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Ionic dependence of slow waves and spikes in intestinal muscle

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LIU, JANE, C. L. PROSSER, AND DONALD D. JOB. *Ionic dependence of slow waves and spikes in intestinal muscle.* Am. J. Physiol. 217(5): 1542-1547. 1969.—Longitudinal muscle fibers of cat jejunum show slow waves, prepotentials, and spikes. Slow waves are reduced to zero amplitude when sodium is replaced by Tris or by lithium or when ouabain is added at concentrations less than required for depolarization. Slow-wave frequency is reduced in lithium (but not Tris) and by ouabain. Intracellular iontophoresis of sodium, but not of potassium, enhances slow-wave amplitude. Longitudinal muscle spikes are reduced to zero in Ca-free medium. are insensitive to sodium, and are eliminated by low concentrations of manganese or cobalt. In circular muscle fibers, triggered spikes are absent in Ca-free medium, go through a maximum at 0.85 mM Ca_2^+, and decline at high calcium concentrations. It is concluded that slow waves result from a rhythmic electrogenic sodium pump and that spikes of both longitudinal and circular fibers reflect calcium influx.

small intestine; smooth muscle; sodium pump; calcium spikes

THE LONGITUDINAL muscle layer of small intestine gives rise to slowly fluctuating potential waves whose function is to synchronize spikes of both muscle layers. These slow waves constitute the cellular basis of the "pacesetter potentials" or "basic electrical rhythm" recorded in vivo (17). At the peak of a slow wave and at the beginning of a spike there may also be recorded a pacemaker potential (5) which appears similar to the slow potentials of taenia coli. The amplitude of duodenal slow waves was shown to be dependent on membrane potential as altered by variation in external potassium and calcium, also to be reduced when sodium was replaced by lithium or sucrose (19). On the basis of effects of inhibitors, particularly strophanthidin (ouabain) in vivo, it was suggested that the slow waves may depend on an electrogenic sodium pump (4). An enhanced efflux of sodium during the falling phase of a slow wave supports this hypothesis (8). Evidence from ion substitutions and from effects of competitive inhibitors indicates that the spikes of taenia coli represent conductance changes for calcium (12, 15). The present study adduces several kinds of observation to elucidate the nature of slow waves and spikes.

METHODS

Segments of cat jejunum were removed from animals anesthetized with α-chloralose (65 mg in 1 ml propylene glycol per kilogram body weight). Tubular muscle preparations consisted of longitudinal and circular layers or pure circular layers. Intracellular recording was by high-resistance (40–80 megohm) microelectrodes filled with 3 M KCl. A Bioelectric preamplifier (NF-1) with its probe control unit was connected to the d-c amplifier of a dual-beam Hewlett-Packard oscilloscope. For measurement of rate of membrane potential changes (dv/dt) an electronic differentiator was used. A bridge circuit (11) was used to inject Na^+ iontophoretically into the muscle cells. Extracellular recording was by pressure electrodes—glass capillaries filled with Tyrode-agar and connected by chlorided silver wire to a preamplifier. All recordings by microelectrodes and pressure electrodes were with reference to an indifferent electrode in the oxygenated Tyrode solution at 35–37 C. In all figures, positivity of the active electrode is upward.

The Tyrode solution had the following composition: NaCl 133 mM; KCl 4.7 mM; $NaHCO_3$ 16.3 mM; NaH_2PO_4 1.2 mM; $CaCl_2$ 1.7 mM; $MgCl_2$ 0.5 mM; glucose 11.5 mM. Tyrode solution containing high Ca^{2+} was buffered with 1 mM Tris-Cl (tris-(hydroxymethyl)aminomethane chloride) instead of sodium phosphate to prevent the precipitation of calcium. Control recordings at normal (1.7 mM) $CaCl_2$ were similar in Tris or phosphate buffer. Sodium replacement was by equivalent concentrations of $Tris^+$ or Li^+.

RESULTS

Pure slow waves are relatively smooth with the rising phase often more rapid than the falling phase. Sometimes a rapid rise or early small spike represent spikes in adjacent cells (15) (Fig. 1*B*). Near the top of the rising phase a change in slope indicates a prepotential from which a spike arises (first spike in Fig. 1, *C* and *D*). The prepotential may be large and the spikes multiple (Fig. 1*A*). A second spike in a cell may fail to show a prepotential (Fig. 1*C*) or may have one (Fig. 1*D*). It is often difficult to be certain whether an initial spike or a second spike arises in the cell in which the microelectrode is inserted or in a nearby cell.

