Cellular regulation of nutrient and energy turnover

https://www.neurodegenerationresearch.eu/survey/cellular-regulation-of-nutrient-and-energy-turnover/

Title of project or programme

Cellular regulation of nutrient and energy turnover

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
Professor	Martin	Brand	MRC Mitochondrial Biology Unit	UK

Address of institution of lead PI

Institution	MRC Mitochondrial Biology Unit
Street Address	Wellcome Trust/MRC Building, Hills Road
City	Cambridge
Postcode	CB2 0XY

Country

- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

4056896.259

Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Alzheimer’s disease and other dementias
- Parkinson’s disease

Keywords

Research abstract in English

We are investigating the efficiency of biological energy conservation, emphasising the mechanism and regulation of a major inefficiency, mitochondrial proton conductance. We are trying to understand

the production of damaging free radicals by mitochondria within cells. This work may allow manipulation of metabolic rate, and so open the way to potential anti-obesity and anti-ageing pharmaceuticals, nutrients and nutriceuticals. It has implications for organ storage and for many progressive diseases that may act through mitochondrial function, including ageing, Parkinson's, Alzheimer's, diabetes and mitochondrial myopathies.

We want to identify the pathways and understand the function, physiological importance, mechanisms and regulation of mitochondrial proton conductance, and to develop ways to manipulate it. In particular, we are working on the function and mechanism of uncoupling proteins, to establish their involvement in physiological uncoupling, regulation of metabolic rate and insulin release, and antioxidant defence. We want to establish the role of mitochondrial proton conductance in the production of reactive oxygen species, to understand how it may affect ageing and progressive mitochondrial and cellular dysfunction and to manipulate it to ameliorate progressive tissue damage. We want to exploit metabolic control analysis to describe and understand the regulation of energy turnover and signal transduction.

– Mechanism of proton conductance: role of UCPs. Brown adipose tissue expresses UCP1, which catalyses proton conductance. Candidate catalysts in other tissues are UCP2 and UCP3. We have expressed the UCPs in yeast and expressed them or deleted them in mice and clonal cell lines and are determining their physiological and mitochondrial phenotypes to establish function and mechanism. We are purifying UCPs and reconstituting them to allow direct measurement of function and regulation by nucleotides

– Regulation of proton conductance. We are establishing the roles of radicals, alkenals, and free and phospholipid fatty acids in proton transport through UCPs and other mitochondrial carriers.

– Dietary restriction and ageing. We are investigating the relationship between diet, ageing, mitochondrial efficiency and reactive oxygen species in mitochondria, cells and organisms, using Drosophila, mammalian and avian models.

– Regulation of energy turnover. We are exploiting control analysis, to investigate signal transduction.

Lay Summary