Caloric Restriction Increases Brain Mitochondrial Calcium Retention Capacity and Protects Against Excitotoxicity

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Caloric restriction (CR) protects against many cerebral pathological conditions that are associated with excitotoxic damage and calcium overload, although the mechanisms are still poorly understood. Here we show that CR strongly protects against excitotoxic insults in vitro and in vivo in a manner associated with significant changes in mitochondrial function. CR increases electron transport chain activity, enhances antioxidant defenses and favors mitochondrial calcium retention capacity in the brain. These changes are accompanied by a decrease in cyclophilin D activity and acetylation and an increase in Sirt3 expression. This suggests that Sirt3-mediated deacetylation and inhibition of cyclophilin D in CR promotes the inhibition of mitochondrial permeability transition, resulting in enhanced mitochondrial calcium retention. Altogether, our results indicate that enhanced mitochondrial calcium retention capacity underlies the beneficial effects of CR against excitotoxic conditions. This protection may explain the many beneficial effects of CR in the aging brain.