Effects of sodium and calcium on slow waves. Sodium concentration in the medium was reduced by substitution of Tris-Cl for NaCl. Sodium replacement by Tris was studied in detail on several preparations from each of eight cats. Figure 2 gives representative records and Fig. 3 indicates the time course of changes in slow waves and spikes when Na^+ was completely replaced by $Tris^+$. The average resting potential, as measured from the bottom of the slow waves, was unaltered (10 experiments at four different sodium concentrations). However, the amplitude of the slow waves gradually decreased, reaching nearly zero after 40–60 min

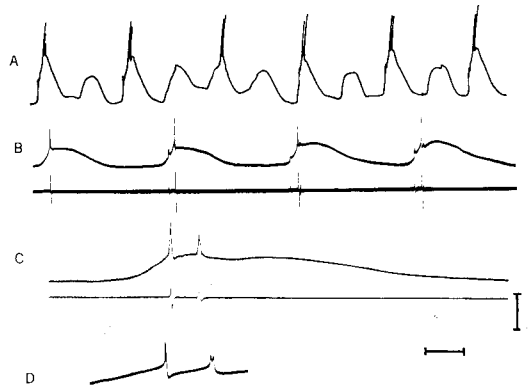

FIG. 1. Spikes, prepotentials, and slow waves. *A:* pressure electrode recording of pure slow waves alternating with slow waves which have prepotentials and spikes; *B:* slow waves, prepotentials, and spikes (differentiated record below); *C:* expanded slow wave with two spikes, prepotential before first; *D:* expanded top of slow wave showing two prepotentials leading to single and double spikes. Vertical calibration 10 mv, horizontal calibration 5 sec in *A*, 1.5 sec in *B*, 0.4 sec in *C*, and 0.5 sec in *D*.

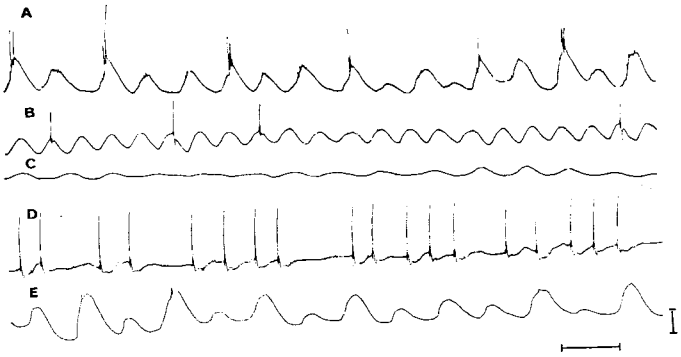

FIG. 2. Effects of Na^+-free solution (Tris substituted) on slow waves and spikes. Pressure electrode recordings, continuous perfusion. *A:* controls (normal Na^+); *B:* Na^+-free (103 min); *C:* period of quiescence (155 min); *D:* period of spontaneous spiking (160 min); *E:* recovery in normal Na^+ solution. Calibrations: 10 sec and 1 mv.

in Na-free medium. Spikes were relatively unaffected. Recovery of slow waves occurred on return to normal Tyrode. In the experiments of Figs. 2 and 3, recovery was not complete and there was some continuing decline of spike amplitude associated with slight deterioration of the preparation. The maximum rate of rise of slow waves, also rate of fall, as measured with intracellular electrodes decreased when extracellular sodium was reduced. For example, in one experiment, at 133 mM NaCl the rate of rise was 75 mv/sec and rate of fall 53 mv/sec, whereas at less than 75 mM NaCl the rates of rise and fall were 10–16 mv/sec

The amplitude of slow waves was linearly related to the log of the extracellular Na^+ with a slope of about 10 mv per 10-fold change in Na^+ (Fig. 4). Frequency of slow waves was relatively constant when amplitude was reduced in Tris-substituted saline.

In three experiments LiCl was substituted for NaCl. The amplitude of slow waves declined faster than in Tris substitution and fell to 50% in 10–14 min and to zero in 15–20 min. In addition, the frequency was reduced by 55% in 10–14 min. Spikes persisted at normal height after the slow waves disappeared.

