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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 plasmalemma 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 Ca^{2+}-ATPases, the Na^+/H^+ exchanger, the ATP-sensitive K^+ channel, cation channels, Na^+ channels, Ca^{2+} channels and other channels involved in intracellular Ca^{2+} 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.

Energy metabolism results in the formation of ATP, which provides energy to reactions as diverse as building cell components, cell motility, muscle contraction, transmission of nerve impulses and excitability. The chief pathways contributing to ATP generation are glycolysis, oxidative phosphorylation and fatty acid metabolism. This review will focus on the process of glycolysis and how glycolytically derived products preferentially regulate the activity of many membrane-localized ion translocators (pumps, exchangers and channels).

Glycolysis

Also known as the Embden-Meyerhof pathway, glycolysis is an evolutionary ancient metabolic process, comprising ten enzymes (see Table 1), in which glucose is converted to two moles of pyruvate and NADH with the concomitant generation of two moles of ATP. The overall reaction is:

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Table 1. The glycolytic enzymes, other enzymes closely related to the glycolytic process, their abbreviations, gene name, an example protein structure number (PDB ID) and example GenBank ID of the protein.

Enzyme	Abbreviation	Gene	Structure	Protein
Hexokinase	HK	HK1	1HKG	NP_000179
Phosphoglucose isomerase	PGI	GP1	1HOX	NP_000166
Phosphofructokinase	PFK	PFKL	4PFK	NP_001002021
Fructose 1,6-bisphosphate aldolase	aldolase	ALDOA	4ALD	NP_000025
Triose phosphate isomerase	TPI	TPI1	1TIM	NP_000356
Glyceraldehyde 3-phosphate dehydrogenase	GAPDH	GAPDH	3GPD	NP_002037
Phosphoglycerate kinase	PGK	PGK1	3PGK	NP_000282
Phosphoglycerate mutase	PGM	PGAM2	1PGM	NP_000281
Enolase	enolase	ENO1	3ENL	NP_001419
Pyruvate kinase	PK	PKM2	1PYK	NP_002645
Pyruvate dehydrogenase	PDH	PDHA1	1JM6	NP_000275
Lactate dehydrogenase	LDH	LDHA	5LDH	NP_005557

Note that various isoforms of many of these enzymes are expressed; this list is not comprehensive and only some of these are shown.

$$glucose + 2 \cdot NAD^+ + 2 \cdot ADP + 2 \cdot P_i \rightarrow$$
$$2 \cdot pyruvate + 2 \cdot NADH + 2 \cdot H^+ + 2 \cdot ATP + 2 \cdot H_2O$$

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 transporters) 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) would 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

of these membrane protein complexes. Since glycolysis is stimulated under hypoxic conditions [12, 13], the contribution of this metabolic pathway in maintaining ionic flux and homeostasis is expected to become highly relevant.

The membrane-bound localization of glycolytic enzymes – a prelude to their function

Consistent with the notion that glycolysis may maintain the energetic states in the close proximity of membrane-bound processes such as ion translocators, overwhelming evidence demonstrates that most (if not all) of the glycolytic enzymes are indeed associated with membranes – both at the cell surface and with membranes of intracellular compartments such as the sarcoplasmic reticulum [14–20]. For example, plasma membrane vesicles (obtained from pig stomach antrum smooth muscle) contain the full complement of glycolytic enzymes, including lactate dehydrogenase (LDH), pyruvate kinase (PK), enolase, phosphoglyceromutase, phosphoglycerate kinase (PGK), GAPDH, aldolase and hexokinase [21, 22]. Although there have been reports suggesting that membrane-bound glycolytic enzymes lose their activity [23], these glycolytic enzymes are functional, since addition of FDP, NAD^+, ADP, and P_i to these membrane vesicles supported ^{45}Ca transport and production of NADH and lactate. Similarly, there is strong evidence for membrane-associated glycolytic enzymes in heart sarcolemmal and sarcoplasmic reticular membrane fractions and for the functional activities of these enzymes [17]. A subsequent study also reported that the entire chain of glycolytic enzymes from aldolase onward, including aldolase, GAPDH, PGK, phosphoglyceromutase, enolase and PK are all associated with sarcoplasmic reticulum (SR) vesicles from both cardiac and skeletal muscle [24].

The mechanism for the membrane-bound subcellular localization has not been fully explored, but is likely to involve the subcortical f-actin network. Experimentally, it has been demonstrated that several of the glycolytic enzymes (including aldolase, GAPDH, LDH, PK and PGK) directly interact with cytoskeletal actin and that this interaction is responsible for their membrane localization [25, 26]. However, not all glycolytic enzymes bind to the cytoskeleton [26]. In all likelihood, therefore, a functional glycolytic unit is only produced at the submembrane space when each of the enzymes complexes with each other in association with the cortical cytoskeleton, which would place the glycolytic ATP-generating factory in close proximity to many membrane-bound ion transporters.

