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Short Communication

Cellular metabolism as a tuneable factor and modulator of intracellular signalling



Ole H Petersen
School of Biosciences, Cardiff University, Wales, UK
PetersenOH@cardiff.ac.uk

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Introduction

Transformations of energy from one form to another are fundamental to life. In this short review, the key processes involved will be discussed together with the important issue of how these events are regulated. Intracellular signalling and tuning of cellular metabolism are closely interrelated in a two-way process in which signalling controls metabolism and metabolism influences signalling. The discussion will focus on the nature of the nano-domains between the endoplasmic reticulum (ER) and the mitochondria and the Ca^{2+}- and ATP-mediated feed-back mechanisms operating in that restricted spot. The consequences for energy production of disrupting the nano-domains, which happens in cancer cells, will also be discussed.

Intracellular signalling and metabolism

The digestive system, and the pancreas in particular, forms one part of the machinery that enables animals to transform the energy inherent in the food consumed (fats, proteins and carbohydrates) to ATP, the energy-rich molecule that fuels all the important physiological and biochemical processes that sustain life and allow work to be done [1]. The other parts of the machinery are the transfers of fatty acids, amino acids and small peptides as well as sugars, across the intestinal epithelium and the uptake mechanisms of glucose, amino acids and fatty acids through the cell membranes in many different tissues, providing the substrates for cellular metabolism. Inside the cells, the mitochondria produces the ATP by oxidative phosphorylation. There is a need for overall regulation, because increasing physical work demands more energy and therefore increased food intake. This requires secretion of more digestive enzymes, activation of cellular uptake mechanisms across cell membranes and increased mitochondrial activity. The most important control points depend on intracellular Ca^{2+} signalling and include: activation of pancreatic enzyme secretion in the acinar cells by hormones/neurotransmitters, stimulation of insulin secretion by glucose-elicited depolarization of pancreatic beta-cells and increased ATP formation

in the mitochondria of many different cell types by activation of three Ca^{2+}-sensitive dehydrogenases in the Krebs cycle [2]. Signalling mechanisms and metabolism are therefore closely interrelated (Fig. 1).

