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Na^+-independent glucose utilization during Mn^{2+}-induced contraction in ileal longitudinal smooth muscle

Tetsuyuki Nasu *, Akiko Shibata

Department of Veterinary Pharmacology, Faculty of Agriculture, Yamaguchi University, Yamaguchi 753, Japan

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Abstract

In Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium, addition of 5 mM Mn^{2+} caused a tension about 2.5 × greater than the tonic response induced by 126 mM K^+ medium (Ca^{2+} 2.5 mM, Na^+ 0 mM) in ileal muscle. When glycogen was depleted by incubation in a glucose-free, hypertonic 60 mM K^+ medium, addition of 5 mM Mn^{2+} induced only a very weak tension in Ca^{2+}-free, isotonic 126 K^+ medium. Phlorizin (10^{-3} M), a blocker of Na^+-coupled glucose cotransporter and ouabain (9×10^{-5} M), an inhibitor of Na^+, K^+-ATPase, failed to inhibit the tension elicited by 5 mM Mn^{2+} in a Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium. Mn^{2+} was accumulated in the intracellular compartment in a Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium. The tissue ATP concentration was significantly reduced in a Na^+-deficient 126 mM K^+ medium. However, it recovered almost completely when 5 mM Mn^{2+} was added to the isotonic 126 mM K^+ medium. These results suggest that the Mn^{2+}-induced contraction in depolarized ileal longitudinal muscle in Na^+-deficient medium may be maintained by a glucose transport which is not dependent on Na^+ and insensitive to phlorizin.

Keywords: Mn^{2+}; Ileum; Smooth muscle; Ca^{2+} channel

1. Introduction

Manganese ions (Mn^{2+}) have generally been used as an 'inorganic Ca^{2+} channel blocker' to investigate the function of Ca^{2+} channels. In facts, Mn^{2+} has been shown to have inhibitory effects on contractions in uterus (Osa, 1974), taenia coli (Nonomura et al., 1966) and portal vein (Collins et al., 1972).

In contrast to the above facts, Mn^{2+} could evoke the contraction in Ca^{2+}-free, high-K^+ medium in various types of smooth muscles including guinea-pig ileum (Nasu et al., 1994), uterus (Sakai and Uchida, 1981) and rat mesenteric portal vein (Sutter et al., 1988). We have found that nifedipine, a L-type Ca^{2+} channel blocker, inhibited dose-dependently both the contraction and manganese uptake elicited by 5 mM Mn^{2+} in a Ca^{2+}-free, high-K^+ medium in ileum (Nasu et al., 1995a,b). It has been reported that Mn^{2+} directly activated contractile proteins of skinned fibres of smooth muscle cells (Savineau et al., 1988). These results suggest that Mn^{2+} is entering via voltage-dependent Ca^{2+} channels when the ileal cell membrane is depolarized and it directly activates the contractile elements.

Sustained contractions evoked by 'added K^+ solution' in taenia coli have been shown to be maintained by energy produced in the oxidative metabolism following the glycolytic breakdown of glucose (Pfaffman et al., 1965; Urakawa et al., 1968; Nasu et al., 1982). In contrast, the 'substituted K^+ solution' where equimolar Na^+ is substituted with K^+ produces a transient contraction followed by a very small sustained response. During the contraction elicited by 'substituted K^+ solution', glucose may not be utilized because Na^+ is absent in the external medium (Karaki et al., 1982; Suzuki et al., 1980) and because Na^+ is essential for active transport of glucose in intestine (Rikis and Quastel, 1958; Csaky, 1961; Karaki et al., 1982).

In the present experiments, we examined whether the Mn^{2+}-induced contraction is also dependent on both glucose and sodium in the guinea-pig ileal muscle.

