5.5: Uncoupling Electron Transport from ATP Synthesis

So, that is oxidative phosphorylation. It productively utilizes the energy of the proton gradient across the inner mitochondrial membrane (created by oxidation-powered pumps) to drive ATP formation at an approximate rate of 3 protons to 1 ATP. The system is normally highly self-regulated due to impermeability of the inner mitochondrial membrane to H\(^+\). If the ATP is not used up quickly, then its concentration slows the action of ATP synthases, which slow the movement of protons out of the intermembrane space. This buildup of protons will eventually be enough that the free energy needed to transfer a proton into the intermembrane space (from the electron transport chain) will not be sufficient to overcome the concentration gradient. Electron transport is slowed, and working backwards, the chain reaction slows respiration rates in general. As the cell/organism requires more energy and uses up the ATP more quickly, protons flow more quickly and the electron transport chain is disinhibited. Thus there is a direct association between respiration rate and physiological energy need.

Interestingly, there is an exception to this tight coupling of the electron transport chain and formation of ATP. The purpose of brown fat (aka brown adipose tissue), which is most often found in newborn and hibernating mammals, is to generate non-shivering (non-movement-based) heat to keep the animal warm. This is accomplished by uncoupling the electron transport chain from the ATP synthesis. This uncoupling is a hormonally controlled process based on the presence of a mitochondrial proton channel called thermogenin. The hormone norepinephrine increases production of free fatty acids, which open the thermogenin channel. This allows protons to flow from the intermembrane space back into the matrix without having to go through ATP synthase. Because of this, the electron transport chain can keep chugging away, ATP levels do not build up, there is no reduction in respiration rate, and the excess energy not being used in ATP production is released as heat.

In fact, 2,4-dinitrophenol, which is used in a variety of research and industrial applications today, was at one time used as dieting drug (in the 1930’s) because through a different mechanism, it too uncoupled electron transport from ATP synthesis. Its mechanism of action derived from its ability to carry and release protons as it freely diffused through the
mitochondrial membrane (since it is a small hydrophobic molecule). As this continues, cells catabolize more and more stores of carbohydrates and fats, which is the reason for the interest by dieters. Unfortunately for some of those dieters, this pharmacological means of uncoupling the electron transport chain from the ATP synthesis had no regulation other than the amount of DNP taken. In cases of overdose, respiration rates could rise dramatically while producing little ATP and a great deal of heat. In fact, overdose illness and death are generally due to the spike in body temperature rather than lowered ATP availability. Unfortunately, there are still some dieters and bodybuilders who self-medicate with DNP despite the dangers.