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Multiscale modelling of saliva secretion

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ABSTRACT

We review a multiscale model of saliva secretion, describing in brief how the model is constructed and what we have so far learned from it. The model begins at the level of inositol trisphosphate receptors (IPR), and proceeds through the cellular level (with a model of acinar cell calcium dynamics) to the multicellular level (with a model of the acinus), finally to a model of a saliva production unit that includes an acinus and associated duct. The model at the level of the entire salivary gland is not yet completed. Particular results from the model so far include (i) the importance of modal behaviour of IPR, (ii) the relative unimportance of Ca^{2+} oscillation frequency as a controller of saliva secretion, (iii) the need for the periodic Ca^{2+} waves to be as fast as possible in order to maximise water transport, (iv) the presence of functional K^+ channels in the apical membrane increases saliva secretion, (v) the relative unimportance of acinar spatial structure for isotonic water transport, (vi) the prediction that duct cells are highly depolarised, (vii) the prediction that the secondary saliva takes at least 1 mm (from the acinus) to reach ionic equilibrium. We end with a brief discussion of future directions for the model, both in construction and in the study of scientific questions.

1. Introduction

The primary physiological role of salivary glands is the production of saliva; a hypotonic fluid containing electrolytes and a complex mixture of macromolecules [1–3]. Saliva begins the initial digestion of food, provides defence from microorganisms and protection from physical and chemical assault on the oral cavity. Saliva is therefore vital for oral health and general well being. The importance of saliva is most acutely appreciated in individuals with salivary gland hypo-function [4,5]. "Dry mouth" most commonly occurs as a consequence of medication and radiotherapy for head and neck malignancies. Dry mouth also can result from organic disease such as duct obstruction in cystic fibrosis patients or frequently in Sjögrens syndrome [6–8], a relatively common autoimmune disease associated with significant morbidity. Patients with Sjögrens syndrome typically have a profound dry mouth resulting in altered perception of taste, difficulty in swallowing and speech, together with an increased susceptibility to dental caries and oral candidiasis.

A fundamental prerequisite for developing therapies for salivary gland dysfunction is a thorough understanding of the entire fluid secretion process, not just its isolated components. Experimental approaches to the study of salivary function and pathology are, of course, crucial. Nevertheless, theoretical methods can also play a vital complementary role. Although it is clear that the behaviour of an organ is the result of the integrated sum of the behaviours of its constituent cells and molecules, it is extraordinarily difficult to make this connection explicit, and therefore to understand it in detail. In general, experiments measure the constituent properties, or the whole-organ behaviour, but cannot easily make a direct link between the two. In addition, measurements of the isolated components of a complex system are not necessarily predictive of the overall behaviour of that system.

Computational models have a vital role to play in helping to understand the relationship between cellular properties and whole-organ behaviour, but come with their own set of difficulties and limitations. It is not a trivial matter to understand, within the framework of a single unified model, the behaviour of cells and organs, from the level of cellular components (with space and time scales on the submicron and millisecond time scales) to the level of the organ (with typical space and time scales of centimetres and minutes). Such models, varying as they do over multiple time and space scales are called *multiscale* models, and are arguably the most important challenge presently facing computational modellers in physiology. The challenge arises not only because

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there are few available methods even for the construction, let alone the analysis, of such models. It also arises from the fact that each multiscale problem in physiology must be treated on its own merits, possibly in a way quite different to every other existing multiscale model – a multiscale model of the heart, for example, may be of quite limited use in the construction of multiscale models of the lung, or the liver, or the salivary gland – and thus, in a sense, different wheels need to be continually reinvented.

The multiscale model of saliva secretion that we present here is still a work in progress, and we can still only ask, not answer, many questions about the interaction of spatial structure and organ function. Nevertheless, it has already contributed a significant amount to our understanding of how parotid acinar cells work, and how they interact, and is the first step along the path towards a greater understanding of salivary gland function, from molecule to organ.

2. The physiology of saliva secretion

Reviews of the physiology of saliva secretion can be found in [9–12,1,13–15]. Saliva is secreted by three major pairs of glands – the sublingual, submandibular and parotid glands – as well as from a large number of minor glands scattered through the oral cavity. In each of the major glands primary saliva is produced by acinar cells, which are grouped in grape-like clusters at the terminal branches of a tree-like branching system of ducts, which are lined by duct cells. The primary saliva then travels along the ducts, where its ionic composition is modified by duct cells, to produce secondary saliva which is secreted into the oral cavity. Acinar cells are either serous or mucus, with the proportion of each type determined by the gland and the species, while duct cells also come in a variety of types each with different ion transport functions.

Secondary saliva is typically about 99% water, although the secretion from some glands can be a lot more viscous, due to the presence of large amounts of mucus. The majority of saliva (humans typically produce about a litre a day) comes from the submandibular and parotid glands.

Here, we focus almost entirely on the parotid gland, although data from other glands is used if there are no other options.

2.1. Acinar cells

Parotid acinar cells are polarised epithelial cells (Fig. 1). The basolateral membrane faces to the extracellular space, while the apical membrane faces into the lumenal compartment, which is where the primary saliva is secreted. Multiple acinar cells secrete into the same lumen, a fact that will become important later when we consider the multicellular spatial structure.

