J. Pharm. Pharmacol. 2000, 52: 1513–1518
Received December 8, 1999
Accepted May 23, 2000

Effects of Ba^{2+} on SK&F 96365-sensitive Sustained Contraction of Rat Pulmonary Artery

KOHSUKE UCHIDA, KYOKO SAITO*, TOSHIMITSU KITAJIMA* AND YUICHIRO KAMIKAWA

*Department of Pharmacology and *First Department of Anaesthesiology, Dokkyo University School of Medicine, Mibu, Tochigi 321-0293, Japan*

Abstract

The effects of Ba^{2+} on receptor-mediated sustained contraction of rat pulmonary artery and guinea-pig oesophageal muscularis mucosae were studied in-vitro.

In rat isolated pulmonary artery, sustained contraction induced by noradrenaline (1 μM) was resistant to nicardipine (1 μM), but this same sustained contraction was completely inhibited by SK&F 96365 (30 μM), a blocker of voltage-dependent L-type Ca^{2+} channels and receptor-activated Ca^{2+} influx. The SK&F 96365-sensitive sustained contraction induced by noradrenaline (1 μM) may be due primarily to Ca^{2+} influx through receptor-activated Ca^{2+} channels resistant to nicardipine. Cumulatively applied $BaCl_2$ (0·1–10 mM) increased the noradrenaline (1 μM)-induced sustained contraction of the pulmonary arterial preparation in the absence of nicardipine, but in the presence of nicardipine (1 μM), $BaCl_2$ (0·1–3 mM) did not affect this contraction. A higher concentration of $BaCl_2$ (10 mM), however, weakly inhibited the noradrenaline (1 μM)-induced tone. In addition, $BaCl_2$ (3–10 mM) increased the tone induced by KCl (60 mM), and the $BaCl_2$-elevated KCl tone was markedly inhibited by nicardipine (1 μM) treatment.

In the guinea-pig isolated oesophageal muscularis mucosae, sustained contraction induced by acetylcholine (3 μM) was resistant to nicardipine (1 μM) but was returned to its basal level by SK&F 96365 (30–60 μM). The SK&F 96365-sensitive, acetylcholine-induced sustained contraction of the oesophageal muscularis mucosae is also likely to link with receptor-activated Ca^{2+} channels resistant to nicardipine. In contrast to the rat pulmonary artery, cumulatively applied $BaCl_2$ (0·3–10 mM) inhibited the acetylcholine (3 μM)-induced sustained contraction of the oesophageal muscularis mucosae in a concentration-dependent manner in the presence of nicardipine (1 μM).

In conclusion, Ba^{2+} presumably activates voltage-dependent Ca^{2+} channels by depolarizing plasma membrane and also passes through voltage-dependent Ca^{2+} channels to contract the pulmonary artery in the absence of nicardipine, and Ba^{2+} also has a minor effect on the nicardipine-resistant, SK&F 96365-sensitive sustained contraction induced by noradrenaline in rat isolated pulmonary artery.

It is well known that extracellular Ba^{2+} can permeate into smooth muscle cells through voltage-dependent L-type Ca^{2+} channels (VDCs) and behave as a substitute for Ca^{2+}, eliciting contraction of arterial smooth muscles (Hansen et al 1984; Karaki et al 1986; Ebeigbe & Aloamaka 1987; Satoh et al 1987). In arterial preparations, the receptor-mediated sustained contraction is due to transmembrane Ca^{2+} influx through ion channels and Ca^{2+} sensitization to contractile elements (Karaki et al 1997). The exact effect of Ba^{2+} on this receptor-mediated contraction of the arterial preparation is not yet clear.

