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REVIEW ARTICLE

K$_{ATP}$ channels process nucleotide signals in muscle thermogenic response

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Abstract
Uniquely gated by intracellular adenine nucleotides, sarcolemmal ATP-sensitive K$^+$ (K$_{ATP}$) channels have been typically assigned to protective cellular responses under severe energy insults. More recently, K$_{ATP}$ channels have been instituted in the continuous control of muscle energy expenditure under non-stressed, physiological states. These advances raised the question of how K$_{ATP}$ channels can process trends in cellular energetics within a milieu where each metabolic system is set to buffer nucleotide pools. Unveiling the mechanistic basis of the K$_{ATP}$ channel-driven thermogenic response in muscles thus invites the concepts of intracellular compartmentalization of energy and proteins, along with nucleotide signaling over diffusion barriers. Furthermore, it requires gaining insight into the properties of reversibility of intrinsic ATPase activity associated with K$_{ATP}$ channel complexes. Notwithstanding the operational paradigm, the homeostatic role of sarcolemmal K$_{ATP}$ channels can be now broadened to a wider range of environmental cues affecting metabolic well-being. In this way, under conditions of energy deficit such as ischemic insult or adrenergic stress, the operation of K$_{ATP}$ channel complexes would result in protective energy saving, safeguarding muscle performance and integrity. Under energy surplus, downregulation of K$_{ATP}$ channel function may find potential implications in conditions of energy imbalance linked to obesity, cold intolerance and associated metabolic disorders.

Keywords: *Kir6.2; SUR; ATPase; energy expenditure; diffusion; metabolism; phosphotransfer; structure modeling*

Introduction

Modern human genotypes have persisted from the prehistoric era of a hunting/gathering lifestyle, in which episodes of feasting followed by rapid energy storage were succeeded by episodes of endurance exercise to obtain more food (Booth *et al.*, 2002; Himms-Hagen, 2004). Hence, evolutionary pressures, in an environment with ample demand for physical activity and restricted food supply, favored biological systems that conserve energy and optimize energy use (Celi, 2009). The central metabolic principle is the combustion of nutrients (mainly carbohydrates and lipids) to carbon dioxide and water transforming consumed energy to a readily usable form,

primarily ATP, which is then utilized by active cellular processes to maintain the whole spectrum of cellular and core body functions concomitantly producing heat, that is, in thermogenesis (Else *et al.*, 2004; Himms-Hagen, 2004; Levine, 2007). The main thermogenic contributors, skeletal and cardiac muscles, account for 10–20% of sedentary daily energy use, and during physical activity increase their energy consumption 20–100 times over basal levels (McArdle *et al.*, 1996). Of note, the relatively high affinity of cellular ATPases for ATP (Läuger, 1991a), compared to the intracellular ATP levels (~6–10 mM; Bittl *et al.*, 1987; Elliott *et al.*, 1989; Weiss *et al.*, 1992), causes these energy consuming systems to operate within a wide range of cellular energy states, virtually independent of

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intracellular ATP levels. Thus, in active muscles, fuel economy would require an intrinsic controlling mechanism capable of adjusting energy expenses in accord with ATP availability (Zingman *et al.*, 2003). Realization of such mechanism implies the existence of an evolutionarily conserved energy sensor capable of processing changes in the intracellular adenine nucleotide pool. Uniquely gated by intracellular adenine nucleotides, ATP-sensitive K$^+$ (K$_{ATP}$) channel complexes have been traditionally recognized as a suitable candidate for this role.
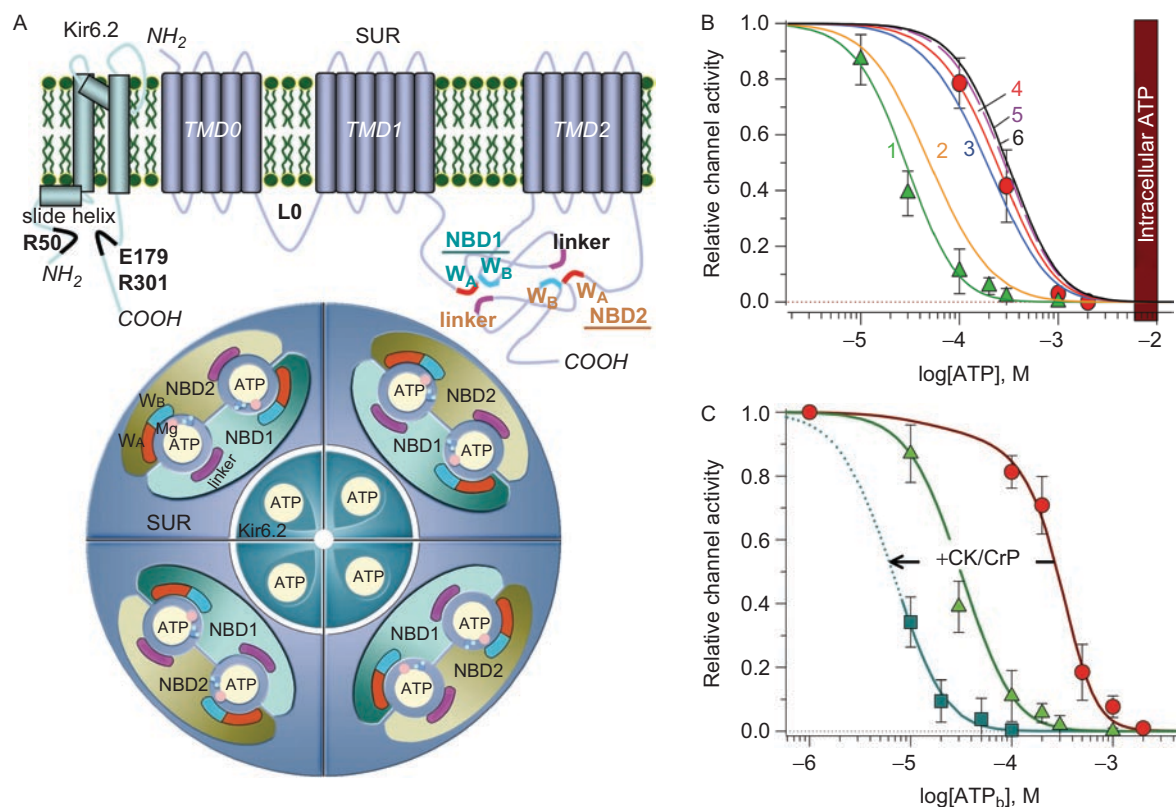
K$_{ATP}$ channels and nucleotide sensing

