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PERSPECTIVES

CICR takes centre stage in β-cells: a cute cascade connects cAMP to CICR

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An estimated 285 million people in the world have overt β-cell failure, and the number is likely to increase to 438 million by 2030 (Islam, 2010). Thus, understanding the signalling mechanisms that control β-cell functions is a matter of crucial interest. Ca^{2+}-induced Ca^{2+} release (CICR), first described in muscle cells, appears to be present in an increasing number of cell types. We now know that CICR is neither restricted to the muscle cells nor an exclusive property of the ryanodine receptors (RyRs). In fact, both the inositol 1,4,5-trisphosphate receptors (IP_3Rs) and the RyRs can act as Ca^{2+}-gated Ca^{2+} channels. CICR through IP_3Rs is sensitized by inositol 1,4,5-trisphosphate (IP_3), whereas CICR through RyRs is sensitized by a variety of small molecules, e.g. fructose 1,6-diphosphate (Kermode *et al.* 1998) and arachidonic acid (Woolcott *et al.* 2006). In β-cells, CICR has taken a two-decade-long journey from being highly controversial to taking centre stage in recent years. In fact, new therapeutic agents that facilitate CICR in β-cells, e.g. several glucagon-like peptide 1 (GLP-1) analogues, are being increasingly used to improve β-cell function in diabetes. An understanding of the molecular mechanisms by which GLP-1 facilitates CICR is thus also of clinical relevance.

GLP-1 facilitates CICR mainly by producing cAMP, which acts through cyclic AMP-dependent protein kinase A (PKA). But, it turned out that activation of PKA could not fully account for the facilitation of CICR by GLP-1. Another direct target for cAMP is a guanine nucleotide exchange factor for the Ras-like small GTPase Rap (Epac). This factor is a product of two genes, *Epac1* and *Epac2*. Epac2 has two domains for binding cAMP and a guanine nucleotide exchange factor for Ras-like small GTPases. In β-cells, activation of Epac2 facilitates CICR. How does Epac2 facilitate CICR? Oestreich *et al.* (2009) have addressed this question in heart muscle cells where the critical importance of CICR is established beyond any doubt. In this issue of *The Journal of Physiology*, Dzhura *et al.* (2010) have addressed the same question in β-cells. Using pharmacological activators of Epac, and Epac2 knockout mice, these authors demonstrate again that this molecule does indeed play a distinct role in facilitating CICR.

An unexpected finding of this study is that β-cells express the phosphoinositide-specific phospholipase C ε (PLC-ε). Like other PLCs, PLC-ε generates inositol 1,4,5-trisphosphate (IP_3) and diacyl glycerol (DAG). In addition, it has both Ras guanine exchange factor (RasGEF) and Ras-associating (RA) domains. Thus, it acts as an activator and an effector of small GTPases, like Ras and Rap. Each molecule of Epac2 binds to two molecules of cAMP and the Epac2:cAMP complex activates Rap1 (Fig. 1). The GTP-bound Rap1 then binds to the RA domain of PLC-ε and increases its phospholipase activity. Using PLC-ε knock-out mice, Dzhura *et al.* demonstrate that PLC-ε is essential for the PKA-independent facilitation of CICR by GLP-1. In a series of carefully designed experiments using molecular techniques and pharmacological tools, the authors demonstrate that the Epac2- and Rap1-mediated activation PLC-ε facilitates CICR through activation of protein kinase C (PKC) and calcium–calmodulin-dependent protein kinase II (CaMKII) (Fig. 1).

Thus, CICR in β-cells is a highly regulated process where cAMP plays an obligatory role. Facilitation of CICR by the two cAMP effectors is also clearly discernable. It should be pointed out that, *in vitro*, half-maximal activation of PKA occurs at ∼1 μM cAMP whereas half-maximal activation of Epac2 (the B domain of Epac2) occurs at ∼40 μM cAMP. One can speculate that the PKA-mediated facilitation of CICR occurs when GLP-1 concentration is low, whereas Epac2-mediated facilitation of CICR occurs during stimulation of the GLP-1R by pharmacological concentrations of GLP-1.

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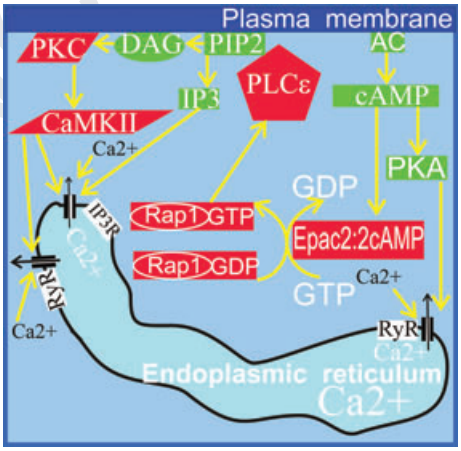

Figure 1. Schematic diagram showing the pathways whereby cAMP facilitates CICR in β-cells

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