Recently, we reported new evidence that $BaCl_2$ selectively inhibits the receptor-mediated (acetylcholine-induced) sustained contraction of guinea-pig oesophageal muscularis mucosae pretreated with nicardipine (Uchida et al 1998a). However, no information is available on the effect of extracellular Ba^{2+} on receptor-mediated sustained contraction of arterial smooth muscle. The aim of this study was to examine the effect of

Correspondence: Kohsuke Uchida, Department of Pharmacology, Dokkyo University School of Medicine, Mibu, Tochigi 321-0293, Japan.
E-Mail: k-uchida@dokkyomed.ac.jp

$BaCl_2$ on receptor-mediated sustained contraction of rat pulmonary artery, and to compare this effect with that of the guinea-pig oesophageal muscularis mucosae in-vitro.

Materials and Methods

Rat pulmonary artery preparation

Male Sprague-Dawley rats, 300–350 g (n = 33), were anaesthetized with sevoflurane (Maruishi Pharmaceutical Co., Osaka, Japan) and were killed by bleeding from the carotid artery. The main pulmonary artery was rapidly excised and placed in a modified Krebs bicarbonate solution (mM: NaCl 120, KCl 4·7, $CaCl_2$ 2·5, $MgCl_2$ 1·2, $NaHCO_3$ 25, KH_2PO_4 1·2, glucose 14) at room temperature. After removal of adhering connective tissue, the artery was cut into rings (1·5–2 mm diameter, 1–2 mm length). The arterial rings were sagittally cut on one side, and were used as open-ring preparations (1–2 mm width, 3–4 mm length) (Uchida et al 1998b). Each open-ring preparation was suspended in an organ bath containing 10 mL of modified Krebs solution. The solution was bubbled with 95% O_2-5% CO_2 and maintained at 37°C. For all of the preparations, the endothelium was mechanically removed by gently rubbing with a cotton swab. Removal of the endothelium was confirmed by the absence of acetylcholine-induced relaxation.

Guinea-pig oesophageal muscularis mucosae preparation

The oesophageal muscularis mucosae isolated from guinea-pigs was used. Longitudinal muscularis mucosae preparations were obtained as described in our previous report (Uchida 1983). After adult male guinea-pigs, 300–400 g (n = 13), were anaesthetized with sevoflurane, they were killed by bleeding from the carotid artery. The oesophagus was excised and pinned on a cork mat immersed in a modified Tyrode's solution (mM: NaCl 136·8, KCl 2·7, $CaCl_2$ 1·8, $MgCl_2$ 1·05, $NaHCO_3$ 11·9, NaH_2PO_4 0·42, glucose 5·56). The outer striated muscle coat was cut longitudinally and gently peeled away leaving an inner tube. This inner tube, including the longitudinal muscularis mucosae, was about 10–15 mm long when unloaded and was suspended in a 10-mL organ bath filled with modified Tyrode's solution. The solution was continually bubbled with 95% O_2-5% CO_2 at 37°C. In experiments using acetylcholine, Tyrode's solution contained physostigmine (20 nM) to inhibit cholinesterase activity in the oesophageal muscularis mucosae.

Measurement of response

The open-ring preparation of rat pulmonary artery was suspended vertically under a 1·0-g load, and isometric tension responses of the preparation were recorded on a polygraph (8K 22-1-S, NEC San-ei, Tokyo, Japan) by a force-displacement transducer (45196A, NEC San-ei). The longitudinal muscularis mucosae of the guinea-pig oesophagus was suspended under a 0·5-g load in an organ bath, and responses of the muscularis mucosae were recorded by an isotonic transducer (TD-112S, Nihon Kohden, Tokyo, Japan) connected to a chart recorder (RJG-4124, Nihon Kohden).

Experiments were begun 60 min after the preparation was suspended in an organ bath. During this equilibration period, each preparation was washed with fresh solution every 20 min. After the 60-min equilibration period, the preparation was maximally contracted with a single concentration of noradrenaline (1 μM, for the pulmonary artery) or of carbachol (10 μM, for the muscularis mucosae). In experiments on responsiveness to $BaCl_2$, the arterial preparation was pre-contracted with noradrenaline (1 μM) or KCl (60 mM), and the muscularis mucosae was pre-contracted with acetylcholine (3 μM). These spasmogens produced a maximum sustained contraction of each preparation. After the sustained contraction induced by noradrenaline, KCl or acetylcholine had reached its plateau, $BaCl_2$ was added to the preparation cumulatively. Responses to $BaCl_2$ were expressed as a percentage of the plateau level of the pre-contraction. In addition, the inhibitory response of SK&F 96365 or nicardipine on the preparation pre-contracted with noradrenaline (1 μM), KCl (60 mM) or acetylcholine (3 μM) was expressed as the amplitude of relaxation by a percentage of the pre-contraction plateau level.