Discovered in the cardiac sarcolemma (Noma, 1983), K$_{ATP}$ channels have been found in high density in all metabolically active tissues, where they are formed by tissue-specific multimerization of four pore-forming Kir6.1 or Kir6.2 with four regulatory SUR1 or SUR2 subunits; the latter existing in two isoforms, SUR2A and SUR2B, as a result of alternative splicing (Inagaki *et al.*, 1995; 1996; Yamada *et al.*, 1997; Clement *et al.*, 1997). The progress in understanding K$_{ATP}$ channel stoichiometry and structure–function relationships is widely discussed in a number of excellent reviews (e.g. Babenko *et al.*, 1998; Seino, 1999; Moreau *et al.*, 2005; Nichols, 2006; Aittoniemi *et al.*, 2009). Briefly, in cardiac and skeletal myocytes, K$_{ATP}$ channel complexes primarily combine Kir6.2 and SUR2A subunits (Inagaki *et al.*, 1996; Lorenz and Terzic, 1999; Lefer *et al.*, 2009). Numerous nucleotide-binding sites within the channel subunits confer a sophisticated nucleotide-dependent gating to K$_{ATP}$ channel complexes (Figure 1A). While intracellular ATP keeps K$_{ATP}$ channels closed by binding to Kir6.2 (Tucker *et al.*, 1997; Drain *et al.*, 1998; Craig *et al.*, 2008), the effectiveness of this binding can be modulated through MgATP/MgADP interactions with nucleotide-binding domains (NBD1 and NBD2) of the SUR2A subunit (Shyng *et al.*, 1997; Hosy *et al.*, 2007) that harbor an intrinsic hydrolytic activity (Matsuo *et al.*, 1999, 2000; Bienengraeber *et al.*, 2000). Stabilization of MgADP at these binding pockets reduces the pore sensitivity to ATP (Zingman *et al.*, 2001; 2007) favoring K$^+$ efflux.

There is a common belief that the nucleotide-gated K$^+$ flux is the central energy controlling mechanism associated with sarcolemmal K$_{ATP}$ channels. Indeed, due to the properties of weak inward rectification, K$^+$ flux through K$_{ATP}$ channels can accelerate repolarization of action potentials (AP) by driving membrane potential towards K$^+$ equilibrium, opposing thereby associated energy expenses. The operation of K$_{ATP}$ channels in response to reduced ATP and increased ADP levels would thus limit processes occurring during the AP propagation, including not only the operational time of L-type Ca^{2+} channels and associated Ca^{2+} release from the sarcoplasmic reticulum, but also the concomitant activity of the Na$^+$/Ca^{2+}

exchanger, myosin-, Ca^{2+}- and Na$^+$/K$^+$-ATPases (Nichols and Lederer, 1991; Gong *et al.*, 2000; Zingman *et al.*, 2002; 2007; Cifelli *et al.*, 2007; 2008). This conventional view, although apparently the most rational, still requires reconciliation of the established IC$_{50}$ for channel inhibition by ATP (in the range of 20–50 μM) with millimolar intracellular ATP levels (Elliot et al., 1989; Nichols and Lederer, 1991; Alekseev *et al.*, 2005). The MgADP-bound state of SUR2A expands the range for ATP inhibition (IC$_{50}$ ~300 μM), which however still remains far below actual intracellular ATP levels (Figure 1B). On saturating all ADP-binding sites, at ADP >150–300 μM, no further reduction in ATP sensitivity can be achieved (Lederer and Nichols, 1989; Weiss *et al.*, 1992; Abraham *et al.*, 2002; Selivanov *et al.*, 2004). Thus, at 6–10 mM of cytosolic ATP, MgADP-dependent K$_{ATP}$ channel regulation would not be translated into channel opening, questioning the homeostatic role of K$_{ATP}$ channels.

It is possible that the sensitivity of K$_{ATP}$ channels towards ATP can be reduced in the intact cell by additional regulators. In fact, modulation of K$_{ATP}$ channels by acidic pH has been proposed and, although found to be very inconsistent among tissues (skeletal versus cardiac muscles) as well as animal species (mammalian versus frog skeletal muscles), could contribute to channel activation, provided that significant changes in intracellular nucleotide levels occur under vigorous metabolic stress (Cook and Hales, 1984; Lederer and Nichols, 1989; Davies *et al.,* 1992; Koyano *et al.*, 1993; Vivaudou and Forestier, 1995; Allard *et al.*, 1995). In addition, membrane negatively charged phosphatidylinositol phosphates (i.e. PIP$_2$, PIP$_3$), when applied exogenously to membrane patches, render K$_{ATP}$ channels insensitive to ATP, suggesting phosphorylation/dephosphorylation-induced changes of membrane phospholipid composition as a mechanism for physiological regulation (Baukrowitz *et al.*, 1998; Shyng and Nichols, 1998; Song and Ashcroft, 2001). The variability in membrane phospholipid content may, in particular, explain the inconsistency in the response to ATP of native K$_{ATP}$ channels identified in excised patches (Findlay and Faivre, 1991; Shyng and Nichols, 1998), indicating a contribution of membrane charges brought by phospholipids in setting nucleotide-sensitivity of the channel pore (Nichols, 2006). However, activation of the creatine kinase/creatine phosphate (CK/CrP) system, that by regenerating ATP should facilitate the phosphorylation of phospholipids, effectively enhances ATP-induced channel inhibition with IC$_{50}$ ~10 μM (Figure 1C; Nichols and Lederer, 1990; Bienegraeber *et al.*, 2000; Abraham *et al.*, 2002), which is even below the minimal IC$_{50}$ values that could be achieved in the presence of lipid kinase inhibitors (Tarasov *et al.*, 2006). Conversely, under decreased ATP/ADP ratio, reduction of lipid kinases phosphorylation rates and the resulting drop of K$_{ATP}$ channel activity would be inconsistent with

Figure 1. Structure and nucleotide-dependent gating of K_{ATP} channel complexes. (A) Kir6.2 possesses two transmembrane (TM) pore-forming α-helices and a slide helix, which by lateral movement contributes to the gating mechanism. The putative ATP binding residues are indicated in black. SUR2A is comprised of three bundles of transmembrane-spanning domains and two cytosolic ATP-binding cassettes (ABC), i.e. nucleotide binding domains (NBD1 and NBD2). W_A and W_B denote the Walker A and Walker B motifs conserved within ABC proteins that, along with the linker regions, are critical for coordination of nucleotides within binding pockets. Each ATP molecule is sandwiched between the Walker motifs of one NBD and the linker region from another NBD. The whole K_{ATP} channel complex is formed by four SUR co-assembled with four Kir6.2 subunits, harboring 12 nucleotide binding sites in total. Cofactors of the hydrolytic reaction, Mg^{2+} (pink) and water molecules (blue), are also indicated. (B) MgADP antagonizes ATP-induced inhibition of cardiac K_{ATP} channels. In excised patches from isolated cardiomyocytes, the ATP sensitivity of K_{ATP} channels is defined by an IC_{50} of $27 \pm 5\,\mu M$ in the absence (triangles) versus $270 \pm 19\,\mu M$ in the presence (circles) of 100 μM ADP. At increasing ADP concentrations (curve 1: 0; 2: 10; 3: 50; 4: 100; 5: 500; 6: 1000 μM), following suturation of all binding sites no further reduction in ATP sensitivity of K_{ATP} channels can be achieved (adapted from Selivanov *et al.*, 2004). The vertical bar corresponds to 6–10 mM intracellular ATP levels. (C) Concentration–response curves defining ATP-induced K_{ATP} channel inhibition in open cell-attached patches, where K_{ATP} channels operate in a relatively intact cellular environment, in the absence (circles) and presence (squares) of 1 mM creatine phosphate (CrP). Intracellular ATPase activities define the right-shift of the concentration-response curve (IC_{50} ~300 μM) in the open-cell attached configuration, relative to the values measured in excised patches (triangles), and can be effectively left-shifted to an IC_{50} ~10 μM by activation of the ATP-regenerating endogenous creatine kinase (CK) when the reaction substrate (CrP) is applied. By itself, CrP has no significant effect on K_{ATP} channel activity (Abraham *et al.*, 2002).

