Does the morphology of the acinar lumen directly affect primary saliva secretion?

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND
SCIENCE

Vera-Sigüenza E, Pages N, Rugis J, Yule I. D, Sneyd J.

NIH National Institutes of Health

Introduction

A hallmark of salivary epithelia is that they do not operate on a single cell basis, instead they come in racemous clusters that form a distinct arborised tubular (luminal) network. Its morphological characteristics have been hypothesised to influence the generation of Ca2+ signalling patterns and, thus determine the production of primary saliva.

Motivation

Defects of cellular process regulation, often resulting from unregulated Ca2+ signalling, are responsible for gland dysfunction and disease. From radiation-induced loss of salivary gland function as well as in the salivary defects associated with the autoimmune exocrinopathy Sjogren's syndrome.

Our study offers an avenue for examining the mechanisms underlying these problems and aims to aid in the development of novel clinical targets and therapeutic strategies.

Methodology

To investigate this, we constructed an anatomically accurate 3D small acinus mathematical model using confocal microscopy images depicting the staining of apical inositol 1,4,5-trisphosphate receptors (InsP3Rs) and basolateral sodium-potassium adenosine triphosphatase pumps (NaK-ATPases) in mouse parotid acini.

Each cell, in our 'in-silico' acinus, runs an individual mathematical model equipped with the associated intracellular machinery required for water transport coupled through Ca2+ and InsP3 cell to cell signalling.

The model uses the Cl- ion as the rate limiting step for fluid secretion. It relies on the activation of apical Cl- Ca2+ Channels (TMeM16a) to generate an osmotic gradient that water follows by osmosis.

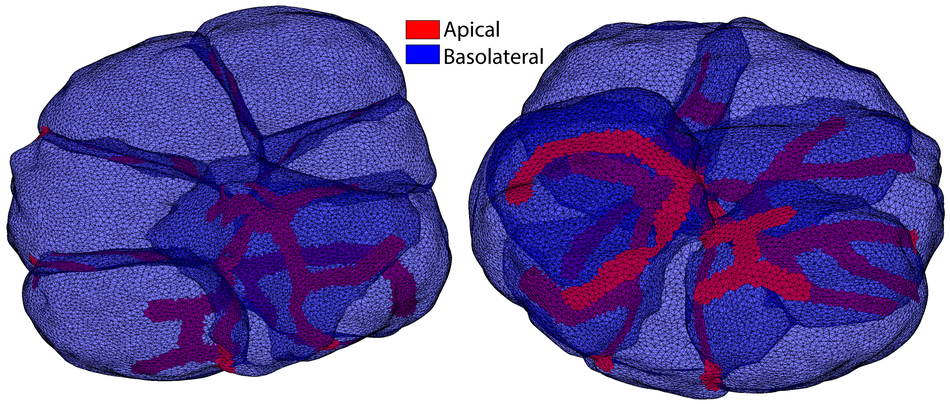

Figure 1. Our model uses a mesh constructed from 31 confocal microscopy images of mouse parotid gland epithelia at 1024 by 1024 pixels, with a resolution of 0.069 microns per pixel and a stack spacing of 0.8 microns. These consist of fluorescent staining of the apical Ca2+-dependent Cl– channels, (TMeM16a), and NaK-ATPases as a way to visualise apical and basolateral plasma membranes of acinar cells.

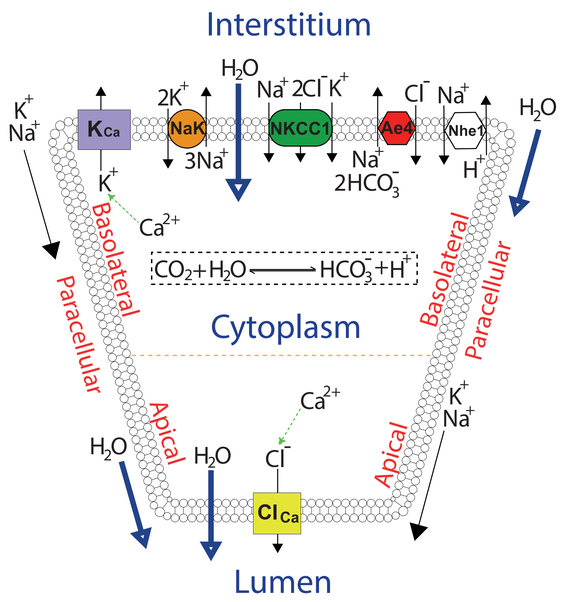

Figure 2. Schematic diagram of a single salivary acinar cell model. The basolateral membrane portion contains Nkcc1 (green), NaK-ATPase (orange), Ae4 (red), Nhe1 (white) and Ca2+-activated K+ channels.
Our model includes the carbonic anhydrases in the cytoplasm that catalyse the reaction of CO2 and water to form carbonic acid, which dissociates into HCO3 and H+.The apicalmembrane contains a Ca2+-activated Cl– channel. Both apical and basolateral membranes are permeable to water.
Finally, we have included paracellular K+ and Na+ currents along with a paracellular water flow.

Results

Results indicate that global synchronisation of Ca2+ signals, at acinus level, must occur for optimal fluid secretion.
We demonstrate that although certain topological features of the lumen are necessary, a specific configuration is not critical for fluid transport.

On a computational level, this is reflected in the fact that a spatial mathematical model may not be necessary, instead, a collection of single cell models suffice to understand and predict the underlying mechanisms of the collective behaviour distinctive of salivary acini, thus reducing the computational effort needed to study the salivary secretion process.

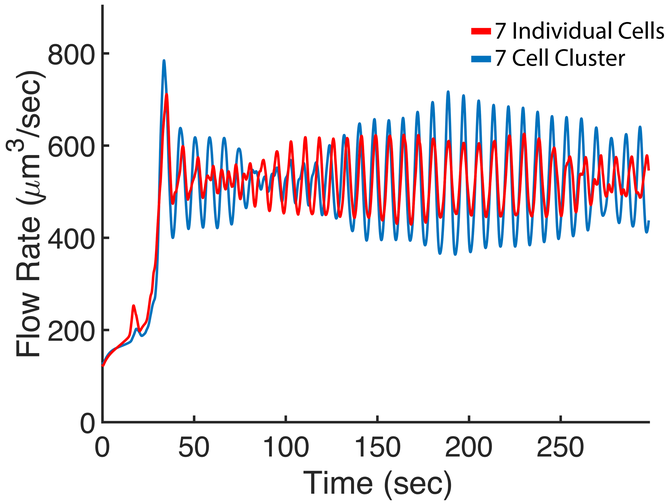

Figure 3. The total fluid flow rate of a seven acinar cell cluster can be obtained by a collection of seven individual model cells. This computational predictionmay indicate that the luminal configuration may not be essential for optimal fluid secretion.

Future Work

New laboratory results and experimental data are required to further fine tune our model. However, the predictions and results, from this and previous models, have proven invaluable in many ways. The next stage is to simulate an entire parotid gland using the ideas and techniques employed here. We will merge acinar and ductal fluid flow models with the sole purpose of creating a fully functional virtual gland that can be used by researchers, and the public alike, to understand the process of salivary secretion.

References

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