Statistical analysis

Each experimental group consisted of 3–10 preparations taken from different animals. The data are expressed as the mean ± s.e.m. Statistical significance was determined by Student's *t*-test. Values of $P < 0{\cdot}05$ were considered significant.

Drugs

The following drugs were used: *l*-noradrenaline bitartrate, carbachol chloride (Sigma, Chemical Co., St Louis, MO), acetylcholine chloride

(Dai-ichi Seiyaku, Tokyo, Japan), $BaCl_2 \cdot 2H_2O$, nicardipine hydrochloride (Wako Pure Chemicals, Osaka, Japan), SK&F 96365 (BIOMOL Res. Lab., Plymouth Meeting, PA). Concentrations of drugs in this study refer to the final bath concentrations.

Results

Effect of $BaCl_2$ on rat isolated pulmonary artery

Noradrenaline (1 nM–1 μM) produced a concentration-dependent contraction of the rat isolated pulmonary artery, and 1 μM noradrenaline caused the maximum contraction in this preparation. This noradrenaline (1 μM)-induced sustained contraction was resistant to nicardipine (1 μM), but was completely inhibited by SK&F 96365 (30 μM) (95·6 ± 2·65%; n = 4) (Figures 1 and 2B). After the sustained contraction induced by noradrenaline (1 μM) had reached its plateau level, $BaCl_2$ (0·1–10 mM) was added cumulatively to the organ bath and increased the noradrenaline-induced tone of the rat pulmonary artery in a concentration-dependent manner (Figures 2A and 3). Such excitatory responses to $BaCl_2$ were not seen in the arterial preparation pre-treated with nicardipine (1 μM), but the higher concentration of $BaCl_2$ (10 mM) caused a weak relaxation of this preparation (13·3 ± 3·05%; n = 6) (Figures 2B and 3). The pulmonary artery

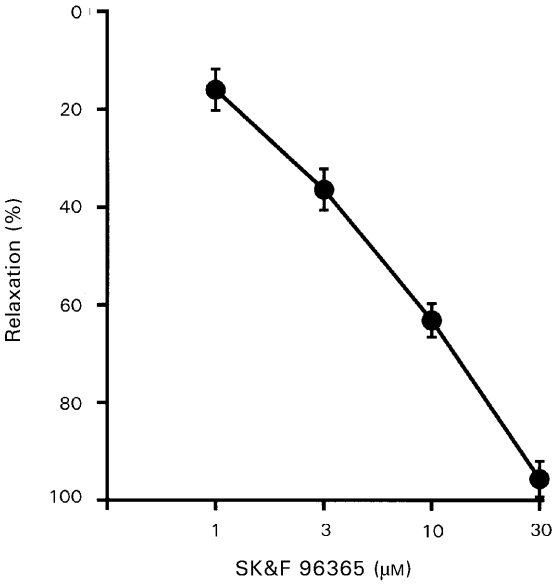

Figure 1. Cumulative concentration–response curve to SK&F 96365 of the noradrenaline (1 μM)-pre-contracted pulmonary artery isolated from rat. SK&F 96365 (1–30 μM) caused a concentration-dependent relaxation of the pulmonary artery pre-contracted with noradrenaline (1 μM). The ordinate scale shows the amplitude of relaxation as a percentage of the plateau level of pre-contraction. Each point represents the mean ± s.e.m. of 4 observations.