Regulation of ion pumps by glycolysis

The Na^+-K^+-ATPase

The Na^+-K^+-ATPase (or Na^+/K^+ pump) is a transmembrane protein present in all eukaryotic cells that transports Na^+ and K^+ ions across the membrane against their electrochemical gradients by using the energy of ATP hydrolysis. The ensuing transmembrane gradients of Na^+ and K^+ are used in diverse physiological processes. For example, the activities of many transporters (e.g. of amino acids), ion exchangers (such as the Na^+/Ca^{2+} exchanger) and ion channels (e.g. the Na^+ channel) depend directly on the potential energy stored in the form of the ensuing Na^+ gradient across the cell membrane. Similarly, the unequal distribution of K^+ is responsible for the establishment of the resting membrane potential of cells and for repolarizing the action potential following the upstroke of the action potential. Furthermore, since the Na^+/K^+ pump translocates an unequal number of Na^+ and K^+ ions with each cycle (three Na^+ ions and two K^+ ions), it is an electrogenic process and as such can directly contribute to the electrical activity of cells. Hence, factors that regulate the Na^+/K^+ pump (such as glycolysis) may indirectly influence a multitude of physiological processes, both in health and disease.

The Na^+/K^+ pump was one of the first membrane proteins to be described to be preferentially regulated by glycolytically derived ATP. The early studies to demonstrate that membrane-bound ATP fuels the Na^+/K^+ pump were performed by examining effects of glycolytic enzyme activity on the Na^+/K^+ pump in human red cell membranes [27]. Since then, ample support in the literature exists for the concept that Na^+/K^+ pump activity is fueled by glycolytically derived ATP. This has been observed in several tissue types, including the squid giant axon, mammalian erythrocytes or red cell ghosts, brain synaptosomes, kidney cells, skeletal muscle, smooth muscle and cardiac myocytes [28–37]. Techniques used to demonstrate this phenomenon range from flux measurements of radioactive ions and electrophysiological approaches to measure the 'pump current' produced by the electrogenic Na^+/K^+ pump. For example, in cardiac Purkinje cells, it has been shown that ATP generated via glycolysis is used preferentially over that generated by oxidative phosphorylation to drive the pump [38]. In the latter study, the Na^+/K^+ pump current, recorded using whole-cell patch clamp techniques, was only modestly affected by inhibition of oxidative phosphorylation when compared to the glycolytic inhibition [with iodoacetic acid (IAA)]. Glycolytically derived ATP was similarly shown to fuel the Na^+/K^+ pump in human red cells, MDCK cells, Rous-transformed hamster cells and Ehrlich

ascites tumor cells [27, 37,39, 40]. The localization of key glycolytic enzymes close to the pump has been postulated to provide the ATP to the pump to carry out this function. For example, GAPDH and PGK have been shown to associate with the Na^+/K^+ pump in human red blood cells [39, 41]. The ATP generated by these enzymes has been suggested to accumulate into a submembrane pool to preferentially regulate the Na/K pump [27, 42, 43]. Another glycolytic enzyme, triosephosphate isomerase which catalyzes the conversion of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate, has also been demonstrated to associate with the Na^+-K^+-ATPase through cofilin, an actin binding protein [44]. Thus, there is clear evidence for preferential regulation of the Na^+/K^+ pump by glycolytically derived ATP.

The proton pump (H^+-ATPase)

The V-type H^+-ATPase transforms the energy of ATP hydrolysis to active proton transport across diverse biological membranes (both intracellular and plasmalemmal). The transmembrane H^+ gradient established is then used to drive several H^+-dependent transport systems (symporters and antiporters) as well as H^+ flux through channels. The V-type H^+-ATPase was first described in endosomal membranes, where it is responsible for acidification of endosomes. It is now known to have important functions in diverse intracellular organelles as well as the plasma membrane and it regulates the functions of secretory vesicles, the trans-Golgi network, endosomes, lysosomes and the yeast vacuole. In some specialized cells, such as kidney epithelial cells and osteoclasts, V-ATPases reside at high levels on the plasma membrane where they are responsible for transepithelial or cellular proton transport [45, 46].

At the molecular level, it is now understood that the V-type H^+-ATPase consists of up to 14 protein subunits arranged in a membrane-embedded V_0 complex, which translocates H^+ across the membrane, as well as a cytoplasmic V_1 complex, which mediates the hydrolysis of ATP [47]. Extracellular glucose regulates V-type H^+-ATPase activity *in vivo* by regulating the extent of association between V_1 and V_0 [48]. It is clearly understood that the ATP is being used to drive the H^+-ATPase, but the mechanism for coupling pump activity to metabolism is less well explored. Early studies suggested a coupling between glycolytically derived ATP and H^+ transport activity. For example, under anaerobic conditions in the turtle urinary bladder, H^+ transport was maintained in the absence of mitochondrially produced ATP [49]. Also, glucose-induced H^+ efflux from Ehrich ascites tumor cells (due to the production of glycolytically produced lactic acid) was strongly correlated with the rate of glycolysis [50]. The strongest argument for an involvement of glycolytically produced ATP to H^+ transport comes from relatively recent studies, where yeast two-hybrid approaches have identified glycolytic enzymes as components of the H^+-ATPase complex. For example, using the E subunit of V-type H^+-ATPase as bait to screen a human kidney cDNA expression library, the glycolytic enzyme aldolase was found to be an interacting partner. Interaction was independent of the presence of actin or glycolytic substrates. In mouse kidney, colocalization was observed for the V-type H^+-ATPase E subunit and aldolase and, finally, aldolase was found to be required for assembly of V_1V_0 complexes [51]. In a subsequent study, aldolase was found to interact directly with three different subunits of V-ATPase (subunits a, B and E) [52]. The role of glycolytic enzymes in V-type H^+-ATPase assembly and function was also demonstrated in other studies. In a phage display and immunoprecipitation analysis, the V-type H^+-ATPase a subunit was found to associate with the glycolytic enzyme PFK-1 and to colocalize with PFK-1 in human kidney tissue sections [53]. Thus, the evidence is overwhelming for a direct interaction between glycolytic enzymes and subunits of the V-ATPase and how this interaction dictates both the assembly and function of this H^+ pump.

