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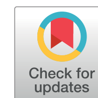

Do We Need a New Hypothesis for K_{ATP} Closure in β-Cells? Distinguishing the Baby From the Bathwater

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Let us first start where we all agree: K_{ATP} channels are the main conductance of the resting pancreatic β-cell, and their closure by changes in the ATP/ADP ratio is the triggering mechanism used by glucose to increase Ca^{2+} flux into the β-cell (1–3). When Cook and Hales (4) and Ashcroft et al. (5) discovered the K_{ATP} channel and showed it was closed by glucose metabolism, the source of the ATP that closed the channel was not stipulated. In fact, we struggled to find the first references to the term consensus model or canonical model in the literature. This is not mere semantics, as it seems most parsimonious to us that both glycolytic and mitochondrially derived ATP should be capable of closing the channel. As Merrins and Kibbey (6) argue in their Counterpoint article in this issue of *Diabetes*, it is difficult to separate glycolysis from oxidative phosphorylation (OXPHOS) because they are tightly linked: inhibiting glycolysis will also affect mitochondria by depriving them of pyruvate.

Merrins and Kibbey (6) present a highly provocative and challenging point of view that the role of mitochondria as key producers of the ATP that closes K_{ATP} needs to be discarded on biochemical and experimental grounds, whereas Rutter and Sweet (7) strongly questioned the need to discard the prevailing model. In the summary that follows, we will review the evidence supporting the novel hypothesis and some problems with it. We direct interested readers to the accompanying articles by Rutter and Sweet (Point) (7) and Merrins and Kibbey (Counterpoint) (6) in this issue of *Diabetes*.

Merrins and Kibbey (6) dispute the idea that β-cells use the ATP made by mitochondria to close their K_{ATP} channels, even though we all learned as students that for every 1 mol glucose, 36 mol ATP is generated by OXPHOS. To be clear, they do not dispute that mitochondrial ATP production is important to the β-cell, only that its main job is not triggering a rise in Ca^{2+} in response to glucose but pumping Ca^{2+} out of the cell after the rise occurs. We do wonder, however, why the β-cell, a highly aerobic cell, would avoid using the ATP made by OXPHOS, as the job of the β-cell is to secrete insulin and sustain glucose homeostasis regardless of the prevailing ADP level. Why should the cell relegate the crucially important job of detecting glucose and responding with the secretion of insulin to a lesser generator of ATP?

No matter how many compelling arguments might be put forth to support the theory that ATP synthesized by pyruvate kinase (PK) from phosphoenolpyruvate (PEP) during glycolysis is the key to understanding how K_{ATP} channels are closed by glucose metabolism through the action of a proposed metabolon, the experimental data supporting this theory are incomplete and contradictory. Furthermore (as we discuss later), arguing over which component of β-cell metabolism serves as the source of the ATP that generates islet oscillations may be asking the wrong question altogether.

Lewandowski et al. (8) provided data showing that K_{ATP} channels are inhibited when a solution containing ADP and PEP is applied to inside-out patches containing K_{ATP} channels, suggesting that close apposition of PK to the channel synthesizes enough local ATP to close the channel because of the action of glycolysis alone (8). This is a key piece of experimental evidence from Merrins' group (9) that is cited in support of the existence of a glycolytic metabolon in β-cells. To those unfamiliar with the idea of a metabolon, it is a closely linked collection of metabolic enzymes that have tight interactions and can be isolated as a biochemical unit (10). Such entities have been proposed for the enzymes of the tricarboxylic acid cycle (11) and other metabolic units in diverse organisms (12).

When we attempted to replicate the experiment of Lewandowski et al. (8) using identical methods and protocols (4) to study the regulation of K_{ATP} channels of mouse β-cells, insulin-secreting INS-1 cells, or human islets, we could not replicate this effect in any of our tests (13). While a negative result like ours does not refute the prior observation, we believe that the reported effect will also fail to be

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COMMENTARY

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observed by other workers, perhaps because other factors controlling the expression or localization of PK are labile, are dependent on cell culture conditions, or are sensitive to cell handling or the vagaries of patch formation.

Recently, we used the same approaches and conditions that failed to demonstrate PEP-induced K_{ATP} closure in patches from β-cells on those obtained from neonatal rat cardiomyocytes (Fig. 1). Cardiac cells were the original cell type in which K_{ATP} channels were discovered (14) and also where Weiss and Lamp (15,16) and Coetzee and colleagues (17) showed that glycolytically generated ATP preferentially suppressed K_{ATP} activity in excised membrane patches. We found that, using this cell type, the combined application of ADP and PEP to the inside-out patches did result in K_{ATP} channel closure (Fig. 1*A*). This positive-control experiment verified that our methods should have worked in β-cells too, but they did not in any instance. While there are biochemical data in heart cells that show that K_{ATP} channel subunits and PK protein can be pulled down together, at present no direct evidence for such a signaling complex exists in β-cells.

