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Original Article

The effect of calcium channels blockade on slow-wave distribution in the electrophysiological model of human gastric wall smooth muscle cells

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ABSTRACT

Introduction: Two of the most important ion channels in the smooth muscle membrane are L-type and T-type calcium channels. L-type calcium channels are responsible for smooth muscle contraction, while T-type calcium channels are involved in cell membrane depolarization.

Methods: In this study, a model consisting of 1200 cells was used to simulate the smooth muscle of the gastric wall. The paper explores the effects of blocking 10%, 50%, 90%, and 100% of L-type and T-type calcium channels on the spatiotemporal wavefront propagation in human gastric wall smooth muscle cells, simulated separately.

Results: The results showed that complete blockage had the most significant effect on the slow-wave. Blockage of the L-type calcium channel led to a reduction of -3.4% and -0.8% in the membrane potential during the spike and plateau phases, respectively. The T-type calcium channel reduced the spike and resting membrane potential by -1.8% and -0.9%, respectively. In addition, the L-type calcium channel exhibited a greater impact on reducing muscle contraction compared to the T-type calcium channel. This suggests that higher blockage of calcium channels led to decreased membrane potential during slow-wave phases and reduced muscle contraction, compared to the physiological state.

Conclusion: Blocking ion channels in electrophysiological models can potentially help control gastrointestinal tract motility disorders and smooth muscle contraction.

Keywords:
Stomach
Smooth Muscle Cell
Slow-wave
Calcium Channel Blockers
Electrophysiology

Introduction

Smooth muscle cells play a vital role in the contractile and motility functions of the Gastrointestinal (GI) Tract. Impaired ion channel function leads to a lack of rhythmic and regular muscle contractions in the human GI tract (Jung et al, 2012; Radulovic et al, 2015). An increase in intracellular calcium is (Jung et al, 2012) one of the causes of GI smooth muscle contractions. Depolar-

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ization allows calcium ions to enter the cell membrane, initiating contraction (Evans and Mangel, 2010). The smooth muscles of the GI tract contain voltage-sensitive L-type and T-type calcium channels. T-type calcium channel is sensitive to mibefradil, while the L-type calcium channel is sensitive to dihydropyridine and nifedipine. The L-type calcium channel provides the calcium required for smooth muscle contraction while the T-type calcium channel depolarizes the cell membrane and activates the interstitial pacemaker cells of Cajal (Beyder and Farrugia, 2012; Chul Kim et al, 2002; Radulovic et al, 2015). Dysfunction of smooth muscle calcium channels leads to various diseases such as dysphagia, Brugada syndrome, paralytic ileus and colon, QT syndrome, and GI dysmotility in humans (Hedley et al, 2009; Radulovic et al, 2015; Wegener et al, 2006).

Some researchers have found that the smooth muscles of the GI tract do not exhibit contractile activity when in contact with calcium-free solutions. This effect has been observed in the smooth muscles of the cat‘s stomach, rat intestine, guinea pig ileum, toad stomach, and rat colon when exposed to calcium-free solutions (Aloamaka et al, 1984; Bayginov et al, 1989; Evans and Mangel, 2010; Nasu et al, 1995; Shinohara and Kosaka 1984; Zhou et al, 2008). These experiments highlight the importance of calcium ions in smooth muscle contraction.

Therefore, researchers have studied the effects of calcium ions in different parts of the GI tract. Calcium ions play a crucial role in the smooth muscle contraction function of the GI tract (Evans and Mangel, 2010). The effect of calcium current blockage on L-type and T-type calcium channels was investigated in a mathematical model of the human colon (Yeoh et al, 2017). The inhibition of calcium channels in the production and propagation of slow-waves was examined in the stomach (Van Helden et al, 2010). Changes in the slow-waves using sensitivity analysis and blocking the L-type calcium channel in the electrophysiological model were studied in the human jejunum (Poh et al, 2012). A similar study showed that the T-type calcium channel does not play a significant role in spontaneous pacemaker and contraction (To et al, 2020). Calcium currents and intracellular calcium concentrations in the human stomach were simulated and the effects of calcium channel blockers were examined (Corrias and Buist, 2008; Corrias and Buist,2007). The effect of calcium channels on gastrointestinal immobility was investigated in patients with spinal cord injury (Radulovic et al, 2015).