stress-induced activation of K_{ATP} channels, indicating that coupling of K_{ATP} channels with cellular energetics is mediated by adenine nucleotide signaling (Tarasov *et al.*, 2006).

While adenine nucleotides have been recognized as the principal regulators of K_{ATP} channels, there is still an obvious lack of solid biophysical and biochemical foundations of how energy signals could be generated and transmitted within the intracellular milieu where metabolic systems are set to buffer nucleotide levels. Hence, the quest to resolve a simple, at first glance, question regarding the incongruity between the nucleotide sensitivity of K_{ATP} channel sensors and the actual, well-maintained intracellular nucleotide levels, involves

several important concepts that will be discussed herein.

Nucleotide signaling in a compartmentalized cellular environment

Lack of correlation between significant changes in bulk nucleotide levels and K_{ATP} channel openings during metabolic challenge (Elliot et al., 1989; Decking *et al.*, 1995; Zingman *et al.*, 2002) has given rise to the suggestion that sarcolemma-associated ATPases could depress local ATP concentration, setting a nucleotide ratio at the channel site distinct from cytosolic levels (Nichols and Lederer,

1991; Weiss *et al.*, 1992; Abraham *et al.*, 2002; Selivanov *et al.*, 2004). This is in accord with the recent finding that K$_{ATP}$ channels complement specific membrane complexes combining Na$^+$/K$^+$ ATPase, voltage-gated Na$^+$, K$^+$ channels and the Na$^+$/Ca^{2+} exchanger, and are anchored through ankyrins to the spectrin-actin based membrane cytoskeleton (Terzic and Kurachi, 1996; Hashemi *et al.*, 2009; Kline *et al.*, 2009). Such compartmentalized complexes appear to function in a microenvironment where local ion and nucleotide contents may be distinct from average cytosolic levels.

Intracellular energy consumption has traditionally been viewed as a process whereby freely diffusing high-energy phosphates are consumed where needed throughout the cytoplasm. However, this concept underwent an essential reevaluation (Saks *et al.*, 2009) since, for instance in the heart, selective inhibition of anaerobic glycolysis versus mitochondrial oxidative phosphorylation has revealed a differential efficacy of these systems in supporting specific membrane versus contractile functions, which cannot be explained by changes in total transcellular high-energy phosphate levels (Doorey and Barry, 1983; Weiss and Hiltbrand, 1985; Kaasik *et al.*, 2001). As the cytoplasm is now considered to be far from a "well-mixed bag", in which high-energy phosphates diffuse readily to various cellular ATPases (Weiss and Korge, 2001), intracellular compartmentalization could in principle offer a rational basis for nucleotide-dependent K$_{ATP}$ channel gating, provided that significant diffusional limitations exist between cellular microdomains.

The value of the diffusion coefficient for ATP in the cytosol, obtained using ^{31}P assisted NMR (e.g. Kinsey and Moerland, 2002), implies a rather regular value of nucleotide diffusion in free space ($\sim 10^{-6}$ cm^2 s^{-1}). However, within the intracellular microenvironment where the cytoskeleton tethers proteins into macro-complexes (Hashemi *et al.*, 2009) the free diffusional space is extremely limited, restricting metabolite mobility (Weiss and Lamp, 1987; Weiss and Korge, 2001; Kaasik *et al.*, 2001). The existence of significant diffusion limitations has been suggested for different subcellular compartments (Saks *et al.*, 2001) including the submembrane "fuzzy space" with a highly restricted diffusion of molecules as small as Na$^+$ ions (Lederer *et al.*, 1990). This "fuzzy space" would further restrict the mobility of bigger molecules to an even higher extent, and, in the presence of local ATPases, could set submembrane nucleotide concentrations distinct from bulk levels. In fact, assuming that bulk ATP is 7 mM and sarcolemmal ATPase flux is 4.7×10^{-6} µmol cm^{-2} s^{-1}, as was estimated in working hearts based on ^{18}O-assisted ^{31}P NMR (Weiss *et al.*, 1992; Pucar *et al.*, 2001; Abraham *et al.*, 2002), even a minimal contribution of sarcolemmal K$_{ATP}$ channels to cardiomyocyte excitability, 1% of the total membrane population (Lederer and Nichols, 1989), would require

a ~ 4 mM drop of submembrane ATP levels. Such ATP gradient can be only achieved at an apparent diffusion coefficient of 2.3×10^{-11} cm^2 s^{-1} (Abraham *et al.*, 2002), which is already 100,000 times lower than nucleotide diffusion in the cytosol. Notably, this is likely an underestimation of the diffusion barrier, which could be even stronger in myocytes where components of the glycolytic system and adenylate kinase (AK) have been identified in the vicinity of K$_{ATP}$ channels (Weiss and Lamp, 1987; Elvir-Mairena *et al.*, 1996; Carrasco *et al.*, 2001; Janssen *et al.*, 2004). By regenerating local ATP, these systems could further diminish the nucleotide gradients between cellular compartments. Considering operation of 1% of the K$_{ATP}$ channel population in the presence of AK alone, a 4 mM ATP gradient between the bulk and the submembrane space, at the same ATPase activity, would require an apparent diffusion coefficient as low as 1.6×10^{-11} cm^2 s^{-1} (Selivanov *et al.*, 2004). Although such extremely high diffusion restrictions have been obtained with certain assumptions, the five orders-of-magnitude difference of this apparent value from the coefficient for free diffusion of nucleotides in the cytosol cannot be compensated by varying several times the diffusion distance, i.e. the thickness of the submembrane space (0.2 µm), ATPase activity, bulk ATP or other parameters. Furthermore, these values for apparent diffusion coefficient are in agreement with estimates ($\sim 10^{-9}$–10^{-13} cm^2 s^{-1}) performed for cAMP and ATP in the subsarcolemmal space implementing alternative approaches (Rich *et al.*, 2000; Kabakov, 1998). A number of observations thus indicate the existence of diffusional hindrances at the submembrane space sufficient to seclude K$_{ATP}$ channels from bulk metabolic pathways, questioning a mechanism that is capable of shunting the existing barrier and secure communication between membrane complexes and cellular energy pools.

