A Is For . . .

Uncoupling Protein

uncoupling protein *A type of mitochondrial anion carrier protein that is activated by free fatty acids and that dissipates a proton gradient built up by the mitochondrial respiratory chain, uncoupling respiration from phosphorylation; proposed to be involved in energy regulation and obesity.*

Oxidation of substrates in mitochondria reduces NAD^+ to NADH and FADH to $FADH_2$. Electrons released by the nucleotides are delivered to the electron transport chain in the inner mitochondrial membrane. Electron transport couples oxidation to the pumping of protons from the mitochondrial matrix into the intermembrane space. Movement of protons creates an electrochemical gradient, called the proton motive force.

Protons return to the matrix through ATP synthase during phosphorylation of ADP to ATP and cannot enter the matrix when there is no ADP. The steeper pH gradient in the absence of ADP inhibits the electron transport chain and the reduction of NAD^+ and FADH. This is the chemiosmotic hypothesis for the close coupling of substrate oxidation to energy needs.

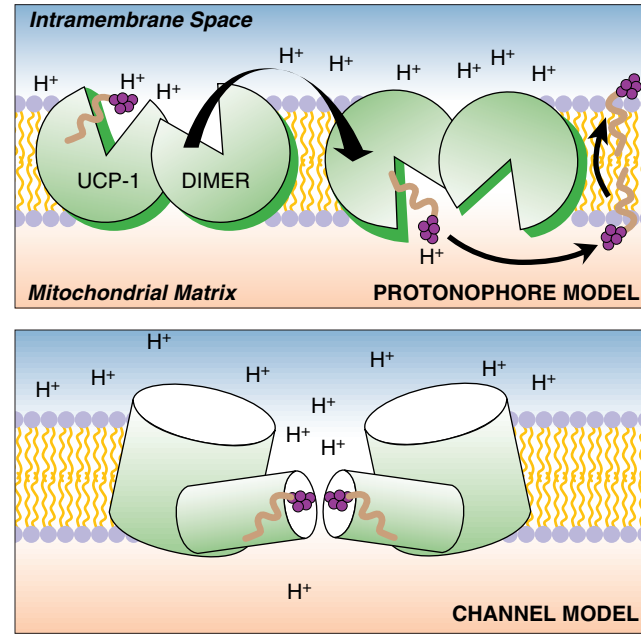
Coupling of substrate oxidation to ATP synthesis is not perfect, for mitochondria consume oxygen even when ADP is not available. "Proton leaks," which are increases in the proton conductance of mitochondria, account for a considerable part of basal (resting) energy expenditure in humans. Increasing energy use by pharmacologically increasing proton leakage would be a way to reduce weight, and this was tried using dinitrophenol back in the 1930s.

In small mammals and human infants, brown adipose tissue is an important site of cold-induced thermogenesis, an adaptive energy expenditure. The mechanism is transport of protons across the inner mitochondrial membrane by a protein originally called thermogenin, later uncoupling protein, and now UCP-1.

Because adult humans have almost no brown adipose tissue, the contribution of UCP-1 to total energy expenditure cannot be large. But the existence of substantial proton leaks in mitochondria extracted from tissue that has no UCP-1 suggested the existence of other such uncoupling proteins. Four of them have been described, among which UCP-2 and 3 are 71% homologous to each other and 55% and 57% homologous, respectively, to UCP-1.

UCP-2 is widely expressed in humans, with the highest levels in white adipose tissue. UCP-3 is found mainly in skeletal muscle, which is also the major site of basal energy expenditure. At least 400 published papers since their discovery in 1997 testify to the interest in UCP-2 and 3, yet no one knows what these proteins actually do.

Almost all of the work on UCP-2 and 3 has reported mRNA content rather than protein content, principally because there are no specific antibodies for the two proteins. No regulators of their uncoupling activity have been found either, whereas UCP-1 is highly regulated. Thus, the link between mRNA expression and protein activity is tenuous.



Two models for proton transport across the inner mitochondrial membrane by UCP-1. Adapted from Dalgaard and Pedersen: *Diabetologia* 44:946-965, 2001.

The weight of evidence at the moment is against any important role for the uncoupling proteins in regulating energy expenditure. Their tissue distribution does not match measured proton leak. Moreover, starvation increases UCP-2 and 3 mRNA and protein in white adipose tissue and skeletal muscle without increasing proton leak.

Thus, the proton leak that is responsible for part of basal energy expenditure probably does not involve uncoupling proteins. Absence of either UCP-2 or UCP-3 in mice does not reduce metabolic rates, and knockout mice lacking UCP-2 or 3 do not become obese.

Genetically engineered mice overexpressing UCP-1 and UCP-3 are resistant to diet-induced obesity, so these proteins are still promising anti-obesity drug targets. Double or triple knockout mouse models should clarify their function, while the physiologic consequences of increases or decreases in proton leak across the inner mitochondrial membrane need to be examined.

Louise T. Dalgaard and Oluf Pedersen: Uncoupling proteins: functional characteristics and role in the pathogenesis of obesity and type II diabetes. *Diabetologia* 44:946-965, August 2001.