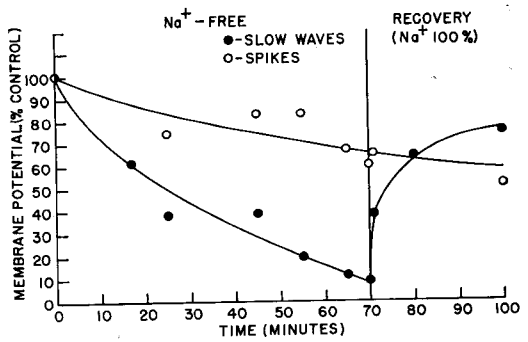

FIG. 3. Time course of effects of Na^+-free (Tris substituted) Tyrode solution on spikes and slow waves.

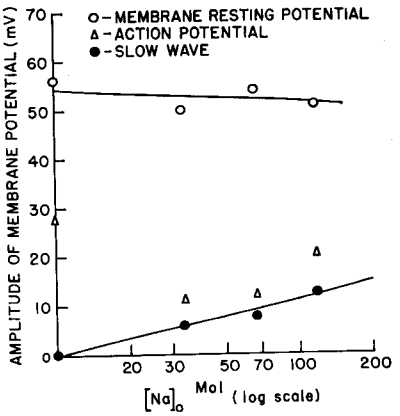

FIG. 4. Effects of varying extracellular Na^+ concentration on resting membrane potentials, action potentials, and slow waves; averages of 6–21 measurements at each point.

The effect of reduced Na^+_o on amplitude of slow waves was assumed to result from a depletion of intracellular sodium rather than from a decrease in inward gradient of Na^+ for the following reasons: the time required for reducing the slow waves is long, there is no tendency for the slow waves to approach the Na^+ equilibrium potential (calculated for taenia to be between +25 and +14 mv (6)), and the slope is only 10 mv. Analyses of longitudinal muscle removed from intestinal segments which have been soaked in Tris-Tyrode solution for 1 hr show reduction in intracellular sodium concentrations by 50–70% (total tissue Na from 88 to 30 mM/g wet wt).

The role of intracellular Na^+ in the generation of slow waves was further studied by iontophoresis. Figure 5 shows the effect of injecting Na^+ into a longitudinal muscle cell by a microelectrode filled with near-saturated NaCl. Positive current (2×10^{-9} amp) was used to drive Na^+ into the cell and approximately 6.7×10^{-11} mEq Na^+ was injected in the experiment shown in Fig. 5*B*. The amplitude of the slow wave was 3.5 times higher than before the current was applied. When the same current was passed by an electrode filled with KCl (Fig. 5*A*) no such enhancement of the slow wave was observed. Also depolarization of the membrane to the same amount by adding potassium to the medium reduced the amplitude of the slow waves rather than enhanced it, as shown in Table 1.

As a further control, resistance of NaCl and KCl electrodes was measured during current pulses when the

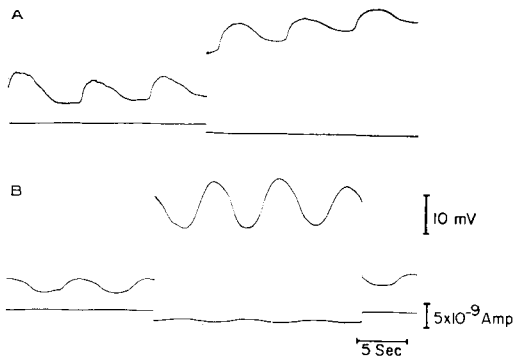

FIG. 5. Effects of injecting Na^+ iontophoretically into a longitudinal muscle cell by a microelectrode filled with saturated NaCl (*B*). Control experiments with microelectrode filled with KCl (*A*).

TABLE 1. *Effects of potassium content of medium on resting potentials and slow-wave amplitude in longitudinal fibers*

Medium		Resting Potential, mv	Slow-Wave Amplitude, mv
½ K	2.3 mM	60.9	18
Normal K	4.7 mM	41.1	14.1
2 × K	9.4 mM	38.8	14.6
4 × K	18.8 mM	29.5	7.0

electrodes dipped into a low-sodium, high-potassium medium. With both types of electrode the measured resistance was constant over a range of positive current from 0.7×10^{-8} to 0.4×10^{-7} amp. Since saturated NaCl was used in the micropipettes, the contribution of electroosmosis is negligible (3). It is concluded that the enhancement of slow-wave amplitude by iontophoresis of Na^+ is not due to change in membrane potential or to alteration of electrode resistance but to increasing intracellular Na^+.

