Title

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Publication Date

2013

Peer reviewed

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Background: Aging is associated with a decline in multiple aspects of cognitive function. Evidence suggests that high fat diet (HFD) consumption and presence of metabolic dysfunction lead to exacerbated brain aging and promote the development of cognitive deficits. The present work investigated whether exposure to HFD accelerates age-related cognitive deficits in adult *vs* aged mice.

Methods: Adult (6-month old; n=32) and aged (16-month old; n=32) C57BL/6J male mice were exposed to regular diet or HFD (60% fat) for 3 months prior to behavioral testing and maintained on the HFD during testing for an additional 2 months. Mice were tested in a battery of cognitive tests including the novel object and novel location recognition tasks, and the Barnes maze. In addition, locomotor activity was assessed.

Results: HFD resulted in a significant body weight gain with adult mice gaining significantly more weight (72% increase from baseline body weight) than aged mice (35% increase from baseline body weight). Weight gain was attributed to food calories sourced from fat and cholesterol, but not total calorie intake. Both age and exposure to HFD decreased locomotor activity. In the novel object recognition task, all mice showed similar discrimination index, indicating no effect of age or exposure to HFD on novel object recognition memory. In the novel location recognition task, independent of exposure to HFD, adult mice showed significant increased discrimination index for the novel location (mean±SEM; 0.26±0.04 test trial *vs* −0.04±0.04 familiarization trial, p<0.001); whereas, aged mice did not positively discriminate the novel location (mean±SEM; 0.11±0.07 test trial *vs* 0.01±0.04 familiarization trial, *n.s.*), indicating age-related deficits in spatial memory. During the 5-day Barnes maze task acquisition (4 trials per day), mice exposed to HFD exhibited a slower rate of improvement (ie, decreasing errors across days of training) compared to mice exposed to regular diet suggesting HFD-induced deficits in spatial learning.

Conclusions: The results indicate that both age and exposure to HFD produced deficits in cognitive function mediated by the hippocampus but the observed deficits were task-dependent. Specifically, exposure to HFD impaired novel location recognition memory; whereas aging was associated with impaired learning and memory in the Barnes maze. Novel object recognition memory mediated by perirhinal cortex was unaffected by age or exposure to HFD. These findings highlight the compelling link between age, diet-induced obesity, and cognitive impairments. Ongoing studies have been designed to determine the neuropathologic and metabolic mechanisms underlying the effects of aging and obesity on cognitive function.

Keywords: aging obesity cognition learning mice.

Disclosures: J. Kesby, Nothing to Disclose; S. Semenova, Nothing to Disclose; J. Kim, Nothing to Disclose; J. Olefsky, Nothing to Disclose; C. Achim, Nothing to Disclose; V. Soontornniyomkij, Nothing to Disclose; B. Soontornniyomkij, Nothing to Disclose; D. Jeste, Nothing to Disclose.