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High-fat diet-induced memory impairment in triple-transgenic Alzheimer's disease (3xTgAD) mice is independent of changes in amyloid and tau pathology☆

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ABSTRACT

Obesity and consumption of a high-fat diet are known to increase the risk of Alzheimer's disease (AD). Diets high in fat also increase disease neuropathology and/or cognitive deficits in AD mouse models. However, the effect of a high-fat diet on both the neuropathology and memory impairments in the triple-transgenic mouse model of AD (3xTgAD) is unknown. Therefore, groups of 2-month-old male 3xTgAD and control (non-Tg) mice were maintained on a high-fat or control diet and memory was assessed at the age of 3–4, 7–8, 11–12, and 15–16 months using a series of behavioral tests. A comparable increase in body weight was observed in non-Tg and 3xTgAD mice after high-fat feeding at all ages tested but a significantly greater increase in epididymal adipose tissue was observed in 3xTgAD mice at the age of 7–8, 11–12, and 15–16 months. A high-fat diet caused memory impairments in non-Tg control mice as early as the age of 3–4 months. In 3xTgAD mice, high-fat consumption led to a reduction in the age of onset and an increase in the extent of memory impairments. Some of these effects of high-fat diet on cognition in non-Tg and 3xTgAD mice were transient, and the age at which cognitive impairment was detected depended on the behavioral test. The effect of high-fat diet on memory in the 3xTgAD mice was independent of changes in AD neuropathology as no significant differences in (plaques, oligomers) or tau neuropathology were observed. An acute increase in microglial activation was seen in high-fat fed 3xTgAD mice at the age of 3–4 months but in non-Tg control mice microglial activation was not observed until the age of 15–16 months. These data indicate therefore that a high-fat diet has rapid and long-lasting negative effects on memory in both control and AD mice that are associated with neuroinflammation, but independent of changes in beta amyloid and tau neuropathology in the AD mice.

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and is a significant health problem worldwide. AD is characterized by the presence of beta amyloid (Aβ) plaques and neurofibrillary tangles within the brain and patients present with cognitive deficits including impairments in learning and memory. The occurrence of AD is mostly sporadic affecting individuals over the age of 65 years. However, there are several factors that can increase AD risk including diabetes, stroke, atherosclerosis, and obesity and/or metabolic syndrome.

Obesity is a major health problem associated with increased risk of several diseases such as diabetes. However, obesity at midlife can also increase the risk of dementia and AD later in life (Beydoun et al., 2008; Fitzpatrick et al., 2009; Gustafson et al., 2003; Hassing et al., 2009; Kivipelto et al., 2005; Profenno et al., 2009; Rosengren et al., 2005; Whitmer et al., 2005, 2007, 2008), an effect that is independent of the conditions associated with obesity that are also risk factors for AD, such as type 2 diabetes and cardiovascular disease (Hassing et al., 2009; Whitmer et al., 2005, 2007). This relationship between obesity and AD appears to depend on age as obesity can decrease the risk of AD in later life (Fitzpatrick et al., 2009) and weight loss actually precedes disease onset (Buchman et al., 2005; Stewart et al., 2005). Obesity is often caused by and is associated with, consumption of diets that are high in fat. The prevalence of AD is greater in countries with higher intake of high fat and/or calorie diets but lower in those that consume diets low in fat (Grant, 1997; Panza et al., 2004). Furthermore, epidemiologic studies suggest diets high in

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saturated fats (especially in midlife) are a major risk factor for the development of AD (Eskelinen et al., 2008; Grant, 1999; Kalmijn et al., 1997; Laitinen et al., 2006; Luchsinger et al., 2002), and this risk is higher in individuals with the APOE ε4 allele (Laitinen et al., 2006; Luchsinger et al., 2002).

Disease neuropathology and/or behavioral deficits are enhanced in mouse models of AD that are maintained on a high-fat diet (without high levels of cholesterol) (Herculano et al., 2013; Ho et al., 2004; Julien et al., 2010; Maesako et al., 2012a; Pedrini et al., 2009; Phivilay et al., 2009). There are several well-characterized mouse models of AD, most with mutations in amyloid precursor protein (APP) and/or presenilin 1/2 (PS1/2) that present with Aβ plaques only. The triple-transgenic AD (3xTgAD) mouse has mutations in APP_{Swe}, $PS1_{M146V}$, and tau_{P301L}, and as a consequence, develops temporal- and region-specific Aβ plaques and tangle-like pathology that closely resemble the pathology seen in the human AD brain, in addition to developing functional impairments, including learning and memory deficits (Billings et al., 2005; Oddo et al., 2003a, 2003b). The 3xTgAD mouse does not present with an aggressive pathology, as we do not observe Aβ plaques and tangle-like pathology until approximately at the age of 12 months, which is after cognitive deficits are detected (Billings et al., 2005; Knight et al., 2012, 2013). The 3xTgAD mouse therefore allows us to identify the effect of a high-fat diet before significant AD neuropathology, and to also study the relationship between Aβ plaques and tau.