In this research, unlike previous studies that presented cell models of the GI tract as single cells, modeling was done on a set of gastric cells, considering their connections with each other through gap junctions. The paper investigates the effect of calcium channel function on the slow-wave distribution in human gastric wall smooth muscle (hGWSM) cells. Computational modeling in electrophysiological studies, especially in the heart (Blanc 2002; Whittaker et al, 2020), and the role of calcium channels in health or heart disease (Kushner et al, 2019) have provided new horizons for researchers. It is expected that with the development of such studies in the electrophysiology of the GI tract, researchers will achieve achievements similar to those in the heart. Electrophysiological modeling significantly reduces the cost and duration of laboratory studies, and allows non-invasive stimulation and investigation of cell and tissue conditions under different circumstances. Considering the importance of calcium ions in the contractile activity and motility pattern of GI smooth muscle, the study aims to evaluate the effect of calcium channels blockade on the distribution and propagation of the slow-wave in the electrophysiological model of human gastric wall smooth muscle cells.

Materials and methods

The Hodgkin-Huxley approach was used to simulate the changes in the gastric cell membrane potential (V_m), over time. Based on this approach, the cell membrane is assumed to be like an electric circuit, and its potential changes depend on the ion current, the stimulus current, and the cell capacitance (Hodgkin and Huxley, 1952). In Eq. (1), capacitance (C_m) and initial resting potential of the gastric cell membrane were chosen to be 77pF and -70mV, respectively (Corrias and Buist 2007).

$$\frac{dV_m}{dt} = -\frac{1}{C_m}(I_{ion} + I_{stimulation}) \qquad (1)$$

To simulate the current of the gastric cell model (I_{ion}), due to the formation of different parts of the GI tract from smooth muscle cells, and almost identical ion currents, the equation of the colon cell current (Eq. (2)) was used (Yeoh et al, 2017).

$$I_{ion} = I_{Ca-L} + I_{Ca-T} + I_{Kni} + I_{Kfi} + I_{Na} + I_{NCX} + I_{NaK} + I_{NSLC} \qquad (2)$$

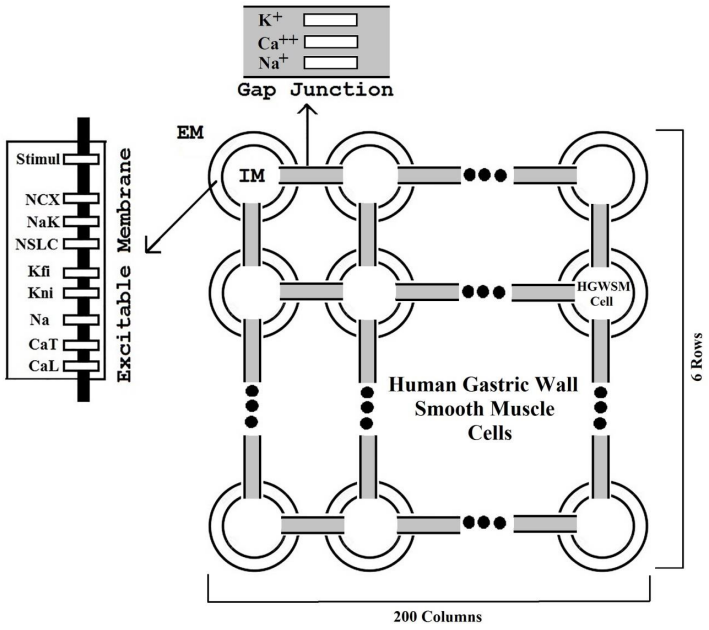

FIGURE 1. Cell viability assay of cells treated with LBS after 24 and 48 h. A). Cytotoxic effects of different concentrations of LBS on MCF-7 cell line. B) LBS cytotoxicity at different concentrations on MDA-MB-231. Results represent the means ± SE of three different experiments. n=3. (P<0.05:*, P<0.01:**, P<0.001: ***).

Where $I_{Ca\text{-}L}$ is the L-type calcium current, $I_{Ca\text{-}T}$ is the T-type calcium current, I_{Kni} is the non-inactivating potassium current, I_{Kfi} is the fast-inactivating potassium current, I_{Na} is the sodium current, I_{NCX} is the sodium-calcium exchanger current, I_{NaK} is the sodium-potassium pump, and I_{NSLC} is the non-selective leakage current. The L-type and T-type calcium channel current equations are shown in Eqs. (3) and (4), respectively (Corrias and Buist 2007; Poh et al, 2012; Yeoh et al, 2017).

$$I_{Ca-L} = G_{CaL} * d_{CaL} * f_{CaL} * (V_m - E_{Ca}) \quad (3)$$

$$I_{Ca-T} = G_{CaT} * d_{CaT} * f_{CaT} * (V_m - E_{Ca}) \quad (4)$$

Where G is the maximum conductance, d is the voltage-dependent activation, f is the voltage-dependent inactivation, V_m is the membrane potential, E_{ca} and is the Nernst potential for calcium ions.