Calcium pumps (Ca^{2+}-ATPases)

Ca^{2+} influx into cells or Ca^{2+} release from intracellular organelles is required for excitation-contraction coupling, stimulus-secretion coupling and receptor-mediated Ca^{2+} signaling. The increase in cytosolic Ca^{2+} is transient and Ca^{2+} must be resequestered in intracellular organelles or extruded from the cell to maintain low resting intracellular Ca^{2+} levels. To this end, mammalian tissues employ a large number of Ca^{2+}-transporting ATPases. They are encoded by at least nine different alternatively spliced genes and belong to three subfamilies of the P-type superfamily of ion transport ATPases. These are the secretory pathway Ca^{2+}-ATPases (SPCAs), the sarco(endo)-plasmic reticulum Ca^{2+}-ATPases (SERCAs) and the plasma membrane Ca^{2+}-ATPases (PMCAs) [54–59].

Plasma membrane Ca^2-ATPases

Glycolysis has long been recognized as an important regulator of Ca^{2+} homeostasis in many eukaryotic cells [e.g. see ref. 60]. One of the ways this is manifested is the regulation of sarcolemmal Ca^{2+}-ATPases by glycolytically derived ATP [21, 22]. There is also evidence for preferential regulation of plasmalemmal Ca^{2+}-ATPases by glycolytically derived ATP (e.g. in peripheral sensory nerve terminals [61]).

Sarco(endo)plasmic reticulum Ca^{2+}-ATPases

In conjunction with the Na^+/Ca^{2+} exchanger, plasmalemmal Ca^{2+} pumps, and the SR Ca^{2+} release channel (see below), SERCAs play a crucial role in the maintenance of Ca^{2+} homeostasis in many cell types, such as smooth muscle, cardiac and skeletal myocytes. Molecular cloning studies have revealed three distinct genes that SERCAs, namely SERCA1, SERCA2 and SERCA3 [57, 58, 62].

There is a fairly large body of literature to demonstrate the preferential regulation of SERCAs by glycolysis [reviewed in ref. 63]. For example, biochemical data obtained with triads from rabbit skeletal muscle have shown that they can synthesize ATP from GAP or FDP and that this ATP is compartmentalized and not in equilibrium with bulk ATP [64]. Although it has been known for some time that glycolytic enzymes are associated with membranes of the cardiac SR [17, 65], their role in regulating SR Ca^{2+} pumps was not established until fairly recently. In a study using sealed right-side-out SR vesicles from rabbit skeletal and cardiac muscle, it was found that ^{45}Ca transport was supported by glycolytic substrates and cofactors specific for each of the glycolytic reactions [24]. Interestingly, Ca^{2+} transport was inhibited by IAA acid (an inhibitor of GAPDH) when the fuel was fructose-1,6-diphosphate (the substrate for aldolase), but restored by phosphoenolpyruvate (the substrate for PK). These functional data demonstrate that enzymes involved in each of the two ATP-producing steps are associated with the SR membrane and are capable of providing ATP for the Ca^{2+} pump. Effects of glycolysis on SR Ca^{2+} transport are also evident in intact myocytes. For example, in isolated cat cardiac myocytes, local application of glycolytic inhibitors (2-DG and IAA) reduced the rate of reuptake of Ca^{2+} into the SR, which was accompanied by a 15–20% decrease of SR Ca^{2+} load [66]. Interestingly, the possibility exists that glycolysis, in turn, may also be dynamically regulated by alterations in intracellular Ca^{2+} levels. A large part of the cellular functions of Ca^{2+} are mediated by the ubiquitous intracellular Ca^{2+} receptor, CaM. The Ca^{2+}·CaM complex allosterically activates numerous proteins, including Ca^{2+}/CaM-dependent protein kinase II (CaMKII). A recent study, performed with SR fractions isolated from rabbit skeletal muscle, showed that the SR membrane-bound CaMKIIβ_M associates with and is able to phosphorylate GAPDH and can regulate its activity in a Ca^{2+}-dependent manner [67]. Thus, Ca^{2+} signaling may serve to modulate GAPDH and thereby ATP and NADH levels at the SR membrane, which in turn will regulate calcium transport processes.

Ion exchangers

Ion exchangers function by transporting ions against their concentration gradients. The energy needed for this 'uphill' transport is derived from the transmembrane concentration gradients of other ions, which in turn were established by ATP-consuming ion pumps. Examples of ion exchangers include the Na^+/Ca^{2+} exchanger, which uses the prevailing inward Na^+ electrochemical gradient to drive Ca^{2+} ions out of the cell, and the Na^+/H^+ exchanger, which utilizes the same Na^+ gradient to maximize the efflux of protons from the cell. Some ion exchangers are electrogenic in that they translocate unequal changes across the cell membrane. For example, the Na^+/Ca^{2+} exchanger translocates three Na^+ ions into the cell for every Ca^{2+} extruded, which causes net movement of charge (i.e. electric current) across the cell membrane. Due to their electrogenic nature, these exchangers can directly contribute to the electrical activity of an excitable cell.