In humans, the severity of AD-related neuropathology especially Aβ plaque burden, does not always correlate with, or is predictive of, cognitive deficits, and memory impairments can occur in mouse AD models in advance of overt Aβ plaque (and tangle) pathology (Billings et al., 2005; Oddo et al., 2003b; Serrano-Pozo et al., 2011). Most studies to date examining the role of high-fat diets in AD mouse models have assessed neuropathology only (Julien et al., 2010; Pedrini et al., 2009; Phivilay et al., 2009) and few have monitored both neuropathology and memory (Herculano et al., 2013; Ho et al., 2004; Maesako et al., 2012a). Furthermore, most of these studies identifying an effect of a high-fat diet in AD on neuropathology and behavior have modified diet in AD mice only and have not studied the effect of diet in control animals (Ho et al., 2004; Maesako et al., 2012a). As high-fat diets have been shown to affect memory in cognitively-normal rodents (McNeilly et al., 2011; Pistell et al., 2010; Winocur and Greenwood, 2005), it is not clear whether the cognitive deficits observed in AD mice fed a high-fat diet are related to or independent of AD pathology. Finally, most reports on the changes in cognition and/or neuropathology in high-fat fed AD mice have studied just one time point, and thus only report effects at a single stage and/or severity of the disease. It is possible that some of the effects of a high-fat diet in AD might be transient, which will be missed in such studies.

The aim of this study therefore was to characterize longitudinally the impact of a high-fat diet on both cognition and neuropathology in male 3xTgAD and non-transgenic (non-Tg) control mice. Memory was assessed using a battery of behavioral tests. No study to date has compared the effects of a high-fat diet on both cognition and neuropathology in 3xTgAD mice and we show that a high-fat diet impairs memory in both the non-Tg control and 3xTgAD mice, the effects of which depend on the behavioral test used and duration of diet. Effects of high-fat diet on cognition in the 3xTgAD mice occurred without any significant effect on AD neuropathology.

2. Methods

2.1. Animals and diet

Male 3xTgAD mice expressing mutant $PS1_{M146V}$, APP_{Swe}, Tau_{P301L}, and control non-Tg (129/C57BL6) mice were originally supplied by Frank LaFerla (Irvine, CA, USA) (Oddo et al., 2003b) and an in-house colony established in Manchester. All mice were kept in standard housing conditions (humidity 50%–60%, temperature 21 ± 1 °C, 12:12 hour light-dark cycle with lights on at 07:00 hours) and given *ad libitum* access to standard rodent chow and water unless stated. All animal experiments were carried out in accordance with the United Kingdom Animals (Scientific Procedures) Act 1986. At the age of 8 weeks 3xTgAD and non-Tg control mice were placed on either a high-fat diet (60% energy from fat, 35% fat content by weight, 13% saturated fatty acids, 58G9, Test Diets, supplied by IPS Product Supplies Ltd, UK) or control diet (12% energy from fat, 5% fat content by weight, 0.78% saturated fatty acids, 58G7). Separate groups of mice were maintained on their respective diets until the age of 3–4 (n = 10–12/group), 7–8 (n = 10–11/group), 11–12 (n = 9–10/group), or 15–16 (n = 6–10/group) months when behavioral tests were performed. Body weight was monitored in all mice from weaning until behavioral assessment. There were a few deaths because of unknown causes over the cause of the study, and these animals were not included in the analyses (7–8 months: non-Tg control n = 1; 11–12 months: 3xTgAD control n = 1, 3xTgAD high-fat n = 1; 15–16 months: non-Tg high-fat n = 3, 3xTgAD control n = 2, 3xTgAD high-fat n = 1).

2.2. Behavioral tests

Male non-Tg control and 3xTgAD mice were subjected to the Y-maze spontaneous alternation, smell recognition, novel object recognition, and Morris water maze (MWM) tests. On the days of behavioral evaluation, home cages were placed in the testing room 30 minutes before testing to allow habituation. All behavioral observations were made between 1000 hours and 1600 hours. The order of observation during this period was randomized across animals and all subsequent analysis was performed blinded to genotype and diet. No more than one behavioral test was completed during any single day. All equipment was cleaned between animals.

2.2.1. Y-maze spontaneous alternation test

Short-term working memory was assessed in the Y-maze spontaneous alternation test using a black opaque Perspex Y-maze with 3 arms (A, B, and C) each containing a visual cue (arm dimensions; 15 cm × 10 cm × 10 cm). Each animal was placed in turn in arm A of the Y-maze and allowed to explore for 8 minutes and the arm entries made by each animal were recorded. Arm entry was defined as having all 4 paws in the arm. Spontaneous alternation was defined as a successive entry into 3 different arms, on overlapping triplet sets (Hiramatsu et al., 1997; Wall and Messier, 2002). The percentage number of alternations was calculated as the number of actual alternations divided by the maximum number of alternations (the total number of arm entries minus 2). The total number of moves was also recorded as an index of ambulatory activity (Hiramatsu et al., 1997).

2.2.2. Smell recognition test

Short-term non-associative memory based on the natural exploration of novelty in mice was assessed in the smell recognition test. All mice were habituated to a black opaque polycarbonate circular arena (diameter, 30 cm × height, 21 cm) for 5 minutes over 2 days. On the day of testing, mice were placed in the arena and allowed to explore 2 identical unfamiliar scented balls for 10 minutes (phase 1). The scented balls were placed in the center of the arena, 5 cm from the edge and 8 cm away from each other. The hollow balls (Chad Valley, UK) were filled with cotton wool and 0.5 mL of scent (orange, lemon, vanilla, or almond, Dr Oetker Ltd, UK) was evenly distributed into the balls via small holes. Mice were then removed, one of the balls was replaced with a novel scented

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