* Corresponding author. Fax: (81-839) 335-820; e-mail: nasu@agr.yamaguchi-u.ac.jp

2. Materials and methods

2.1. Preparation, physiological solution and tension recording

Strips of longitudinal smooth muscle were isolated from ileum of male Hartley strain guinea pigs (400 g), and were immersed in modified Tyrode's solution saturated with 100% O_2 at 37°C. The solution contained (mM): NaCl 123.7, KCl 2.7, $CaCl_2$ 2.5, $MgCl_2$ 1.0, tris(hydroxymethyl) aminomethane 25 and glucose 5.5. The pH of the solution was adjusted to 7.4 with HCl at 37°C. The 'added K^+ solution' (40–60 mM) was prepared by adding an appropriate amount of 2 M KCl solution to the normal medium. The 'substituted K^+ solution' was prepared by replacing NaCl in the normal solution with equimolar KCl. Manganese ions (as $MnCl_2 \cdot 4H_2O$) were directly added to the bathing solution.

The muscle strips were suspended at a resting tension of 0.6 g and allowed to equilibrate for 40 min with several changes of the Tyrode's solution. After equilibration, the tissue was conditioned by adding 40 mmol/l K^+ to the bath. Isometric contraction of the muscle was measured by a strain gauge transducer (Nihon Kohden, RM-6000).

Quick release was performed to assess the intensity of the active state of a Mn^{2+}-induced contraction in a Ca^{2+}-free, isotonic 126 mM K^+ medium by the method described by Bose and Bose (1975).

2.2. Manganese uptake

To determine tissue Mn^{2+} concentrations in ileal longitudinal muscles, the strips were incubated in various constituent medium containing 5 mM Mn^{2+} for various periods. Successively, the strips were washed with both Ca^{2+}- and Mg^{2+}-free Tyrode solution containing 5 mM chelating agent, EDTA, which does not penetrate the cell membrane of guinea-pig taenia coli (Brading and Jones, 1969) for 30 min. After removing from the bath, strips were blotted on filter paper, weighed, transferred to a quartz cuvette with 0.5 ml solution containing equal amount of $HClO_4$ (60%) and HNO_3 (60%) and heated in a muffle furnace at 200°C for 3 h. The samples were dissolved in 0.1 M HCl and Mn^{2+} concentrations were measured with an atomic absorption spectrophotometer (Hitachi, Z-8200).

2.3. Tissue ATP concentration

The tissue ATP concentrations were measured by the method of Ishida et al. (1984). The muscles were removed from the bath at the end of each experiment and boiled for 5 min in the test tubes containing 1 ml of water. The ATP concentration in the extract was measured with a luminometer (Lumac, M1070), using a luciferine-luciferase reagent. We also ascertained that ATP was not broken in the boiled water for 5 min.

