

Hypermetabolism in a triple-transgenic mouse model of Alzheimer's disease

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Abstract

A common feature of Alzheimer's disease (AD) is weight loss, even though there is often an increase in food intake in AD patients. The reasons for this weight loss are unknown, but may be due to increased energy expenditure (metabolic rate) or a reduction in energy intake. This was investigated in the present study, using a triple-transgenic (3xTgAD) mouse model of AD. Two-month-old 3xTgAD mice displayed greater food intake (17%) and body weight (34%) but no difference in metabolic rate, as compared with nontransgenic controls (non-Tg). At 12 months of age, 3xTgAD mice still consumed more food (30%), but their body weight was significantly lower (15%) than non-Tg controls. This reduction in body weight was accompanied by a significant rise in metabolic rate, indicated by greater oxygen consumption (24%) and carbon dioxide production (29%); the effects were also observed in 18-month-old 3xTgAD mice. These data demonstrate for the first time the existence of a hypermetabolic state in an experimental model of AD, but whether this can explain the weight loss observed in AD patients remains to be determined.

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1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by a progressive decline in cognitive function that is associated with the presence of amyloid-beta ($A\beta$) plaques and neurofibrillary tangles. Although obesity in midlife has been identified as a risk-factor for AD, weight loss is a common feature of the disease, affecting 30%–40% of patients with mild to moderate AD (Gillette et al., 2007; Gillette-Guyonnet et al., 2000; Guerin et al., 2005; White et al., 1996). This weight loss leads to poorer health outcomes, such as an increased risk of infections, falls and muscular atrophy, with a resultant reduction in quality of life and an increase in morbidity. The risk of

weight loss increases with the severity and progression of AD, and is a predictor of mortality (White et al., 1998, 2004). Prevention of this life-threatening weight loss in AD is therefore a major goal, but currently the mechanisms responsible are unknown. To lose lean or fat mass, energy intake must be lower than demand (expenditure and storage). However, food intake in people with AD is usually adequate or even increased (Burns et al., 1989; Keene and Hope, 1997a, b; Niskanen et al., 1993; Smith et al., 1999; Spindler et al., 1996).

Weight loss can occur if energy expenditure (metabolic rate) is raised. It is uncertain whether abnormalities in metabolism exist in AD patients because no change, an increase, or a reduction in metabolism has been reported (Donaldson et al., 1996; Poehlman et al., 1997; Niskanen et al., 1993; Prentice et al., 1989; Wang et al., 1997; Wolf-Klein et al., 1995). Although no direct measurements of metabolic rate in animal models of AD have been reported to date, the existence of a hypermetabolic state is supported

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indirectly by the finding that energy intake is elevated, but body weight is lower, in some transgenic mouse AD strains (Pugh et al., 2007; Vloeberghs et al., 2008). Therefore, the aim of this study was to examine longitudinally body weight, food intake, and metabolic rate in a triple-transgenic (3xTgAD) mouse model of AD. These mice overexpress human amyloid precursor protein (APP_{Swe}), presenilin-1 (PS-1_{M146V}) and tau_{P301L}, and develop progressive age-dependent cognitive deficits as well as A β plaque pathology and neurofibrillary tangles (Oddo et al., 2003).

2. Methods

2.1. Procedure

3xTgAD and background strain, wild-type nontransgenic mice (non-Tg) (C57BL6/129sv), were originally supplied by Frank LaFerla and Salvatore Oddo (University of California, Irvine, CA, USA), and in-house colonies were established as separate littermates.