Ion exchangers do not depend directly on ATP hydrolysis for their activities. However, they do indirectly depend on energy derived from ATP, which is used by ionic pumps to establish the ionic gradients on which they depend. The preceding section outlined the preferential role for glycolytically derived ATP in the function of several of these pumps, the most notable being the Na^+/K^+ pump. Conceptionally at least, alterations in pump function (and the ensuing changes in the transmembrane Na^+ gradient) may impact the activity of several of the ion exchangers (including the Na^+/Ca^{2+} exchanger and the Na^+/H^+ exchanger). However, it is not clear whether this is in fact the case. For example, there is very little evidence that the Na^+/Ca^{2+} exchanger is specially regulated by glycolysis. In contrast, the Na^+/H^+ exchanger appears to be preferentially regulated by glycolysis [68–71]. In an interesting study, however, the suppression of Na^+/H^+ exchange activity by glycolytic inhibitors was found to occur in the absence of alterations in the cytosolic Na^+ activity (measured with ion-sensitive electrodes) [72], as would be expected if the effect was secondary due to Na^+/K^+ pump blockade. It should be noted, however, that experiments performed with intact hearts suggested that there is indeed an involvement of glycolysis in Na^+ homeostasis [8, 73]. Furthermore, it is entirely possible that the Na^+ activity only changed locally in a submembrane compartment (the so-called 'fuzzy space' [74, 75]), which may in turn affect the Na^+/H^+ activity. The latter explanation is unlikely given the effect of glycolysis on the Na^+/H^+ exchanger without an apparent strong inhibition on other Na^+-dependent exchangers (such as the Na^+/Ca^{2+} exchanger). Since the Na^+/H^+ exchanger is less sensitive to inhibitors of

oxidative phosphorylation compared to inhibitors of glycolysis [72, 73], it is likely that one or more glycolytic intermediates or products directly affect the activity of the Na^+/H^+ exchanger. Without excluding other possibilities, an attractive candidate is that glycolytically produced ATP may directly participate in the direct phosphorylation of the Na^+/H^+ exchanger, which is known to increase its function [76]. Alternatively, it is possible that locally produced ATP may participate in other phosphorylation reactions, such as those in the phosphatidylinositol pathway, which may affect the Na^+/H^+ exchanger by alterations in PIP_2 levels. Further exploration of these pathways is warranted – also in the context of other pumps, exchangers and channels.

Regulation of ion channels by glycolysis

Ion channels are responsible for setting the membrane potential in both excitable and non-excitable mammalian cells. They play an important role in a host of biological activities (such as excitation-contraction coupling and excitation-secretion coupling). By sensing the metabolic state of the cell, they can also couple the intracellular oxidative or energy status of the cell to alterations in metabolism. Several ion channels are sensitive to glycolytic activity and as such couple glucose metabolism directly to excitability.

ATP-sensitive K^+ (K_{ATP}) channels

ATP-sensitive potassium (K_{ATP}) channels derive their name by virtue of their regulation by intracellular nucleotides. First described to be blocked by cytosolic ATP [77], we now know that the channel is also activated by Mg-ADP [78] and that it is the ATP:ADP ratio that controls K_{ATP} channel opening. The best described role for K_{ATP} channels is in the pancreatic β-cell, where ATP production from glucose closes the normally open K_{ATP} channel, which results in membrane depolarization, excitability, elevation of intracellular Ca^{2+} and secretory insulin release [79]. The K_{ATP} channel is also strongly expressed in glucose-sensing neurons [80], which modulate their firing rate in response to blood glucose levels (thus linking food intake to behavior). In the cardiovascular system, K_{ATP} channels are responsible for maintenance of the basal vascular tone and regulate processes such as autoregulation of coronary blood flow and hypoxic vasodilation [81]. Recent data assign a role for K_{ATP} channels in the vascular endothelium to the regulation of secretory release of the vasoconstrictor, endothelin-1 [82]. In the cardiac myocyte, K_{ATP} channels have been implicated in protection of the heart against stress responses[83, 84] and pathophysiological processes such as protection from ischemic insults [85]. The sensitivity of these channels to intracellular nucleotides places these channels in the unique position to couple cellular energy metabolism directly to excitability and secretion.

At a molecular level, K_{ATP} channels are hetero-octameric complexes, consisting of four pore-forming subunits belonging to the inward rectifier family (Kir6.1 and Kir6.2) and four regulatory subunits (SUR1 and SUR2) belonging to the ATP-binding cassette superfamily (ABC proteins) [86]. Increasingly, the K_{ATP} channel (as is the case with many other membrane proteins) is recognized as belonging to a macromolecular complex that includes other subunits with non-channel functions, which may modulate the functional properties and regulation of the channel. For example, K_{ATP} channels were found to couple to metabolic enzymes such as creatine kinase and adenylate kinase, which participate in the phosphotransfer reactions that link mitochondrial ATP production to K_{ATP} channel activity [87]. Despite this important mode of regulation of K_{ATP} channel activity, it has been recognized for some time now that K_{ATP} channel activity is preferentially regulated by glycolytically derived ATP. In a series of elegant experiments, the Weiss laboratory have demonstrated that in the open-cell patch clamp configuration, K_{ATP} channels could be closed equally well by ATP production produced when perfusing cells with substrates of oxidative phosphorylation, the creatine kinase system or glycolysis. However, in the presence of an intracellular ATP-consuming system, glycolytic enzymes were far more efficient in blocking K_{ATP} channel activity, suggesting that glycolytic ATP (or intermediates) formed in the immediate vicinity of the K_{ATP} channel preferentially blocks K_{ATP} channels [88]. From these data came the interpretation that key glycolytic enzymes are located near K_{ATP} channels at the plasma(sarco)lemma. The regulation of K_{ATP} channels by glycolysis has also been demonstrated in tissues other than the heart. Dubinsky et al. [89] showed that the activity of K_{ATP} channels in the basolateral membranes of *Necturus* enterocytes is influenced by ATP formed in the vicinity of these channels through the action of PK that is associated with this membrane. A structural basis for these data was recently obtained by our finding that K_{ATP} channel subunits physically associate with key glycolytic enzymes [90]. In a two-hybrid screen, using a K_{ATP} channel subunit as bait in a screen against a rat heart cDNA library, we found GAPDH and triosephosphate isomerase as putative interacting proteins. Indeed, interaction was confirmed by coimmunoprecipitation assays; both in transfected cells as well as membrane prepared from rat hearts. Others have also

