



Coenzyme Q10 a potential therapeutic target for ataxia: Evaluation of therapeutic strategies

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Scientific summary

A coenzyme Q₁₀ (CoQ₁₀) deficiency has been identified as a potentially important cause of cerebellar ataxia. This project will investigate the pathogenic mechanisms associated with CoQ₁₀ deficiency and evaluate the biochemical efficacy of quinone treatment to restore mitochondrial energy metabolism and replenish cellular antioxidant capacity. In this study, which will form the basis for a PhD studentship, cellular models of neuronal CoQ₁₀ deficiency will be established by both pharmacological manipulation and interference RNA strategies. These neuronal cell models together with fibroblasts from a patient with a confirmed CoQ₁₀ deficiency will be used to assess the effect of a deficit in CoQ₁₀ status upon integrated function of the mitochondrial electron transport chain (ETC), fatty acid β -oxidation, cellular antioxidant status and oxidative stress generation. Since $\geq 55\%$ of cellular CoQ₁₀ is extramitochondrial, assessment will be undertaken of the subcellular distribution of a CoQ₁₀ deficiency. Cellular uptake and distribution of potentially therapeutic quinones CoQ₁₀, idebenone, decylubiquinone and MitoQ in the CoQ₁₀ deficient cells will be evaluated. Determination will be made of the effect of quinones upon integrated ETC function, ETC enzyme activity and fatty acid β -oxidation in CoQ₁₀ deficient cells. The effects of quinone supplementation will also be monitored on cellular superoxide generation and cellular antioxidant status.

Lay summary

Coenzyme Q₁₀ (CoQ₁₀) is used by the cell to produce energy for maintaining growth of the cell. It also acts as an effective antioxidant protecting the cell from chemicals called free radicals that can cause cellular dysfunction. A CoQ₁₀ deficiency has been identified as a potentially important cause of cerebellar ataxia. In this project we will investigate the effect of a CoQ₁₀ deficiency upon the ability of cells (fibroblasts and neurones) to produce energy and protect themselves against free radical-induced dysfunction. In addition, this project will be the first study to evaluate and assess potential treatments targeted at restoring the energy production and antioxidant potential of cells with a CoQ₁₀ deficiency. The results of this project will therefore have therapeutic potential for providing a more effective treatment for cerebellar ataxic patients with a CoQ₁₀ deficiency.

The student awarded this PhD studentship will hopefully contribute to the next generation of scientists investigating inherited ataxias.

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