Calorie Restriction in Old Rhesus Monkeys Confers Protection Against Adverse Physiological Processes in Critical Brain Regions Affected by Normal Aging


INTRODUCTION

- Projected health care cost of aging by 2050: 63 trillion dollars.
- Problems with forming new memories and higher order cognition partly happen because of atrophy in the hippocampus and the top of the frontal lobe (i.e. the dorsal convexity).
- The atrophic influence of toxic products such as iron in the brain, inflammatory proteins (e.g. IL-6), and the vascular risk marker homocysteine (Hcy) is poorly understood.
- 30% calorie restriction (CR) in rodents and monkeys improves health and may reduce the influence of these toxic products on the brain.

METHODS

Subjects and Physiology

- 17 controls, 26 CR monkeys. 19-31 years old. 30% CR diet relative to baseline food intake consumed for 12-17 years. Control had unrestricted food access for ~8 hrs/day. IL-6 & Hcy collected in blood. Brain iron assessed with MRI scan.

Volumetrics

- T1-weighted brain volume scan. TR = 8.772 ms; TE = 1.876 ms; inversion time = 900 ms; flip angle = 10°; number of excitations = 2; acquisition matrix = 256x256; field of view = 160mm. 124 coronal sections. 0.625 x 0.625 x 0.7 mm voxels.
- T2-weighted relaxation brain iron scan. TR/TE=2000/45ms; flip angle = 90°; excitations = 2; acquisition matrix = 256x256; field of view = 160mm. 124 coronal sections. 0.625 x 0.625 x 1.7 mm voxels.

Diffusion Tensor Imaging

- DWI-EPI sequence in 12 optimal directions. b = 1000 s/mm²; NEX = 6; FOV = 160 mm, in-plane matrix = 120x120, slice thickness = 2.5mm. Resampled at 0.5 x 0.5 x 0.5 voxels.

Statistics

- T-tests for analyzing CR effect on physiological variables.
- Voxel and cluster thresholds for brain-physiological correlations:
  - p < .005 (uncorrected) and p < .05 (corrected). Age, gender, condition, and the total volume of the brain appropriately taken into account as covariates. Protective effects of CR analyzed with physiology or age interactions.

RESULTS

CR and Physiology

- CR monkeys showed significantly less brain iron deposition in several motor function areas.
- CR monkeys had 1.12µg/ml lower median IL-6 concentrations, which would confer health benefits.
- CR monkeys had no change in homocysteine levels.

Hippocampus

- Brain iron: CR monkeys had greatly reduced iron deposition & atrophy in areas like hippocampus as a function of age (see graph A for illustrative example).
- Inflammation (IL-6): Due to lower IL-6 levels, CR Monkeys showed less atrophy in hippocampus.
- Vascular degeneration (Homocysteine): Despite no effect of CR on Hcy levels, CR monkeys showed less atrophy in hippocampus as a function of age.

Dorsal Convexity

- Brain iron: No relationship was seen in either group.
- Inflammation (IL-6): CR monkeys had greatly reduced IL-6 related atrophy as a function of age (see graph B).
- Vascular degeneration (Homocysteine): Hcy was related to atrophy for both CR and controls. Because CR did not reduce Hcy levels in our sample, CR would not protect against atrophy due to vascular damage in the dorsal convexity.

Summary

- Long-term 30% CR in rhesus monkeys reduces levels of toxic compounds in the blood and brain that can cause brain atrophy.
- CR led to substantial brain protection in the hippocampus and dorsal convexity.
- These physiological processes influence atrophy in these regions differently.
- CR does not confer protection in all cases, such as vascular-related atrophy in the convexity.

Objectives

1) Test if CR reduces levels of these indices.
2) Assess associations of physiological indices to atrophy in hippocampus and dorsal convexity.
3) Examine if CR monkeys show reduced associations b/w indices and brain atrophy.