found GAPDH to coimmunoprecipitate with K_{ATP} channel subunits [91]. Similarly, we also found that PK coimmunoprecipitated with K_{ATP} channel subunits. Supportive of their interaction, immunocytochemistry of isolated cardiac myocytes demonstrated membrane localization of PK and GAPDH, where they colocalized with K_{ATP} channel subunits. Finally, substrates for these glycolytic enzymes inhibited K_{ATP} channel activity (both in the open-cell and inside-out configurations), suggesting that glycolytic activity (such as ATP formation in the immediate environment of the K_{ATP} channel complex) directly blocks K_{ATP} channel activity. These data provide a structural basis for the early observations of a preferential role of glycolytically produced ATP in inhibiting K_{ATP} channel activity.

The functional and physiological significance of glycolysis in regulating K_{ATP} channels is widespread. For example, during myocardial ischemia, K_{ATP} channels open and account partially for K^+ loss from the ischemic myocardium [92]. The action potential shortening during hypoxia and metabolic inhibition that occurs as a result of K_{ATP} channel opening is rapidly reversed by glucose [93, 94], suggesting that the glycolytic process may limit K_{ATP} channel opening during metabolic impairment. It is interesting to note a published report suggesting *activation* of K_{ATP} channels by the glycolytic intermediate, 1,3-bisphosphoglycerate [91]; these data may be relevant in pathophysiological conditions of severe hyperglycemia, where K_{ATP} channel activation may be protective. Similarly, other end-products of glycolysis (such as lactate) may activate the K_{ATP} channel [95, 96]. In the coronary vascular smooth muscle, inhibition of glycolysis causes almost maximal K_{ATP} channel-mediated vasodilation [97], suggesting a strong coupling between glycolysis, K_{ATP} channel activity and coronary blood flow. In the pancreatic β-cell, insulin release is strongly correlated with glucose uptake, glycolytic ATP production and K_{ATP} channel activity, both from glycolytic ATP production as well as from the production of other glycolytic intermediates, such as NADH [98]. The NADH shuttle system, composed of the glycerol phosphate and malate-aspartate shuttles, may efficiently couple glycolysis to mitochondrial ATP generation, which may be important for both K_{ATP}-channel-dependent and -independent steps of insulin release [99]. Thus, inhibition of K_{ATP} channels by glycolytic products has the potential to regulate insulin secretion. Finally, K_{ATP} channels may compete with other physiological processes for the same glycolytically derived ATP, such that the activity of one process may regulate the other. For example, there is an interesting functional interaction between K_{ATP} channels and the Na^+/K^+ pump, whereby the activity of one determines the activity of the other, most likely by competition for the same glycolytically derived ATP [100–104]. Whereas the role of such an interaction during metabolic impairment is easy to rationalize, the significance in a physiological context remains to be determined.

Other K^+ channels

Apart from K_{ATP} channels, there is not much evidence for the regulation of other types of K^+ channel by glycolysis. Hyperglycemia and hypoglycemia can both cause prolongation of the Q-T interval and ventricular arrhythmias. An important repolarizing K^+ current is the human ether-a-go-go-related gene (HERG) K^+ channel. It was found that HERG channels are indeed inhibited by hypoglycemia [105], but there did not appear to be a distinctive role for glycolysis. In contrast, the inward rectifier K^+ current in Muller (glial) cells of the vertebrate retina, which are pathways for the redistribution of excess extracellular K^+, was found to be ATP sensitive [106]. Furthermore, it was found that the activity of the channels was maintained by ATP synthesized at sites located in close proximity to the channel, suggestive of a role for glycolysis in K^+ homeostasis in glial cells. A likely candidate for these channels is the Kir4.1 subunit [107], which forms channels known to be ATP regulated [108]. These subunits are also expressed in other tissues such as the mammalian cochlea, central chemoreceptors in brainstem neurons and gastric smooth muscle [109–111], but the functional relevance of possible glycolytic control of K^+ conductances in these tissues remains to be determined.

Cation channels

In visceral smooth muscle, a non-selective cation channel is involved in pacemaker activity and is strongly modulated by neuromodulation, for example by muscarinic stimulation [112, 113]. There are reports suggesting that these non-selective cation channels are regulated by glycolytic ATP. For example, in guinea pig ileal myocytes, deprivation of external glucose or its replacement with 2-deoxyglucose significantly reduced the magnitude of the non-selective cation current. In the nystatin-perforated patch clamp recording technique, glycolytic inhibition was more effective in reducing the current than blockade of oxidative phosphorylation or the creatine-phosphocreatine system [114], suggestive of a preferential regulation of these channels by glycolysis. TRPC subunits (in particular TRPC4 and TRPC7 [112, 115]) are thought to be components of non-selective cation channels in mammalian gastric smooth muscle. The canonical TRPC channels are expressed ubiquitously in a variety of other cell types

[116] and future studies are needed to determine to what extent TRPC channel activity is mediated by glycolytically derived ATP.