The electrophysiological model of the colon cell (Yeoh et al, 2017) was used as a basis to obtain the gastric cell model. The reasons for using the colon model as a basic model for the stomach cell model were the formation of the GI tract from smooth muscles, the presence of similar ion channels, and the similarity of slow-wave phases. Another reason was the closer concentration values of ions in both cells. Then this model was optimized using the electrophysiological characteristics of gastric cells and considering the parameters of ion channel gating from the corrias model (Corrias and Buist 2008; Corrias and Buist, 2007). The electrophysiological properties of gastric cells were considered to adapt and optimize this model (Corrias and Buist, 2007). Intracellular sodium and potassium concentrations were chosen to be 10 and 164mM, respectively. Extracellular potassium, sodium, and calcium concentrations were chosen to be 5.9, 137, and 2.5mM, respectively. The volume, surface area, capacitance, and membrane potential of the stomach cell were chosen to be 3.5 pL, 41e-6 cm^2, 77 pF, and -70 mV, respectively (Corrias and Buist, 2007).

The slow-wave is generated by the pacemaker cells and the electrophysiological interactions of the cells with the extracellular environment through the excitable membrane. The electrophysiological wave generated is passed through the surrounding cells through gap junctions (Brandstaeter et al, 2018). The propagation of a slow-wave at the surface of the gastric wall causes its smooth muscles to contract. The cells were arranged in 200 columns and 6 rows (Figure 1) to simulate hGWSM. The excitable membrane of each cell is assumed to interact with the extracellular environment (interstitial fluid) with ion channels. Also, to model the ion interactions of cells with each other, gap junctions are considered

TABLE 1: The values of the selected parameters of the slow-wave profile in different states of L-type calcium channel blockage compared to the physiological state

Blockage (%)	MS (mV)	MP (mV)	MR (mV)
10	-36.84 (-0.3%)	-40.95 (-0.1%)	-70.07 (-0.01%)
50	-37.32 (-1.6%)	-41.07 (-0.4%)	-70.08 (-0.03%)
90	-37.83 (-3.1%)	-41.20 (-0.7%)	-70.09 (-0.04%)
100	-37.96 (-3.4%)	-41.23 (-0.8%)	-70.10 (-0.06%)

MS=Max Spike Value; MP=Max Plateau Value; MR=Max Rest Value; The percentage of parameter changes comparative to the physiological state is shown in parentheses.

between the two adjacent cells.

Using this model, slow-wave distribution and propagation can be shown in hGWSM cells. In this model, to investigate the effect of L-type and T-type calcium channels and pharmacological and pathological interventions on the slow-wave, the conduction of calcium channels was changed separately. First, the channels are assumed to be normally conductive, then 10, 50, 90, and 100% channel blockage is applied, respectively. Other researchers have used similar methods to block ion channels (Poh et al, 2012). Finally, each state was compared to the physiological state. The results were described based on the changes of the slow-wave phases in the physiological and blocked state. This paper is based on the method previously presented for the effect of potassium channels on the slow-wave (Taghadosi et al, 2021).

Results

The model used in this paper was based on the colon model (Yeoh et al, 2017) and the electrophysiological characteristics of the human stomach (Corrias and Buist, 2007). In the physiological state, the potential values of the start, maximum spike, maximum plateau, and maximum resting potential were -70.06, -36.72, -40.92, and -70.06 mV, respectively. One slow-wave cycle occurred in about 21.4 seconds, and three slow-wave cycles took about 64 seconds (approximately 2.8 cycles-per-minute). These results are shown in Figures 2a, 2b. Simulations of slow-wave distribution in hGWSM cells are shown in Figure 2c in the physiological state. This phenomenon was displayed in three different time intervals in the gastric body: a) at the beginning of the body (BoB), b) in the middle of the body (MoB), and c) at the end of the body (EoB). The initial potential, depolarization, spike, plateau, repolarization, and resting phases are visible in this wave. After simulating the slow-wave distribution on the physiological state of the gastric wall in Figure 2c, the effects of channel blockers and pharmacological factors can be applied to the model, and the resulting changes can be observed. Using this method, the changes in different phases of the slow-wave can be investigated using blockers.

