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Review

Effects of high-fat diet exposure on learning & memory

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HIGHLIGHTS

- This review examines the effects of high-fat diet exposure on learning and memory.
- Techniques most often used to assess cognition in rodent models are also summarized.
- There is a strong association between HF diet exposure and cognitive impairment.
- Mechanisms may involve insulin, leptin, BDNF, inflammatory pathways & BBB dysfunction.
- Maternal HF diet consumption may affect the cognition of offspring.

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ABSTRACT

The associations between consumption of a high-fat or 'Western' diet and metabolic disorders such as obesity, diabetes, and cardiovascular disease have long been recognized and a great deal of evidence now suggests that diets high in fat can also have a profound impact on the brain, behavior, and cognition. Here, we will review the techniques most often used to assess learning and memory in rodent models and discuss findings from studies assessing the cognitive effects of high-fat diet consumption. The review will then consider potential underlying mechanisms in the brain and conclude by reviewing emerging literature suggesting that maternal consumption of a high-fat diet may have effects on the learning and memory of offspring.

Contents

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1. Introduction

Consumption of a high-fat (HF) diet has long been known to increase one's risk for a number of medical conditions including obesity, diabetes, and the metabolic syndrome. Further evidence in humans and rodents suggests that these same conditions are associated with an increased risk of Alzheimer's disease and other forms of cognitive impairment [1–3]. Given the expanding global burden of high fat diet consumption and obesity, and an emerging crisis of dementia due to a rapidly aging population, understanding the effects of high-fat diet consumption on cognition, gaining insights into potential underlying mechanisms, and developing effective treatment strategies are of critical importance. Here, we will review the methods that are most commonly used to assess learning and memory in rodent models, and we will then summarize findings from behavioral studies of the effects of HF diet before discussing potential underlying mechanisms. Finally, we will briefly examine emerging data suggesting that maternal high fat diet consumption may have effects on the offspring's metabolism, neurodevelopment, and cognition.

2. Behavioral phenotypes

First, it should be noted that in rodent studies of the effects of HF diet on learning and memory, there is tremendous diversity in the choice of animal strain, age, diet, length of exposure, and method of assessing behavioral outcomes with very few studies using multiple tests of cognition. In order to avoid over-generalization of findings from various studies, we have organized this review by behavioral test. The tests included here are not intended to be exhaustive, but they include those that are among the most common in studies of cognition. For each test of 'learning' and/or 'memory', we begin by summarizing the most common methods employed and the brain regions that are thought to be involved before discussing the effects of HF diet on performance. Regarding the various diets, we have described each as it appears in the methods section of the original manuscript (i.e. 60% HF diet, Western diet, HF/high sucrose diet, etc.). While there may be some discrepancies in the ways that different authors describe various diets, we hope that this approach will avoid misinterpreting or misrepresenting views of the authors of the original work.

2.1. Morris Water Maze

The Morris Water Maze is perhaps the most well-known and commonly used test of spatial learning and memory in rodents. The standard protocol requires rodents to swim from a start location to a pre-viously unknown escape platform that is submerged below the surface of opaque water, and therefore hidden from sight. The test requires rodents to orient themselves and navigate to the hidden escape platform using cues located on the perimeter or outside of the arena. Spatial learning can be assessed by measuring latency to finding the escape platform across multiple trials, and memory is most often assessed by removing the platform and measuring a preference for the quadrant in which the platform had previously been located [4–6]. Performance in the Morris Water Maze is correlated with hippocampal function, and has been specifically associated with hippocampal NMDA receptor function by two studies using NMDA receptor antagonists [7,8]. Similarly, performance in the Morris Water Maze has been correlated with hippocampal long-term potentiation (LTP) [7–9]. Reversal learning, which is a common addition to the standard protocol, requires rodents to learn a new location of the platform and, based on lesion studies, is thought to be more heavily dependent on the prefrontal cortex and striatum ([10], reviewed in [11]). Additional lesion studies suggest that other brain areas including the prefrontal cortex, basal forebrain, striatum, and cerebellum are involved in various aspects of the Morris Water Maze (reviewed in [6,11]).

In studies that have assessed the effects of HF diet exposure on cognition, the Morris Water Maze is by far the most frequently used. Of the more than 40 studies in rodents that have been published to date, the overwhelming majority has found that HF diet consumption impairs hippocampal dependent performance in the Morris Water Maze. This robust association, which has been previously reviewed [12], has been described in various wild type mouse and rat models that have been exposed to a HF diet for between 1 month [13] and 8 months [14]. Among the various diets used in these experiments are 21% HF [15], 32% HF [16], 42% HF [17], 58% HF [18], 59.3% HF [19–21], 60% HF [22–25], and 'HF, refined sugar' [13,14,26,27]. Of these reports, only one found that HF diet exposure resulted in deficits in the Morris Water Maze without affecting body weight [27]. This is in contrast to several studies (summarized below) that found HF diet-related impairment in other behavioral tests without an associated increased in body weight.

Only a few studies have reported no change in Morris Water Maze performance after HF diet consumption. In one, mice were exposed to 45% HF diet for 5 or 10 months [28]. In another, 24% HF exposure impaired performance of juvenile but not adult rats [29], and in two additional studies, rats were fed diets enriched with polyunsaturated fatty acids (PUFAs), which had been expected to improve cognitive function [30,31].

Finally, while extensive discussion is outside of the scope of this review, the Morris Water Maze has additionally been used to demonstrate that various HF diets can exacerbate cognitive deficits found in the HF diet + streptozotocin (STZ) model of diabetes [32–35] as well as models of stroke [36,37], traumatic brain injury [38,39], and Alzheimer's disease [40].

2.2. Barnes Maze

The Barnes Maze is closely related to the Morris Water Maze in that the test requires rodents to find a hidden escape using external spatial cues. The primary variation from the Morris Water Maze is that, rather than relying on swimming, the Barnes Maze uses a dry, elevated circular platform with multiple potential escape holes located at the periphery. A hidden escape box is placed under only one hole at any given time. Also like the Morris Water Maze, learning, memory, and cognitive flexibility can be assessed by measuring latency to completion of the task across multiple trials, time spent in the area that had previously contained the escape box, and reversal learning, respectively. Based on early electrophysiological recordings from live animals, performance in the Barnes Maze is also thought to be largely hippocampal dependent [41] though lesion studies of Morris Water Maze performance suggest that other brain regions such as the prefrontal cortex and striatum are likely more involved in reversal learning tasks ([10], reviewed in [11]). While used less frequently than the Morris Water Maze, the Barnes Maze may have an advantage in cases where swimming speed, motivation, or motor coordination is impaired as may be the case with obesity and other metabolic conditions resulting from HF diet consumption. Also, use of the Barnes Maze may avoid confounding factors associated with stress responses that are known to be activated by the Morris Water Maze. This is supported by at least one study which found that,

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