The effect of reduced chloride concentration was studied by substituting Na propionate for NaCl. After 90 min in a propionate-substituted solution, slow waves of normal amplitude and frequency were recorded and there was no change in resting potential. These results suggest that Cl^- ions do not play a significant role in the generation of slow waves.

Ouabain at 10^{-6} M or higher concentration depolarized the muscle membrane and abolished slow waves. However, at lower concentrations, slow waves were reduced or eliminated with depolarization by only one-half to two-thirds the voltage of the slow wave (Fig. 6). Figure 7 shows the time course of the effect of 10^{-7} M ouabain. Resting potential as measured from bottom of the waves was reduced from 50 to 46 mv or to the midpoint of control slow waves, but amplitude of slow waves diminished rapidly and after 20 min the slow waves were completely abolished. After as short a time as 2 min in 10^{-7} M ouabain, the amplitude was reduced to 50% of control values. Frequency of slow waves was also reduced in ouabain. At 10^{-6} M ouabain, reduction of slow waves was accompanied by enhanced spiking.

Tetrodotoxin was applied to several preparations under different recording conditions (experiments in collaboration with T. Nagai and M. Kobayashi). At concentrations of 3.8×10^{-7}–6.8×10^{-7} M (in some experiments as high as 2.4×10^{-6} M) tetrodotoxin had no observable effect on

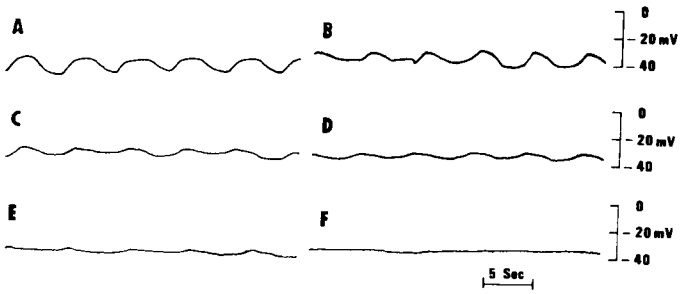

FIG. 6. Effect of ouabain (10^{-7} M) on slow waves and resting potential, intracellular recordings. *A:* control; *B:* ouabain, 3 min; *C:* 5 min; *D:* 7 min; *E:* 9 min; *F:* 11 min.

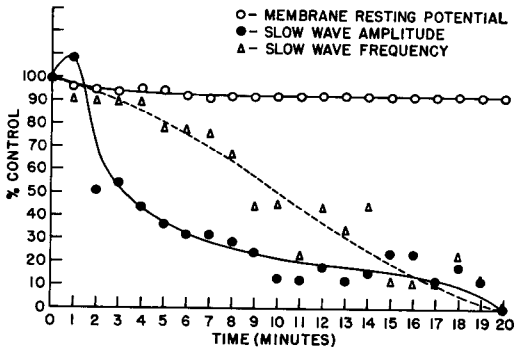

FIG. 7. Time course of effects of ouabain 10^{-7} M on resting membrane potential and amplitude and frequency of slow waves.

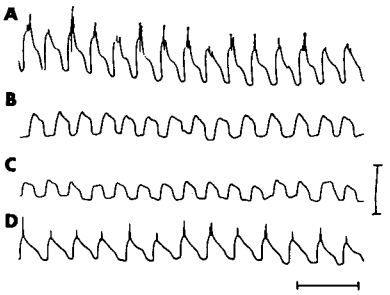

FIG. 8. Effects of reduced extracellular Ca^{2+} on spikes and slow waves (pressure electrode recordings). *A:* normal Ca^{2+} (control); *B:* 15 min; *C:* 60 min in Ca^{2+}-free Tyrode solution; *D:* normal Ca^{2+} (recovery). Calibrations: 10 sec, and 1 mv.

slow-wave amplitude or frequency or on spikes of either longitudinal or circular muscle.

