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Manganese Ions Induce Tonic Contraction after Relaxation in a High-K^+ Medium in Ileal Longitudinal Smooth Muscle of Guinea-pig

T. NASU, H. MURASE AND H. SHIBATA

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

Abstract—In ileal longitudinal muscle 5 mM Mn^{2+} inhibited completely the K^+ (60 mM)-induced tonic tension to the base line; however, the tension progressively increased to above the level of original tonic response evoked by K^+ after 3 h in the presence of Mn^{2+}. Tetrodotoxin (5×10^{-5} M) had no influence on the tension development in the presence of Mn^{2+} in the high-K^+ medium. Mn^{2+} also increased the tension in a high-K^+, Ca^{2+}-free medium. The Ca^{2+} antagonist, gallopamil (10^{-6} M) inhibited the development of tension in the presence of Mn^{2+} in the high-K^+ medium. The ^{45}Ca uptake determined by the lanthanum method remained unchanged from control levels after 3 h of the 5 mM Mn^{2+} application in the high-K^+ medium in spite of the development of the tension. The manganese uptake in the high-K^+ medium, increased in accordance with the increase of duration of 5 mM Mn^{2+} application. Gallopamil inhibited manganese uptake in the high-K^+ medium. These results suggest that Mn^{2+} firstly reduces K^+-induced tension by inhibition of Ca^{2+} influx; subsequently, Mn^{2+} ions accumulate in the intracellular compartments through voltage-operated Ca^{2+} channels and may activate contractile proteins in the ileal muscle.

Manganese ions (Mn^{2+}) are known to inhibit specifically the action potential discharge in the membranes in barnacle muscle fibres (Hagiwara & Nakajima 1966) and in various smooth muscles such as the guinea-pig taenia coli (Nonomura et al 1966; Brading et al 1969), the mouse myometrium and the guinea-pig ileum (Osa 1974), and the rabbit and guinea-pig portal vein (Collins et al 1972; Nanjo 1984). Previous reports have shown that Mn^{2+} inhibits contractile responses to K^+ in ileum (Osa 1974) and taenia coli (Nonomura et al 1966) and the responses evoked by K^+ or noradrenaline in the portal vein (Collins et al 1972). Moreover, Mn^{2+} has also been found to inhibit the binding of a Ca^{2+}-channel antagonist, nitrendipine, to a microsomal fraction in intestinal muscle (Ehlert et al 1982). These data indicate that Mn^{2+} has a strong inhibitory action on Ca^{2+} channels in the cell membrane of smooth muscles.

In contrast, Mn^{2+} has been shown to induce contractile responses under certain conditions in mesenteric portal vein (Sutter et al 1988) and taenia coli (Lategan & Brading 1988). The purpose of this study was to gain further insight into the mechanism of the contractile action of Mn^{2+} in high-K^+ medium in ileal longitudinal muscle of guinea-pig.

Materials and Methods

Preparations

Strips of longitudinal smooth muscle were isolated from the ileum of male Hartley guinea-pigs, 400 g, and were immersed in modified Tyrode solution bubbled 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 high-K^+ (40–60 mM) solution was prepared by adding an appropriate amount of 2 M KCl solution to the Tyrode solution. Manganese ions as $MnCl_2 \cdot 4H_2O$ were directly added to the bathing solution. To produce the anoxic condition, 100% N_2 gas was used instead of 100% O_2.

The muscle strips were suspended at a resting tension equivalent to 0·6 g and allowed to equilibrate for 40 min with several changes of Tyrode solution. Isometric contraction of the muscle was measured by a strain-gauge transducer (Nihon Kohden, RM6000). After equilibration, the tissue was conditioned by adding 40 mM K^+ to the bath.

La^{3+}-resistant residual ^{45}Ca uptake

^{45}Ca uptake into the ileal longitudinal muscle was measured by a modification of the lanthanum method described by Karaki & Weiss (1979). The muscle samples were exposed to 2·5 mM Ca^{2+} (+ ^{45}Ca, 5 μCi mL^{-1}, New England Nuclear), K^+ (60 mM) medium containing 5 mM Mn^{2+} for 3 h, after which they were rinsed with a lanthanum solution ($LaCl_3$ 68·7, glucose 5·5 and Tris-HCl 25 mM) (pH 7·4), which was gassed with 100% O_2 at 1°C for 50 min. The strips were blotted and then treated with a solubilizer (Soluene TM-350, Packard) and the radioactivity was measured with a liquid scintillation spectrophotometer (Aloka, LSC-602).

