EDITORIAL

An introduction to the Bioscience Birthday Symposium held in honour of Ole Petersen CBE, FRS

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This issue contains five review articles summarizing talks that were presented at a 2-day Physiology and Pathophysiology symposium held in the elegant setting of the National Museum in Cardiff to celebrate the seventieth birthday of Ole Petersen, Chair of the Cardiff School of Biosciences. Ole trained in medicine in Copenhagen and, whilst a student, became fascinated by the physiology of the exocrine glands, leading him to spend much of his spare time investigating ion transport mechanisms in the salivary glands together with a fellow medical student (J. H. Poulsen). After qualifying in medicine and a brief period as a faculty member in the medical school in Copenhagen, Ole took up the Symers Professorship of Physiology at Dundee University followed by the George Holt Chair in Physiology at Liverpool. Ole remained in Liverpool for almost 30 years before succeeding Nobel Laureate Sir Martin Evans as head of the Cardiff School.

For several decades, Ole's laboratory has provided fundamental insight into the role of ion channels and calcium signals in regulating secretory cell physiology and how aberrant activity of these pathways can engender disease, particularly acute pancreatitis. Acute pancreatitis is a devastating disease in which pro-enzymes such as trypsinogen that are stored in zymogen granules become activated prematurely. This results in autodigestion of the gland, usually in response to excessive alcohol abuse and biliary disease, and death often follows. Pioneering work by Ole's group established that excessive Ca^{2+} signals, particularly Ca^{2+} influx through store-operated Ca^{2+} channels, constituted the primary event that triggered the autodigestion process (Raraty *et al.* 2000). These Ca^{2+}-selective channels are activated by depletion of Ca^{2+} within the endoplasmic reticulum (ER) and are a major conduit for Ca^{2+} in most cell types (Parekh & Putney, 2005). Loss of Ca^{2+} from the stores leads to multimerization of ER-resident Ca^{2+} sensor stromal interaction molecule (STIM) proteins, which then migrate across the ER membrane to reach specialized ER–plasma membrane (PM) junctions (Hogan *et al.* 2010). Here, they bind to and gate Orai proteins, which are the pore-forming subunit of store-operated channels. These punctate-like clusters of STIM and Orai proteins result in hot spots of Ca^{2+} entry. Javier García-Sancho describes how these local Ca^{2+} signals can be generated and how sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) pumps on the ER membrane take up some of the Ca^{2+} into the ER, thereby ensuring adequate replenishment of the Ca^{2+} store (García-Sancho, 2014). By contrast, in excitable cells such as chromaffin cells, the higher local Ca^{2+} arising from larger conductance voltage-gated Ca^{2+} channels is buffered by closely apposed mitochondria rather than SERCA pumps, presumably reflecting the relative differences in SERCA pump and mitochondrial uniporter affinities for Ca^{2+}. Gerasimenko *et al.* describe the elegant recent work from Ole's laboratory that raises the exciting prospect that inhibition of store-operated Ca^{2+} channels might provide an effective therapy against acute pancreatitis (Gerasimenko *et al.* 2014). Pharmacological block of store-operated Ca^{2+} channels in pancreatic acinar cells with small molecule inhibitors afforded protection against cytoplasmic Ca^{2+} overload, premature protease activation and necrosis following challenge with alcohol and fatty acids, stimuli that induce pancreatitis. This adds to the growing list of indications where Orai channel blockers could provide a new therapeutic approach (Parekh, 2010). Neurodegenerative diseases are also associated with altered Ca^{2+} signalling. Michael Berridge presents a fascinating account of Ca^{2+} deregulation in Alzheimer's disease and how a gradual rise in resting Ca^{2+} concentration, in response to accumulation of amyloid β oligomers, may lead to memory erasure during sleep (Berridge, 2014). Amyloid β affects neurons directly as well as indirectly, the latter by inducing inflammatory responses in microglia and astrocytes. Because store-operated Ca^{2+} channels often provide the Ca^{2+} necessary to induce inflammatory mediator expression and secretion, targeting the channels might also be of some benefit to Alzheimer's disease.

Store-operated Ca^{2+} channels are not the only route for non-voltage-activated Ca^{2+} entry in cells. Another important class of channel is the transient receptor potential (TRP) channel. Mammalian TRP proteins form six transmembrane domain-spanning cation-permeable channels, which can be grouped into six subfamilies. Patch clamp work by Ole's group revealed the presence of agonist-activated non-selective cation channels in the acinar cell (Thorn & Petersen, 1992), now known to be members of the TRPC subfamily. TRP channels are widely expressed and exhibit polymodal activation. Bernd Nilius and colleagues describe the properties and function of Ca^{2+}-permeable TRPV3 channels, which are found mainly in keratinocytes of skin (Nilius *et al.* 2014). Although the role of these channels as thermosensors is controversial, they are involved in somatosensation, barrier function and hair development. TRPV3 is tightly associated with the rare skin disease Olmsted syndrome, where gain-of-function mutations lead to constitutive channel activity.

Cytoplasmic Ca^{2+} can be taken up rapidly into mitochondria, stimulating metabolic enzymes producing ATP. Whilst cross-talk between Ca^{2+} and other signalling pathways such as the cAMP second messenger system has been known for many years, recent work has revealed important functional interaction at the level of mitochondria between these fundamental intracellular signals. Tullio Pozzan and colleagues have identified a cAMP-generating system within the matrix itself, which is activated by matrix Ca^{2+}. Transient increases in matrix Ca^{2+} induce more prolonged cAMP production. This discovery, which is described in their review (Di Benedetto *et al.* 2014), establishes mitochondria as important signalling hubs, integrating multiple second messenger pathways to regulate ATP production.

These reviews provide insight into the breadth of research contributions of Ole Petersen over the last forty years (Ca^{2+} signalling, ion channels, mitochondria

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and Ca^{2+} dysregulation in disease). The symposium was a tremendous success, with numerous excellent talks and sharing of much unpublished data, all conducted in a very friendly and relaxed atmosphere. One looks forward with great anticipation to the next series of major contributions that Ole will make in the coming years.

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