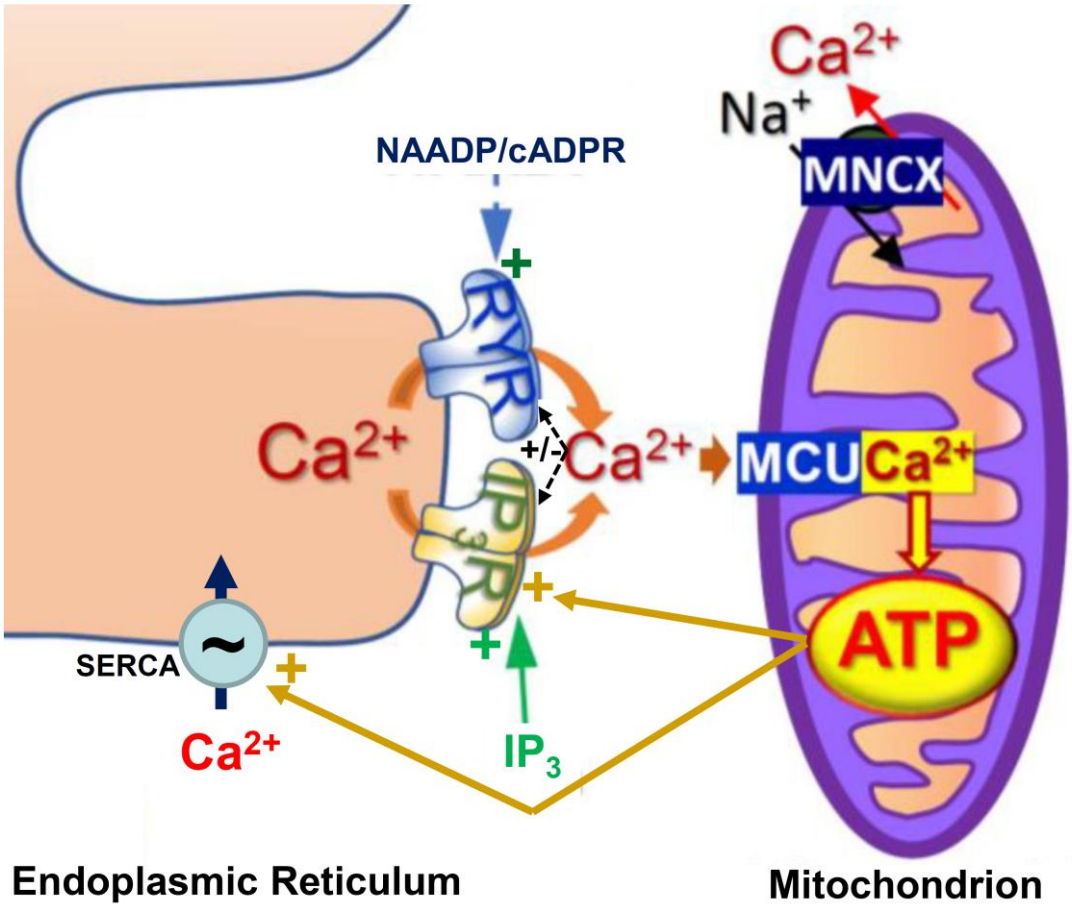


Figure. 1. Simplified diagram illustrating the close relationships between the signalling molecule Ca^{2+} and the primary energy carrier ATP. For details, see text. SERCA, Ca^{2+} ATPase in endoplasmic reticulum membrane; NAADP, nicotinic acid adenine dinucleotide phosphate; cADPR, cyclic ADP ribose; RyR, ryanodine receptor; IP_3, inositol trisphosphate receptor; MNCX, mitochondrial Na^+/ Ca^{2+} exchanger; MCU, mitochondrial Ca^{2+} uniporter.

In nano-domains between the endoplasmic reticulum (ER) and the mitochondria, a small Ca^{2+} release from the ER can create a substantial rise in the local cytosolic Ca^{2+} concentration enabling uptake through the channel protein MCU (mitochondrial Ca^{2+} uniporter). Ca^{2+} uptake is facilitated by the huge electrical potential difference (~200 mV, negative in mitochondrial matrix) across the inner mitochondrial membrane (IMM). This causes a rise in the mitochondrial Ca^{2+} concentration ($[Ca^{2+}]_m$), dictating increased Krebs cycle activity and therefore ATP formation. ATP release from the mitochondria into the cytosol increases the open state probability of the IP_3Rs as well as providing energy for reuptake of Ca^{2+} into the ER (Fig. 1). Recent data indicate a much more subtle control of intracellular Ca^{2+} release than the traditional IP_3 system alone [3] and this has consequences for mitochondrial Ca^{2+} uptake. Qualitatively, the

scheme outlined here is relatively simple, but quantitatively it is complicated because small changes can have huge consequences for physiology and pathology. In general, the key regulator – the free Ca^{2+} concentration inside cells - needs to be kept low because otherwise Ca^{2+}-phosphate precipitates will damage the cells. Therefore, intracellular Ca^{2+} signals are best kept small and short-lasting, which is what generally happens in normal physiology [2]. The mitochondria also have to protect themselves against an excessive $[Ca^{2+}]_m$ elevation. Under many pathological conditions the cytosolic Ca^{2+} concentration becomes excessively elevated, resulting in excessive mitochondrial uptake, which then – via opening of the Ca^{2+}-sensitive mitochondrial permeability transition pore in the IMM – causes depolarization of the IMM. A collapse of the electrical potential across the IMM prevents ATP formation and further Ca^{2+} uptake. The intricate quantitative interrelationships between Ca^{2+} signalling mechanisms and ATP production as well as recently discovered promising pharmacological interventions at critical control points will be discussed.

Conflicts of interest: The author declares no conflict of interest.

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