Tissue manganese (Mn^{2+})

To determine tissue Mn^{2+} concentrations in ileal longitudinal muscles, the strips were removed from the bath after incubation in a medium containing an appropriate amount of Mn^{2+}. They were blotted on filter paper, then weighed and heated in a muffle furnace at 550°C for 2 h. The samples were dissolved in 0·01 M HCl and Mn^{2+} concentrations were measured with an atomic absorption spectrophotometer (Hitachi, 308).

Correspondence: T. Nasu, Department of Veterinary Pharmacology, Faculty of Agriculture, Yamaguchi University, Yamaguchi 753, Japan.

Results

Effects of Mn^{2+} on high-K^+-induced contraction

When ileal longitudinal muscles were treated with high-K^+ (hypertonic, 60 mM) medium, the phasic contraction ($2{\cdot}9 \pm 0{\cdot}2$ g, n = 35) was followed by a tonic contraction ($2{\cdot}1 \pm 0{\cdot}2$ g). After the muscles were incubated in the high-K^+ medium for 30 min, Mn^{2+} was applied at various concentrations. Mn^{2+} 5 mM reduced the tonic K^+ response to the base-line level within 1 min, then after approximately 15 min, the muscle progressively contracted until 3 h after the reappearance of tone, the response reached 178 ± 12 (n = 20) of the original K^+-induced tonic levels. The recovered tension persisted for more than 5 h after the peak tension was reached (Fig. 1). Based on these preliminary findings, the effects of 5 mM Mn^{2+} on the high-K^+ (60 mM)-induced tonic contraction were studied in detail, because this concentration of Mn^{2+} completely inhibited the tonic response to K^+ and because the contraction evoked subsequently was greatest. On the other hand, instead of 60 mM KCl an addition of twice the number of millimoles, sorbitol or sucrose, both unable to penetrate into the smooth muscle cell membrane (Goodford & Leach 1966), had no effect on the contraction when similar experiments were performed, suggesting that the effects of 60 mM K^+ is not the result of changes in osmolarity.

Neither the nerve-conduction blocker, tetrodotoxin (5×10^{-5} M), nor the muscarinic antagonist, atropine (10^{-6} M), had an influence on the development of contraction after the inhibition of high-K^+ (60 mM)-induced tonic response by 5 mM Mn^{2+} (data not shown).

When 5 mM Mn^{2+} was added alone to the Tyrode solution, the muscles failed to contract even after more then 4 h (data not shown).

Mn^{2+} (5 mM) decreased the contractile effects evoked by 10, 20 or 30 mM K^+ but did not cause a subsequent contraction. However, the tension in the presence of 5 mM Mn^{2+} increased, depending on the K^+ concentration of above 35 mM (Table 1).

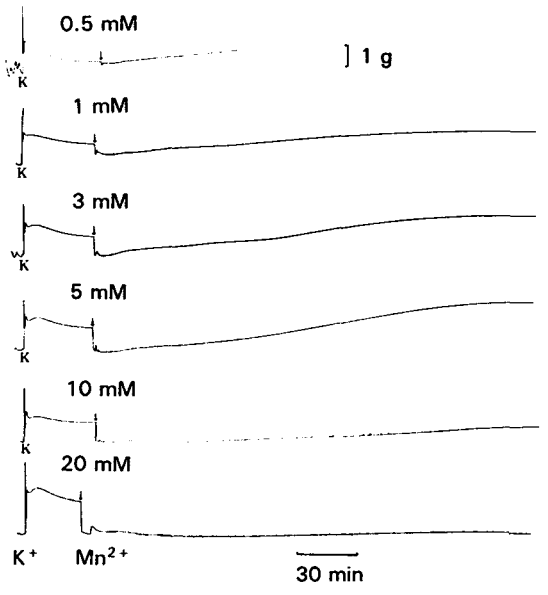

FIG. 1. Effects of Mn^{2+} on high-K^+ (hypertonic, 60 mM)-induced contraction in ileal longitudinal muscle. $MnCl_2$ was applied 30 min after the addition of 60 mM K^+.

Table 1. Effects of 5 mM Mn^{2+} on various concentrations of K^+-induced contractions of ileal longitudinal smooth muscle.

K^+ (mM)	Recovered tone (%)
0	0
10	0
20	0
30	0
35	$25 \pm 7{\cdot}5$
40	$67 \pm 9{\cdot}5$
50	$102 \pm 10{\cdot}1$
60	178 ± 8

Mn^{2+} 5 mM was applied 30 min after the addition of K^+ (10–60 mM). The recovered responses of 3 h after 5 mM Mn^{2+} application are expressed as a percentage of each K^+-induced tonic response before addition of 5 mM Mn^{2+}. Each value represents the mean of 12–20 experiments (mean ± s.e.).

