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Research report

Partial rescue of memory deficits induced by calorie restriction in a mouse model of tau deposition

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HIGHLIGHTS

- Tg4510 mice showed smaller body weights despite increased food intake.
- Short-term memory was enhanced by CR in the novel object recognition test.
- A trend for improvement in contextual memory was observed in CR Tg4510 mice.
- No changes in spatial memory deficits were observed in Tg4510 mice submitted to CR.
- No impact on tau deposition markers was observed.

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ABSTRACT

Calorie restriction (CR) was shown previously to improve cognition and decrease pathology in transgenic mouse models with Alzheimer-like amyloid deposition. In the present study, we investigated the effects of CR on the Tg4510 model of tau deposition. Mice in the calorie restriction group had food intake gradually decreased until they reached an average of 35% body weight reduction. Body weight and food intake were monitored throughout the study. After being on their respective diets for 3 months, all animals were submitted to behavioral testing. Tg4510 mice fed *ad libitum* showed lower body weight than nontransgenic littermates despite their increased food intake. Additionally, Tg4510 showed increased locomotor activity in the open field regardless of diet. Calorie restricted Tg4510 mice performed significantly better than *ad libitum* fed mice in the novel object recognition test, suggesting improved short-term memory. CR Tg4510 mice also performed significantly better in contextual fear conditioning than mice fed *ad libitum*. However, in a modified version of the novelty test that allows for interaction with other mice instead of inanimate objects, CR was not able to rescue the deficit found in Tg4510 mice in this ethologically more salient version of the task. No treatment differences in motor performance or spatial memory were observed in the rotarod or radial arm water maze tests, respectively. Histopathological and biochemical assessments showed no diet-induced changes in total or phospho-tau levels. Moreover, increased activation of both astrocytes and microglia in Tg4510 mice was not rescued by calorie restriction. Taken together, our data suggests that, despite an apparent rescue of associative memory, CR had no consistent effects on pathological outcomes of a mouse model of tau deposition.

1. Introduction

Calorie restriction (CR) is the most robust intervention capable of prolonging lifespan in multiple species from yeast to smaller mammals [reviewed in [1]]. Its neuroprotective effects have been implicated in several neurological disease

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models [2,1,3]. CR has been reported to increase metabolic efficiency which is often associated with enhanced processes providing resistance to cellular stress such as improved mitochondrial function, enhanced antioxidant defenses [4] and decreased production of reactive oxygen species (ROS) [5–8]. Other possible mechanisms are: decreased activity of pro-apoptotic and inflammatory factors [9], increased neurogenesis [10] and increased levels of molecular chaperones in the brain [11,12].

Alzheimer's disease (AD) is the most prevalent type of dementia and a common age-related condition, clinically described by progressive cognitive decline. Pathologically, it is characterized by post-mortem findings of widespread deposition of amyloid-beta peptide (Aβ) forming plaques and neurofibrillary tangles, which are aggregates of hyperphosphorylated forms of tau protein. Previously, we showed that short-term calorie restriction in early adulthood significantly reduced the number and size of amyloid plaques in the brains of two transgenic mouse models of amyloid deposition (APP and APP+PS1) that express mutations associated with familial or early onset AD [13]. These transgenic mice presented increased GFAP immunoreactivity that was attenuated in the CR group. Mouton et al. [14] submitted middle-aged (13–14 months old) APP+PS1 mice to a 40% CR for 18 weeks to address the question of whether CR would be beneficial in decreasing amyloid load after heavy accumulation has taken place. Stereological analysis of amyloid deposits showed reductions of 33% in the neocortex and 32% in the hippocampus for the CR group compared to the same brain regions in the *ad libitum* fed mice [14].

Reducing caloric intake by 30% in rhesus monkeys for up to 20 years lowered the incidence of age-related diseases, predominantly cancer, diabetes and cardiovascular disease. In addition to a subjective more youthful appearance, CR animals displayed attenuated brain atrophy [15]. Recent studies carried out at the National Institute of Aging (NIA) showed that CR did not affect longevity but significantly impacted health span in non-human primates. Additionally, fasting glucose, serum cholesterol and triglyceride levels were also improved in CR animals [16]. Surprisingly, the reduction in amyloid load described in mouse models was not replicated in studies of nonhuman primates. Post-mortem histological analysis confirmed that CR attenuated astrogliosis, but failed to change amyloid load compared to controls [17].

