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CONTRACTILE ACTIVITY OF THE HUMAN STOMACH UNDER COMPLEX STIMULATION

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ABSTRACT

The effect of multiple co-transmission by acetylcholine (ACh) and substance P (SP) on the biomechanics of the antrum of the human stomach has been investigated *in silico*. The results demonstrate the intense excitatory effect of ACh and SP on the firing rate of interstitial cells of Cajal on myoelectrical activity of the smooth muscle syncytium, and on contractility of the antrum. Quantitative analysis of co-transmission by ACh and SP and the regulation of antral gastric motility provide an insight into the hidden mechanisms on physiological activity and suggest pathological mechanisms at work in the development of, e.g., gastric arrhythmia, retrograde peristalsis, etc.

Keywords: human stomach, acetylcholine, substance P, biomechanics, contractility.

INTRODUCTION

Acetylcholine (ACh) is a ubiquoutous neurotransmitter in the stomach. It is released upon stimulation by electrical stimulation and it exerts metabotropic and ionotropic responses by binding to muscarinic G - protein coupled receptors linked to the phospholipase C (PLC) and the activation of ligand gated Ca^{2+} - channels. The result is the generation of fast excitatory postsynaptic potentials (EPSP). Substance P (SP) is a neuropeptide that exhibits a plethora of effects including the production of prolonged EPSP and contraction/relaxation of gastric smooth muscle cells (SMCs), by binding selectively to two distinct ionotropic, NK_1, and metabotropic, NK_3, receptors. Both receptors are members of the G-protein coupled receptor family and employ the IP_3 as well as adenylate cyclase - 3'5' adenosine cyclic monophosphate and protein kinase C signaling pathways. These enhance the release of Ca^{2+} from the sarcoplasmic reticulum through ryanodine receptor channels and its influx by opening transmembrane L-type Ca^{2+} channels on SMCs. ACh and SP are co-stored in the primary sensory and motor neurons. In this study it is assumed that: i) ACh release precedes SP, ii) ACh and SP interact synergistically, rather than additively, iii) there are muscranic type receptors and NK_1 and NK_2 type receptors on SMCs, and also NK_1, NK_3 receptors on the motor neuron and on interstitial cells of Cajal (ICC).

The aim of the study was to investigate *in silico* the effect of co-transmission by ACh and SP and receptor polymodality on the dynamics of myoelectrical and contractile activity in the antrum of the human stomach.

RESULTS AND CONCLUSION

The trigger in the release of SP is the rise of intracellular calcium. This induces exocytosis of the neurotransmitter from the vesicular stores. As a response to a single excitation 0.2 μM, SP

is released and increases 14.5 times after a high frequency, 0.5 Hz, stimulation. The free fraction of SP diffuses further into the synaptic cleft where max[SP_c] = 0.056 μM is recorded, Figure 1. A general tachykinin conformer of the NK receptor binds to SP to form a complex, max[SP-NK] = 0.042 μM. The latter activates guanine-nucleotide G protein which initiates the PLC signaling pathway. The final step in the cascade is the phosphorylation/ dephosphorylation of intracellular proteins by protein-phosphatase. The quantity of active proteins rises to 166 nM and remains at this level for the duration of stimulation. They alter the permeability of ion channels and cause the generation of long lasting EPSPs of low amplitude, 20 - 40 mV.

SP and ACh have a profound effect on the firing rate of ICC and myoelectrical response of the antrum. The frequency of ICC discharges increases nearly fourfold from the normal value. SMCs become depolarized and produce regular slow waves of average amplitude 26 mV at a ν = 4 Hz. The amount of [Ca_i^{2+}] quickly reaches 0.49 μM and stays at this level during the continued presence of reactive proteins. As a result, a long lasting tonic-type contraction of intensity max T^a = 25.4 mN/cm develops.

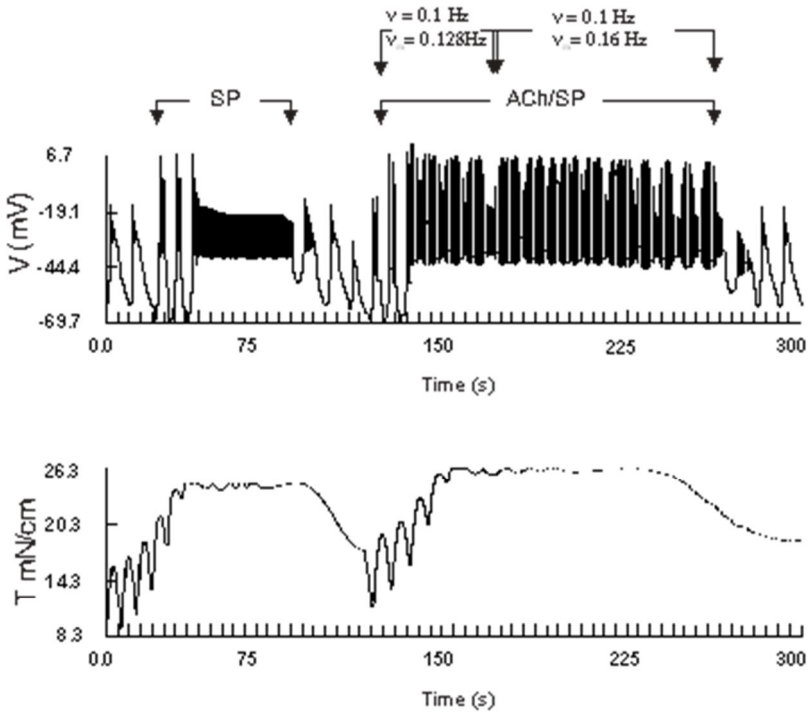

Fig. 1 - The electrical activity and total force variations in presence of ACh and SP

The observed results of numerical simulations provide an insight into the intricate intrinsic mechanisms apparent in the regulation of antral gastric motility. Pathological changes in the dynamics of excitatory neurotransmitters, ACh and SP, may lead to abnormal contractility, e.g., gastric arrhythmia, retrograde peristalsis and spastic contractions of the antrum.