The calcium antagonist, gallopamil caused a dose-related reduction of the development of contractions in the presence of Mn^{2+} after the inhibition of high-K^+ (60 mM) tonic response. The concentration of above 10^{-6} M gallopamil completely inhibited the contraction (Table 2). Furthermore, the contraction evoked by 5 mM Mn^{2+} in high-K^+ medium was progressively decreased by subsequent addition of 10^{-6} M gallopamil (data not shown).

High-K^+ (60 mM) did not produce a contraction in a Ca^{2+}-free medium. In a Ca^{2+}-free, high-K^+ medium, 5 mM Mn^{2+} was still capable of causing the same level of contraction as in normal Ca^{2+}, high-K^+ medium. Gallopamil (10^{-6} M) completely inhibited the progressive rise in tension by 5 mM Mn^{2+} in a Ca^{2+}-free, high-K^+ medium.

The contractile effect caused by 5 mM Mn^{2+} in a high-K^+ medium recovered more rapidly until the level of 187 ± 7 (n = 8)% of original K^+ response after 3 h, when anoxia was induced by replacing 100% O_2 by 100% N_2 gassing the tissue.

Effects of Mn^{2+} on La^{3+}-resistant residual ^{45}Ca uptake

In the high-K^+ medium during 30 min, the Ca^{2+} uptake increased to $0{\cdot}78 \pm 0{\cdot}028$ (n = 12) mM (kg wet tissue)$^{-1}$ from $0{\cdot}42 \pm 0{\cdot}035$ (n = 12) mM (kg wet tissue)$^{-1}$ in normal medium. To determine the effects of Mn^{2+} on the low affinity binding sites of Ca^{2+}, muscle was incubated for 3 h

Table 2. Effects of calcium antagonist, gallopamil, on the effects of 5 mM Mn^{2+} on high-K^+-induced contraction of ileal longitudinal smooth muscle.

Gallopamil (μM)	Recovered tone (%)
0	178 ± 8
0·01	$133 \pm 7{\cdot}5$
0·03	$66 \pm 6{\cdot}3$
0·1	$34 \pm 7{\cdot}5$
0·3	$11 \pm 5{\cdot}1$
1	0

Gallopamil (10^{-8}–10^{-6} M) was administered 10 min after the inhibition of high-K^+ (60 mM)-induced contraction by 5 mM Mn^{2+}. The recovered responses of 3 h after 5 mM Mn^{2+} application in the presence of gallopamil are expressed as a percentage of the K^+-induced tonic response before addition of Mn^{2+}. Each value represents the mean of eight experiments (mean ± s.e.).

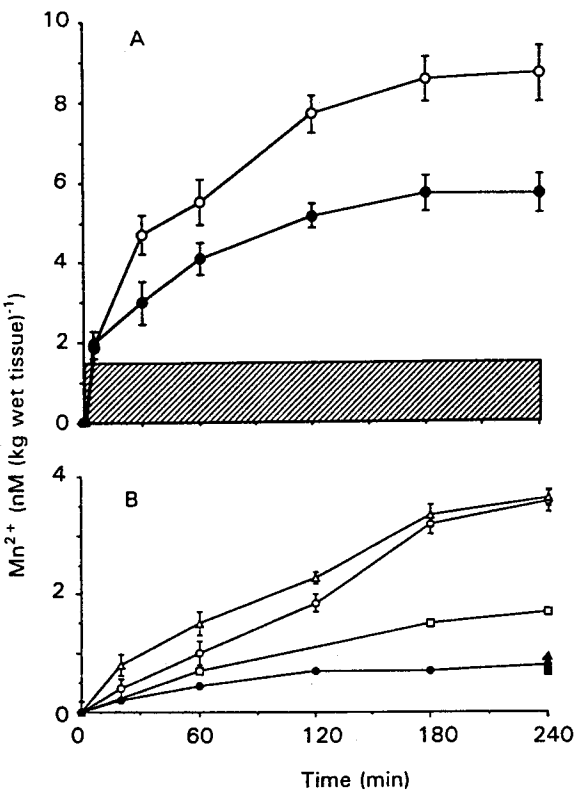

FIG. 2. Time course of Mn^{2+} uptake by ileal longitudinal muscle. A. Mn^{2+} was applied in normal (●) or high-K^+ (○) medium. The tissue Mn^{2+} concentrations were determined without washing. The hatched area represents the amount of Mn^{2+} that existed in the extracellular space. Each point represents the mean of eight experiments (mean ± s.e.). B. After the incubation for various periods following addition of 5 mM Mn^{2+} on normal (●), K^+ (○), Ca^{2+}-free, K^+ (△), 10^{-7} M gallopamil, K^+ (□), 10^{-6} M gallopamil, K^+ (■), Ca^{2+}-free, 10^{-6} M gallopamil, K^+ (▲) medium, the muscles were washed with Ca^{2+}- and Mg^{2+}-free medium containing 5 mM EDTA for 30 min. Each point represents the mean of 8–12 experiments (mean ± s.e.).