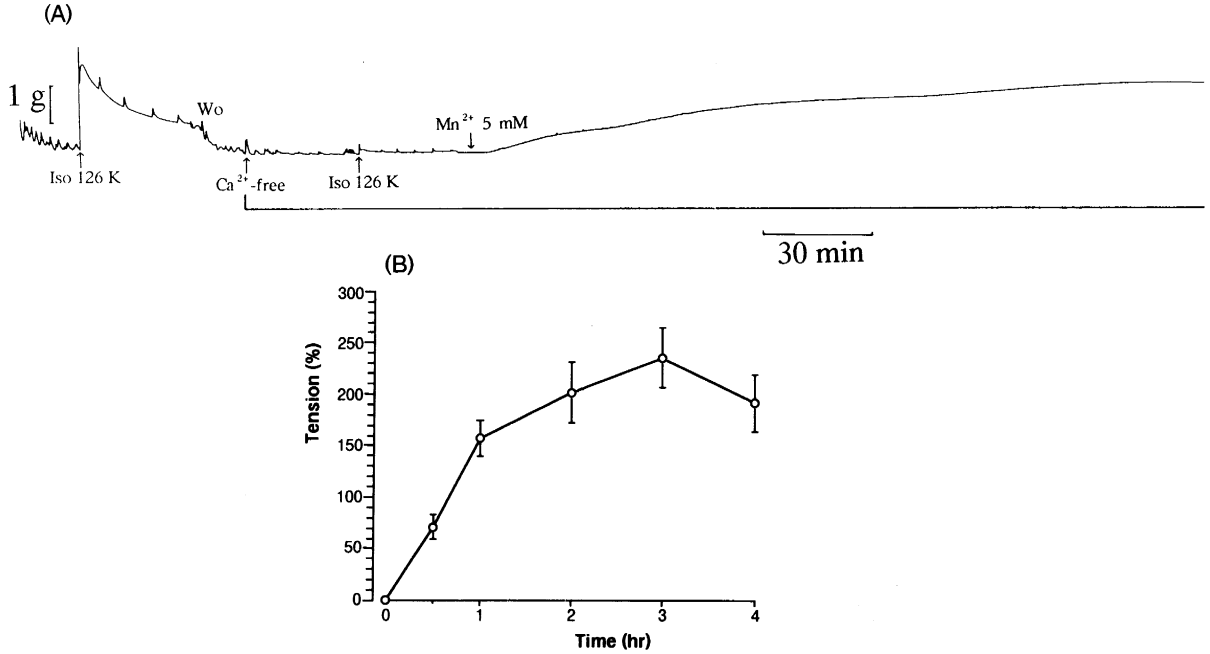

Fig. 1. Effects Mn^{2+} on contraction in Na^+-deficient, isotonic 126 mM K^+ medium in ileal longitudinal muscle. The muscle was suspended in Ca^{2+}-free medium for 30 min and successively in Ca^{2+}-free, isotonic 126 mM K^+ medium for 30 min. Thereafter, 5 mM Mn^{2+} was added to the Ca^{2+}-free, isotonic 126 mM K^+ medium. The repetitive small contractions during isotonic 126 mM K^+ medium or during Ca^{2+}-free, isotonic 126 mM K^+ medium in these figures are artifacts due to changes of the isotonic 126 mM K^+ medium or Ca^{2+}-free, isotonic 126 mM K^+ medium, respectively. Iso 126 K, isotonic 126 mM K^+. (B) The responses (mean ± S.E., $n = 8$) elicited by 5 mM Mn^{2+} in Ca^{2+}-free, isotonic 126 mM K^+ medium were expressed as percentages of the isotonic 126 mM K^+ (+2.5 mM Ca^{2+})-induced tonic response after 30 min.

2.4. Chemicals

The following drugs were used: phlorizin (Sigma, St. Louis, MO, USA) and ouabain (Merck, Darmstadt, Germany). Other chemicals used were of analytical grade.

2.5. Statistics

All data are expressed as means ± S.E.M. with the number of tissues. Student's *t*-test was used to compare data with $P < 0.05$ considered significant.

3. Results

3.1. Effects of Mn^{2+} on isometric responses in Ca^{2+}- and Na^{+}-deficient isotonic high-K^{+} medium

The substituted K^{+} (126 mM K^{+}, 0 mM Na^{+}) solution (isotonic 126 mM K^{+}) caused an initial transient contraction (2.6 ± 0.2 g, $n = 20$) in ileal longitudinal muscle. Successively, the tension was decreased and its tonic contraction was sustained at a steady low level of 22.5 ± 4.4% of the initial transient response after 30 min (Fig. 1)

In a Ca^{2+}-free medium, the isotonic 126 mM K^{+} did not produce a contraction. Mn^{2+} at 5 mM could evoke the contraction in this medium. The response 3 h after elicited by 5 mM Mn^{2+} in Ca^{2+}-free, isotonic 126 mM K^{+} medium reached 237 ± 30% ($n = 10$) of the original K^{+} (+2.5 mM Ca^{2+})-induced tonic levels (Fig. 1).

The role of the external glucose on the tension development elicited by Mn^{2+} in Ca^{2+}-free, isotonic 126 mM K^{+} medium was studied. After the muscles had been exposed to a glucose-free, Ca^{2+}-free, isotonic 126 mM K^{+} medium, 5 mM Mn^{2+} was added. During the next 2 h 5 mM Mn^{2+} developed a small increase in tension of 23 ± 6.8% (n = 8) of it after addition of 5 mM Mn^{2+} in a Ca^{2+}-free, 126 m K^{+} medium containing 5.5 mM glucose (Fig. 2).

In the glycogen-depleted preparations (see legend to Fig. 2), 5 mM Mn^{2+} added to the glucose-free, Ca^{2+}-free, isotonic 126 mM K^{+} medium exhibited only a very weak tension of 12 ± 2.9% ($n = 8$) of it 2 h after the addition of 5 mM Mn^{2+} in Ca^{2+}-free, 126 mM K^{+} medium containing 5.5 mM glucose (Fig. 2).

