Regulation of the Mitochondrial Permeability Transition Pore by Arginine Residues of F-ATP Synthase

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Arginine-glyoxal adducts can lead to either suppression or induction of permeability transition (PT) of isolated rat liver mitochondria (1). We find that purified bovine F-ATP synthase reconstituted into planar lipid bilayers displays channel activity after the addition of *p*-hydroxyphenyl glyoxal (OH-PGO) in presence of Ca^{2+}, even in the absence of BZ423 and of oxidants, previously shown to be required for Ca^{2+}-induced activation of the channel. OH-PGO is thus a strong inducer of PTP, and these results indicate that the reactive arginine(s) are located in the F-ATP synthase. Phenylglyoxal (PGO) is the most extensively used reagent for the site-specific chemical modification of arginine in proteins. We show that phenylglyoxal (PGO) affects the PT in a species-specific manner: inhibitory effects in mouse and yeast, inducing effects in human and *Drosophila*. Subunits e and g are essential for the dimerization of F-ATP synthase and mitochondrial cristae formation (2). Remarkably, we demonstrate that mitochondria from a yeast mutant strain lacking subunit g (*ΔATP20*) is resistant to the PT inhibitory effects of PGO, and that the effect is phenocopied in a subunit g R107A mutant. Thus, the effect of PGO on the PT is specifically mediated by R107, the only subunit g arginine that is conserved across species. These findings identify the target of PGO and strongly indicate that the PT is mediated by F-ATP synthase.

Reference

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