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PERSPECTIVES

Blockade of calcium entry provides a therapeutic window in acute pancreatitis

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Acute pancreatitis (AP) is a serious disease with rising incidence and no specific treatment. Shockingly, the mortality of severe AP is still between 30 and 50%, which makes the disease as harmful as stroke or acute myocardial infarction. It goes almost without saying that any study offering insights into this challenge is of high importance.

What are the difficulties in developing a therapy?

AP is a multifactorial disorder involving many cell types such as the acinar, ductal, stellate and inflammatory cells (Hegyi & Petersen, 2013). In the past many investigators have targeted only one of the cell types (for example trypsin inhibitor targeting acinar cells, biological treatment targeting inflammatory cells or secretin targeting ductal cells); however, these efforts failed. Recently, two major intracellular events have been reported in AP which seem to be uniformly presented in all cell types, namely ATP depletion (Maléth *et al.* 2013) and the consequent calcium (Ca^{2+}) overload (Maléth & Hegyi, 2014). Ole Petersen's laboratory (in the past based in Liverpool and most recently in Cardiff) has been at the forefront of the investigations into these mechanisms, and with striking success.

Do we know why these two mechanisms are so harmful?

Before answering it has to be stated immediately that elevation of intracellular Ca^{2+} can be either advantageous or detrimental (Maléth & Hegyi, 2014). Oscillatory Ca^{2+} signalling plays a pivotal role in the physiological regulation of the exocrine pancreas. Physiological stimuli will usually cause fast elevation of intracellular Ca^{2+} level due to the activation of the inositol trisphosphate (IP_3)-mediated Ca^{2+} release from the endoplasmic reticulum (ER) store. After the stimuli, the energy-demanding sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and the plasma membrane Ca^{2+}-ATPase (PMCA) pumps move Ca^{2+} out from the cytosol back to the ER and to the extracellular space. This intracellular Ca^{2+} signalling causes the acinar cells to secrete enzymes and the ductal cells to generate fluid and bicarbonate, and importantly the stellate cells will be able to migrate and proliferate.

However, the pancreatitis-inducing factors such as ethanol, fatty acids and bile acids can turn this physiological Ca^{2+} signal to a dangerous, toxic and sustained Ca^{2+} elevation that drives the cell to an early death (Hegyi & Petersen, 2013; Maléth & Hegyi, 2014). The non-oxidative ethanol metabolites, fatty acid ethyl esters, and the fatty and bile acids induce calcium release from the ER stores, causing severe mitochondrial damage with marked ATP depletion both in acinar and ductal cells. These changes will switch off the ATP-dependent SERCA and PMCA, resulting in consistent intracellular Ca^{2+} elevation and severe Ca^{2+} depletion in the ER. This latter effect in the ER causes translocation of the Ca^{2+}-sensing protein STIM1 (which is distributed in the ER membrane) leading to conformational changes and the clustering of this unique protein into specific ER–plasma membrane junctions, also called puncta formation. This biophysical change will open the store-operated calcium channels, including the Ca^{2+} release-activated Ca^{2+} channel (CRAC), which will continuously elevate the intracellular Ca^{2+}, eventually leading to cell death.

In this issue of *The Journal of Physiology*, Gryshchenko *et al.* have found a way to interfere with this calcium overload (Gryshchenko *et al.* 2016). They examined bradykinin- and cholecystokinin-elicited Ca^{2+} signal generation both in acinar and stellate cells. They found that pathophysiologically relevant bradykinin concentrations induce Ca^{2+} signals via B2 receptors in stellate cells but not in acinar cells. In contrast, cholecystokinin evoked Ca^{2+} signals in acinar, but not in stellate cells. They showed that inhibition of CRAC channels strongly reduces the Ca^{2+} entry phase in stellate cells and decreases necrosis in acinar cells. Previously it has been documented that CRAC channel blockade provides effective protection against alcohol-related intracellular protease activation and necrosis in acinar cells (Gerasimenko *et al.* 2013). The palmitoleic acid ethyl ester, an important mediator of alcohol-related pancreatitis, inducing sustained intracellular Ca^{2+} elevation, could have been markedly inhibited by CRAC blockade. Importantly, this blockade had only a marginal effect on the physiological Ca^{2+} oscillations evoked by physiological stimuli (Gerasimenko *et al.* 2013).

All in all, CRAC blockade is highly beneficial both in acinar and stellate cells, inhibiting only the bad and not the good Ca^{2+} signal; therefore this pharmacological intervention offers the potential for the first specific therapy in AP.

References

Gerasimenko JV, Gryshchenko O, Ferdek PE, Stapleton E, Hébert TO, Bychkova S, Peng S, Begg M, Gerasimenko OV & Petersen OH (2013). Ca^{2+} release-activated Ca^{2+} channel blockade as a potential tool in antipancreatitis therapy. *Proc Natl Acad Sci USA* **110**, 13186–13191.

Gryshchenko O, Gerasimenko JV, Gerasimenko OV & Petersen OH (2016). Ca^{2+} signals mediated by bradykinin type 2 receptors in normal pancreatic stellate cells can be inhibited by specific Ca^{2+} channel blockade. *J Physiol* **594**, 281–293.

Hegyi P & Petersen OH (2013). The exocrine pancreas: the acinar-ductal tango in physiology and pathophysiology. *Rev Physiol Biochem Pharmacol* **165**, 1–30.

Maléth J & Hegyi P (2014). Calcium signaling in pancreatic ductal epithelial cells: An old friend and a nasty enemy. *Cell Calcium* **55**, 337–345.

Maléth J, Rakonczay Z Jr, Venglovecz V, Dolman NJ & Hegyi P (2013). Central role of mitochondrial injury in the pathogenesis of acute pancreatitis. *Acta Physiol (Oxf)* **207**, 226–235.

Additional information

Competing interests

None declared.

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