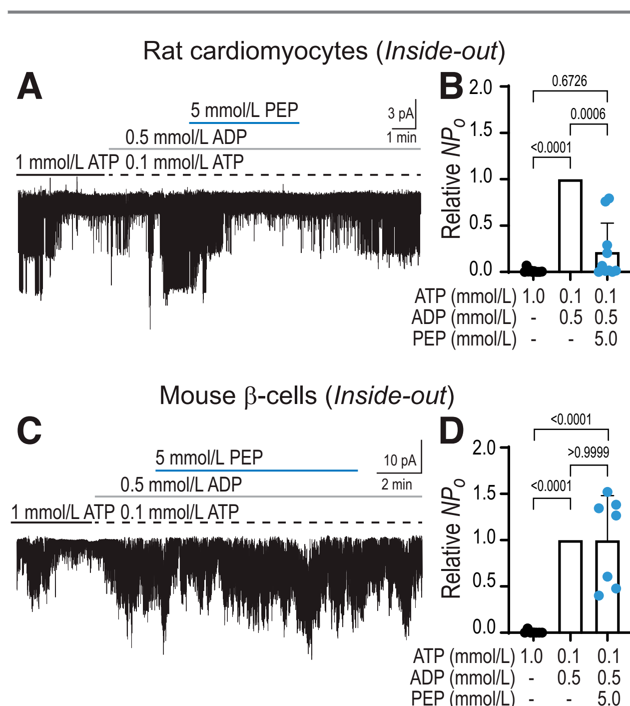

Figure 1—K_{ATP} channel activity in the presence of PEP. K_{ATP} activity was studied from inside-out recordings obtained from two different tissues. Channel activity was evaluated in cardiomyocytes isolated from neonatal rats (*A*) or in mouse β-cells (*C*). *A* and *B*: When PEP was perifused, a clear reduction in K_{ATP} activity was observed from recordings obtained from cardiomyocytes. In 4 out of 17 recordings, we did not observe a significant reduction in channel activity during PEP application, and these traces were removed for the final analysis. *C* and *D*: From mouse β-cells, however, PEP did not provoke a significant change in channel activity in any of the total traces we recorded. Openings were recorded at a holding potential of −50 mV and are displayed as downward deflections. Channel activity was quantified as *NPo* (*Po*, open probability; *N*, number of channels in the patch). Values are shown as the mean ± SD, with *P* values indicated.

Of course, β-cells and heart cells differ not only in their metabolism but also in the physiological role played by K_{ATP} channels in the two tissues. In the heart, K_{ATP} channels do not appear to be critical for the normal heartbeat, while under pathophysiological conditions, such as ischemia, the normally closed channels open as ATP/ADP falls, limiting Ca^{2+} influx and reducing the workload of the cell as a protective mechanism (18–20). In β-cells, the closure of K_{ATP}, in contrast, is part and parcel of the physiological triggering mechanism of β-cell stimulus-secretion coupling (1,2,21). The energy demands of the β-cell are also different from those of heart cells. Heart cells must beat continuously for the organism to survive, while the β-cell is a glucose sensor that increases its metabolic activity as glucose rises to trigger Ca^{2+} influx and insulin secretion, not primarily to meet its own energy needs.

One must be cautious about extrapolating results obtained from excised patches to the whole cell when trying to interpret the metabolic source of the ATP that mediates K_{ATP} channel closure. Merrins and Kibbey (6) dispute the existence of mitochondria in their excised patches in their Counterpoint article but cannot rule out that possibility for each and every excised patch. They show that applying pyruvate to the patches failed to close K_{ATP}. In fact, in some instances, pyruvate increased K_{ATP} activity for some reason. However, excising patches from the cell may also pull K_{ATP} channels away from any mitochondria that normally might be in the channel vicinity in situ and be the dominant source of ATP. More than 10 years ago, Rutter and colleagues (22) proposed that submembrane domains near the K_{ATP} channel are regulated by ATP that is locally generated by the close proximity to mitochondria. Recent work by Fraser and colleagues (23), who have developed new optical methods to measure submembrane glycolytic and OXPHOS activity in real time in β-cells, has shown that mitochondria are closely apposed to the plasma membrane.