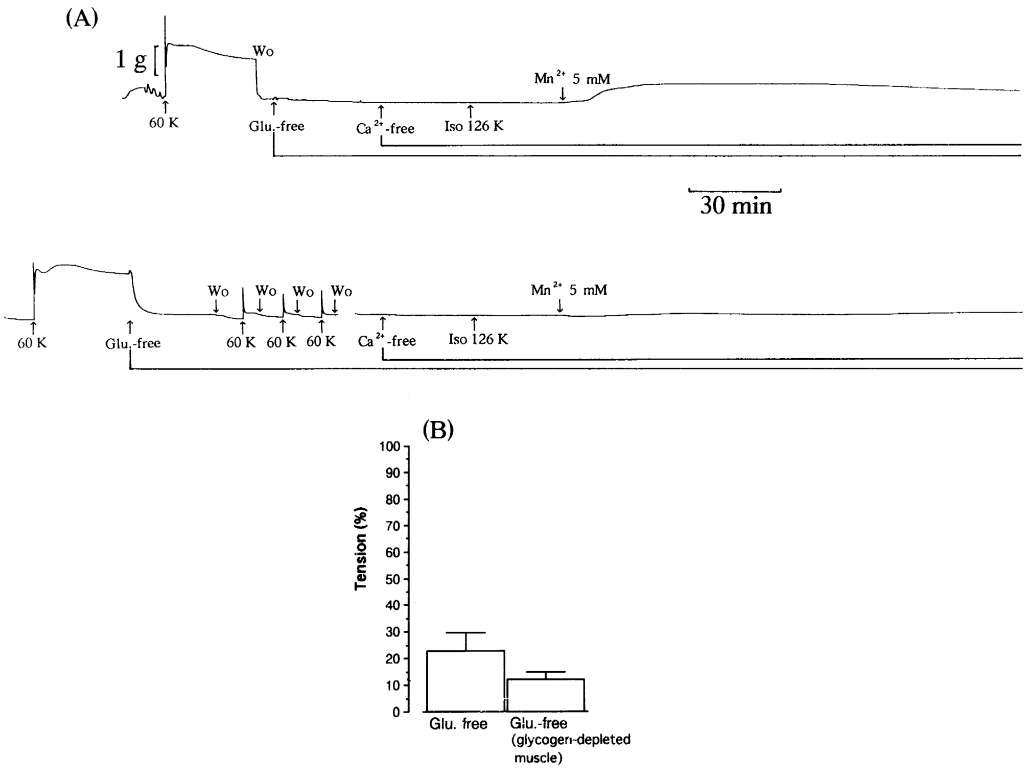

Fig. 2. Effects of external glucose-depletion on contraction by Mn^{2+} in Ca^{2+}-free, isotonic 126 mM K^{+} medium. (A) (upper figure) Muscle was first exposed to glucose-free medium for 30 min and reexposed to both glucose- and Ca^{2+}-free medium for 30 min. Successively, following 30 min of exposure to both glucose- and Ca^{2+}-free, isotonic 126 mM K^{+} medium, 5 mM Mn^{2+} was added. (lower figure) In the next series of experiments, muscle was exposed to a glucose-free medium (+60 mM K^{+}) after stimulation with hypertonic 60 mM K^{+} medium. The muscle caused a decrease in tension and, successively, they were repeatedly stimulated with hypertonic 60 mM K^{+} for 5 min at 12 min intervals in glucose-free medium until only a transient contraction was observed. In this glycogen-depleted preparation, 5 mM Mn^{2+} was added to the both glucose- and Ca^{2+}-free, isotonic 126 mM K^{+} medium. 60 K, hypertonic 60 mM K^{+}; Glu-free, glucose-free; 126 K, isotonic 126 mM K^{+}. (B) The tension development 2 h after the addition of 5 mM Mn^{2+} in both glucose- and Ca^{2+}-free, isotonic 126 mM K^{+} medium. The responses were expressed as percentages of the tension development 2 h after the addition of 5 mM Mn^{2+} in Ca^{2+}-free, isotonic 126 mM K^{+} medium containing normal glucose (5.5 mM) (mean ± S.E., $n = 8$).