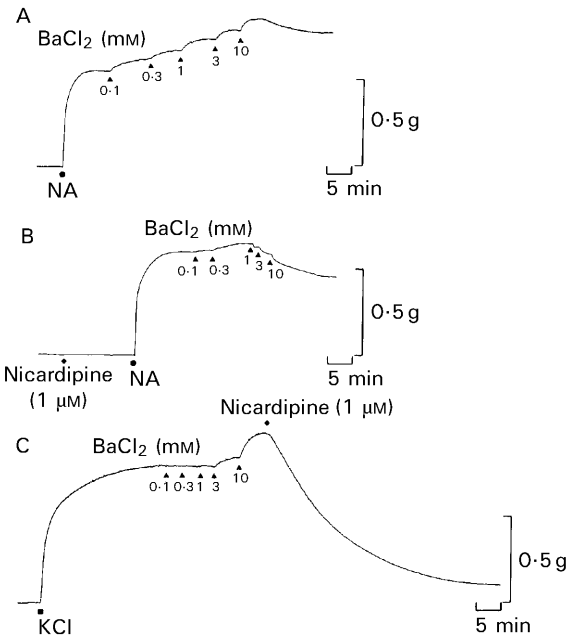

Figure 2. Typical traces showing the effect of cumulatively increased concentrations of $BaCl_2$ on the pulmonary artery pre-contracted with noradrenaline (NA 1 μM, A and B) or KCl (60 mM, C) isolated from rat. A. $BaCl_2$ elevated the tone of noradrenaline (1 μM)-pre-contracted pulmonary artery. B. In the presence of nicardipine (1 μM), $BaCl_2$ (1–10 mM) did not elevate the tone, but rather slightly inhibited the tone of noradrenaline (1 μM)-pre-contracted pulmonary artery. C. $BaCl_2$ elevated the tone of KCl (60 mM)-pre-contracted pulmonary artery. The $BaCl_2$-elevated tone was inhibited by nicardipine (1 μM).

responded to an application of KCl (60 mM) with a sustained contraction, and the magnitude was almost the same as that induced by noradrenaline (1 μM). The magnitude of sustained contraction induced by noradrenaline (1 μM) was 0·63 ± 0·035 g (n = 10) and that induced by KCl (60 mM) was 0·52 ± 0·085 g (n = 10). The KCl (60 mM)-induced sustained contraction was almost abolished by nicardipine (1 μM) (96·2 ± 2·72%; n = 3) (typical trace not shown). Cumulatively applied $BaCl_2$ (3–10 mM) increased the KCl (60 mM)-induced tone (Figures 2C and 3), and the $BaCl_2$-elevated KCl tone was markedly inhibited by treatment with nicardipine (1 μM) (Figure 2C). This inhibition caused by nicardipine (1 μM) was 92·6 ± 2·70% (n = 6) of the plateau tension level induced by $BaCl_2$ (10 mM).

Effect of $BaCl_2$ on guinea-pig isolated oesophageal muscularis mucosae

The muscularis mucosae of the guinea-pig oesophagus responded to an application of KCl (60 mM) with a sustained contraction, which was completely inhibited by nicardipine treatment (0·3–1 μM) (99·8 ± 0·76%; n = 3) (Figure 4A). Acetylcholine