Merrins and Kibbey (6) emphasize that their work with mutant mice lacking specific PK isoforms is further proof of their hypothesis. However, their study of mutants lacked clear findings at the islet/cell and whole-animal levels; only modest changes were seen in islet Ca^{2+} oscillations, in insulin secretion, or in whole-body glucose metabolism, which were attributed to molecular redundancy (24). An alternative explanation, however, is that the PK isoforms are not critical to the control of insulin secretion or β-cell function and that the lack of robust responses they reported at the islet, cell, or whole-animal level instead reflect only subtle actions, not key ones. Similarly, the loss of β-cell PEPCK also did not produce a strong phenotype (25). Can these mutants become glucose intolerant, perhaps under stress of a high-fat diet?

One of the strongest pieces of data presented by the group is their demonstration that the addition of amino

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acids to the recording chamber during cell-attached patch recordings of K_{ATP} channels was able to close K_{ATP}, presumably by activating the PEP cycle (24), and that mutant PK isoforms are unable to replicate this effect. It was surprising that this same setup was not used to show that raising glucose in the medium also closed the channel in wild-type PK but not mutants lacking specific isoforms. We also worry that alternative pathways for amino acid metabolism involving OXPHOS via the generation of pyruvate from PEP were not considered (26–28). For example, Foster et al. (24) tested the ability of amino acids to close K_{ATP} channels in β-cells lacking PKM1. Since these cells only expressed PKM2, they were not responsive to addition of amino acids and K_{ATP} activity was unaffected; however, channel activity was reduced after perifusion of amino acids in the presence of a PK activator, which suggested that allosteric activation of PKM2 was necessary to metabolize PEP, as previously reported by other groups (29,30). What is surprising is that this sole observation was taken as a confirmation of the hypothesis that PK makes the ATP that closes K_{ATP} channels. However, once pyruvate is synthesized in β-cells by PK, it can be transported and metabolized into the mitochondria to make even more ATP. This possibility was not discussed in Foster et al. (24) or in the article that followed from Merrins' group (9).

Another point worth considering is how mitochondrial PEP in their scheme can diffuse from where it is made in supposedly distant mitochondria to the vicinity of PK colocalized with K_{ATP} channels, while the ATP made by mitochondria cannot diffuse similarly to close K_{ATP}. We agree with Rutter and Sweet (7) that this seems implausible.

As also discussed in the Point article by Rutter and Sweet (7), there is little or no direct evidence that ADP falls so low during islet oscillations that OXPHOS is rendered incapable of synthesizing ATP while PK can keep chugging on to make ATP (8,31). This has not been proven directly via experiments (which would likely require a robust ADP sensor), and the data we (13) recently published indicates the opposite: using Perceval, we and others have shown that the profile of ATP/ADP measured during calcium oscillations has a sawtooth shape (see Fig. 4 in Corradi et al. [13]), the symmetrical shape of which shows that average ATP/ADP is the same during the silent and active phases of bursting. Further, the rapid addition of the OXPHOS inhibitor sodium azide profoundly reduces ATP/ADP, whether applied during the silent or the active phase of bursting, refuting the claim of Merrins and Kibbey that OXPHOS is switched off during the silent phase. Moreover, an unbiased reading of the literature does not support the contention that the affinity of PK for ADP is greater than that of OXPHOS; the literature shows the opposite (32–35).

We are aware of the criticism that mitochondrial inhibitors of OXPHOS such as azide might disrupt PEP formation and block glycolysis by substrate accumulation (36). However, in our hands, azide has very rapid effects that work within seconds, seemingly too fast to cause a buildup of glycolytic end products. We note that Sekine et al. (36) incubated cells in rotenone for 30–60 min.

Rutter and Sweet (7) argue that the true motor for calcium oscillations is likely calcium itself, which provides both positive feedback on ATP through mitochondrial activity and negative feedback through ATP consumption by pumps. This idea is at the core of the Integrated Oscillator Model (37). Simulations with the model agreed in detail with our experimental findings on azide and OXPHOS activity in the silent phase (13). More generally, the long history of mathematical modeling of metabolic oscillations in islets has shown that, depending on conditions, oscillations in Ca^{2+}, ATP/ADP, and insulin secretion can be driven either by oscillations in glycolysis or by Ca^{2+}-dependent variation of ATP production and consumption. The characteristics of the oscillations studied by Merrins and Kibbey (e.g., sawtooth oscillations in ATP/ADP and fructose 1,6-bisphosphate) align best with the latter type (37,38). In that class of oscillations, Ca^{2+}-dependent variations in consumption (by Ca^{2+} ATPases) are dominant (Fig. 2*A*), as originally proposed by Detimary et al. (39) and shown in Marinelli et al. (40). In fact, Ca^{2+} and ATP/ADP oscillations can occur in the model even with constant ATP production (Fig. 2*B*). Oscillations in fructose 1,6-biphosphatase similarly are not required. Thus, when Merrins and Kibbey say "PKM2 activity peaks at the time K_{ATP} channels close," they are correct, and the model agrees but says the PKM2 activity just passively follows calcium through its stimulation of pyruvate dehydrogenase. These points together suggest that the precise location and timing of ATP production are not critical for K_{ATP} closure during oscillations.