Na^+ channels

In many excitable cells (including cardiac myocytes and neurons), Na^+ channels are responsible for the rapid depolarization during the onset of the action potential. The rate of rise of the action potential partly determines the conduction velocity. Furthermore, as has been demonstrated in some forms of the hereditary long-QT syndrome, alteration in Na^+ channel gating kinetics may cause life-threatening arrhythmias [117]. Very little is known regarding the role of glycolysis in Na^+ channel activity. In excised patches obtained from neonatal rat cardiac myocytes, it was found that the glycolytic intermediates 2,3-diphosphoglycerate and glyceraldehyde phosphate facilitate channel opening at micromolar concentrations [118]. However, glycolysis appears not to affect the *amplitude* of the cardiac Na^+ current [119]. Interestingly, in the former study, channels were more likely to reopen during a maintained depolarization, suggesting that Na^+ channel inactivation kinetics may be regulated by glycolysis. The physiological or pathophysiological consequences of this putative regulatory mechanism of Na^+ channel activity are not known.

Ca^{2+} homeostasis

This section will largely focus on Ca^{2+} homeostasis of cardiac muscle; in principle, many of these concepts can be extrapolated to Ca^{2+} regulatory mechanisms in other tissues. In cardiac muscle, a contractile event is initiated by influx of Ca^{2+} into the cell through voltage-gated Ca^{2+} channels (and to some extent via the 'reverse' mode of the Na^+-Ca^{2+} exchanger). This small amount of Ca^{2+} triggers a large efflux of Ca^{2+} from the SR through specialized Ca^{2+} channels (the ryanodine receptors), which causes the contraction. During relaxation, the excess Ca^{2+} is pumped back into the SR by ATP-driven Ca^{2+} pumps (SERCAs) and also extruded to the exterior via the Na^+-Ca^{2+} exchanger and sarcolemmal Ca^{2+} pumps. There are many reports demonstrating that intracellular Ca^{2+} levels are under dynamic regulation of energy metabolism, and more specifically, the glycolytic process. Evidence was discussed above for regulation of PMCAs and SERCAs by glycolysis. The remainder of this section will deal with evidence summarizing an involvement of the glycolytic process in some of the other processes involved in Ca^{2+} homeostasis.

L-type calcium channels

The L-type voltage-dependent Ca^{2+} channel, also known as the dihydropyridine receptor due to its blockade by this class of compounds, opens in response to membrane depolarization, to allow Ca^{2+} influx into the cytosol. In cardiac cells, Ca^{2+} influx through L-type Ca^{2+} channels initiates contraction and in some cells (such as pancreatic β-cells or neurons) initiates secretory release of hormones and neurotransmitters. The L-type Ca^{2+} channel consists of a hetero-octameric polypeptide comprised of α1, α2/δ and β subunits. The α2/δ subunits are closely associated with the α1 subunit by surface interaction and are intracellularly linked through a disulfide bridge to the δ subunit [120].

As is the case for several other ionic channels, the L-type Ca^{2+} channel is regulated by intracellular ATP. Early data obtained using guinea pig ventricular papillary muscle found that the action potential shortening during hypoxia was sensitive to glycolytic ATP. For example, increasing extracellular glucose counteracted action potential shortening, whereas agents that inhibited glucose transport or glycolysis caused action potential shortening [121]. These results, along with measurements of muscle ATP content and lactate production [122], suggest that the duration of the action potential is dependent on the level of glycolytic ATP. Intracellular injection of ATP in whole-cell patch clamp studies of guinea pig myocytes resulted in a 40–60% prolongation of action potential duration [123], which correlated with a corresponding increase in L-type Ca^{2+} current [124]. Some of these effects may well be mediated through glycolytically mediated alterations in K_{ATP} channel activity (see earlier). Nevertheless, there is direct evidence from experiments utilizing whole-cell voltage-clamped rabbit cardiomyocytes to suggest that Ca^{2+} channels themselves may also be regulated by glycolysis [125]. In the latter study, glycolytic inhibition (2-deoxyglucose plus pyruvate) caused a substantial decrease in the whole-cell Ca^{2+} current, whereas oxidative inhibition (cyanide plus glucose) had no effect on current amplitude. Similar decreases in the Ca^{2+} current occurred when glycolysis was inhibited by 2-deoxyglucose or iodoacetamide. This study also provided insight into the possible mechanism; in cells dialyzed with AMP-PCP, glycolytic inhibition failed to decrease the Ca^{2+} current, suggesting that the Ca^{2+} current is regulated by intracellular ATP derived from glycolysis, but that it does not require the hydrolysis of ATP, as has been previously suggested in the literature [126, 127]. Direct phosphorylation-independent regulation of the Ca^{2+} current has also been demonstrated in smooth muscle cells from rat mesenteric artery and in portal vein, which also appear to be preferentially regulated by glycolytically derived ATP [128, 129], which provides a link between vascular contractility and the its

dependence on the glycolytic energy status of the vascular myocyte [60]. The preferential utilization of glycolytic ATP by L-type Ca^{2+} channels is consistent with the observation that glycolytic enzymes are colocalized with Ca^{2+} channels, for example, as found in skeletal muscle [130].