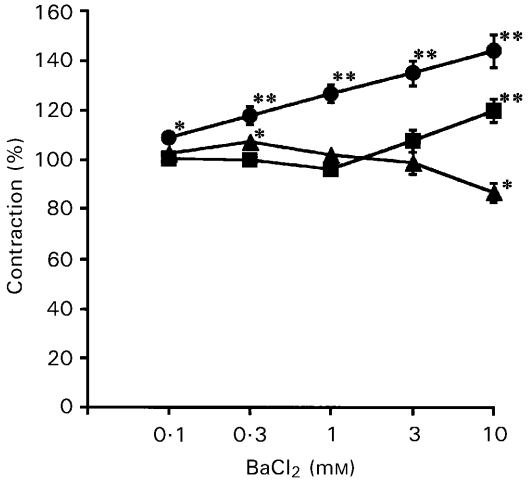

Figure 3. Cumulative concentration–response curves to $BaCl_2$ of rat isolated pulmonary artery. Effect on noradrenaline (1 μM)-pre-contracted pulmonary artery without nicardipine (●); effect on noradrenaline (1 μM)-pre-contracted pulmonary artery with nicardipine (1 μM, ▲); effect on KCl (60 mM)-pre-contracted pulmonary artery (■). The ordinate scale shows the amplitude of contraction as a percentage of the plateau level of pre-contraction. Each point represents the mean ± s.e.m. of 5–6 observations. $*P < 0.05$, $**P < 0.01$, vs the plateau level of the tone induced by noradrenaline (1 μM) or KCl (60 mM).

(3 μM) also produced the maximum sustained contraction of the oesophageal muscularis mucosae, and this sustained contraction was not affected by pre-treatment with nicardipine (1 μM) (Figure 4A).

In the muscularis mucosae pre-treated with nicardipine (1 μM), $BaCl_2$ (0·3–10 mM) concentration-dependently inhibited the acetylcholine-induced tone, and at 10 mM the acetylcholine-induced tone was almost abolished (94·1 ± 2·07%; n = 5) (Figure 4A). The nicardipine-resistant acetylcholine-induced sustained contraction was completely inhibited by SK&F 96365 (30–60 μM) (99·1 ± 0·98%; n = 5) (Figure 4B).

Discussion

The exact effect of Ba^{2+} on noradrenaline-induced sustained contraction of vascular smooth muscles is not yet clear. Recently, in rat isolated thoracic aorta, Noguera et al (1999) reported that Ba^{2+} (2·4–24 mM) augmented the magnitude of the residual contraction induced by noradrenaline after nifedipine treatment. Non-selective cation channels are permeable to Ba^{2+} (Byrne & Large 1988; Amédée et al 1990), and Ba^{2+} blocks K^+ channels (Benham et al 1985) on the plasma membrane of vascular smooth muscles. Therefore, Ba^{2+} presumably increased Ca^{2+} influx through VDCs by depolarizing the plasma membrane. In these experiments, $BaCl_2$ produced a further contraction of both noradrenaline- and KCl-induced tone of the rat pulmonary artery. The $BaCl_2$-elevated KCl tone