The basolateral membrane has a variety of ion exchangers and channels (Fig. 1), including the Na^+/K^+ ATPase, a $Na^+/K^+/Cl^-$ cotransporter and a Ca^{2+}-dependent K^+ channel. On the apical membrane the most important ion channel is a Ca^{2+}-dependent Cl^- channel.

Control of Ca^{2+} is crucial (Fig. 2). Binding of an agonist to G-protein-coupled receptors (P2Y purinergic receptors, for example, or alpha-adrenergic receptors) results in the activation of phospholipase C (PLC) and thus production of inositol trisphosphate (IP_3). This pathway is important for the control of Ca^{2+} dynamics in almost all cell types, and is described in much more detail in [16–21]. IP_3 binds to IP_3 receptors (IPR), which are Ca^{2+} channels situated on the membrane of the endoplasmic reticulum (ER), resulting in the release of Ca^{2+} from the ER. Ca^{2+} can also be released from the ER through ryanodine receptors (RyR) or through a generic small background leak (J_{er}), and is taken up into the ER by SERCA pumps. Finally, Ca^{2+} is removed from the cell by ATPase pumps on the plasma membrane and enters the cell through a

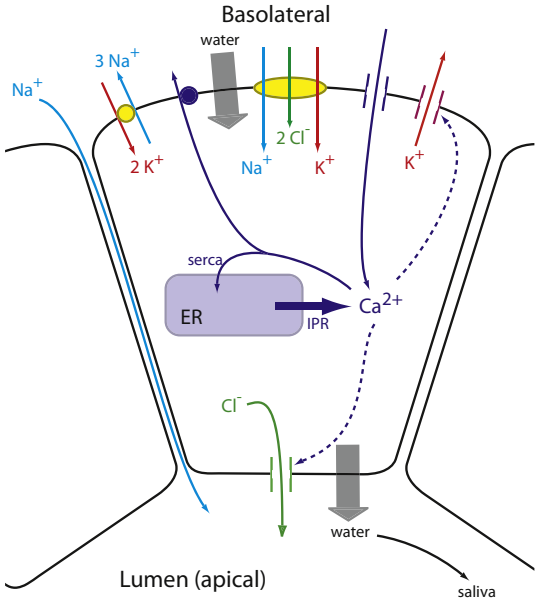

Fig. 1. The major ion channels involved in the secretion of saliva, and their control by Ca^{2+}. Although Ca^{2+}-sensitive K^+ channels are also situated on the apical membrane, they are omitted here for clarity.

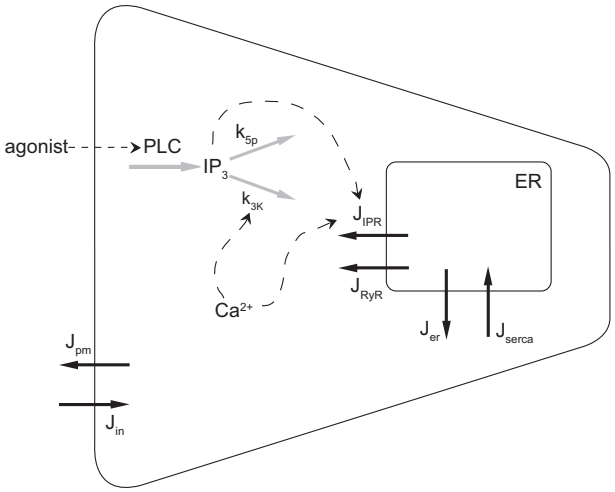

Fig. 2. Summary of the important reactions involved in the control of Ca^{2+} in a salivary acinar cell. Agonist stimulation induces the formation of IP_3, which releases Ca^{2+} from the endoplasmic reticulum (ER) via the opening of IP_3 receptors (IPR). The rate of degradation of IP_3 is Ca^{2+}-dependent. Calcium is pumped into the ER, and out of the cell, by ATPase pumps, while it can also leave the ER through ryanodine receptors (RyR). J_{pm} represents the removal of Ca^{2+} from the call by plasma membrane ATPase pumps, while J_{in} represents a generic influx of Ca^{2+}, most likely through receptor-operated or store-operated Ca^{2+} channels.

variety of channels (although we shall simplify the modelling of Ca^{2+} entry by presuming only a single channel type). The rate of degradation of IP_3 is controlled by Ca^{2+} via its effect on the 3-kinase that converts IP_3 to IP_2. Thus, k_{3K} is an increasing function of Ca^{2+}.

The basic mechanism of saliva secretion is thus as follows. Stimulation of the cell by agonist results in the release of Ca^{2+} from the ER, and the resultant increased $[Ca^{2+}]$ activates the Ca^{2+}-dependent Cl^- channel on the apical membrane. Cl^- thus flows out of the cell, down its electrochemical potential gradient into the lumenal space, depolarising the cell. If there were no other ion currents, this Cl^- current would quickly cease as the membrane depolarises.