INTRODUCTION

Caloric restriction (CR) protects against many neurodegenerative conditions and neuronal damage associated with calcium overload. The role of mitochondria, which play an important role in cellular calcium handling, is poorly understood in the context of CR.

OBJECTIVES

This study aims to understand the effect of CR in the brain and its effects on calcium handling by mitochondria, as well as to identify possible mechanisms by which CR protects against calcium-overload insults.

MATERIALS & METHODS

Experiments were performed using Sprague-Dawley rats, Swiss mice and cellular models. Standard bioenergetic and molecular biology techniques were adopted.

DISCUSSION AND RESULTS

CR protects against kainic acid, an excitotoxic insult that over-activates glutamate receptors and induces calcium-overload in neurons. CR also increases electron transport activity and enhances calcium retention capacity in brain mitochondria without changing the mitochondrial mass. The expression of Mfn-2, a protein involved in mitochondrial morphology regulation, was increased, and could account for the higher electron transport activity observed. The increase in calcium retention seems to be mediated by post-translational modifications in cyclophilin D, as it is not further increased with cyclosporin A and the levels of cyclophilin D in the brain do not change with the diet. We also observed an increase in the phosphorylation state of ERK in brains from CR animals, which has been previously associated with phosphorylation and inhibition of cyclophilin D. Serum from CR animals is sufficient to mimic some of these features in primary neuronal cultures and protects against calcium-overload death in glioblastoma cells.

CONCLUSIONS

We propose that enhanced calcium retention capacity could underlie the beneficial effects of CR against pathological conditions that induce calcium overload in neuronal cells. Protection could be triggered by a molecule present in serum that acts on cyclophilin D, inhibiting it, thereby increasing calcium retention capacity in mitochondria and limiting calcium-induced damage to the cell.