Nucleotide signal transmission and processing

Coupling of K$_{ATP}$ channel proteins with cellular energetics is underscored by spatial association of the channel subunits with phosphotransfer (AK and CK) and glycolytic enzymes (Weiss and Lamp, 1987; Jovanović *et al.*, 2007) that are capable of facilitating energy transfer (Nichols and Lederer, 1990; Elvir-Mairena *et al.*, 1996; Carrasco *et al.*, 2001; Abraham *et al.*, 2002; Crawford *et al.*, 2002; Dzeja and Terzic, 2009), and in association with cytoskeleton-bound complexes (Hashemi *et al.*, 2009; Kline *et al.*, 2009), could form a complete cellular metabolic unit.

The role of these reactions in the transmission of nucleotide signals may not be so evident. In particular, the phosphotransfer reaction, ADP + CrP $\leftrightarrow$ Cr + ATP catalyzed by CK, phosphorylates ADP to ATP by transferring the phosphate group from creatine phosphate (CrP) producing creatine (Cr). The high value of the equilibrium

constant for this reaction, $K_{CK} = 160$ (Lawson and Veech, 1979), indicates that augmentation of total ATP turnover would deplete the intracellular pool of CrP to a greater extent than the pool of ATP. Hence, CK buffers changes in ATP and ADP levels throughout the cell, which, at first glance, contradicts the concept of nucleotide signaling. On the other hand, such buffering could be interpreted as "shuttling" of high-energy phosphates between sites of energy production and consumption (Dzeja and Terzic, 1998) or as a mechanism of nucleotide carrying or facilitated ATP diffusion flux (Meyer *et al.*, 1984), which implies that delivery of ATP from one cellular compartment to another is accompanied by diffusion of high-energy phosphate equivalents (CrP), which then are locally involved in CK-catalyzed ATP synthesis.

Theoretical analysis of the relationships between metabolite concentrations and fluxes in the presence of strong diffusion hindrances revealed that the CK and AK reactions, in contrast to their role to void changes in cytosolic ATP levels, may acquire properties of amplification and attenuation of nucleotide signals, respectively (Selivanov *et al.*, 2004). Such modulation of nucleotide gradients at a diffusion barrier can be readily understood from the basic properties of phosphotransfer reactions. Assuming absence of the CK system, one may expect that a difference between bulk and submembrane ATP levels imposed by membrane ATPases is independent of bulk ATP, i.e. a drop in bulk ATP ($\Delta[ATP]_b$) would be passively followed by the same drop of submembrane ATP levels ($\Delta[ATP]_m$), with no signal modulation: $\Delta[ATP]_m = \Delta[ATP]_b$ (Figure 2A, blue dashed line). In the presence of CK, the substantial levels of intracellular CrP maintain nucleotide content, voiding the concentration gradient between compartments. However, due to the high value of the equilibrium constant of the CK reaction, even a small reduction of bulk ATP would result in a significant drop of bulk CrP and, thereby, a reduction of CrP flux over the diffusion barrier (Figures 2B–2D). A fall of CrP in the submembrane space would result in efficient amplification of an ATP drop in this compartment: $\Delta[ATP]_m > \Delta[ATP]_b$ (Figure 2B).

This analysis also has predicted that as long as CK effectively supports $[ATP]_m$ the contribution of AK in setting nucleotide gradients is negligible. Only when CK fails to maintain $[ATP]_m$, switching on the AK reaction will support $[ATP]_m$ attenuating submembrane ATP changes (Selivanov *et al.*, 2004; Alekseev *et al.*, 2005). Such a profile of interplay between phosphotransfer systems is in agreement with experimental observations that reduction of CK flux is accompanied by up-regulation of AK-mediated phosphotransfer (Janssen *et al.*, 2000; Pucar *et al.*, 2001).

While these new properties for phosphotransfer reactions were drawn based on a submembrane diffusion restriction that was theoretically derived considering minimal contribution of K_{ATP} channels to membrane excitability, in a real intact cell nucleotide signal modulation would depend on the actual value of the subsarcolemmal diffusion hindrance (Figures 2C–2D), which remains undefined. In general, the concept of energy signaling in a compartmentalized environment suggests that, at diffusion barriers secluding cellular compartments, bioenergetic *trends* can be amplified and then processed by membrane nucleotide sensors. Therefore, by virtue of processing even minor changes in cellular nucleotide content (Abraham *et al.*, 2002; Selivanov *et al.*, 2004), K_{ATP} channels could decode cellular metabolic dynamics and control muscle energy expenditure not only under stress conditions but also at any level of activity, continuously promoting body energy conservation.