In this study, five steps were considered to investigate the effect of L-type calcium channel blockade. Here, these effects were simulated by reducing channel conduction. 1) Physiological state. 2) 10% channel blockage. 3) 50% channel blockage. 4) 90% channel blockage. 5) Complete (100%) channel blockage. These changes are shown on the selected slow-wave parameters [Max Spike Value (MS), Max Plateau Value (MP), and Max Rest Value (MR)] in Table 1. The results showed that with increasing blockage of the L-type calcium channel compared to the physiological state, the potential value of MS, MP, and MR decreased. The most changes in the complete blockage state were a 3.4% decrease in MS, a 0.8% decrease in MP, and a 0.06% decrease in MR (Table 1).

The physiological slow-wave curve is shown as a dotted line in Figures 3a, 3b. Also, half and full blockage of the L-type calcium channel were shown by the dashed line and the solid line, respectively. Figures 3a, 3b showed that the potential value of the spike and plateau in the state of complete blockage had the greatest reduction. These changes were not significant in other slow-wave phases. In addition to single-cell results, the effect of complete blockage in the L-type calcium channel on the spatiotemporal wavefront distribution in hGWSM cells was also modeled. The range of hGWSM cells from the beginning of the body to the end of the body was considered. The first region was the BoB, the second region was the MoB, and the third region was the EoB. The wave propagation in the MoB in complete blockage of the L-type calcium channel is shown in Fig-