Male mice at 4–5 weeks of age were group-housed in standard housing conditions (temperature, 20°C \pm 2°C; humidity, 55% \pm 5%; 12-hour light/12-hour dark cycle with lights on at 8:00 hours), and given ad libitum access to standard rodent chow and water. All studies were conducted in accordance with the UK Animals (Scientific Procedures) Act, 1986. Separate groups of 3xTgAD and non-Tg mice had body weight and food intake measured weekly until 2 ($n = 4$ per group) and 12 months of age ($n = 5$ for 3xTgAD and $n = 6$ for non-Tg). At these time points, mice were housed individually in calorimetric cages (Columbus Instruments, Columbus, OH, USA) to allow for measurements of metabolic rate. After 24-hour habituation, oxygen consumption (VO₂, in mL/kg/h), carbon dioxide production (VCO₂, in mL/kg/h), and respiratory quotient (RQ; ratio of VCO₂ to VO₂ that is used as an indicator of composition of metabolic fuel being oxidized for energy) were measured by indirect calorimetry every 10 minutes for 4 days. Body weight and food intake were also measured daily and a 24-hour average was calculated. Mean heat production (kcal/d) was calculated and used as a measure of energy expenditure. Mean energy balance over the 4-day monitoring period was calculated from the difference between energy intake (kcal/d) and energy expenditure and expressed as average energy gained or lost per day. A separate group of non-Tg and 3xTgAD mice at 18 months of age were analyzed for body weight, food intake, and metabolic rate over 4 days in calorimetry cages as mentioned earlier ($n = 4$ per group). To confirm AD pathological changes, immunohistochemistry for A β and hyperphosphorylated tau was performed using 6E10 and AT8 antibodies, respectively, on brain sections from all mice.

2.2. Statistical analyses

Data are represented as mean \pm standard error of the mean. For group-housed animals, individual body weight

was measured, but average weekly food intake was calculated by dividing weekly food consumption per group by the number of mice per group. Statistical differences in longitudinal body weight (in group-housed animals) were determined using repeated measures analysis of variance. Statistical differences in mean body weight, food intake, VO₂, VCO₂, RQ, and energy balance over the 4-day monitoring period in calorimetric cages were analyzed using a Student's *t*-test. Statistical significance was taken when $P < .05$.

3. Results

3.1. Food intake, body weight, and metabolic rate in 2-month-old 3xTgAD mice

Between 6 and 8 weeks of age, body weight of 3xTgAD mice was significantly higher by 27%–31% compared with that in age-matched non-Tg control mice ($P < .05$, Fig. 1A). Average weekly food intake per mouse between 5 and 8 weeks of age appeared to be higher (18%–55%) in 3xTgAD versus non-Tg mice (Fig. 1B), but as these data were derived from group-housed animals no statistical analysis was performed. When housed individually in calorimetry cages at 2 months of age, a significantly greater mean body weight (34%; $P < .001$, Fig. 1C) and mean 24-hour food intake (17%; $P < .05$, Fig. 1D) was observed in 3xTgAD mice, when compared with age-matched non-Tg controls.

Indirect calorimetry to measure metabolic rate revealed that at 2 months of age, no statistical differences in mean daily VO₂ ($P > .05$, Figs. 1E and H), VCO₂ ($P > .05$, Figs. 1F and I) or RQ ($P > .05$, Figs. 1G and J) were detected between 3xTgAD and non-Tg mice. During the metabolic monitoring period, both groups of mice exhibited a similar degree of positive energy balance (non-Tg, 5.2 \pm 0.3 kcal/d vs. 3xTgAD, 5.4 \pm 0.7 kcal/d, $P > .05$).

Pathological analysis of brains from 2-month-old 3xTgAD mice confirmed the presence of intraneuronal A β in the hippocampus, cortex, and amygdala. No hyperphosphorylated tau was detected in the hippocampus, cortex, and amygdala of 2-month-old 3xTgAD mice. No A β or tau pathology was observed in control non-Tg mice (data not shown).

3.2. Food intake, body weight, and metabolic rate in 12-month-old 3xTgAD mice

Over a 12-month period, male 3xTgAD mice displayed different body weight (Fig. 2A) and food intake (Fig. 2B) profiles compared with non-Tg mice. In support of the data reported earlier, the body weight of 3xTgAD mice aged between 5 weeks and 4 months was 12%–33% higher ($P < .05$) than that of non-Tg animals. In contrast, between 7.5–8.5 and 9.5–12 months of age, body weight was significantly lower (by 8%–9% and 11%–18%, respectively) in 3xTgAD compared with non-Tg mice ($P < .05$). However, despite these biphasic differences in body weight in 3xTgAD mice, the estimated average weekly food intake per

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