When $CaCl_2$ was omitted from the Tyrode solution, slow waves continued with unaltered amplitude although the rate of rise and fall of potential was less than normal (Fig. 8) Maximal rates of rise and fall were recorded from muscle cells in Tyrode solution containing 0.85–1.7 mM Ca^{2+}. The apparent reduction in slow waves is due to a decline in prepotentials.

Spikes in longitudinal muscle. Action potentials (spikes) in longitudinal fibers are very sensitive to calcium concentration. Figure 8 illustrates the effect of Ca^{2+} depletion on slow waves and spikes as measured with pressure electrodes. After 17 min in Ca-free solution, prepotentials and spikes were completely abolished, whereas after 60 min in a Ca-free medium slow waves persisted. The time course of the effect of Ca^{2+} depletion on slow waves and spikes is shown in

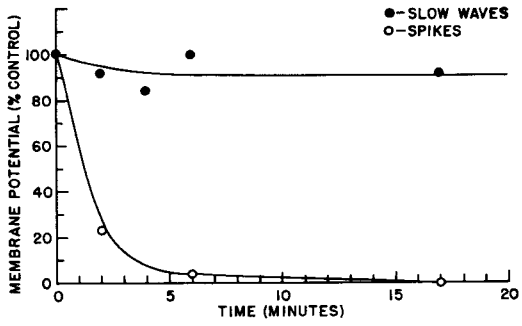

FIG. 9. Time course of effects of Ca^{2+} depletion on slow waves and spikes.

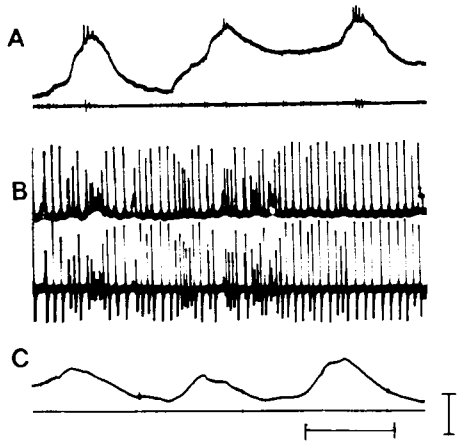

FIG. 10. Representative records showing effects of varying extracellular Ca^{2+} concentration on slow waves and spikes. Intracellular recordings with differentiated spikes below. *A:* control (normal Ca^{2+}); *B:* Ca^{2+} 2 times (3.4 mM) for 3 hr; *C:* Ca^{2+} 25% (0.43 mM) for 1 hr. Note prepotentials at base of spikes in *B*. Calibrations: 10 mv, 5 sec.

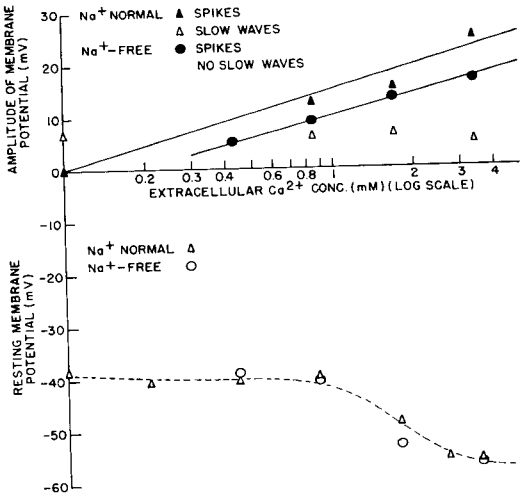

FIG. 11. Effects of varying extracellular Ca^{2+} concentration on resting membrane potentials, slow waves, and spikes as measured by intracellular microelectrodes, averages of 7–16 preparations from 4 cats.

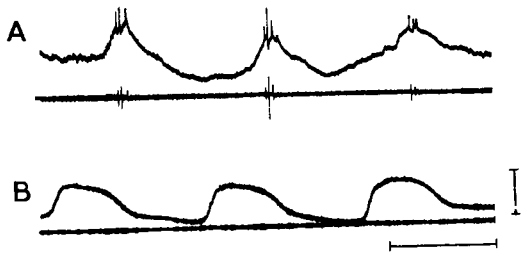

FIG. 12. Effects of Mn^{2+} on slow waves and spikes as recorded intracellularly. *A:* control; *B:* Mn^{2+} 5×10^{-7} M (15 min). Calibrations: 5 sec, 10 mv.

