Biological electron transfer captured in real time

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Two research teams led by Dr. Michael Verkhovsky and Prof. Mårten Wikström of the Institute of Biotechnology of the University of Helsinki have for the first time succeeded in monitoring electron transfer by Complex I in real time. In the future, this work might, for example, have medical relevance, because most of the maternally inherited so-called mitochondrial diseases are caused by dysfunction of Complex I.

This achievement required developing and building of a special device by which the enzyme-catalysed electron transfer could be captured at different time points by stopping the reaction at liquid nitrogen temperatures, on a microsecond (one millionth of a second) time scale. The electrons are very small elementary particles, which is why their transfer is very fast. This work is published this week in *PNAS*. The results give certain hints of the function of Complex I at the molecular level.

Electron transfer is central to many chemical reactions in the cell. It has particular functional importance in cell respiration, which in eukaryotes takes place in the inner mitochondrial membrane, and in the cell membrane of prokaryotes. In cellular respiration molecules stemming from food are oxidised to carbon dioxide, and the electrons liberated in the process are "fed" into the so-called respiratory chain, which consists of three successive membrane-bound enzyme complexes, finally to react with the oxygen we breathe, which is reduced to water using these electrons.

The purpose of electron transfer in cellular respiration is to release the major part of the energy of foodstuffs and to conserve it in a suitable form, ATP (adenosine triphosphate), which the cell may use in its energy-requiring reactions (e.g. biosynthesis, active transport, mechanical work), which are essential e.g. during fetal development and growth, in neural and kidney function, muscle contraction, etc.

The energy captured in cellular respiration is transduced to ATP in two phases. The role of the respiratory chain is to couple electron transfer to the translocation of positively charged protons across the membrane, so that the mitochondrial membrane (or the cell membrane in bacteria) becomes electrically polarised, just like charging up a battery. In the second phase, the voltage difference of the battery is used to drive the protons back across the membrane, coupled to the synthesis of ATP by very special molecular machinery.

The first enzyme complex of the respiratory chain is called Complex I. High-energy electrons are fed into this complex in the form of a reduced coenzyme, NADH (nicotinamide adenine dinucleotide), which is oxidised to NAD+ having donated its two electrons. After this, the electrons are transferred along several protein-bound iron/sulphur centres in Complex I until they reach their destination, a molecule of ubiquinone, which is thus reduced to ubiquinol. This reaction, as catalysed by Complex I, is linked to proton translocation across the membrane and thus leads to "charging the battery". At a later stage ubiquinol donates its electrons further in the respiratory chain (ultimately to oxygen), by which it is oxidised back to ubiquinone to allow continuation of Complex I function.

Source: University of Helsinki