in the high-K^+ (60 mM) medium (Ca^{2+} 2·5 mM) containing ^{45}Ca added 5 min after the application of 5 mM Mn^{2+} in the high-K^+ medium. The ^{45}Ca uptake into the low-affinity Ca^{2+}-binding sites remained unchanged from control levels in spite of the development of tension in the presence of 5 mM Mn^{2+} in the high-K^+ medium.

Manganese uptake in ileal muscle

To investigate the time course of Mn^{2+} uptake into ileal tissues, the muscles were incubated in a normal or high-K^+ (60 mM) medium containing 5 mM Mn^{2+}. The rate and extent of manganese uptake in the high-K^+ medium was greater than in the normal medium (Fig. 2A). If we assume that extracellular space is saturated with the same concentration of substrate as the external medium, the hatched area (5 mM Mn^{2+} in external medium×0·35 in the extracellular space as measured by [^{14}C]sorbitol) in Fig. 2A represents the Mn^{2+} level that existed in the extracellular space.

In the next series of experiments, the extent of Mn^{2+} accumulation in the intracellular compartment that EDTA cannot reach, was investigated. After incubation in the presence of 5 mM Mn^{2+}, the muscles were washed for 30 min with Ca^{2+}-free and Mg^{2+}-free Tris Tyrode solution containing 5 mM EDTA. The Mn^{2+} uptake in the high-K^+ medium was greater than in normal medium. In addition, gallopamil inhibited dose-dependently the Mn^{2+} uptake in the high-K^+ medium (Fig. 2B).

When 5 mM Mn^{2+} was added in the Ca^{2+}-free, high-K^+ (60 mM) medium, the Mn^{2+} uptake was increased, but this was inhibited by gallopamil (10^{-6} M).

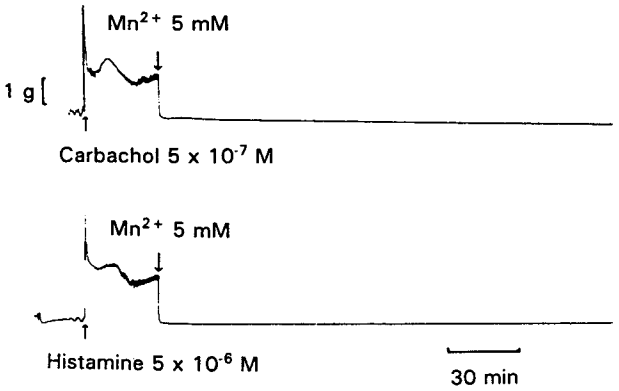

FIG. 3. Effects of Mn^{2+} on carbachol- or histamine-induced contraction in ileal muscle. Mn^{2+} (5 mM) was applied 30 min after the addition of carbachol or histamine.

Effects of Mn^{2+} on carbachol- or histamine-induced contraction

The effects of Mn^{2+} on the ileal contractions induced by stimulation through muscarinic or histamine receptors were examined. Mn^{2+} (5 mM) completely inhibited the tonic contraction induced by either 5×10^{-7} M carbachol or 5×10^{-6} M histamine, and there was no subsequent development of contraction when responses were monitored for more than 3 h (Fig. 3).

Discussion

In the present studies, Mn^{2+} at concentrations above 3 mM completely inhibited the K^+-induced ileal tonic contraction within 1 min; thereafter, the contractions progressively increased to above the level of the original K^+ tonic response after 3 h in the presence of 5 mM Mn^{2+} in the high-K^+ medium. The contraction by Mn^{2+} in the high-K^+ medium did not involve neural elements, since it was not affected by pretreatment with tetrodotoxin. After the application of other heavy metals such as Cd^{2+} (Nasu 1983; Nasu et al 1983), Co^{2+} (Nasu 1992) or Pb^{2+} (Nasu et al 1993) to the high-K^+-induced contractions in ileal or aortic smooth muscles, the responses were also inhibited; however, the contractions did not develop entirely thereafter.