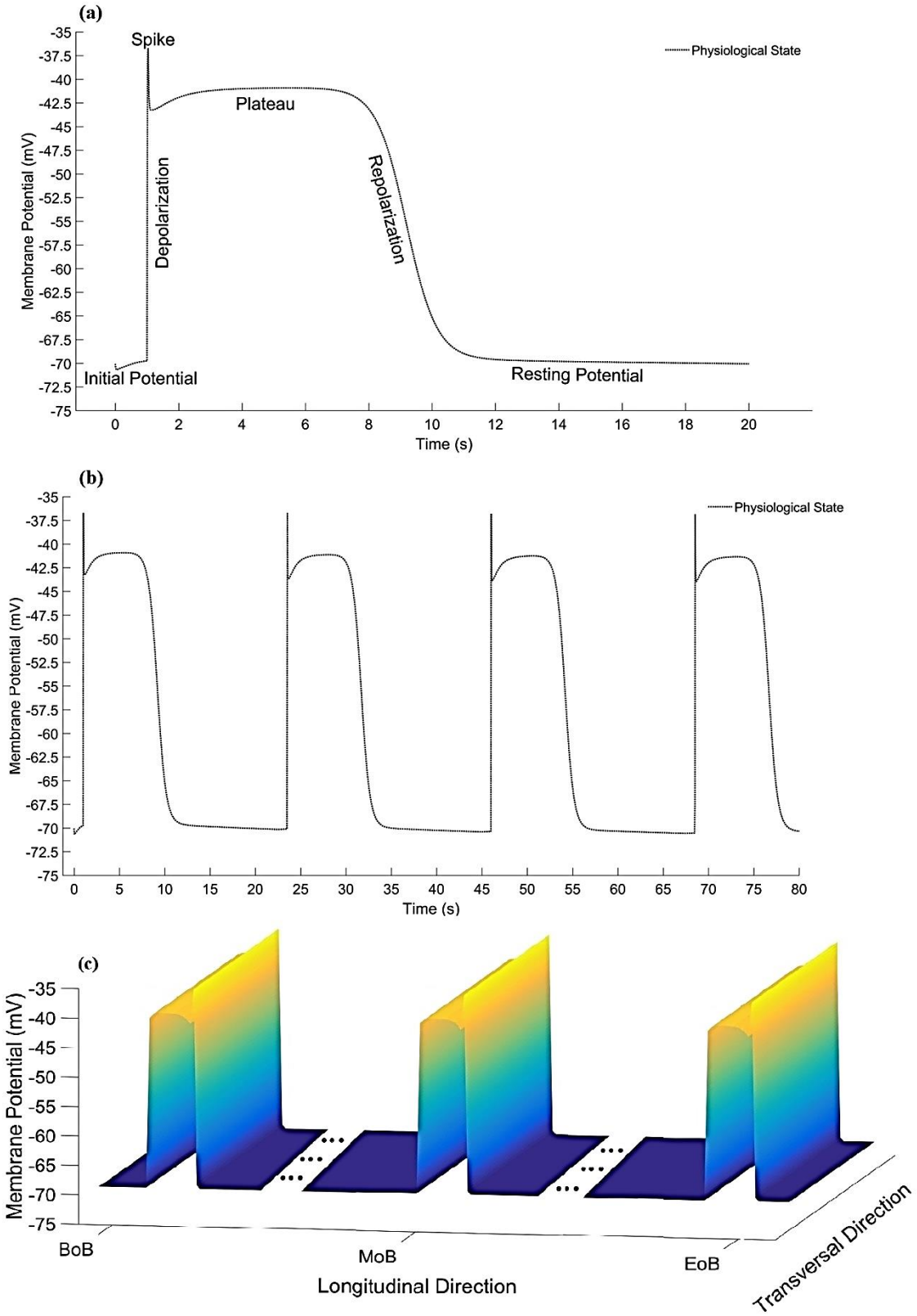

FIGURE 2. Simulation of physiological slow-wave profile in a) One cycle, b) Four cycles, and c) hGWSM cells in three temporal intervals: Beginning of the body (BoB), Middle of the body (MoB), and End of the body (EoB).

