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Impaired spatial memory in APP-overexpressing mice on a homocysteinemia-inducing diet

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Abstract

Consumption of a diet that significantly elevates homocysteine (homocysteinemia) induces cell death in the CA3 hippocampal subfield in amyloid precursor protein (APP) over-expressing transgenic mice but not in wild-type controls. We assessed behavioral and other neuropathological effects of a homocysteinemia-inducing diet in aged APP-overexpressing mice. Starting at 16–18 months of age, mice were fed either a treatment diet lacking folate, choline, and methionine, and supplemented with homocysteine, or a control diet containing normal amounts of folate, choline and methionine but no homocysteine. After 5 months on the experimental diets, performance on a delayed non-matching-to-position working-memory task was unimpaired. In contrast, spatial reference memory in the water maze was impaired in transgenic mice on the treatment diet. Transgenic mice had higher homocysteine levels than wild-type mice even when fed the control diet, suggesting an effect of genotype on homocysteine metabolism. Methyl-donor deficiency did not alter amyloid deposition in the transgenic mice. These results suggest that disrupted homocysteine metabolism may induce Aβ-associated memory impairments and neurodegeneration in APP overexpressing mice.
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1. Introduction

One of the primary features of Alzheimer's disease is neuronal cell loss in the hippocampus and cerebral cortex, areas of the brain involved in memory and cognition. As neurons die, short-term memory fails, followed by a decline in language, reasoning, and the ability to perform everyday tasks. Although the cause of cell death in Alzheimer's disease is not known, considerable evidence implicates β-amyloid (Aβ), a 39–43 amino-acid peptide cleaved from the amyloid precursor protein (APP). Aβ has been shown to induce DNA damage and neuronal death *in vitro*, and memory deficits *in vivo* [22,24,38,47]. When APP is overexpressed or abnormally cleaved, Aβ forms toxic oligomers that aggregate into amyloid plaques and are associated with age-related memory impairment [7,47]. This process has been modeled in several APP-overexpressing transgenic mouse lines bearing mutations linked to familial Alzheimer's disease in humans [9,14,30].

Although such genetic factors are sufficient to cause Alzheimer's disease, most cases are sporadic and other potentially-modifiable risk factors may be required for pathogenesis. One such factor is homocysteinemia—elevated plasma levels of the non-protein forming, sulfur amino acid homocysteine. Homocysteinemia is associated with

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increased risk of Alzheimer's disease and stroke [39], and moderate elevations of plasma homocysteine in cognitively intact individuals are associated with increased risk of subsequent incident dementia [34].

The relationship of homocysteinemia to Alzheimer's disease is uncertain. At high concentrations, homocysteine is neuro- and vasotoxic. In addition, conditions that lead to homocysteinemia have been shown to increase vulnerability to primary brain insults in animal models [8,40] and to inhibit the proliferation of hippocampal neuroprogenitor cells [19]. The effect of homocysteinemia on cell death has been studied in 10-month-old APP-overexpressing mice bearing the Swedish double mutation (K595N, M596L). Three months of a methyl-donor-free diet supplemented with homocysteine induced a reduction in the number of CA3 pyramidal cells in the APP transgenic mice but not in wild-type controls [18]. The CA1 subfield and soluble amyloid levels were unaffected by the homocysteinemia-inducing diet. It is not known whether the reduction in CA3 cell numbers in the homocysteinemic transgenic mice was due to increased neuronal death or to an inhibitory effect on neural progenitors, or both. Alzheimer's patients have a similar loss of cells in CA3, and lesions of this hippocampal subfield induce memory deficits in experimental animals [3,11,32,35,37]. The effect of the homocysteinemia-inducing diet on memory and neuropathology in APP-overexpressing mice is not known. The present experiments examined short-term working memory, spatial memory, and neuropathology in Tg2576 transgenic mice exposed to chronic homocysteinemia.

2. Methods

2.1. Study population

Female Tg2576 APP-overexpressing transgenic mice bearing the Swedish double mutation (K670N, M671L) were generated on a B6SJLF1 hybrid background [4,14]. Wild-type X APP transgenic matings were used to produce hemizygous transgenic mice ($n = 14$) and wild-type littermate controls ($n = 19$) for all experiments. One transgenic mouse died after hidden-platform training in the water maze, but before cued-platform training. Because the retinal degeneration (*rd*) gene is known to segregate with the B6SJLF1 strain, all mice were screened for the presence of *rd* using polymerase chain reaction (PCR), and *rd*-positive mice were eliminated from the study. Mice were housed in an AALAC-approved vivarium, and temperature, humidity, and lighting levels were in accordance with AALAC guidelines. The colony room was kept on a 14:10 light/dark cycle, with lights on at 6 am.

2.2. Experimental diets

Mice were maintained on standard lab chow (Purina #5001) until 16–18 months of age, after which the mice were divided into two groups that were fed amino-acid defined, control or treatment diets. The control diet contained 2 mg folic acid, 14.48 g choline, and 1.70 g L-methionine per kg diet, and no homocysteine (Dyets Inc., diet #518754). The treatment diet completely lacked the methyl donors folic acid, choline, and L-methionine (Dyets Inc., diet #518806) but was supplemented with 4.5 g/kg D,L-homocysteine (Sigma #H4628). The diets did not contain sulfa drugs, thus providing conditions that permit limited folate intake via coprophagy and allowing the mice to tolerate a long-term dietary deficiency. Mice were maintained on their assigned experimental diets for 6 months. The working memory task was conducted during the first 5 months of the diet, followed by 2 weeks of water–maze testing. The mice were then left undisturbed on the experimental diets for 2 weeks before being sacrificed for histology.

Mice had free access to food and water throughout the study, except when performing the food-motivated short-term working-memory task. During the working-memory task, mice were put on a food-restriction regimen of 8 h free access per day, decreasing over 2 weeks to 4 h per day. Under this regimen mice typically fall to ~90% of their free feeding weights within the first week. Following the initial weight loss they gain weight slowly, reaching their free-feeding weights ~1 month after initiation of the restriction regimen. Behavioral testing was conducted in two cohorts of mice. The first cohort was trained on the working-memory task followed by water–maze testing. The second cohort was naïve when water–maze testing commenced. There were no genotype- or diet-dependent differences in body weight during the last week of food restriction (F's < 0.64; p's > .435).

2.3. Delayed non-matching to position (DNMTP)

Mice were trained on a discrete-trial delayed conditional discrimination, a short-term working memory task commonly used with rodents and primates, including Alzheimer's patients [2,23,33]. We used a version of the task known as delayed non-matching to position (DNMTP), in which mice were required to choose a spatial location different than the one presented at the beginning of the trial [21,25,26]. DNMTP testing began at the age of 12–14 months, and continued until water maze training began at 21–23 months. At 16–18 months of age, all mice had reached criterion-level performance and were started on either the treatment or control diet, matched for performance on the DNMTP task. Thus the mice were fed standard lab chow for the first 4 months of DNMTP testing, and the experimental diets for the last 5 months.

The DNMTP task was conducted in commercially-available operant chambers (MED Associates, Georgia VT). The operant chambers were housed within light-and sound-attenuating cubicles, each containing a fan that provided constant background noise (~65 dB). Each chamber was outfitted with three nose-poke response holes, one on each side of the front wall equidistant from the food-delivery well, and a third in the center of the rear wall. A houselight located

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