Mn^{2+} itself at low concentrations (10^{-5}–10^{-6} M) has been reported to cause a transient contractile response which ceased within several minutes (Schnieden & Weston 1969; Satoh et al 1986). Satoh et al (1986) also have noted that the transient response caused by Mn^{2+} was inhibited by cooling, tetrodotoxin, hyoscine and use of Ca^{2+}-free medium. Furthermore, Mn^{2+} of low concentration has been shown to increase the release of [^{14}C]acetylcholine in ileum (Satoh et al 1986). This probably indicates that Mn^{2+} of low concentration induces a transient contraction through acetylcholine release from intramural cholinergic nerves.

In contrast, when 5 mM Mn^{2+} alone was added to the normal solution, the ileal muscle failed to contract even after more than 4 h.

The tension development in the presence of Mn^{2+} in high-K^+ medium increased, depending on the K^+ concentration (above 35 mM) used. In taenia coli studies, when the K^+ concentration was increased from 4·6 to 30 mM, the membrane potential decreased from 51·5 to 37 mV (Holman 1958). This may indicate that Mn^{2+} of millimole concentration can cause ileal contraction when the cell membrane is in a state of depolarization.

The contraction did not develop after the inhibition by 5 mM Mn^{2+} of the tonic contraction induced by 5×10^{-7} M carbachol or 5×10^{-6} M histamine. It is reported that the extent of membrane depolarization induced by carbachol or histamine was smaller than that caused by K^+ in ileal muscle (Bülbring & Burnstock 1960; Bolton 1971).

We have found that when 5 mM Mn^{2+} was added to a Ca^{2+}-free, high-K^+ medium, the tension also increased progressively. Moreover, in spite of treatment with ryanodine (10^{-5} M), which diminished release of Ca^{2+} from intracellular stores (Ito et al 1986), 5 mM Mn^{2+} was still capable of causing a contraction in the high-K^+ (normal Ca^{2+}) medium (data not shown). This suggests that the contraction by Mn^{2+} in high-K^+ medium did not depend on either Ca^{2+} influx from extracellular Ca^{2+} or Ca^{2+} release from an intracellular store. In support of this view, the ^{45}Ca uptake remained unchanged from control levels in spite of the development of the contraction after 3 h of 5 mM Mn^{2+} in the K^+ medium.

Mn^{2+} has been reported to cause contraction of skinned fibres of guinea-pig stomach (Ito et al 1982) and the chicken gizzard (Hoar & Kerrick 1988) in a Ca^{2+}-free medium. Hoar & Kerrick (1988) have shown that Mn^{2+} can cause myosin to interact in a rigor-like state by the direct oxidizing action on the myosin without myosin light-chain phosphorylation. Therefore, if Mn^{2+} penetrates the cell membrane of ileal smooth muscle, it will have an effect on the contractile proteins.

The chelating agent, EDTA, does not penetrate the cell membrane of guinea-pig taenia coli (Brading & Jones 1969) and its action appears to be restricted to the smooth muscle cell membrane (Weiss & Goodman 1976). Therefore, when the ileal strips were washed with Ca^{2+}- and Mg^{2+}-free medium containing EDTA after Mn^{2+} treatment, it is thought that Mn^{2+} which existed in the extracellular space and bound to the cell membrane, is eliminated. The Mn^{2+} uptake in high-K^+ medium which was washed with EDTA, increased slowly in accordance with the increase of duration of 5 mM Mn^{2+} application. In Ca^{2+}-free, K^+ medium, the Mn^{2+} uptake also increased. The Ca^{2+} antagonist, gallopamil (10^{-6} M) inhibited both the contraction and the Mn^{2+} uptake in the Ca^{2+}-free, high-K^+ medium. These results suggest that Mn^{2+} penetrates the cell membranes of ileal smooth muscle through voltage-operated Ca^{2+} channels in the ileal muscle membrane.

The ileal tonic contraction to K^+ is thought to be maintained by energy produced during oxidative metabolism, since the inhibitors of respiration in mitochondria, such as N_2 gas (Pfaffman et al 1965) or KCN (Nasu & Ishida 1990), preferentially inhibit the tonic response in taenia coli. However, in anoxic conditions, the ileal tension increased in the presence of 5 mM Mn^{2+} in a high-K^+ medium. This may suggest that Mn^{2+} accumulates in an intracellular compartment to cause rigor-like contractions in ileal muscle as proposed by Hoar & Kerrick (1988).

In summary, it is probable that Mn^{2+} firstly reduces K^+-induced tension by inhibition of Ca^{2+} influx. Subsequently, Mn^{2+} is slowly accumulated in the intracellular compartment in the presence of the high concentration of K^+ and activates contractile proteins in the ileal muscle. While the concentration of Mn^{2+} in the external medium was raised to the high concentration of 20 mM, the ileal response did not develop even after 3 h in the high-K^+ medium.

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