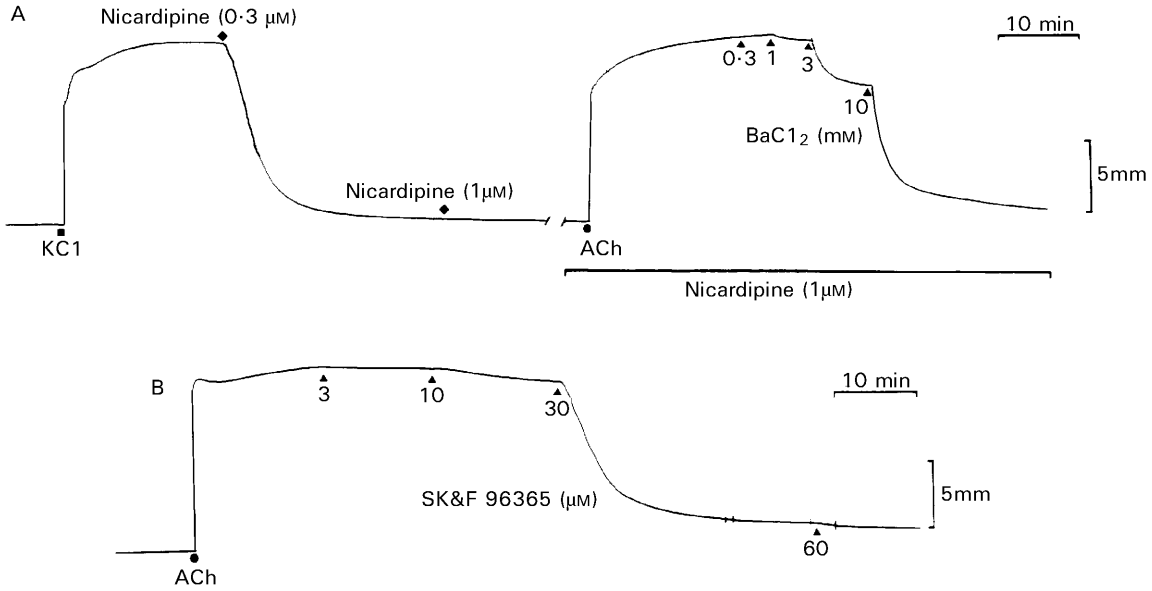

Figure 4. Typical traces showing the effect of cumulatively increasing concentrations of $BaCl_2$ or SK&F 96365 on the acetylcholine (ACh, 3 μM)-pre-contracted muscularis mucosae isolated from guinea-pig oesophagus. A. The KCl (60 mM)-induced contraction of muscularis mucosae was completely inhibited by nicardipine (0·3–1 μM). In the presence of nicardipine (1 μM), $BaCl_2$ caused a concentration-dependent relaxation of the muscularis mucosae pre-contracted with acetylcholine (3 μM). B. SK&F 96365 (1–60 μM) caused a relaxation of the oesophageal muscularis mucosae pre-contracted with acetylcholine (3 μM) in a concentration-dependent manner.

was markedly inhibited by nicardipine treatment, and $BaCl_2$ did not increase the noradrenaline-induced tone in the presence of nicardipine. These results suggest that Ba^{2+} activates VDCs by depolarizing the plasma membrane and permeates into smooth muscle cells through VDCs to produce a contraction of rat isolated pulmonary artery. Nicardipine may block Ca^{2+} and Ba^{2+} influx through VDCs that are opened by Ba^{2+}-evoked depolarization.

Agonist-induced contractions of vascular smooth muscle are mediated by Ca^{2+} release from intracellular storage sites, transmembrane Ca^{2+} influx through ion channels and an increase in Ca^{2+} sensitivity of contractile elements (Rembold et al 1992; Orallo 1996; Karaki et al 1997). In our experiment using rat isolated pulmonary artery, the noradrenaline-induced sustained contraction was resistant to nicardipine, a blocker of VDCs (Terai et al 1981), but was almost completely inhibited by SK&F 96365, a blocker of both VDCs and receptor-activated Ca^{2+} influx (Merritt et al 1990; Gorenne et al 1998; Tosun et al 1998). Recently, capacitative Ca^{2+} entry, which is the Ca^{2+} influx through Ca^{2+} channels activated in response to Ca^{2+} depletion within the intracellular Ca^{2+} stores, has been found to occur following receptor activation of smooth muscle (Gibson et al 1998). De La Fuente et al (1995) reported that Ca^{2+} depletion within sarcoplasmic reticulum induced by thapsigargin or cyclopiazonic acid seemed to facilitate Ca^{2+} influx through a verapamil-resistant pathway in rat pulmonary artery, and there are some reports that SK&F 96365 inhibits capacitative Ca^{2+} entry (Demaurex et al 1992; Burt et al 1995). The noradrenaline-induced sustained contraction of rat isolated pulmonary artery is likely to be mediated primarily by receptor-activated Ca^{2+} influx resistant to nicardipine. In this study, $BaCl_2$ caused a weak relaxation of the noradrenaline-pre-contracted arterial preparation with nicardipine treatment. Ba^{2+} has a minor effect on the SK&F 96365-sensitive, receptor-mediated sustained contraction induced by noradrenaline in rat isolated pulmonary artery.