Membrane nucleotide sensing and optimal muscle activity thermogenesis

This homeostatic role of K_{ATP} channels has been recently demonstrated by implementing indirect calorimetry measurements in normal and K_{ATP} channel deficient mice obtained by targeted disruption of the *KCNJ11* gene encoding the pore-forming Kir6.2 subunit (Kir6.2-KO) and in Tg[MyoD-Kir6.1AAA] mice with skeletal muscle specific ablation of K_{ATP} channel activity (Alekseev *et al.*, 2010). Indeed, mice lacking K_{ATP} channels demonstrate a higher rate of oxygen consumption under sedentary conditions, reflecting increased energy expenditure and thereby heat production. In spite of the established role of K_{ATP} channels in glucose homeostasis (Miki *et al.*, 1998; Aguilar-Bryan *et al.*, 2001; Ashcroft, 2005) and possibly in appetite control (Spanswick *et al.*, 1997), while unchallenged, mice lacking K_{ATP} channels did not exhibit a deficit in caloric intake or blood energy substrates (Alekseev *et al.*, 2010). The analysis of calorimetric data at a low exercise regimen further revealed that the K_{ATP} channel deficit raises energy use through an extra energy cost of physical activity, which is primarily determined by skeletal and cardiac muscle performance (Ghanassia *et al.*, 2007). The accelerated metabolism profile of the K_{ATP} channel-deficient animal models may, in certain aspects, resemble metabolic states associated with hyperthyroidism (Sugden *et al.*, 1992; Chen-Zion *et al.*, 1995) or overexpression of mitochondria uncoupling proteins in skeletal muscles (Li *et al.*, 2000). Although sharing with hypermetabolic phenotypes the properties of enhanced insulin sensitivity and glucose uptake (Miki *et al.*, 2002; Minami *et al.*, 2003), lack of sarcolemmal K_{ATP} channel function does not affect mitochondrial oxidative phosphorylation capacity or nucleotide levels in myocytes (Zingman *et al.*, 2002; Alekseev *et al.*, 2010). Maintenance of phosphocreatine and nucleotide pools thus imposed mobilization of glycogen and fat stores resulting in the
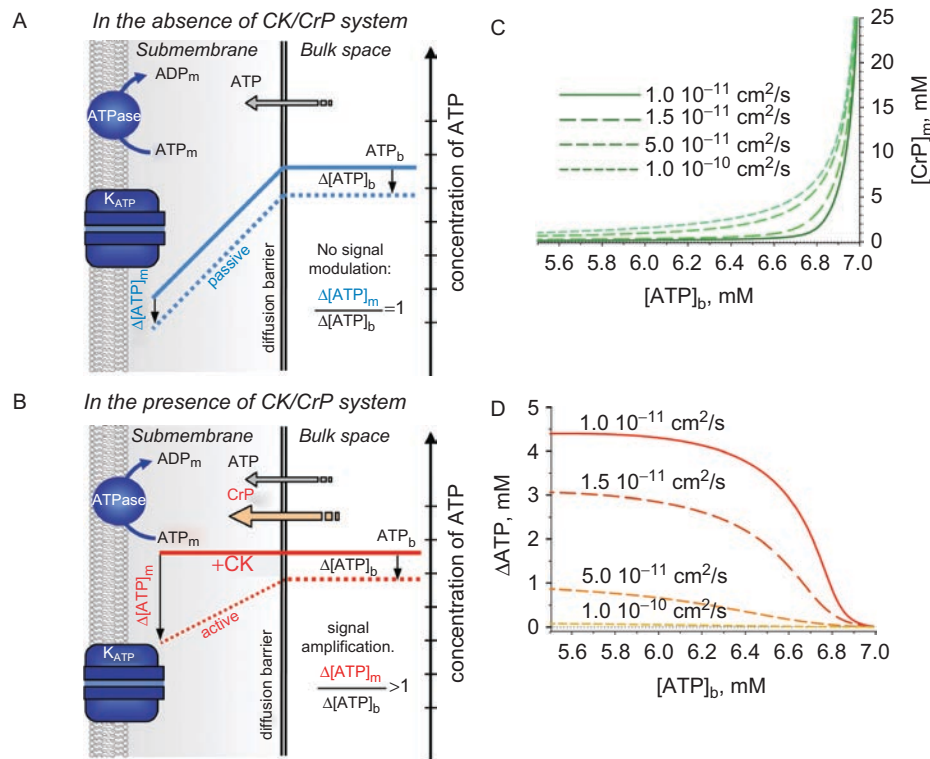
Figure 2. Nucleotide signals at a strong diffusion barrier secluding submembrane space. (A) In the absence of the creatine kinase/creatine phosphate (CK/CrP) phosphotransfer system, local ATPase activities set a nucleotide gradient between cellular compartments (blue solid line). A drop in bulk ATP levels ($\Delta[\text{ATP}]_b$) is passively followed by changes in submembrane concentrations ($\Delta[\text{ATP}]_m$), i.e. the gradient remains unchanged (blue dotted line) with no signal modulation. (B) In the presence of CK/CrP system, the facilitated diffusion catalyzed by CK virtually voids the concentration gradient (red solid line), but actively modulates (i.e. amplifies) changes in submembrane nucleotide content ($\Delta[\text{ATP}]_m$, red dotted line) that exceed the deviation of bulk ATP. (C and D) Submembrane concentrations of creatine phosphate ([$\text{CrP}]_m$) and ATP gradients (ΔATP) between bulk and submembrane space, respectively, calculated at the different values of apparent diffusion coefficients (system of equations 13, Selivanov *et al.*, 2004) following a drop of bulk ATP ([$\text{ATP}]_b$). Calculations were performed with 7 mM total nucleotide content; 40 mM total Cr/CrP level; sarcolemmal ATPase flux $4.7 \cdot 10^{-6}$ µmol/cm^2/s; $\Delta x = 0.2$ µm and $K_{CK} = 160$.

elevation of both muscle and whole body thermogenesis. The enhanced energy use in K_{ATP} channel-deficient cardiac and skeletal muscles resulted in limited body weight gain and restrained physical endurance (Alekseev *et al.*, 2010). In this way, K_{ATP} channels emerge as an important evolutionary preserved energy-sparing system that defines muscle thermogenic response through optimization of energy use.

This finding postulates that the operational principle of this system is the feedback processing of bioenergetic cues into constraints of membrane excitability. Indeed, measurement of oxygen consumption in isolated hearts revealed that increasing pacing rates produces a moderate elevation of energy expenditure in line with K_{ATP} channel-dependent shortening of action potential duration (Alekseev *et al.*, 2010). Lack of compensatory K_{ATP} channel-driven shortening of action potentials in K_{ATP} channel-deficient hearts was associated with significant elevation of oxygen consumption. However, paradoxically, even at the lowest workload rate (460 bits per min), when wild-type and knockout groups demonstrated

indistinguishable durations of action potentials, hearts lacking K_{ATP} channels still consumed more oxygen compared to normal hearts (Alekseev *et al.*, 2010). One possible explanation is that microscopic changes in individual action potential duration, while undetectable by MAP (monophasic action potential) recording, as implemented in the study, when integratively accumulated during thousands of cardiac cycles may contribute to energy saving. In this way, one may anticipate an advantage of progressive membrane potential shortening that may be achieved by a more robust activation of K_{ATP} channels. However, transgenic mice expressing K_{ATP} channels with a 40–100-fold reduced ATP sensitivity revealed no benefit from ischemic preconditioning, no improvement of functional recovery following metabolic inhibition along with no protection against intracellular Ca^{2+}-induced rigor contracture (Koster *et al.*, 2001; Rajashree *et al.*, 2002), i.e. phenomena that are also characteristic of K_{ATP} channel-deficient hearts (Zingman *et al.*, 2002; Gumina *et al.*, 2003; 2007). Taken together these data suggest that a molecular mechanism responsible for the

K_{ATP} channel-driven feedback control of cellular energy balance remains unresolved.