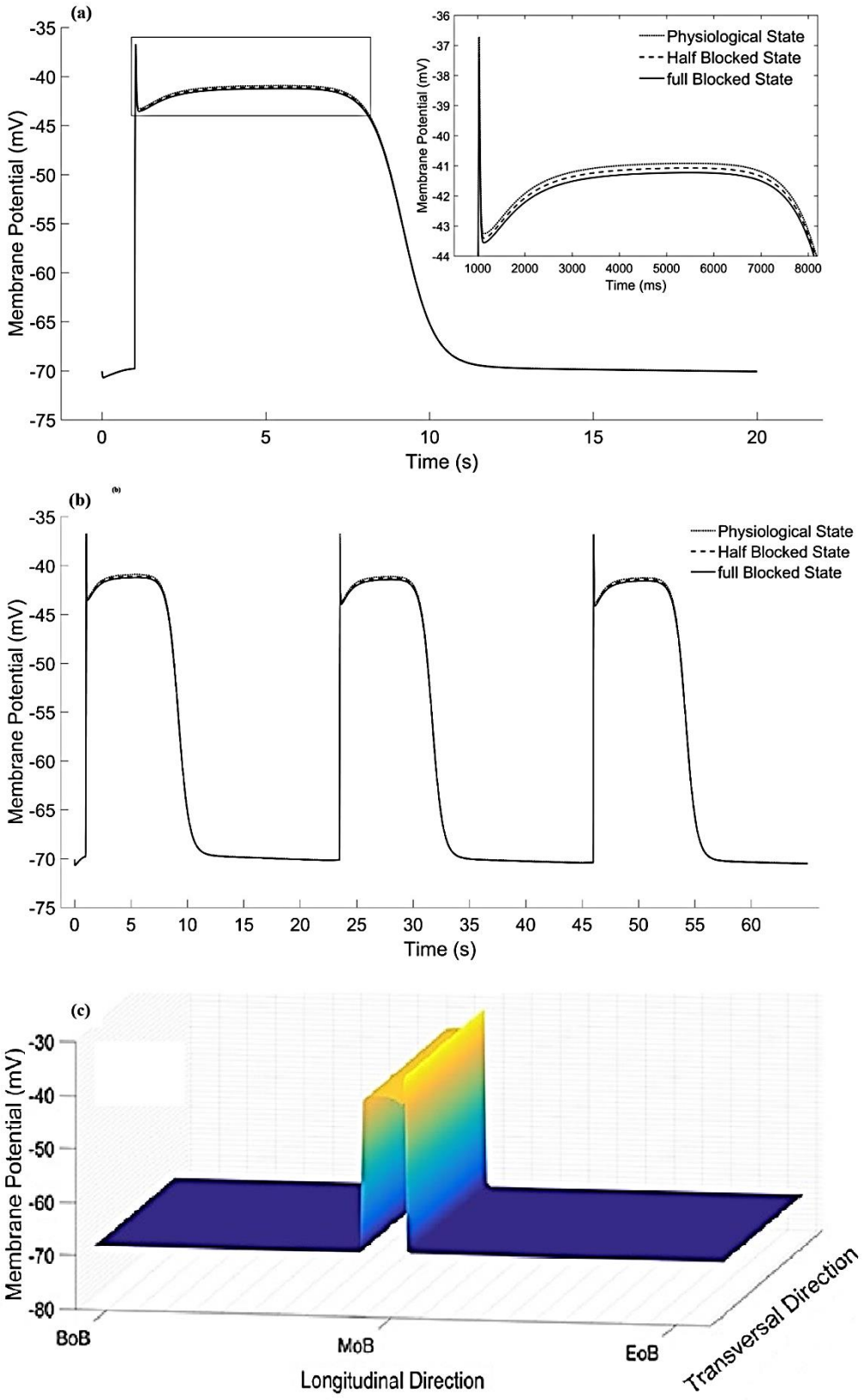

FIGURE 3. Simulation of L-type calcium channel blockers on slow-wave profile in a) One cycle, b) Three cycles. Physiological State (dotted line), Half Blocked State (dashed line), Full Blocked State (solid line) and c) hGWSM cells in middle of the body (MoB) in the full blocked state.