Most of the evidence to date has focused on amyloid pathology in rodent models. Although several groups have shown the effects of calorie restriction on Aβ accumulation, only recently researchers have studied its effects on tau and phospho-tau level alterations. Besides improvement in cognitive performance, significant reduction in phosphorylated tau in the cortex of conditional double knockout of PS1 and PS2 transgenic mice has been previously reported [18] after 4 months of 30% calorie reduction. However, the absence of tangle formation despite substantial phosphorylation of tau observed in this model limits our interpretation of this finding. Furthermore, when the triple transgenic mouse model of AD (3xTgAD) was submitted to 40% calorie restriction for 7 or 10 months, reductions in both Aβ and phospho-tau in the hippocampus were observed compared to a control group maintained on an *ad libitum* diet [19]. Considering that tau pathology is largely driven by the presence of amyloid in this model [20,21], using a tau depositing model would permit discrimination of effects on amyloid from those on tau. Based on the above mentioned results, we hypothesized that CR would prevent tau-associated pathology and behavioral deficits in a well established mouse model of tau deposition.

Table 1
Composition of diets used in this study.

	Ad libitum diet-NIH-31 (g/kg)	Calorie restriction diet (g/kg)
Casein	210	210
L-Cystine	3	4
Sucrose	200	199
Maltodextrin	100	99
Corn starch	369	369
Cellulose (fiber)	40	40
Flaxseed oil	21	21
Canola oil	19	19
79055 MM Ca-P deficient	13.4	13.4
Calcium phosphate dibasic ($CaHPO_4$)	7	7
Calcium carbonate ($CaCO_3$)	7.3	7.3
40060 VM, Teklad	10	14
Ethoxyquin (Liquid)	0.01	0.01
Total	1000	1000
Protein, % by weight	17.9	17.9
Protein, % of kcal	23.8	23.8
Carbohydrate, % by weight	46.8	46.6
Carbohydrate, % of kcal	62.2	62.1
Fat, % by weight	4.7	4.7
Fat, % of kcal	14	14.1
kcal/g	3.0	3.0

2. Materials and methods

2.1. Mice

Parental mutant tau and tetracycline-controlled transactivator protein lines were maintained separately and bred to produce Tg4510 mice and nontransgenic littermates as described previously [22]. The Tg4510 mouse has a human P301L mutation, which is associated with an autosomal dominantly inherited dementia referred to as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) [23]. This model differs from other tau transgenic mice in that the major tau pathology is found in the forebrain rather than the spinal cord. This is due to the tet response element driven expression, with the tet activator regulated by the CaM kinase II promoter, resulting in expression predominantly in forebrain neurons. These mice develop progressive pathology with histologically discernible tau deposits consistently observed at 3 months, progressing through a series of conformational and hyperphosphorylated forms analogous to that found in AD patients leading to neuron loss and atrophy by 6 mo ([22,24]). All animals were 3 months old at the start of the study and nontransgenic littermates were used as control groups for behavioral and histological changes (FVB/129S F_1 hybrid background). Mice were maintained on a twelve-hour light/dark cycle. Water was provided *ad libitum* throughout the experiment.

2.2. Calorie restriction

All animals were individually caged before the commencement of the study for individual assessments of food intake and body weight. Measurements of daily food consumption started when the animals were 3 months old and were carried out for 4 weeks before the start of the calorie restriction procedure. The CR group received a diet identical to the *ad libitum* diet except that it was supplemented with micronutrients to maintain normal vitamin and mineral intake [diet devised by Dr. Robert Engelman [13]] and manufactured at Harlan Teklad (Madison, WI). A detailed list of macronutrient components of each diet used in this experiment is presented in Table 1. For one week prior to initiation of CR, mice were slowly transitioned into either the fortified CR or to NIH-31 *ad libitum* (AL) control diet ($n=10$ per group). In a preliminary study, CR was introduced with 10% increments per week