Mechanisms for the energy-saving operation of K_{ATP} channels

The known structure–function properties of K_{ATP} channels suggest at least two possible mechanisms by which they could affect cellular energy balance. The first, mentioned above, is the constraint of cellular energy expenses on myofibrillar contraction and re-sequestration of Ca^{2+} and Na^+ ions by opposing membrane depolarization (Nichols and Lederer, 1991; Gong et al., 2000; Zingman et al., 2002; 2007; Cifelli et al., 2007; 2008; Alekseev et al., 2010). The second could be associated with the enzymatic properties of the regulatory SUR subunit of the channel complex and resembles the mechanism realized in a number of molecular pumps and ABC transporters. Although the molecular mechanisms of operation of different ATPases are not identical, the general principle of coupling between ion flux and associated catalytic activity is underscored by the ability of ATPase pumps to synthesize ATP using ion movement down the electrochemical gradient (Boyer et al., 1973; Läuger, 1991b; Boyer, 1997). For instance, in the F_0F_1 mitochondrial ATPase, due to the

reversibility of this catalytic reaction, proton permeation through the F_0 pore-forming subunit reduces the affinity of the F_1-ATPase towards synthesized ATP (Boyer, 1997; Kagawa et al., 1997; Figure 3A). Furthermore, the reversibility of hydrolysis associated with the functioning of some ABC multidrug transporters has been demonstrated in response to downhill substrate uptake (Balakrishnan et al., 2004). In fact, even though SUR belongs to the ABCC subfamily of ABC transporters and also exhibits hydrolytic activity measured in isolated SUR proteins (Matsuo et al., 1999, 2000), in truncated NBDs fusion constructs (Zingman et al., 2001; Bienengraeber et al., 2004; Masia et al., 2005; de Wet et al., 2007; Park et al., 2008; Park and Terzic, 2010), as well as in purified recombinant Kir6.2/SUR1 complexes (Mikhailov et al., 2005), it is still unknown whether the identified intrinsic catalytic reaction possesses properties of reversibility. So far, the hydrolysis reaction rate measured in NBD fusion constructs was found to be insensitive to inorganic phosphate (Bienegraeber et al., 2004), but the catalytic properties of isolated NBDs may not necessarily correspond to properties within the whole complex. By analogy to other ATPases, the reversibility of interconversions between ATP- and ADP-P_i bound states of SUR would underscore the independence of the specific catalytic reaction upon external energy input (Boyer, 1997). Therefore, there is a
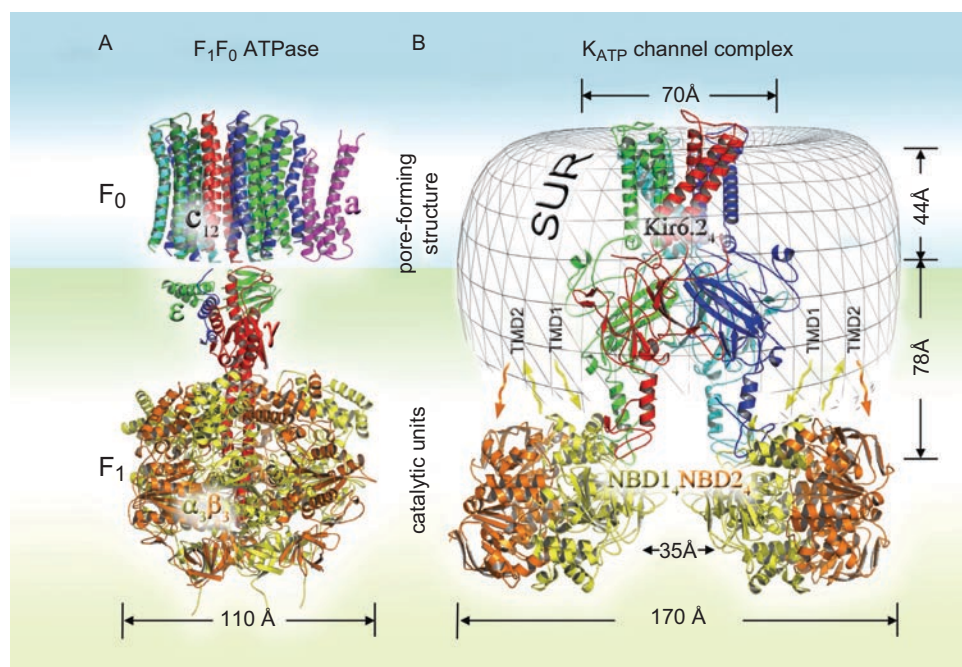
Figure 3. Topological features of F_1F_0 ATPase and K_{ATP} channel complexes. (A) Molecular architecture of the rotary motor in F_1F_0 ATPase (PDB: 1C17 and 1E79) comprises the pore forming F_0 unit of 12 *c* and *a* subunits (magenta) as well as the catalytic nucleotide-binding F_1 unit of three α (yellow) and three β (orange) subunits connected by the axle of ε and γ subunits (stator is not shown). (B) Molecular architecture of K_{ATP} channels is presented by four full-length Kir6.2 subunits (red, blue, cyan, green) embedded in the unresolved transmembrane domain (TMD0-TMD1-TMD2) structure (gray mesh). Catalytic quaternary structure of four NBD1 (yellow) and four NBD2 (orange) subunits reveals a 35 Å inner cleft (Park and Terzic, 2010) dictating the putative plane of NBDs and pore interaction at the bottom of the Kir6.2 cytoplasmic domain.

theoretical possibility that K$^+$ flux through the channel pore in response to MgADP binding to SUR could facilitate conformational transitions within SUR to release synthesized ATP. Although speculative, the latter suggestion may shed light upon some apparently unorthodox structure–function relationships, primarily associated with the unsettled role of the SUR ATPase in the regulation of K$^+$ permeation through the channel pore, which does not require energy input, as well as upon the role of the apparently redundant nucleotide-binding sites within the constitutive complex subunits (Alekseev *et al.*, 2005; Nichols, 2006; Aittoniemi *et al.*, 2009).

What evidence could favor the ATP-synthesis hypothesis? Although the K$_{ATP}$ channel complex apparently cannot be associated with any known types of ATPase it shares some structural topology with A-/F-/V- or K$^+$ translocating P-type ATPases, which are composed of distinct oligomeric segments including a catalytic unit and a membrane-embedded component, which functions in ion conduction (Müller and Grüber, 2003; Bramkamp *et al.*, 2007; Figures 3A and 3B). Indeed, the combination of molecular simulation with single particle electron microscopy and small angle X-ray scattering (SAXS) revealed that, as in other macromolecular transporters, the ion-conducting Kir6.2 subunit is wrapped by the associated SUR unit (Mikhailov *et al.*, 2005; Hosy *et al.*, 2007; de Wet *et al.*, 2007; Park and Terzic, 2010). Although the topology of cytoplasmic NBD1 and NBD2 is a matter for debate, recent SAXS analysis revealed that the inner cleft delineated by four NBDs (~35 Å) was narrower than the predicted near-to-membrane dimension of the Kir6.2 structure (~55 Å). Therefore, four pairs of NBD1–NBD2 dimers could be located at the bottom of the cytoplasmic Kir6.2 terminus (Park and Terzic, 2010), thus forming a macromolecular organization that is typical for other ATPase complexes (Figure 3B). Lack of tight physical association between NBD1/NBD2 and Kir6.2 (Schwappach *et al.*, 2000; Mikhailov and Ashcroft 2000) provides the basis for a flexible mechano-molecular interaction between conformational transitions of Kir6.2 and nucleotide-binding TMD1-NBD1/TMD2-NBD2 cytoplasmic regions (Chan *et al.*, 2003; Rainbow *et al.*, 2004; Dupuis *et al.*, 2008). Furthermore, the catalytic activity of SUR is sensitive to classical ATPase inhibitors such as ortho-vanadate or beryllium fluoride mimicking organic phosphates in binding pockets, indicating the ability of the SUR binding sites to coordinate P$_i$ with prebound MgADP (Zingman *et al.*, 2001). The properties of stable nucleotide binding resulting from cooperative interaction of NBDs in SUR (Ueda *et al.*, 1999; Matsuo *et al.*, 2000; Karger *et al.*, 2008) may also favor the reversibility of the catalytic reaction. There is evidence that allosteric coupling between constitutive channel subunits confers not only SUR-mediated Kir6.2 channel gating but also a reversed effect of Kir6.2 on the catalytic rate of the SUR subunit (Aittoniemi *et al.*,