The ryanodine receptor

Ca^{2+} is released from the endo- and sarcoplasmic Ca^{2+} stores via specific Ca^{2+} channels, named ryanodine receptors (RyR; named after the plant alkaloid that specifically blocks these channels). Three isoforms have been identified: RyR1 that is mostly expressed in skeletal muscle; RyR2 in cardiac muscle; RyR3 in the nervous system [131]. RyRs are regulated by a variety of physiological factors and pharmacological agents. The main physiological modulators are calcium, protein phosphorylation, the redox state and the cellular energy status.

In cardiac and skeletal muscle, the RyRs are located at the junctional SR of the triad. This localization ensures efficient Ca^{2+} release to the contractile proteins. Evidence for regulation of SR membrane proteins by glycolysis stems from the observation that glycolytic enzymes associate with SR membranes (see earlier). For example, isolated skeletal muscle triads were found to contain a compartmentalized glycolytic reaction sequence catalyzed by aldolase, triosephosphate isomerase, glyceraldehyde-3-phosphate dehydrogenase and phosphoglycerate kinase. Using different substrates for these various enzymes, it has been found that the RyR was particularly sensitive to the glycolytic intermediate, fructose 1,6-bisphosphate, which both increased ryanodine binding and increased the open probability of RyR channels [64]. Similar data have been reported for RyR2 isolated from cardiac muscle [132], suggesting that sugar phosphate glycolytic intermediates may regulate RyR gating and function. Physiological data directly support this concept. In isolated cat atrial myocytes, focal inhibition of glycolysis caused subcellular alterations of Ca^{2+} homeostasis, consistent with an effect mediated by alterations in SR Ca^{2+} release [133]. These effects are likely to be mediated directly by the sugar phosphates, since application of phosphocreatine, fructose-1,6-bisphosphate and fructose-6-phosphate causes a transient increase of Ca^{2+} spark frequency and a depletion of SR Ca^{2+} load in permeablized cardiac myocytes, which was not prevented by inhibitors of glycolysis [134]. FBP and F6P directly increased RyR channel activity. These effects of glycolysis may be partly responsible for the oscillations in SR Ca^{2+} release that are associated with alterations in glycolytic rate [135].

Physiological and pathophysiological relevance

Given that a number of ion transporters and ion channels are preferentially affected by glycolysis, the physiological role of glycolysis in tissue and cellular function can be assessed in this context. This topic is quite comprehensive by its very nature and is beyond the scope of this review. The text below serves to illustrate some specific examples where glycolytic regulation of channels and transporters can be relevant in the context of cellular function.

Insulin release and the control of blood glucose

Glucose is a major source of energy for most living organisms. It is not surprising, therefore, that specialized systems are in place to sense blood glucose levels and to couple glucose levels to excitability and cellular function. One of the best characterized examples of where changes in blood glucose levels are translated to alterations in cellular excitability and function is the regulation of insulin release by pancreatic β-cells in response to increased plasma glucose levels. It is thought that after entry of glucose into the cell, acceleration of glucose metabolism occurs, which increases the ATP content (or more correctly, the ATP/ADP ratio), which in turn leads to closure of K_{ATP} channels, membrane depolarization, opening of voltage-dependent Ca^{2+} channels, increases in Ca^{2+} influx and intracellular Ca^{2+} activity, which stimulates exocytosis of insulin-secreting granules [136]. It is clear that both glycolysis and mitochondrial metabolism may be important to regulate any of these processes. A role for glycolysis can be visualized at several of these steps. First, the essential role of glucokinase should be recognized as an essential glycolytic enzyme in regulating the rate of islet glucose utilization [137]. In support, population studies have shown that mutations in the glucokinase gene can lead to development of an autosomal dominant form of diabetes [138]. There are indications from the literature that inhibitors of glycolysis suppress glucose-stimulated insulin secretion, whereas blockers of pyruvate transport or Krebs cycle enzymes are without effect [139], suggestive of an essential role of glycolysis in the glucose response. Although not all studies are in complete agreement with this finding, there is clear evidence for a role of glycolysis in glucose-stimulated insulin releasee [139 but see ref. 140]. Glucose additionally induces complex patterns of oscillations in intracellular excitability, the Ca^{2+} activity and insulin secretion. There is evidence to suggest an involvement of glycolysis in these oscillations [141, 142]. The mechanisms(s) responsible have not been elucidated, but K_{ATP} channels are attractive candidates, given their established role in the first

phase of insulin release [79] as well as their preferential regulation by glycolysis [143]. Their regulation can be mediated both by alterations in the ATP/ADP levels in the immediate microenvironment of the channel that are caused by the glycolytic enzymes that form part of the K_{ATP} channel macromolecular complex [90] and by regulation of channel activity due to the glycolytically produced NADH, which through an NADH shuttle system may couple glycolysis to mitochondrial ATP generation [99]. Of course, it may also be possible for glycolysis to co-regulate any of the other steps (in addition to other ion pumps, exchangers and channels) involved in coupling glucose metabolism to insulin secretion, but their relative contributions to overall insulin secretion remain to be examined. Indeed, mathematical modeling of metabolic processes and pancreatic β-cell excitability suggest a clear involvement of glycolysis in alterations in membrane potential, ion channels and cytosolic Ca^{2+} [144].