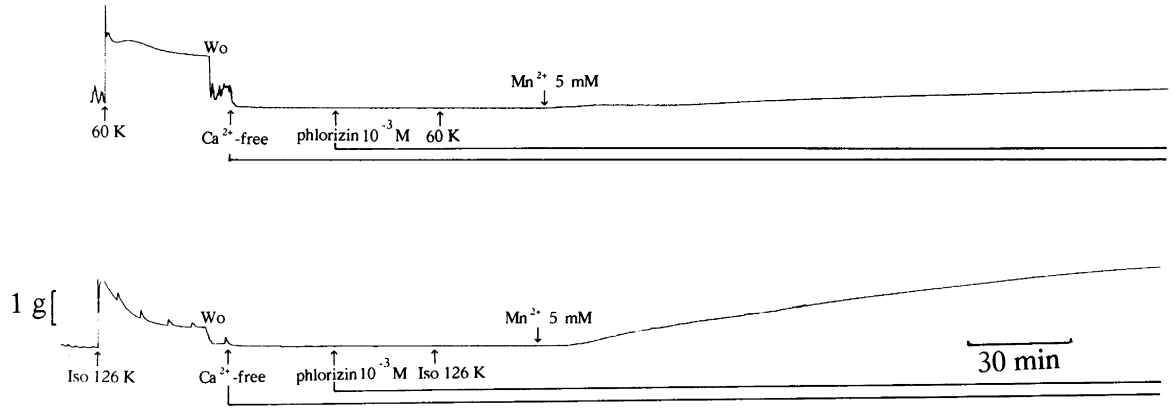

Fig. 3. Effects of phlorizin on contraction by Mn^{2+} in Ca^{2+}-free, hypertonic 60 mM K^+ or Ca^{2+}-free, isotonic 126 mM K^+ medium. (top panel) Effect of 10^{-3} M phlorizin on response by 5 mM Mn^{2+} in Ca^{2+}-free, hypertonic 60 mM K^+ medium (Na^+ 123.7 mM). (bottom panel) Effect of 10^{-3} M phlorizin on response by 5 mM Mn^{2+} in Ca^{2+}-free, isotonic 126 m K^+ medium (Na^+ 0 mM).

Phlorizin has been shown to inhibit glucose entry by blocking the Na^+-coupled glucose cotransporter in the intestinal brush border (Parsons et al., 1958; Lostao et al., 1994). Phlorizin at the concentrations lower than 10^{-4} M had no effect on the hypertonic 60 mM K^+-induced contraction of ileal muscle. When the muscle was pretreated with 10^{-3} M phlorizin, the hypertonic 60 mM K^+-induced tonic tension after 30 min was reduced to $25 \pm 4.7\%$ ($n = 8$) of the control.

Phlorizin at 10^{-3} M almost completely abolished the tension development by 5 mM Mn^{2+} in a Ca^{2+}-free, hypertonic 60 mM K^+ medium in the presence of Na^+. In Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium, in contrast, 10^{-3} M phlorizin failed to inhibit the tension development by 5 mM Mn^{2+} (Fig. 3).

Ouabain has been reported to have inhibitory effects on intestinal active transport of glucose resulting from the inhibition of Na^+, K^+-ATPase in the cell membranes (Csaky and Hara, 1965; Schultz and Curran, 1970). When 9×10^{-5} M ouabain was administered to ileal muscle, there was an increase in tension and the response decreased slowly to the initial level within 15 min. Hypertonic 60 mM K^+ was then added in the presence of ouabain. The tonic response to hypertonic 60 mM K^+ after 30 min was reduced to $38 \pm 4.2\%$ ($n = 8$) of the control.

In Ca^{2+}-free, hypertonic 60 mM medium in the presence of Na^+ in the pretreatment with 9×10^{-5} M ouabain, addition of 5 mM Mn^{2+} did not increase in tension. In Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium, 9×10^{-5} M ouabain did not inhibit the tension elicited by 5 mM Mn^{2+} (Fig. 4).

