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MODELLING OF THE EFFECT OF METOCLOPRAMIDE ON THE BIOMECHANICS OF THE GASTROPARETIC HUMAN STOMACH

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ABSTRACT

A computational model was used to study the effect of metoclopramide on the biomechanics of the gastroparetic human stomach. The results show that metoclopramide can reinstate focally normal patterns of myoelectrical and mechanical activity at discrete sites of the stomach. The drug, however, neither organizes nor sustains a coordinated propagation of electromechanical waves in the organ. The integrity and functionality of the regulatory system is essential in achieving the desirable pharmacological effect, i.e., the synchronization and restoration of the rhythmicity of slow waves and phasic (propulsive) contractions.

Keywords: biomechanics, gastroparesis, human stomach, metoclopramide.

INTRODUCTION

Gastroparesis is manifested by altered gastric movements in the form of either atony, or hypo or hypermotility. These are a result of pathological changes in the anatomy of the organ, the myenteric nervous system, interstitial cells of Cajal (ICC) and the interplay amongst them. The treatment of gastroparesis relies mainly on the use of metoclopramide, the only US FDA-approved medication. *In vitro* investigations of the effect of metoclopramide on isolated specimens from the human stomach have shown that the drug facilitates cholinergic neurotransmission induced by subtle stimulation of 5-HT₄ receptors. Transmembrane 5-HT₄ receptors are a part of the G-protein coupled receptor family positively linked to the stimulatory G_s protein pathway. These receptors are expressed on smooth muscle cells (SMCs). The resultant effects of their activation are: an increase in Na⁺, BK_{Ca}, Ca²⁺ and a decrease in K⁺ ion channel permeability; enhanced neuronal acetylcholine (ACh) release; strengthened contractility. The aim of this study is to analyze the effect of metoclopramide on the biomechanics of the gastroparetic human stomach.

The mathematical model of the gastroparetic human stomach and numerical algorithm are described elsewhere [1]. It is noteworthy that structural damages are incurred in the myenteric nervous plexus. SMCs, although entangled in the network of excessive collagen fibers, sustain their functionality and react to direct 5-HT₄ receptor stimulation. Viable ICC and motor neurons discharge at their natural frequencies with a phase shift (time-disintegrated).

RESULTS AND CONCLUSION

The effect of metoclopramide on the myoelectrical activity of the SIP/ganglion unit is dose-dependent. Acting conjointly with endogenous ACh, the drug: reduces the amplitude of Ca²⁺; intensifies BK_{Ca}, and decreases K⁺,Cl⁻ ion currents; depolarizes the resting membrane

potential of SMCs; decreases the amplitude, and restores and stabilizes the rhythmicity of slow waves; induces phasic bursting of spikes at a constant frequency of 2.5 Hz. At low concentrations the drug initiates phasic contractions, whilst at moderate concentrations tonic-type contractions is produced. Myoelectrical and phasic contractile activity cease at high concentrations.

The reaction of the SIP/ganglion unit to the drug changes if its morphofunctional integrity is preserved, along with the ability of the motor neuron to respond directly to the stimulation of somatic and presynaptic nerve-terminal 5-HT₄ receptors. Metoclopramide acting specifically at neuronal 5-HT₄ receptors increases 2-fold the frequency of discharges by the motor neuron. The motor neuron entrains ICC and synchronizes oscillatory myoelectrical activity of the stomach. A larger amount of free ACh is released and regular rhythmic slow waves of high amplitude and spikes are generated. SMCs produce strong regular phasic contractions. The recorded amplitude of total force is 12.27 mN/cm with max*T*, 20 mN/cm.

The following concomitant stimulation of 5-HT₄ receptors on SMCs at a low dose sustains phasic contractility with a positive effect on the strength, max*T* = 22 mN/cm. The qualitative and quantitative effects of metoclopramide on the myoelectrical activity of the stomach are similar to those described above. At high concentrations the drug changes the pattern of spiking from phasic bursting to beating and ceases regular phasic contractions. SMCs develop a long-lasting contraction of max*T* = 26 mN/cm.

The results of numerical simulations demonstrate that in the case of structural disarrangement within and between the MP and ICC network, metoclopramide can reinstate focally normal patterns of myoelectrical and mechanical activity at discrete sites of the stomach. Metoclopramide does not organize and sustain a coordinated propagation of electromechanical waves in the organ. The integrity and functionality of the myenteric nervous plexus is essential in achieving the desirable pharmacological effect. Only then does the drug synchronizing discharges of inter- and motor neurons, entrain firing of detached ICC, and restore the rhythmicity of occurrence and propagation of slow waves and phasic (propulsive) contractions (Figure 1).

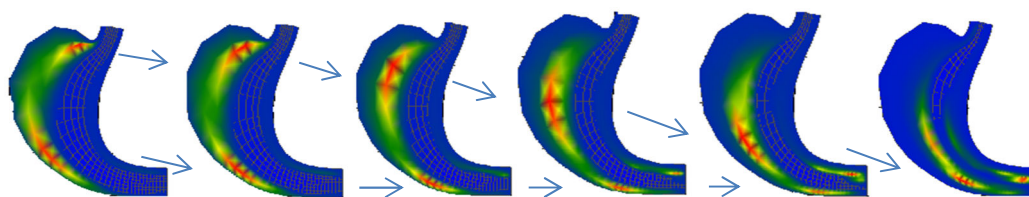


Fig. 1 - Synchronization of myoelectrical activity in the stomach by metoclopramide

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