Neuronal function

Although the brain represents only 2% of the total body weight, it is responsible for 25% of total body glucose utilization. Glucose is essentially the sole energy substrate in the normally functioning brain. For a review of glucosensing mechanisms in the brain, the reader is referred to Levin [145]. It has been known for some time, for example, that glycolysis mediates K^+ uptake into brain cells by preferential activation of the Na^+/K^+ pump [146, 147] and that this phenomenon partially accounts for the dependence of brain function on glycolysis. Astrocytes, which are largely responsible for K^+ equilibration in the brain, receive up to 40% of their total ATP production from glycolysis [148]. In support, functional compartmentalization of energy production was demonstrated in neural tissue, with glycolytic energy production shown to be preferentially used by Na^+/K^+ pumps to maintain normal ionic homeostasis [6]. During anoxic conditions, glycolysis may well protect neuronal function, for example as illustrated by a preferential role for glycolysis in preventing the anoxic depolarization of rat hippocampal area CA1 pyramidal cells [149] and damage to synaptic transmission [150]. Glycolysis may serve other facets of neural function as well. Hypoglycemia causes impaired synaptic transmission, which takes place well before there are changes in the global cellular ATP concentration. Interestingly, the glycolytic enzymes GAPDH and 3-PGK were found to be enriched in synaptic vesicles, where they participate in accumulation of the excitatory neurotransmitter, glutamate [151]. This is another example of how the preferential regulation of a transporter (the glutamate transporter) by glycolytically derived ATP mediates important aspects of cellular function and provides insight into how glycolysis sustains normal synaptic transmission.

The regulation of blood flow

The regulation of blood flow is under strong control of metabolic demand. This is particularly true for cerebral and coronary blood flow, which exhibit autoregulatory control mechanisms of basal flow rates to ensure a steady supply of nutrients to the brain and heart. Cerebral blood flow is regulated by glycolytic activity [152], as attested by the ability of IAA to alter local cerebral blood flow [153]. In coronary vessels, there is also strong evidence for regulation of blood flow by glycolysis. For example, inhibitors of glycolysis cause near maximal vasodilation of coronary arteries in the intact heart and in isolated coronary arteries [97, 154] as well as hyperpolarization of the smooth muscle membrane potential [154]. These effects are blocked by glibenclamide (a sulfonylurea inhibitor of K_{ATP} channels). Furthermore, coronary hypoxic vasodilation, which is mediated by vascular K_{ATP} channels [155], has the same time course and magnitude as that produced with 2-DG [97]. These data suggest a direct coupling between glycolytic activity, K_{ATP} channel activity and the coronary vascular tone. The direct role of glycolysis on vascular K_{ATP} channels has not been examined. Endothelial K_{ATP} channels, which mediate the release of the vasoconstrictor endothelin-1 [82], may add another dimension to the local control of coronary blood flow. Since aortic endothelial cells synthesize ATP mainly through glycolysis [156] and K_{ATP} channels are remarkably sensitive to glycolytically derived ATP (see earlier), it would be of interest to examine whether glycolysis also regulates this aspect of blood flow control.

Glycolysis and the heart

In contrast to the brain, which relies mainly on glucose for metabolism, the heart mainly utilizes fatty acids and lactate as the preferred fuels for energy production under physiological conditions [157, 158]. However, during energy-delimited situations such as hypoxia or myocardial ischemia, the heart switches over to preferential use of glucose as its energy source [159]. Glycolytically derived ATP has historically been deemed to be protective against ischemic insults. For example, in the isolated, perfused rat heart, glycolytically produced ATP is thought to preserve and maintain action potential and membrane integrity in the underperfused, ischemic heart [2, 160]. A protective role of glycolysis during ischemia and reperfusion following an ischemic insult has also been noted by others [161–164]. The ‘glucose hy-

pothesis' therefore holds that enhanced glucose metabolism and glycolysis exert anti-ischemic cardioprotective effects. In general, this hypothesis is supported by the subcellular linkage that exists between key glycolytic enzymes and the activity of survival-promoting membrane-bound pumps, such as the Na^+-K^+-ATPase [27, 36, 41, 165] and Ca^{2+} transport by the SR [24, 66, 67, 159, 166, 167]. The relative interaction between increased glycolytic flux and K_{ATP} channel activity has been noted earlier but not investigated in the context of ischemia of the heart and coronary vasculature. There is a need for studies to examine the role of channels, exchangers and pump in the complex relationship between glycolysis and cardiac protection afforded by glycolysis during metabolic impairment.

Conclusions

In recent years evidence has accumulated to demonstrate that glycolysis preferentially regulates membrane ion transport mechanisms. This tight functional coupling between glycolysis and ion transport mechanisms (both at the plasmalemma and membranes inside the cell) appears to stem from a close association of glycolytic enzymes, ion channels, transporters and pumps. The regulation of ion transporters in response to changing energy demand in an attempt to maintain intra- and extracellular ionic gradients is met by a network of interlinked pathways including glycolysis, oxidative metabolism, glycogenolyis and fatty acid oxidation. We have highlighted the specific role of glycolysis in regulating the functions of several ion channels, transporters and pumps. Overall, these data suggest the existence of a well-coordinated and complex signaling cascade occurring at membranes that ensures optimal delivery of energy for channels and transporters to regulate cellular activity. This notion is in direct support of the emerging concept for functionally compartmentalized energetic networks, such that oxidative phosphorylation, glycolysis and glycogenolysis preferentially channel ATP to ATPases in different cellular compartments [168], orchestrating the robust functioning of energy delivery and consumption that ensures the functioning of a living organism.

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