Review

The regulation of ion channels and transporters by glycolytically derived ATP

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Abstract. Glycolysis is an evolutionary conserved metabolic pathway that provides small amounts of energy in the form of ATP when compared to other pathways such as oxidative phosphorylation or fatty acid oxidation. The ATP levels inside metabolically active cells are not constant and the local ATP level will depend on the site of production as well as the respective rates of ATP production, diffusion and consumption. Membrane ion transporters (pumps, exchangers and channels) are located at sites distal to the major sources of ATP formation (the mitochondria). We review evidence that the glycolytic complex is associated with membranes; both at the plasma membrane and with membranes of the endo/sarcoplasmic reticular network. We examine the evidence for the concept that many of the ion transporters are regulated preferentially by the glycolytic process. These include the Na+/K+-ATPase, the H+-ATPase, various types of Ca2+-ATPases, the Na+/H+ exchanger, the ATP-sensitive K+ channel, cation channels, Na+ channels, Ca2+ channels and other channels involved in intracellular Ca2+ homeostasis. Regulation of these pumps, exchangers and ion channels by the glycolytic process has important consequences in a variety of physiological and pathophysiological processes, and a better understanding of this mode of regulation may have important consequences for developing future strategies in combating disease and developing novel therapeutic approaches.

Keywords. Glycolysis, ion channel, transporters, regulation.
Some of the glycolytic products (pyruvate and NADH) can enter the mitochondria, where they are subject to oxidative phosphorylation reactions to produce larger amounts of ATP, which is responsible for sustaining the majority of high-ATP-consuming cellular functions (such as contraction) in mammalian cells. However, it has become increasingly clear that glycolytic intermediates and end-products are by themselves capable of regulating the activity of specific proteins, including some membrane ion translocators. Not surprisingly, these ion translocators are often those that are intimately involved in coupling cellular energy metabolism to cellular excitability or to the regulation of ion homeostasis. The aim of this review is to focus on the glycolytic regulation of some of these ion translocation processes and to put this regulation in the context of cellular physiology and pathophysiology.

**Compartmentalization of glycolysis**

For glycolysis to be able to regulate the activities of proteins and ion translocators (as will be discussed below), it stands to reason that the source of glycolytic intermediates and end-products (such as NADH and ATP) must be compartmentalized and produced in close proximity to the target proteins. This concept is not new [1], and functional compartmentalization of both oxidative and glycolytic metabolism has been described for a variety of tissues, including cardiac, skeletal and smooth muscle myocytes, neuronal cells and the pancreatic insulin-secreting β-cell [2–9]. The model that has evolved, therefore, is that glycolysis preferentially regulates physiological processes located in the micro-environment of the cell boundary.

### ATP gradients exist inside cells

It is important to note that the ATP concentration inside cells may not be uniform at a subcellular level [10]. Unequal spatial ATP distribution may be accounted for by several factors, among which are the site (and rate) of ATP production, the rate of ATP diffusion and the rate of ATP consumption. Thus, radial diffusion of ATP from mitochondria predicts that the ATP concentration will decrease as a function of distance from the mitochondria and that more distally located process (such as membrane ion translocators) may be subjected to lower mitochondrial ATP levels in comparison to cytosolic proteins (such as contractile proteins). This idea has been verified experimentally by (among others) the demonstration that in liver cells, the plasma membrane Na⁺-K⁺-ATPase is substantially more sensitive to alterations in ATP supply than the cytosolic ATP-sulfurylase enzyme [11]. Metabolically active cells (such as contractile myocytes) are expected to have steeper ATP gradients relative to the site of production due to their higher rates of ATP consumption. Also, the ATP gradients between mitochondria and more distally located membrane-bound proteins (such as ion translocators) may be subjected to lower mitochondrial ATP levels in comparison to cytosolic proteins (such as contractile proteins). This idea has been verified experimentally by (among others) the demonstration that in liver cells, the plasma membrane Na⁺-K⁺-ATPase is substantially more sensitive to alterations in ATP supply than the cytosolic ATP-sulfurylase enzyme [11]. Metabolically active cells (such as contractile myocytes) are expected to have steeper ATP gradients relative to the site of production due to their higher rates of ATP consumption. Also, the ATP gradients between mitochondria and more distally located membrane-bound proteins (such as ion translocators) may be exacerbated during conditions of metabolic impairment, when mitochondrial ATP production rates decrease and ATP demand increases [11]. It is therefore easy to visualize how glycolytic enzymes (if located at submembrane locations) might be able to control these membrane-bound processes by the production of glycolytic intermediates and delivery of ATP in the immediate micro-environment.