Fig. 9. The decline of spikes is rapid and it is evident that prepotentials and spikes are more sensitive to Ca^{2+} depletion than are slow waves.

Figure 10 shows the effects of varying extracellular Ca^{2+} concentration on slow waves and spikes as measured by intracellular microelectrodes. The upper traces show membrane potentials and the bottom traces give dv/dt or slopes of membrane-potential changes. *Record A* gives control recordings in Tyrode solution with 1.7 mM Ca^{2+}; slow waves with small spikes were recorded. After 3 hr in high-Ca^{2+} (3.4 mM) solution, large spikes at high frequency (5/sec) and with prepotentials at their initiation were recorded (Fig. 10*B*). Slow waves were virtually gone. The average maximal rates of rise and fall of action potentials were 5.5 and 3.2 v/sec. Figure 10*C* shows that in the same preparation after 1 hr in 25% Ca^{2+} (0.43 mM) Tyrode solution, only slow waves were recorded. The conversion to a "spiking state" with reduction in slow waves was seen in 10 experiments after prolonged soaking in high-Ca^{2+} Tyrode solution. Spontaneous prepotentials and spikes can, therefore, occur in the absence of slow waves, but they are not synchronized as when slow waves are present.

Action potentials were also recorded in Na^+-free solution (Tris substituted) containing different concentrations of Ca^{2+}. The averaged results of three such experiments are plotted in Fig. 11. The lower part of Fig. 11 shows the effect of Ca^{2+} on resting membrane potentials; low Ca^{2+} (0–0.85 mM) depolarized the muscle membrane slightly and high Ca^{2+} (3.4 mM) hyperpolarized it. The upper part of Fig. 11 shows that spikes varied in amplitude with $Ca^{2+}{}_o$ with a slope of 15 mv per 10-fold change in $Ca^{2+}{}_o$. The effect of calcium on spikes was similar in 133 mM NaCl and in Na-free medium as measured by the slope; the absolute level of spike recorded was higher in the normal medium because it was on the top of slow waves, whereas in Na-free medium there were no slow waves, but only spikes. The reduction in spike height in low-calcium medium is not due to a lowering of membrane potential, since the resting potential was unaffected by calcium in the range 0–0.8 mM. Tetrodotoxin had no noticeable effect on spikes.

Manganese and cobalt ions have been used as competitive inhibitors for calcium conductance changes (7). Figure 12 shows that Mn^{2+} at 5×10^{-7} M in the bath completely abolished spikes in longitudinal muscle. Cobalt was found to be even more effective and Fig. 13 shows that after 8 min exposure to Co^{2+} at 10^{-8} M, prepotentials and spikes were abolished. Recovery was incomplete after prolonged treatment with cobalt. Mn^{2+} and Co^{2+} had no effect on slow waves, even at concentrations of 10^{-4}–10^{-3} M.

To ascertain whether the membrane processes underlying the action potential are Ca^{2+} specific, three experiments were performed with 1.7 mM Sr^{2+} substituted for Ca^{2+}. Figure 14 shows microelectrode recordings for 40 min (*B*),

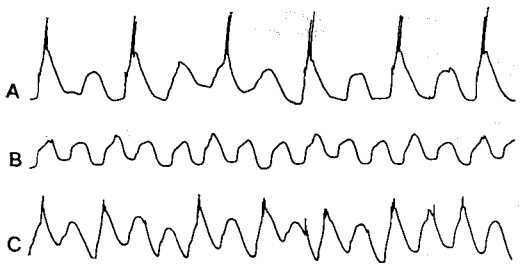

FIG. 13. Effect of Co^{2+} on slow-wave prepotentials and spikes. *A:* control; *B:* Co^{2+} 10^{-8} M (8 min); *C:* recovery in normal Tyrode solution.