2009). Of note, incidents of anoxia-induced nucleotide oscillations in whole cardiomyocytes were detected only at the outward K$_{ATP}$ current set by a positive (+40 mV) holding potential but not at a negative holding potential (−80 mV), which may indicate a possible contribution of K$^+$ flux-dependent ATP synthesis by K$_{ATP}$ channels to the cellular nucleotide pool (Ganitkevich *et al.*, 2010).

The main argument against this hypothesis appears to be the proximity of membrane potentials in resting myocytes to the potassium equilibrium, where no net K$^+$ fluxes are expected, questioning the proposed mechanism for ATP synthesis. However, during propagation of action potentials, where major cellular energy expenses occur, K$^+$ efflux may contribute to the process. The proton-motive force implemented in ATP synthesis can be estimated as $\Delta\mu H^+ = 2.3RT\Delta pH + F\Delta\Psi$, where ΔpH and $\Delta\Psi$ denote proton gradient (~0.8) and mitochondria membrane potential (~160 mV), respectively. Analogously, a sarcolemmal potassium-motive force can be defined as: $\Delta\mu K^+ = 2.3RT\cdot\log[K]_i/[K]_o + F\Delta E$, where logarithm of the ratio between intracellular and extracellular K$^+$ denotes potassium gradient ($\Delta pK \sim 1.4$) and ΔE represents a shift of membrane potential from K$^+$ equilibrium during action potentials (60–80 mV at the phase of plateau). Regardless of the particular synthetic mechanism, direct comparison of ΔpH and $\Delta\Psi$ with ΔpK and ΔE, respectively, without specific constant values, reveals close estimations for $\Delta\mu H^+$ and $\Delta\mu K^+$ indicating the feasibility of a K$^+$ electromotive force for the suggested K$_{ATP}$ channel ATP-synthase activity. This plain energy analysis also indicates that the direct measure of sarcolemmal ATP production by K$_{ATP}$ channel complexes could be performed only at a shift of the membrane potential away from the K$^+$ equilibrium, typical for resting excitable cells, and would require the combination of a reliable nucleotide reporter with the maintenance of constant electromotive force to secure a substantial K$^+$ efflux through the channel pore, a challenging experimental task.

A synthetic function of the K$_{ATP}$ channel complex in general does not contradict the established nucleotide-dependent channel gating and may provide an additional basis for understanding specific nucleotide interactions with constitutive channel subunits. Indeed, the proposed synthetic mechanism implies that binding of MgADP to NBD2 in SUR allosterically antagonizes inhibition of the channel pore by ATP conferring K$^+$ efflux to switch SUR conformation to a low-affinity ATP bound state. Thus, the micromolar range of pore inhibition by ATP, at millimolar intracellular levels, becomes evidently a prerequisite to prevent futile K$^+$ efflux and explains why a significant K$_{ATP}$ channel current has not been detected at physiological stimuli. In this way, the question regarding channel opening at millimolar intracellular ATP levels may seem immaterial, because at basal physiological states the proposed synthetic function mandates an exclusive K$_{ATP}$

channel complex response to ADP regardless of ATP levels, in accord with the traditional signaling mechanism based on receptor–ligand interaction. From this point of view, the amplification and tuning of nucleotide signals in the submembrane space may be considered as an ADP signaling process that switches on K_{ATP} channel complexes to compensate a deficit of local ATP in order to support the operation of ATPases in sarcolemmal metabolic units. Finally, the proposed intrinsic synthetic activity of K_{ATP} channel complexes does not deny the energy saving imparted by K_{ATP} channel-induced shortening of action potentials, because K^+ permeation coupled to catalytic machinery would manifestly restrain membrane excitability at significant K^+ efflux under severe energy deficit.

## A generalized homeostatic role for K_{ATP} channels

The recently documented K_{ATP} channel-driven control of energy-consuming processes under physiological states (Alekseev *et al.*, 2010) extrapolates the homeostatic role of channel complexes to a wider range of environmental cues affecting physiological well-being. While activation of K_{ATP} channels can be implemented in limiting energy consumption by cellular ATPases during metabolic insult, interruption of K_{ATP} channel-dependent control of ATPase activities could be useful in elevating muscle energy expenditure and thereby total body thermogenesis under excessive energy input and impaired physical performance. Hence, intercommunication between cellular energetics and K_{ATP} channels allows the suggestion of a paradigm shift from the protective channel-driven shortening of action potentials towards the bidirectional (up/down) K_{ATP} channel-dependent control of muscle thermogenesis. Metabolic adaptation in the absence of K_{ATP} channels was accompanied by elevated rates of carbohydrate and lipid utilization compared to WT (Alekseev *et al.*, 2010), which, in line with proteomic data, alters nearly 9% of all detected protein species, predominantly bioenergetic complexes including several dehydrogenases and transferases involved in the TCA (tricarboxylic acid) cycle or fatty acid β-oxidation pathway (Arrell *et al.*, 2009). In this way, inefficient cellular energetics induced by K_{ATP} channel malfunction seems to be a common denominator for a spectrum of pathological remodeling and metabolic disorders (Figure 4).

Energy saving has been typically assigned to a protective response of sarcolemmal K_{ATP} channels under energy deficits, such as acute ischemia (Gumina *et al.*, 2003; Moses *et al.*, 2005), sympathetic distress (Zingman *et al.*, 2002; Kane *et al.*, 2004; Liu *et al.*, 2004; Reyes *et al.*, 2007; 2009a) or muscle fatigue (Renaud *et al.*, 2002). It has been also demonstrated that K_{ATP} channels play a crucial role in other syndromes of energy overload. In particular, K_{ATP} channels influence outcome in sympathetic overstimulation such as in endurance exercise or cocaine intoxication (Zingman *et al.*, 2002; Kane *et al.*, 2004; Reyes *et al.*, 2007; 2009a) as well as pressure and volume overload (Kane *et al.*, 2006; Yamada *et al.*, 2006). Defects in nucleotide-dependent channel gating and/or disturbed communication between K_{ATP} channels and intracellular energy routes could all be envisioned as molecular mechanisms contributing to cardiac remodeling and impaired performance induced by energy imbalance (Hodgson *et al.*, 2003; Kane *et al.*, 2005; Zingman *et al.*, 2007). Indeed, mutations in the regulatory SUR2A subunit predispose to dilated cardiomyopathy and adrenergic atrial fibrillation (Bienengraeber *et al.*, 2004; Olson *et al.* 2007; Olson and Terzic, 2010), while a common single nucleotide polymorphism in the pore-forming Kir6.2 subunit has been associated with increased left ventricular size in the setting of hypertension (Reyes *et al.*, 2008) and with reduced heart rate response to exercise in patients with heart failure (Reyes et al., 2009b).