As a measure of a series of elastic element stiffness during Mn^{2+}-induced contraction in a Ca^{2+}-free, isotonic 126 mM K^+ medium, the quick release method was used. The ileal muscle length (1.5 cm) was rapidly reduced by 1 mm 3 h after the addition of 5 mM Mn^{2+} in the Ca^{2+}-free,

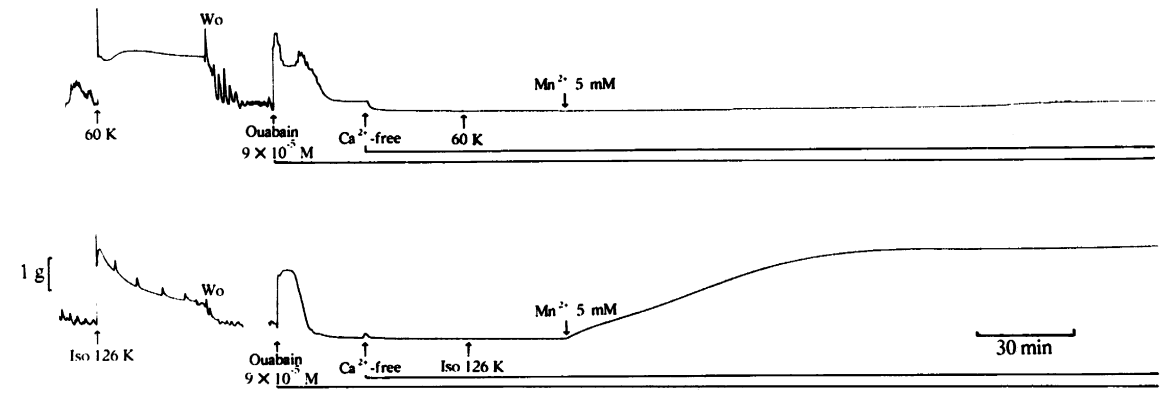

Fig. 4. Effects of ouabain on contraction by Mn^{2+} in Ca^{2+}-free, hypertonic 60 mM K^+ or Ca^{2+}-free, isotonic 126 mM K^+ medium. (top panel) Effect of 9×10^{-5} M ouabain on response by 5 mM Mn^{2+} in Ca^{2+}-free, hypertonic 60 mM K^+ medium (Na^+ 123.7 mM). (bottom panel) Effect of 9×10^{-5} M ouabain on response by 5 mM Mn^{2+} in Ca^{2+}-free, isotonic 126 mM K^+ medium (Na^+ 0 mM).

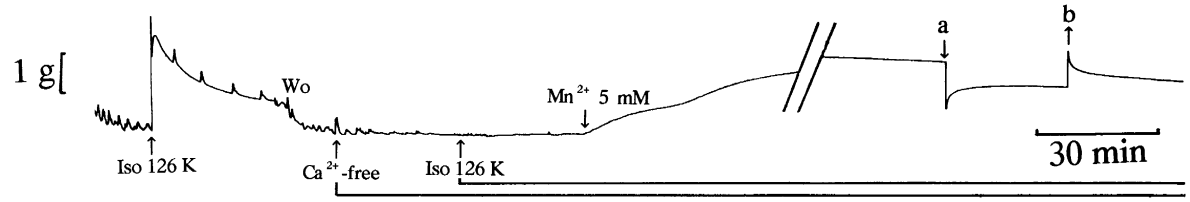

Fig. 5. Effects of quick release on tension development by Mn^{2+} in Ca^{2+}-free, isotonic 126 mM K^+ medium. The ileal muscle length (1.5 cm) was rapidly reduced by 1 mm after 3 h (a) of the addition of 5 mM Mn^{2+} in the Ca^{2+}-free, isotonic 126 mM K^+ medium. After muscle was left 30 min following quick release, rapid restoration of the previous muscle length was done at (b).