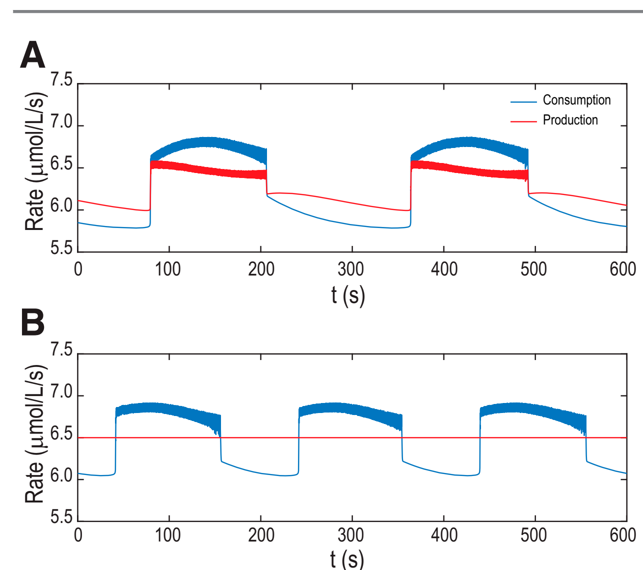

Figure 2—Simulation of ATP consumption rate and production rate using the Integrated Oscillator Model ver. 1.7 (42). *A*: Both consumption and production increase during the active phase of oscillations when intracellular calcium (not shown) is high and decrease during the silent phase when calcium is low. *B*: The variation in consumption rate is larger, and oscillations still occur when the production rate is held fixed.

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An important caveat is that the models only address whole-cell ATP and ADP concentrations. We currently have neither models nor data about whether those concentrations may have different dynamics in close proximity to K_{ATP} channels. We do note, however, that ATP measured under the plasma membrane showed a profile of submembrane ATP that resembled the patterns we and others have monitored in the cytosol (41). The critique by Merrins and Kibbey (6) in their Counterpoint that the sensor used by Tengholm's group (41) was not tethered to the plasma membrane, and therefore lacked specificity as a submembrane sensor, is mitigated by their use of total internal reflection fluorescence microscopy to illuminate a restricted region within 50–100 nm of the plasma membrane. We are therefore not convinced that differences in submembrane ATP, as proposed by Merrins, Kibbey, and colleagues (6,8,9), are necessarily relevant. More data are clearly needed to investigate this further.

Resolution of this important controversy will require new experimental evidence. First, it must be demonstrated that K_{ATP} channels (themselves complexes of SUR1 and Kir6.2 subunits) indeed form a stable, biochemically functional complex with PK that is in close proximity to the plasma membrane. Furthermore, these complexes must also possess the ability to exclude mitochondrially generated ATP within their channel microdomain, so that K_{ATP} is exclusively inhibited by PK-generated local ATP. According to the model outlined in the Point article by Rutter and Sweet (7), disruption of the complexes by, for example, preventing critical protein-protein interactions between the channel and PK would result in significant disruption of β-cell function. This should manifest as a loss of islet oscillatory activity or reduced glucose-induced insulin secretion. The authors of both the Point and Counterpoint articles in this issue suggested the need for experimental evidence along these lines. As the model simulations shown here suggest that oscillations in ATP production may not be required for the production of oscillatory islet Ca or electrical activity, oscillatory PK-induced oscillations in submembrane ATP must be shown experimentally as well. Conversely, according to the canonical model defended by the Point article, block of mitochondrial ATP production should markedly impair K_{ATP} channel closure. Note that impairment of Ca or membrane potential oscillations alone would not be definitive, because both models predict this by different mechanisms.

In sum, we caution readers not to throw the baby out with the bathwater. More research is still needed to fully understand whether there is a direct glycolytic contribution to the ATP that mediates K_{ATP} channel closure in β-cells, and this needs to be done by more groups and with additional tools, some of which remain to be developed. Merrins and Kibbey (6) have proposed a provocative model of β-cell stimulus-secretion coupling that challenges the prevailing gestalt. While that is how science can move forward, the idea needs to be more rigorously tested. As Rutter and Sweet (7) point out clearly, that will likely be difficult to accomplish.

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