In the muscularis mucosae of guinea-pig oesophagus, acetylcholine-induced sustained contraction was resistant to nicardipine but was completely inhibited by SK&F 96365. The sustained contraction induced by acetylcholine was abolished in a Ca^{2+}-free solution containing EGTA (0·1 mM) (Kamikawa et al 1985). These observations suggest that the acetylcholine-induced sustained contraction is primarily mediated by a nicardipine-resistant, receptor-activated Ca^{2+} influx. In contrast to the pulmonary artery, the acetylcholine-induced sustained contraction of the oesophageal muscularis mucosae was nearly returned to the basal level by $BaCl_2$ (10 mM) in the presence of nicardipine. Murray & Kotlikoff (1991) reported that Ba^{2+} inhibited the Ca^{2+}-channel antagonist-resistant, receptor-activated Ca^{2+} influx in airway smooth muscle. In addition, Ohta et al (1995) reported that the Ca^{2+}-channel antagonist-resistant Ca^{2+} entry in rat ileal smooth muscle was inhibited by Ba^{2+}. In the oesophageal muscularis mucosae of guinea-pig, Ba^{2+} may inhibit the nicardipine-resistant, receptor-activated Ca^{2+} influx and markedly inhibits the SK&F 96365-sensitive, receptor-mediated sustained contraction.

The difference in the inhibitory action of $BaCl_2$ on the sustained contraction in the presence of nicardipine in the pulmonary artery and the oesophageal muscularis mucosae seems to be due to different characteristics of the receptor-activated Ca^{2+} influx pathway to produce the contraction of the smooth muscle. Our results suggest that the SK&F 96365-sensitive, receptor-mediated sustained contraction may be subclassified into contraction that is less sensitive to Ba^{2+} (pulmonary artery) and one that is Ba^{2+}-sensitive (oesophageal muscularis mucosae).

In conclusion, Ba^{2+} presumably activates VDCs by depolarizing the plasma membrane and it also permeates into the cell through VDCs, increasing the noradrenaline-induced tone of rat pulmonary artery in the absence of nicardipine. In the presence of nicardipine, Ba^{2+} has a minor effect on the noradrenaline-induced sustained contraction of rat pulmonary artery.

Acknowledgements

This study was supported in part by a grant from the Japan Health Science Foundation, Tokyo, Japan.

References

Amédée, T., Benham, C. D., Bolton, T. B., Byrne, N. G., Large, W. A. (1990) Potassium, chloride and non-selective cation conductances opened by noradrenaline in rabbit ear artery cells. J. Physiol. 423: 551–568

Benham, C. D., Bolton, T. B., Lang, R. J., Takewaki, T. (1985) The mechanism of action of Ba^{2+} and TEA on single Ca^{2+}-activated K^+-channels in arterial and intestinal smooth muscle cell membranes. Pflügers Arch. 403: 120–127

Burt, R. P., Chapple, C. R., Marshall, I. (1995) The role of capacitative Ca^{2+} influx in the α_{1B}-adrenoceptor-mediated contraction to phenylephrine of the rat spleen. Br. J. Pharmacol. 116: 2327–2333

Byrne, N. G., Large, W. A. (1988) Membrane ionic mechanisms activated by noradrenaline in cells isolated from the rabbit portal vein. J. Physiol. 404: 557–573

De La Fuente, P. G., Savineau, J.-P., Marthan R. (1995) Control of pulmonary vascular smooth muscle tone by sarcoplasmic reticulum Ca^{2+} pump blockers: thapsigargin and cyclopiazonic acid. Pflügers Arch. 429: 617–624

Demaurex, N., Lew, D. P., Krause, K-H. (1992) Cyclopiazonic acid depletes intracellular Ca^{2+} stores and activates an influx pathway for divalent cations in HL-60 cells. J. Biol. Chem. 267: 2318–2324

Ebeigbe, A. B., Aloamaka, C. P. (1987) Mechanism of contractile action of barium ion on rat aortic smooth muscle. Can. J. Physiol. Pharmacol. 65: 2454–2458

Gibson, A., McFadzean, I., Wallace, P., Wayman, C. P. (1998) Capacitative Ca^{2+} entry and the regulation of smooth muscle tone. Trends Pharmacol. Sci. 19: 266–269