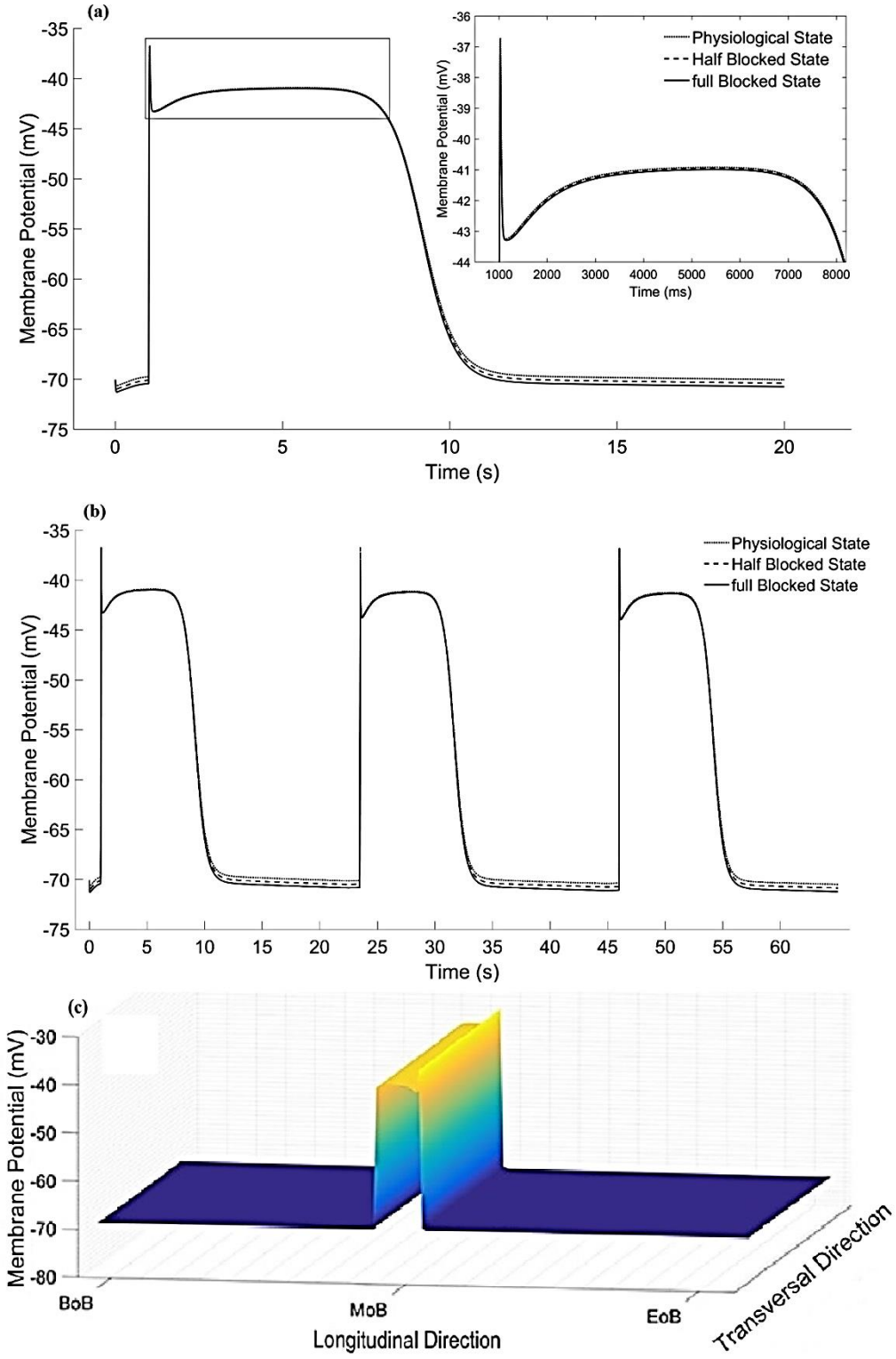

FIGURE 4. Simulation of T-type calcium channel blockers on slow-wave profile in a) One cycle, b) Three cycles. Physiological State (dotted line), Half Blocked State (dashed line), Full Blocked State (solid line) and c) hGWSM cells in middle of the body (MoB) in the full blocked state.

TABLE 2: The values of the selected parameters of the slow-wave profile in different states of T-type calcium channel blockage compared to the physiological state

Blockage (%)	MS (mV)	MP (mV)	MR (mV)
10	-36.79 (-0.2%)	-40.93 (-0.02%)	-70.13 (-0.1%)
50	-37.06 (-0.9%)	-40.96 (-0.1%)	-70.41 (-0.4%)
90	-37.31 (-1.6%)	-40.99 (-0.2%)	-70.69 (-0.8%)
100	-37.37 (-1.8%)	-41.1 (-0.4%)	-70.76 (-0.9%)

MS=Max Spike Value; MP=Max Plateau Value; MR=Max Rest Value; The percentage of parameter changes comparative to the physiological state is shown in parentheses.

ure 3c.

Similarly, five steps were considered to evaluate the effect of T-type calcium channel blockage. The same selected slow-wave parameters (MS, MP, and MR) were used to ensure comparability between the two types of blocking channels. These parameters are shown in Table 2. With the gradual increase in blockage of the T-type calcium channel, the membrane potential during the spike, plateau, and rest phases decreased compared to the physiological state. The most significant changes in the complete blockage state were a 1.8% decrease in MS, a 0.4% decrease in MP, and a 0.9% decrease in MR (Table 2).

The half-block (dashed line) and full-blocked (solid line) curves of the T-type calcium channel compared to the physiological state (dotted line) are shown in figures 4a, 4b. According to Figures 4a, 4b, it was clear that the amount of initial potential, spike, and rest in the state of complete blockage had the greatest decrease, and in the plateau phase, the decrease was less than 0.4%. As the blockage increased from physiological to half and then to full, the curves shifted to lower values. The simulation of spatiotemporal wavefront propagation in hGWSM cells in the T-type calcium channel in the physiological state and complete blockage was performed. The wave propagation in the MoB in complete blockage of the T-type calcium channel along the longitudinal hGWSM is shown in figure 4c.

Discussion

So far, limited studies have been conducted in the field of mathematical modeling of the GI tract. This may be due to the complexity and diversity of cells and smooth muscle layers. For this reason, this study aims to expand modeling in the field of the GI tract and especially the stomach. The hGWSM cell model was simulated based on the colon model (Yeoh et al, 2017) and considering the electrophysiological characteristics of stomach cells (Corrias and Buist, 2008;2007). The hGWSM model was made by connecting 1200 cells and includes the following features: 1) Considering the excitable membrane for each cell for interactions between the intracellular and extracellular environment. 2) Considering ionic, pump, exchanger, and stimulation currents. 3) The presence of gap junctions between each cell with adjacent cells for electrophysiological interactions between cells.

The findings of the research showed that the values of the membrane potential in different phases of the slow-wave are similar to the human stomach study (Corrias and Buist, 2007) and are also consistent with experimental findings from the canine gastric antrum (Ward et al, 2004). The simulation results are consistent with the experimental findings in terms of slow-wave shape and amplitude (Huizinga, 2001; Rhee et al, 2011; Sanders et al, 2006; Ward et al, 2004). These results are also in agreement with experimental findings on the duration of slow-wave (3 cpm) (Hocke et al, 2009; Miedema et al, 1992; O'Grady et al, 2010; Sha et al, 2009).

