogenous Ca, in the Ca-free BS, the NA-induced contraction disappeared and the Ba-induced contraction remained constant at the magnitude of 10-20 % of the initial height in the normal BS. This application of EDTA is supposed to cause Ca depletion in the membrane without influence on the muscle contractile system. 4) The K-induced contraction, which had disappeared in the Ca-free BS, was rapidly recovered by means of the re-exchange of BS to the normal, but could not be recovered by the procedure of Ca uptake (2.2 mM Ca for 20 min and washout). On the other hand, the NA-induced and Ba-induced contractions, which had disappeared and decreased respectively after application of EDTA in the Ca-free BS, were recovered considerably by the Ca uptake and were completely recovered 30 min after re-exchange of BS to the normal. The sum of the above findings leads us to the following assumptions: (1) The K-induced contraction is caused by the passive influx of Ca and Ca release. (2) The NA-induced contraction is caused mainly by Ca release and partly by the subsequent active influx of Ca. (3) The Ba-induced contraction is caused mainly by Ca release and partly by direct stimulation to the contractile element (the latter corresponds to the residual contraction by Ba in the Ca-free BS after application of EDTA). (4) In the muscle cell membrane of pulmonary artery from rabbits, there are two kinds of the Ca stores: the one (hereinafter termed as "S_1") containing loosely-bound Ca and the other (hereinafter termed as "S_2") containing tightly-bound Ca. K releases Ca from S_1 for producing contraction, NA does so mostly from S_2 and partly from S_1, and Ba does so from S_2.

The absence of apparent differentiation between the phasic and the tonic components in the contraction curves of this strip as stated before agree with the Sitrin and Bohr's report on the mesenteric artery of dogs.[18] Furthermore, the fade produced by metabolic inhibition in the NA-induced contraction is consistent with the inhibition of the S-component referred to by Sitrin & Bohr.[18] The interpretation concerning the mechanism of the NA-induced contraction stated above is also similar to the view of Sitrin & Bohr[18] and Peiper et al. (rat aorta).[15] However, the mechanisms of the K- and the Ba-induced contractions are not explicable by Sitrin & Bohr's view[18] with regard to the adrenaline-induced contraction. The K-induced contraction was, in agreement with the view of Peiper et al.,[15] depending

greatly upon the Ca amount in BS. Moreover, as to the metabolic inhibition, our findings are similar to the report[17] mentioning that anoxia inhibited strongly the NA-induced contraction but did not influence the K-induced contraction in the aorta strips from rabbits. The assumption of the above-stated division in the Ca store, which is utilized by drugs for producing Ca release leading to contraction, is consistent with the similar view of Hudgins and Weiss[7] in rabbit's aorta strips and also consistent with our view[1] previously reported in rabbit's ileum strips.

With regard to the mechanism of the Ba-induced contraction of smooth muscle organs, there are different views: (1) direct action on the contractile element,[16] (2) indirect action through Ca release[6, 11, 12, 14, 19] and (3) the combined action of (1) and (2).[1, 4, 13, 20, 22] The reason why discrepancies exist about the direct stimulation of Ba to the contractile element in smooth muscle organs is probably due to the variability in the amount of Ba accessible to this element according to organs.

3. *Relation between drug-induced contraction and the amount of Ca in BS viewed from the concentration-action (C-A) curve*

(1) *Effect of Ca-free BS*

In a short time (2-3 min) after the Ca removal from BS, the log C-A curve of K showed a rightward shift only at low concentrations but not at high concentrations of K. Taking the contracting mechanism of K (ED_{50}) above mentioned into consideration, this finding suggests that the decrease in the contraction by K at the low concentrations is caused by the interruption of Ca influx, and that the ratio of Ca influx to Ca release conccerned with K-induced contraction becomes as small as negligible at high concentrations. In 1 hr after the Ca removal from BS when the K (ED_{50})-induced contraction disappeared, the log C-A curve of K was shifted remarkably to the right and downward. It is considered that this shift is produced by decreased release of Ca by K due to depletion of the K-sensitive store (S_1) containing loosely-bound Ca. Furthermore, although this shift increased gradually with a lapse of time, the log C-A curve of K did not disappear even after a long time. This makes a striking contrast to the findings[1, 13, 20] obtained in various other smooth muscle organs where the log C-A curve of K disappeared in the Ca-free BS and this also suggests that in this strip a complete depletion of Ca store can hardly occur in Ca-free BS because the Ca store is large and/or the binding of Ca is tight.

The log C-A curve of NA remained unchanged in a short time after the Ca removal from BS and was shifted slightly to the right and downward at 4 hr after. This shift became much larger with the subsequent application of EDTA which accelerated the Ca depletion of membrane without affecting the muscle contractile system, suggesting that this shift is produced by the decrease in the NA-induced Ca release due to depletion of the Ca store.

The log C-A curve of Ba remained unchanged in a short time after the Ca removal from BS and showed a slight rightward shift only at low concentrations 4

hr later. With subsequent application of EDTA, this shift became larger only at low concentrations of Ba, the contractions by high concentrations of Ba being unaffected. This finding is consistent with the above presumption that a direct stimulation to actomyosin, besides Ca release, is involved (particularly at high concentrations) in the contracting mechanism of Ba.

(2) *Effect of Ca decrease in BS*

At 30 min after the Ca decrease (1/80) in BS, the log C-A curve of Ba did not change, but the log C-A curve of K was shifted to the right and downward. It is considered that this shift is produced by the decrease in Ca release (due to reduction of Ca in the Ca store S_1) and the decrease in Ca influx, which are concenrned with the K-induced contraction. The log C-A curve of NA showed a rightward shift at low concentrations. This is probably caused by the Ca depletion of S_1, in consideration of the above-mentioned mechanism of the NA (ED_{50})-induced contraction.

(3) *Effect of Ca increase in BS*

At 30 min after the Ca increase (10 mM) in BS, the log C-A curves of NA and Ba were shifted to the right at low concentrations. This may be explained by the assumption that the increased stability of membrane due to the Ca increase in BS inhibits the Ca release which is produced by low concentrations of these agonists. On the other hand, the log C-A curve of K was shifted to the right and upward, showing an intersection with the control curve. Supposedly the rightward shift is brought about by the membrane stabilizing action of Ca, while the upward shift is caused by acceleration of the Ca influx specifically related to the K-induced contraction as a result of the well-known membrane exciting property of K.

SUMMARY

Using the pulmonary artery strips from rabbits, the mechanism of the contractions by K, noradrenaline (NA) and Ba were comparatively investigated in relation to Ca.

1. The shapes of the contraction curves of K, NA and Ba were exponential. Based on the influences of metabolic inhibition (anoxia and dinitrophenol), removal of Ca from bath solution (BS) and application of EDTA on the contraction curves, the following presumptions have been obtained: (1) The K-induced contraction is caused by the passive influx of Ca and the Ca release. (2) The NA-induced contraction is mostly due to Ca release and partly due to subsequent active influx of Ca. (3) The Ba-induced contraction is mostly due to Ca release and partly due to direct stimulation to the contractile element. (4) Evidences have been obtained that Ca stores in the muscle cell membrane of pulmonary artery from rabbits are classified into two kinds; the one (S_1) containing loosely-bound Ca and the other (S_2) con-

taining tightly-bound Ca. K releases Ca from S_1, NA mostly from S_2 but partly from S_1, and Ba from S_2, respectively, for producing contraction.

2. By means of the concentration-action curves, detailed findings (Figs. 7–9) have been obtained concerning the influence of Ca amount in BS on the action of contracting drugs. Discussions have been made on these findings.

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