An Investigation Into The Effect Of An Australian-Type Rodent Diet, With And Without Nutritional Supplementation On The Behavioural Deficits, Neuropathology And Telomere Length In An Amyloid Mouse Model Of Alzheimer's Disease.

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Summary

Alzheimer's disease (AD) is an incurable, terminal, neurodegenerative disease that occurs primarily in people over 65. Life-style interventions including diet are potential candidates for prevention and management of AD. This thesis aims to investigate the role of diet in an AD-type mouse model (APPSWE/PSENdE9) that over expresses amyloid, called Amy mice. It is hypothesised herein that:

1. An Australian-type rodent diet accelerates the behavioural deficits and β-amyloid neuropathology that are observed in Amy mice.

2. Nutrient supplements can reduce the severity of genotype or diet-type induced behavioural deficits and β-amyloid neuropathology in Amy mice.

First, an Australian-type (Oz-AIN) diet was designed to reflect the current nutrient intake of Australians. Second, nutrient supplements that have the potential to slow progression of behavioural or neurological deficits in AD were added to the Oz-AIN diet to create the Oz-AIN Supp diet. The effects of both of these diets are compared with an optimal rodent diet, the AIN93-M diet. The rationale for these diets and their effect on weight gain, food consumption, and organ size are described. Amy mice that were fed the Oz-AIN diet were susceptible to diet-induced weight gain and obesity, which was not observed in Amy mice that were fed the Oz-AIN Supp diet, indicating that nutrient supplements prevent weight gain in Amy mice.

Spatial learning and spatial memory were assessed in the Morris Water Maze. The Oz-AIN diet impaired spatial learning in 15 month old Amy mice. This was prevented with nutrient supplementation, as Amy mice that were fed the Oz-AN Supp diet performed similarly to control mice. At 18 months, the Amy mice fed the Oz-AIN diet demonstrated intact spatial memory. This suggested that the Oz-AIN diet protects spatial memory in aging mice. Olfactory ability (sense of smell) was assessed in the Buried Chocolate Test. Olfactory ability of Amy mice that were fed the Oz-AIN diet was impaired relative to control groups at 12 months of age.

Diet did not affect amyloid load or the number of amyloid deposits. However, the Oz-AIN and Oz-AIN Supp diets were both associated with larger deposits, compared to the AIN93-M diet, suggesting that total fat content and not micro-nutrient intake, facilitates aggregation of amyloid into larger deposits.

Confocal microscopy revealed that three different β-amyloid pathologies occur in brains of Amy mice: (1) intracellular amyloid that was associated with necrotic cells; (2) extracellular diffuse deposits of amyloid; and (3) diffuse deposits that were associated with blood vessels. Whilst the Oz-AIN diet did not have an effect on pathology type, the Oz-AIN Supp diet was associated with increased diffuse deposits associated with blood vessels. It was not determined whether this was invasion or clearance of β-amyloid from the brain, and it is suggested that it is a combination of both.

Genotype and diet-type effects were observed on telomere length (aTL) and oxidative DNA damage in the brains of aging Amy mice. 18 month old Amy mice that were fed the Oz-AIN diet had significantly longer telomeres and significantly more oxidative DNA damage throughout their brains than Amy mice that were fed the an optimal rodent diet.

In conclusion, whilst nutrient supplementation prevented diet-type- and genotype induced spatial learning deficits, high total fat content conserved spatial memory in aged Amy mice. Furthermore, whilst a sub-optimal diet did not have an effect on β-amyloid pathology, nutrient supplements may alter β-amyloid clearance from the brain.

Declaration

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree of diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Sarah M. Brooker, February, 2014.

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Conference presentations

Brooker, S. (2013, June). *The effect of an Australian-type diet on cognitive decline, pathology and telomere length in a mouse model of Alzheimer's Disease.* Paper presented at meeting of Flinders Centre for Neuroscience, Flinders University, SA.

Brooker, S., McIver, C., Patten, G., Power J., & Fenech, M. (2013). *The effect of an Australian-type diet with and without nutritional supplements on cognitive decline and pathology in an AD mouse model.* Poster presented at the 33rd meeting of Australian Neuroscience Society (ANS) Melbourne, Vic.

Brooker, S. (2012). *You are what you eat: The effect of an Australian-type diet, with and without nutritional supplements on weight gain, cognitive decline and brain pathology*. Paper presented at the annual meeting of Australian Society for Medical Research (ASMR), Adelaide, SA.

Brooker, S. (2012). *An Australian Type diet and cognitive decline: Is there a benefit to nutrient supplements?* Paper presented at the meeting of 'Lifestyle Approaches for the Prevention of Alzheimer's disease", McCusker Alzheimer's Foundation, Perth, WA

Brooker, S., McIver, C., Patten, G., & Fenech, M. (2012). *An Australian Type diet and cognitive decline: Is there a benefit to nutrient supplements?* Poster presented at the annual meeting of Lifestyle Approaches for the Prevention of Alzheimer's Disease, McCusker Alzheimer's Foundation , Perth, WA

Brooker, S., McIver, C., Patten, G., & Fenech, M. (2012). *Dietary intervention studies in Alzheimer's disease-prone mice*. Poster presented at the annual meeting, CSIRO, Melbourne, Vic

Brooker, S. (2011). *The effect of an Australian-type diet on rodent models of behavior.* Paper presented at the annual meeting of Australian and New Zealand Obesity Society Annual Scientific (ANZOS), Adelaide, SA

Brooker, S. (2010). *DNA damage and dietary intervention in the Alzheimer's disease-prone mouse.* Paper presented at the annual post-graduate student presentations, CSIRO, Adelaide, SA

Brooker, S. (2009). *Food for thought: Nutrition and cognitive decline.* Paper presented at the post-graduate student Wednesday Wrap, University of Adelaide, Adelaide, SA

Brooker, S. (2009). *Olfactory Dysfunction in an animal model of Alzheimer's Disease.* Paper presented at post-graduate student presentation, NeuroJam, Flinders University