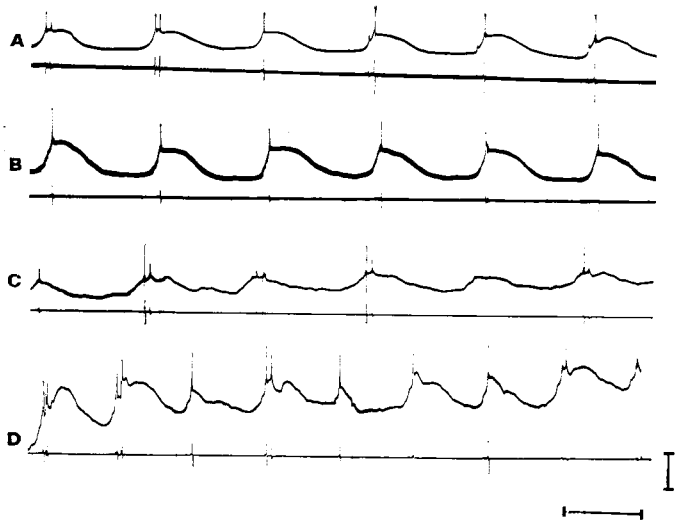

FIG. 14. Effects of substitution of strontium for calcium. *A:* control microelectrode recordings in normal Ca^{2+} Tyrode solution; *B:* Sr^{2+}-substituted solution 40 min; *C:* 60 min; *D:* recovery in normal Ca^{2+} Tyrode solution. Calibrations: 10 sec, 10 mv.

60 min in Sr-Tyrode (*C*), and after return to normal Tyrode solution (*D*). Since recordings were from different cells, amplitudes of spikes and slow waves differed slightly, but it is apparent that Sr^{2+} can be substituted for Ca^{2+} in the membrane processes underlying action-potential production. Magnesium was omitted from the Tyrode solution, it was also increased by 2 and 5 times in concentration while calcium was at normal concentration. In neither low nor high magnesium was any change in spikes or slow waves observed during 0.5 hr. However, when calcium was omitted, increased magnesium could not support spikes. Hence magnesium cannot substitute for calcium in spike production but strontium appears to be able to replace calcium.

Effects of calcium on spikes in circular muscle fibers. Figure 15 shows action potentials and local potentials elicited from strips of circular jejunal muscle fibers by electrical stimulation and recorded in media in which calcium varied from 0 to 2.55 mM. Figure 16 summarizes the effects of calcium on resting potential, on action potentials, and on rates of rise and fall of spike in circular muscle cells. In contrast to the longitudinal cells, resting potentials of circular muscle were relatively unaffected by Ca^{2+}. However, both spike height and rates of rise and fall increased to a maximum at 0.85 mM Ca^{2+} and both lower and higher concentrations reduced the action potentials. In the low-concentration

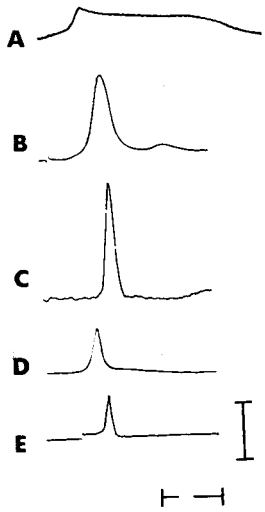

FIG. 15. Effects of varying extracellular Ca^{2+} on action potentials recorded from circular muscle cells in response to shocks. *A:* Ca^{2+} 0 mM; *B:* Ca^{2+} 0.43 mM; *C:* Ca^{2+} 0.85 mM; *D:* Ca^{2+} 1.7 mM; *E:* Ca^{2+} 2.55 mM. Calibrations: 100 msec, 10 mv.

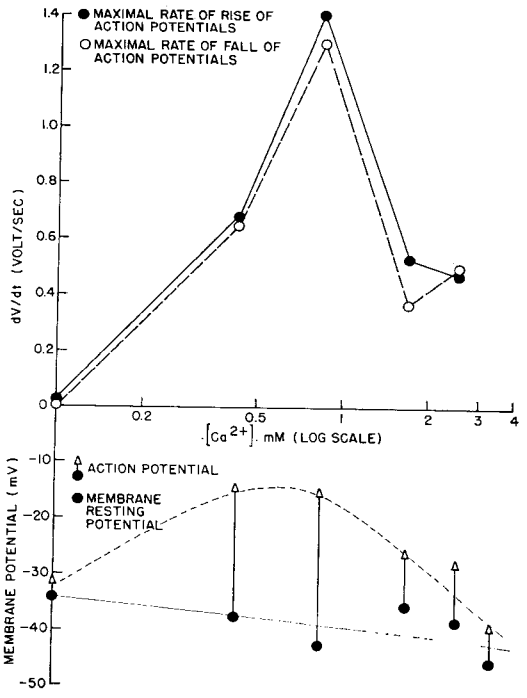

FIG. 16. Effects of varying extracellular Ca^{2+} concentration on resting membrane potentials, action potentials, rates of rise and fall of action potentials recorded from circular muscle cells, 8–10 cells per point.

range, the slope of spike amplitude in circular fibers was 33 mv per 10-fold change in $Ca^{2+}{}_o$, much steeper than in longitudinal fibers. It appears that calcium has dual effects on the membrane processes involved in action potentials from circular muscle cells.

