Differential metabolic and nucleotide sensitivity of beta-cell and cardiac K_{ATP} channels

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ATP-sensitive potassium (K_{ATP}) channels couple the metabolic state of a cell to its electrical activity and play important physiological roles in many tissues. In contrast to beta-cell (Kir6.2/SUR1) channels, which open when extracellular glucose levels fall, cardiac (Kir6.2/SUR2A) channels remain closed. We investigated the molecular basis of this difference by two-electrode voltage clamp (TEVC) and patch clamp of Kir6.2/SUR1 and Kir6.2/SUR2A channels heterologously expressed in *Xenopus* oocytes.

Differential sensitivity to metabolic inhibition (azide) was observed in TEVC of intact oocytes, indicating it results from differences in SUR, and not differences in beta-cell and cardiac metabolism. In inside-out patches, both channel types were inhibited by ATP and activated by MgADP to similar extents. However, when both nucleotides were present, the results were strikingly different. Thus, 100µM MgADP reduced MgATP block of Kir6.2/SUR1 from 24µM to 504µM (when measured immediately after patch excision), but had little effect on MgATP inhibition of Kir6.2/SUR2A. The difference in ATP block in the presence of 100µM MgADP was sufficient to explain why beta-cell K_{ATP} channels open in the absence of glucose and cardiac channels do not. Deleting the last 42 amino acids 'the tail' of SUR abolished MgADP activation of both channels. Replacing the tail of SUR2A with that of SUR1 switched the ATP sensitivity in the presence of MgADP to that of SUR1 (and *v.v.*). These data suggest that the 'tail' of SUR plays a critical role in coupling nucleotide binding/hydrolysis to channel activation, and that this differs between cardiac and beta-cell K_{ATP} channels.