Due to the importance of calcium ions in gastric smooth muscle cells, the function of L-type and T-type calcium channels in slow-wave production and gastric contractions was considered. The calcium channels (L-type and T-type) blockade was applied in a step-by-step manner and increased gradually from the physiological state to 10, 50, 90, and 100% channel blockage. The greatest effect of blockage of both types of calcium channels was observed on the spike phase, which seems to be related to the muscle contraction factor. Muscle contraction may be reduced by further blocking calcium channels (Evans and Mangel, 2010; Radulovic et al, 2015). Comparing the blockage of two calcium channels, it can be concluded that the T-type calcium channel affects the initial membrane potential and the spike potential in the depolarization phase, while the L-type

calcium channel has a greater effect on the spike and the plateau phases. These results are also in agreement with experimental findings from the murine proximal colon (Hotta et al, 2007).

Membrane potential increases by halving the conductivity of the L-type calcium channel in the canine colon (Franck et al, 1999) and human colon model (Yeoh et al, 2017), which is not consistent with the results of this study. This difference was also evident by blocking the T-type calcium channel in the human colon model (Yeoh et al, 2017) and the dog colon (Huizinga et al, 1991). The only similarity was the small changes in the plateau phase due to the rapid inactivation of the T-type calcium current (Yeoh et al, 2017). The results of 50% blockage of the L-type calcium channel are consistent with the results of research on the human jejunum (Poh et al, 2012) and reduce the membrane potential. It has been specified that the use of nifedipine (L-type calcium channel blocker) reduces the duration of the plateau phase, and the use of mibefradil (T-type calcium channel blocker) reduces the spike rate in the depolarization phase in the rat colon (Hotta et al, 2007). In a similar study on the human stomach, it was shown that blocking the T-type calcium channel using nickel reduces the amplitude and frequency of the slow-wave and increases the duration of the plateau phase (Rhee et al, 2011). This may be due to the blocking of calcium ions from entering the cell.

The results showed that smooth muscle contraction depends on the influx of calcium ions into the cell membrane through the L-type calcium channel. Increased intracellular calcium causes contraction of GI tract smooth muscles (Evans and Mangel, 2010). The entry of calcium ions into the membrane is reduced by blocking the L-type calcium channel. This blockage reduces the amplitude of the slow-wave and the muscle contraction. Previous studies have identified diltiazem, verapamil, nifedipine, and nicardipine as L-type calcium channel blockers (Hotta et al, 2007; Lees-Green et al, 2011; Seth and Seth, 1991; Suzuki and Hirst, 1999; Yoneda et al, 2002). This method can improve motility disorders in the stomach wall, intestine, colon, and GI tract (Annaházi et al, 2014; Rychter et al, 2014; Zhou et al, 2019).

It is recommended to block L-type and T-type calcium channels simultaneously to study tissue behavior due to channel blockage. In addition to the membrane potential values, the duration of the slow-wave phases and the depolarization and repolarization rates should also be considered, and other ion channels can also be blocked for more details. By increasing the number of cells and considering electrophysiological parameters, the accuracy of computational models can be increased and evaluated the behavior of the tissue under certain conditions in more detail. By generalizing this method, more accurate and practical models for the GI tract can be modeled in 2D and 3D with considering more details (Taghadosi et al, 2022a; Taghadosi et al, 2022b), and different models can be presented like the heart, including the electrophysiological model, the three-dimensional model, and the finite element model (Du et al, 2018; Kushner et al, 2019; Whittaker et al, 2020). Also, the need to design and use implantable electronic devices within the smooth muscles of the GI tract is strongly recommended. Finally, the electrical activity of the smooth muscles can be recorded in the event of movement disorders, and implantable stimulus or pharmacological factors can be considered to eliminate these disorders. Recently, electronic devices have been developed to control the electrophysiological and motility disorders of the stomach (Farajidavar, 2018) and help distribute electrophysiological waves using electrical stimulation (Carson et al, 2021; Du et al, 2020; Lin and Chen, 2017).

Conclusion

L-type and T-type calcium channels play an important role in gastric smooth muscle contractions. The results of this study showed that the effect of L-type channels on muscle contraction is greater than T-type channels. By blocking these channels and preventing the entry of calcium ions, the phases of spike and plateau can be optimized in a slow-wave, reducing muscle contraction and motility disorders of the stomach wall. Finally, Using the electrophysiological model of cells, the role of ions can be investigated in regulating the potential of cell membranes and muscle contractions non-invasively and with the help of pharmacological agents can reduce GI motility disorders.

Conflict of interest

The authors have no conflict of interest regarding the manuscript.

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Ethics approval

There were no human or animal subjects in this study.

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