DISCUSSION

That prepotentials and spikes of longitudinal intestinal muscle are due to increased conductance of calcium is indicated by: *1)* the elimination of these action potentials in low concentrations of calcium, *2)* the action of competitive inhibitors Mn^{2+} and Co^{2+} in very low concentrations, *3)* the

linear relation of spike height with log Ca^{2+}_o, and *4*) enhanced influx of calcium at the time of spiking (8). The change in spike height for 1 log unit change in calcium was 10 mv, somewhat less than 17 mv found by Tamai and Prosser (19), but similar to the slope of 8 mv for taenia (2). The evidence for calcium involvement in action potentials is similar to that for taenia coli (12, 15), vas deferens (1), and barnacle muscle (7) where calcium spikes occur. Intestine is apparently different from uterus where spikes may involve enhanced Na^+ conductance (13) and from ureter where sodium and calcium appear to move in parallel (10). At high concentrations of calcium, some hyperpolarization was observed in longitudinal but not in circular muscle; this may reflect changes in p*K*. In addition to calcium conductance associated with spikes, variations in external calcium may alter membrane resistance. In circular muscle, spikes are absent in a calcium-free medium, and both amplitude of spike and rates of rise and fall are maximal at an intermediate concentration. It is possible that, in circular muscle, in addition to an apparent conductance change in calcium evident at lower concentrations, there may also be a reduced permeability of the membrane at higher concentrations of calcium which would counteract increased conductance during a spike. It is impossible to make meaningful calculations of concentration gradients because of ignorance of calcium-binding at the membrane.

The state of intense spiking after long soaking in high calcium concentrations has also been reported for taenia coli (12). Similar enhanced spiking is noted after ouabain treatment in longitudinal muscle of cat stomach (16). These effects suggest an interaction between areas of calcium conductance change and of the sodium flux associated with slow waves such that at high concentrations, the calcium effect becomes dominant.

Evidence that the slow waves result from rhythmic efflux of sodium is as follows: *1*) slow waves (but not spikes) are lost in a sodium-free medium, *2*) slow-wave amplitude varies with log Na^+_o with a slope of 10 mv and this is the same at two calcium concentrations, *3*) slow waves are eliminated by ouabain in concentrations which do not depolarize by as much as the slow-wave amplitude, *4*) amplitude is increased when sodium (but not potassium) is iontophoresed into the cell interior, and *5*) efflux of radioactive sodium is at a peak in the early part of the polarizing phase of a slow wave (8). Similar inhibition of slow waves by ouabain and by metabolic inhibitors was seen in vivo (3). Similar enhancement of an electrogenic sodium pump by an increase in intracellular sodium has been observed in *Helix* ganglion cells (9) in posttetanic hyperpolarization of stretch receptors (14), and in heart muscle recovering from cold storage (18). The "true" resting potential appears to be near the membrane potential at the peak of the slow wave.

Frequency of slow waves is relatively unaffected by sodium concentration (Tris replacement) but is highly temperature sensitive (8). However, frequency may be reduced by ouabain and by replacement of sodium by lithium, hence there must be some feedback from the electrogenesis to the pacemaker process, which is presumed to be metabolic. The difference between Li^+ and $Tris^+$ as substitutes for Na^+ may be that Li^+ may be able to replace intracellular Na^+ but may not be pumped, whereas $Tris^+$ may not enter the cell; both permit a reduction in intracellular concentration of Na^+.

The data of this and the accompanying paper (8) suggest that the depolarization phase of the slow wave is due to influx of sodium; this inward current of depolarization presumably provides the basis for the known conduction of slow waves (17). The repolarization phase appears to be due, at least in part, to a rhythmic active extrusion of sodium ions by a ouabain-sensitive pump.

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