The previously unrecognized role for sarcolemmal K_{ATP} channels in the continuous regulation of cellular energy use under non-stressed physiological states suggests a potentially advantageous K_{ATP} channel downregulation under conditions of energy surplus, such as in obesity (Alekseev *et al.*, 2010). The protective function of K_{ATP} channels against body weight gain at the expense of physical endurance would be in accord to inefficient energy use by cardiac and skeletal muscles lacking the K_{ATP} channel energy-controlling mechanism. Downregulation of K_{ATP} channel function specifically in skeletal muscle, despite exposing this tissue to risk of injury, under certain circumstances may have a net benefit. Indeed, the consequences imposed on health by morbid obesity are so severe that current strategies are associated with risks that are deemed acceptable in order to achieve weight loss or control. Moreover, the consequences of K_{ATP} channel downregulation on muscle fiber integrity were found as a result of intense exercise and were not identified in control sedentary animals (Thabet *et al.*, 2005), i.e. under conditions consistent with the population at greatest risk for obesity.

An area of investigation unveiled by an energy-management role of K_{ATP} channels is that of the involvement of the channel complex in temperature control. By setting exercise and non-exercise activity thermogenesis (Alekseev *et al.*, 2010), sarcolemmal K_{ATP} channels could also contribute to heat production during acute cold exposure. As part of a peripheral system aimed at controlling muscle energy economy, it is conceivable that K_{ATP} channels, downregulated at reduced ambient temperature, could increase thermogenesis during muscle shivering, thus elevating heat to maintain core body temperature. While this hypothesis remains to be tested, recent data
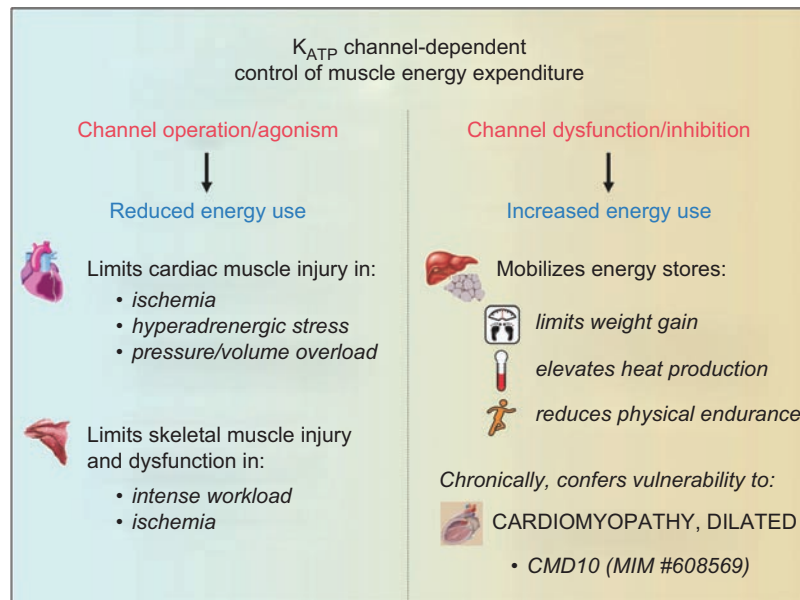
Figure 4. Bi-directional control of muscle energy expenditure by K$_{ATP}$ channel complexes. Active sarcolemmal K$_{ATP}$ channels constrain energy use and protect striated muscles during excessive energy demand. Downregulation of channel function results in increased mobilization of energy resources limiting body weight gain and increasing heat production.

suggests that increasing muscle-specific thermogenesis confers protection against acute cold exposure (Brand and Esteves 2005; Wijers *et al.*, 2008), setting the basis for possible K$_{ATP}$ channel involvement in thermoregulation.

Concluding remarks

Sarcolemmal K$_{ATP}$ channel complexes have been recognized as important components of an evolutionarily conserved biological system aimed at energy conservation and optimization of energy use (Alekseev *et al.*, 2010). This recently acquired physiological function of K$_{ATP}$ channels in striated muscles, beyond the commonly accepted response to severe energy deficit, invites the reevaluation of the conventional view on the role, regulation and therapeutic implication of sarcolemmal K$_{ATP}$ channels. Although the central feature underlying this homeostatic role is the established sensitivity of K$_{ATP}$ channels toward changes in intracellular adenine nucleotides, nucleotide-dependent channel operation cannot be exclusively resolved based on the homogeneity of intracellular energy pool and could rather rely upon compartmentalization of protein complexes and nucleotide fluxes between intracellular microdomains. The vast population of sarcolemmal K$_{ATP}$ channels is thus a prerequisite to support energy homeostasis through the maintenance of local ATPase activities within local metabolic units, secluded at sarcolemma by strong diffusion barriers, contributing to muscle thermogenesis. The operational paradigm of K$_{ATP}$ channel-driven thermogenic response provides at least two possible

mechanisms of the control of energy use that may not be mutually exclusive. First, K$_{ATP}$ channels reduce energy consumption, operating as a "safety valve" against action potential prolongation, which, however, is not readily applicable under physiological stimuli in the absence of detectable changes in action potentials duration. Second, K$_{ATP}$ channels may support energy resources in the submembrane compartment, acting as ATP synthases utilizing K$^+$ ion flow down the electrochemical gradient, which at present remains hypothetical and requires gaining insight into the properties of reversibility of SUR-associated ATPase activity. Alternatively, a distinct yet unrecognized function of K$_{ATP}$ channel complexes that revolves around SUR hydrolytic activity may be further suggested. Recent advances in the K$_{ATP}$ channel field suggest that these sarcolemmal energy sensors may serve as a peripheral target for bi-directional regulation of muscle energy utilization, which may find implication in a broad range of energy imbalance conditions linked, for instance, to heart disease, muscle myopathy, obesity and cold intolerance. In this way, the K$_{ATP}$ channel-dependent muscle thermogenic response could be evaluated for rational diagnosis, prognosis and selection of preventive personalized therapy supported by the newest developments in proteomics, metabolomics and pharmacogenomics (Waldman *et al.*, 2009).

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Declaration of interest

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