Gorenne, I., Labat, C., Gascard, J.-P., Norel, X., Nashashibi, N., Brink, C. (1998) Leukotriene D_4 contractions in human airways are blocked by SK&F 96365, an inhibitor of receptor-mediated calcium entry. J. Pharmacol. Exp. Ther. 284: 549–552

Hansen, T. R., Dineen, D. X., Petrak, R. (1984) Mechanism of action of barium ion on rat aortic smooth muscle. Am. J. Physiol. 246: C235–C241

Kamikawa, Y., Uchida, K., Shimo, Y. (1985) Heterogeneity of muscarinic receptors in the guinea pig esophageal muscularis mucosae and ileal longitudinal muscle. Gastroenterology 88: 706–716

Karaki, H., Satake, N., Shibata, S. (1986) Mechanism of barium-induced contraction in the vascular smooth muscle of rabbit aorta. Br. J. Pharmacol. 88: 821–826

Karaki, H., Ozaki, H., Hori, M., Mitsui-Saito, M., Amano, K., Harada, K., Miyamoto, S., Nakazawa, H., Won, K.-J., Sato, K. (1997) Calcium movements, distribution, and functions in smooth muscle. Pharmacol. Rev. 49: 157–230

Merritt, J. E., Armstrong, W. P., Benham, C. D., Hallam, T. J., Jacob, R., Jaxa-Chamiec, A., Leigh, B. K., McCarthy, S. A., Moores, K. E., Rink, T. J. (1990) SK&F 96365, a novel inhibitor of receptor-mediated calcium entry. Biochem. J. 271: 515–522

Murray, R. K., Kotlikoff, M. I. (1991) Receptor-activated calcium influx in human airway smooth muscle cells. J. Physiol. 435: 123–144

Noguera, M. A., Chuliá, S., Ivorra, M. D., D'Ocon, M. P. (1999) Effect of divalent cations on KCl- and noradrenaline-induced contractile responses in rat aorta after nifedipine treatment. Gen. Pharmacol. 33: 43–50

Ohta, T., Kawai, K., Ito, S., Nakazato, Y. (1995) Ca^{2+} entry activated by emptying of intracellular Ca^{2+} stores in ileal smooth muscle of the rat. Br. J. Pharmacol. 114: 1165–1170

Orallo, F. (1996) Regulation of cytosolic calcium levels in vascular smooth muscle. Pharmacol. Ther. 69: 153–171

Rembold, C. M. (1992) Regulation of contraction and relaxation in arterial smooth muscle. Hypertension 20: 129–137

Satoh, S., Kubota, Y., Itoh, T., Kuriyama, H. (1987) Mechanisms of the Ba^{2+}-induced contraction in smooth muscle cells of the rabbit mesenteric artery. J. Gen. Physiol. 89: 215–237

Terai, M., Takenaka, T., Maeno, H. (1981) Inhibition of calcium influx in rabbit aorta by nicardipine hydrochloride (YC-93). Biochem. Pharmacol. 30: 375–378

Tosun, M., Paul, R. J., Rapoport, R. M. (1998) Role of extracellular Ca^{++} influx via L-type and non-L-type Ca^{++} channels in thromboxane A_2 receptor-mediated contraction in rat aorta. J. Pharmacol. Exp. Ther. 284: 921–928

Uchida, K. (1983) Pharmacological characterization of the adrenoceptors in the muscularis mucosae of the guinea-pig esophagus. Folia. Pharmacol. Jpn 82: 223–235

Uchida, K., Yuzuki, R., Kamikawa, Y. (1998a) Ba^{2+} selectively inhibits receptor-mediated contraction of the esophageal muscularis mucosae. Eur. J. Pharmacol. 362: 83–86

Uchida, K., Nagai, S., Shimada, K., Ohno, Y., Kamikawa, Y. (1998b) Responsiveness of human and guinea-pig isolated pulmonary arteries to α-agonists in-vitro. Pharm. Pharmacol. Commun. 4: 349–353