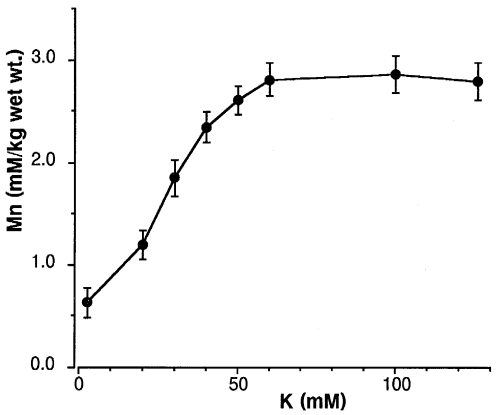

Fig. 6. Manganese uptake in isotonic medium containing various concentrations of K^+. The tissue manganese concentrations were determined following washing with 5 mM EDTA for 30 min 3 h after administration of 5 mM Mn^{2+} in Ca^{2+}-deficient, substituted K^+ medium where the each equimolar Na^+ is substituted with 20–126 mM K^+. Each point represents the mean of 10 experiments (mean ± S.E.).

isotonic 126 mM K^+ medium. After the shortening of the preparation, the tension rapidly decreased, followed by an initial fast and a late slow redevelopment of tension during the observation of 30 min (Fig. 5).

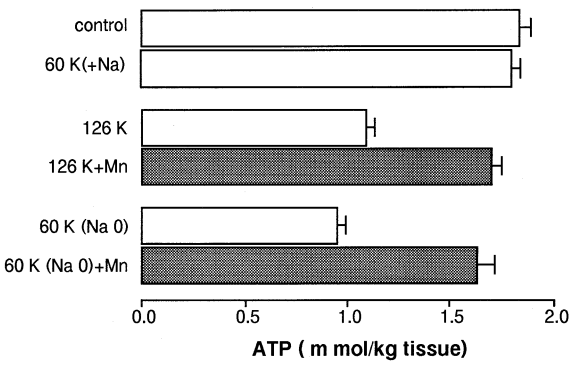

Fig. 7. Effects of Mn^{2+} on tissue ATP concentrations of ileal muscle in Na^+-deficient, isotonic 60 mM K^+ or isotonic 126 mM K^+ medium. Tissue ATP concentrations were determined 3 h after exposure to normal medium (control), hypertonic 60 mM K^+ (Na^+ 123.7 mM) medium (60 K+(Na)), Na^+-deficient, isotonic 126 mM K^+ (126 K), Na^+-deficient, isotonic 126 mM K^+ medium containing 5 mM Mn^{2+} (126 K+Mn), Na^+-deficient, isotonic 60 mM K^+ medium (60 K (Na 0)) or Na^+-deficient, isotonic 60 mM K^+ medium containing 5 mM Mn^{2+} (60 K (Na 0)+Mn). Each bar represents the mean of 8–12 experiments (mean ± S.E.).

3.2. Manganese uptake in Ca^{2+}- and Na^+-deficient isotonic high-K^+ medium

In Ca^{2+}- and Na^+-deficient, isotonic high K^+ medium, the extent of manganese accumulation in the intracellular compartment that EDTA cannot reach, was investigated. Mn^{2+} 5 mM was added to the muscles for 3 h in Ca^{2+}-deficient, substituted K^+ medium where the each equimolar Na^+ is substituted with various concentrations of K^+. The manganese uptake by ileal muscle was dependent on the external K^+ concentration in the Ca^{2+}- and Na^+-deficient, substituted K^+ medium and it reached equilibrium level at 60 mM of K^+ concentration (Fig. 6).

3.3. Tissue ATP concentration in Ca^{2+}- and Na^+-deficient isotonic high-K^+ medium

The tissue ATP concentration measured 3 h after the addition of hypertonic 60 mM K^+ medium (+123.7 mM Na^+) in ileal muscle was almost the same as that in normal Tyrode solution. The tissue ATP concentrations were significantly decreased after a 3 h incubation in Na^+-deficient, isotonic 126 mM K^+ medium or Na^+-deficient, isotonic 60 mM K^+ medium. When 5 mM Mn^{2+} was added to the Na^+-deficient, isotonic 126 mM K^+ medium or Na^+-deficient, isotonic 60 mM K^+ medium, the tissue ATP concentrations increased to the level similar to control in 3 h (Fig. 7).

