P001 UCP2 contributes significantly to high mitochondrial proton leak in INS-1E pancreatic beta cells and attenuates glucose-stimulated insulin secretion

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Proton leak exerts stronger control over ATP/ADP in mitochondria from INS-1E insulinoma cells than in those from rat skeletal muscle, due to the higher proton conductance of INS-1E mitochondria [Affourtit, C. and Brand, M. D. (2006), Biochem. J. 393, 151-159]. Here we demonstrate that high proton leak manifests itself at the cellular level too: the leak rate (measured in trypsinized cells as myxothiazol-sensitive, oligomycin-resistant respiration) was nearly 4-fold higher in INS-1E cells than in myoblasts, and was responsible for 68 ± 3% of INS-1E respiration (n=12). Upon knock-down of uncoupling protein-2 (UCP2) by RNAi, oligomycin-insensitive respiratory activity decreased to 54 ± 3% of the resting activity (n=22). The high contribution of UCP2 to leak suggests that proton conductance through UCP2 accounts for more than 20% of INS-1E respiration. UCP2 knock-down enhanced glucose-stimulated insulin secretion, consistent with a role for UCP2 in beta cell physiology. We propose that the high mitochondrial proton leak in beta cells is a mechanism to amplify the effect of physiological UCP2 regulators on cytoplasmic ATP/ADP and hence on insulin secretion.