4. Discussion

When Mn^{2+} at 5 mM was added to the both Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium in ileal muscle, there was a large tension development. This contraction was inhibited by removing external glucose. In the glycogen-depleted ileal muscle, Mn^{2+} did not induce a tension in a glucose-free, Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium. Quick release experiment indicated that Mn^{2+}-induced contraction is due to active interaction between actin and myosin. From these results, it seems likely that Mn^{2+}-induced contraction is maintained by the external glucose utilized as substrate of energy supply. This suggestion is supported by the facts that the tissue ATP concentrations recovered to the control

level when Mn^{2+} was added to the Na^+-deficient, isotonic 126 mM K^+ medium (Fig. 7).

Smooth muscle of taenia coli has been shown to develop tonic tension principally by using energy produced by aerobic metabolism in mitochondria through glycolytic pathway following glucose uptake at the cell membranes (Urakawa and Holland, 1964; Pfaffman et al., 1965). It has also been shown that glucose is accumulated by glucose cotransporter within intestinal epithelial cells across the brush border (Wright, 1993; Hediger and Rhoads, 1994). However, there are few studies on the mechanism of glucose transport through the cell membrane of ileal smooth muscle. Phlorizin has been shown to competitively inhibit the binding of the glucose site of Na^+-dependent glucose cotransporter in the intestinal brush border (Ugolev and Metel'skii, 1990; Peerce, 1990; Lostao et al., 1994). In ileal muscle, phlorizin (10^{-3} M) inhibited the tonic contraction induced by hypertonic 60 mM K^+ medium containing normal Na^+ (126 mM). In addition, phlorizin (10^{-3} M) also markedly inhibited the contraction elicited by 5 mM Mn^{2+} in Ca^{2+}-free, hypertonic 60 mM K^+ medium containing normal Na^+. In contrast, phlorizin had no effect on the contraction by 5 mM Mn^{2+} in Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium (Fig. 3). Thus, phlorizin inhibited Mn^{2+}-induced contraction in the presence of Na^+ but not in its absence.

It is well established that the Na^+ concentration difference across the cell membrane of ileal muscle could constitute a potential energy source that could be employed for the active transport of glucose (Schultz and Curran, 1970). Ouabain causes an increase in intracellular Na^+ concentration by inhibition of Na^+ extrusion due to the inhibitory action on Na^+, K^+-ATPase in taenia coli (Kishimoto et al., 1980). The abolition of Na^+ concentration difference across the cell membrane by ouabain has been thought to cause the inhibition of active transport of glucose. Ouabain 9×10^{-5} M completely inhibited the contraction elicited by 5 mM Mn^{2+} in Ca^{2+}-free, hypertonic 60 mM K^+ medium containing normal Na^+. In contrast, the ouabain had no effects on the contractions by 5 mM Mn^{2+} in both Ca^{2+}- and Na^+-deficient, isotonic 126 mM K^+ medium.

These results indicate that during contraction due to Mn^{2+} in Na^+-abundant, hypertonic 60 mM K^+ medium, glucose may be taken up through Na^+-coupled glucose cotransporter which is sensitive to phlorizin. In comparison, during contraction due to Mn^{2+} in Na^+-deficient, isotonic 126 mM K^+ medium, glucose uptake may occur through Na^+-independent glucose transport system. It has also been reported that Na^+-dependent glucose and galactose uptake which is sensitive to phlorizin, and the Na^+-independent uptake exists in jejunal enterocytes (Debnam et al., 1990) and renal mesangial cells (Wakisaka et al., 1995).

It has been shown that Mn^{2+} dose-dependently induced contractions of skinned fibres of uterine smooth muscle and that maximum tension by Mn^{2+} was achieved at the concentration of 10^{-5} M (Savineau et al., 1988). We have previously reported that the increase of tension due to Mn^{2+} was dependent on the external K^+ concentrations above 35 mM and the maximal tension reached an equilibrium level at the concentration of 60 mM K^+ (Nasu et al., 1995b). At the same time, the manganese accumulated in intracellular compartment which EDTA cannot reach, attained an equilibrium level at the concentration of 60 mM K^+ (Fig. 6). These facts indicate that the large tension elicited by Mn^{2+} in isotonic 126 mM K^+ medium does not explain solely by the increase in Mn^{2+} concentration of the contractile elements.

In conclusion, Mn^{2+}-induced contraction in ileal smooth muscle in Na^+-deficient, high K^+ medium might be maintained by glucose transport which is not dependent on the external Na^+.

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