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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,

while stress hormone levels are increased in both the Barnes Maze and Morris Water Maze, the stress response is significantly greater in the Morris Water Maze and test performance is correlated with stress hormone level only in the Morris Water Maze [42].

Only a few studies thus far have assessed the effects of HF diet consumption on Barnes Maze performance and the data are mixed. In one, adult female C57BL/6 and Swiss Webster mice were fed a diet containing either 10% or 60% fat. No deficits were seen in either strain after 8 weeks, but after 6 months, the Swiss Webster mice fed a HF diet were found to have impaired acquisition and memory retention. Despite the learning and memory deficits found in HF fed Swiss Webster mice, the authors found increased body weight, hyperglycemia, and hyperlipidemia only in HF fed C57BL/6 mice. Interestingly, they also found increased food intake only in HF fed Swiss Webster mice suggesting that differences in Barnes Maze performances may be related to either the amount of HF diet consumed independent of body weight, or genetic differences between the strains [43]. Another small study using pathogen-free mice found that 3 weeks of access to a high fat/high carbohydrate 'Western diet' had no effect on short-term retention memory despite causing significant weight gain [44]. A third study using CD-1 mice also supports the possibility that HF diet exposure might have independent effects on body weight and cognition. When male CD-1 mice were given ad libitum access to standard chow or 45% HF diet, the authors found that HF fed mice showed no differences in Barnes Maze performance despite being nearly 50% heavier than controls [45].

2.3. Radial Arm Maze

The Radial Arm Maze consists of an elevated platform with several equally spaced arms (most often 8) radiating from a small, open central area and visual cues positioned around the maze. The test usually involves 'baiting' all or a subset of the arms with a food pellet and measuring latency to retrieval of pellets and errors over multiple trials. Latency to completion of the task across trials is thought to assess spatial learning while entry to a non-baited arm is usually considered an error of reference memory and re-entry to a previously baited arm is considered an error of working memory [46,47]. In another commonly used set-up known as the Radial Arm Water Maze, 6 arms radiate from a central area and only one arm contains an escape platform that is hidden under the surface of opaque water. Performance in the Radial Arm Water Maze is assessed in much the same way as the Morris Water Maze [48]. Also like the Morris Water Maze and Barnes Maze, the Radial Arm Maze is usually thought of as a test of hippocampal function based on lesion studies [48]. A study using NMDA receptor antagonists linked Radial Arm Maze performance to hippocampal LTP and NMDA receptor function [49]. However, several studies using reversible, region specific sodium channel blockade have reported that Radial Arm Maze performance may be dependent on more widely distributed neural network involving the hippocampus, prefrontal cortex, nucleus accumbens, striatum, and thalamus [50,51].

Regarding the effects of HF diet on Radial Arm Maze performance, in series of studies one group found that exposing adult male Wistar rats to either a 25% HF diet [52,53] or a 'Western Diet' [54] impaired both short- and long-term memory. Interestingly, in one of these studies, the authors found that Vitamin E treatment prevented HF diet-related performance deficits in the Radial Arm Maze without normalizing body weight [53], and in another, the authors found a similar phenomenon with caffeine treatment [54] again suggesting possible mechanisms of HF diet-induced cognitive impairment that may be independent of obesity. Further support is provided by studies of the effects of a 'HF, high cholesterol' diet among C57Bl/6 mice [55], and a 'high saturated fat, high cholesterol' diet among male Fischer 344 rats [56], both of which found working memory deficits in the Radial Arm Maze but no changes in body weight among HF fed rodents. In another study, male Sprague–Dawley rats were exposed to a 'high saturated fat, high glucose' diet and tested for spatial and non-spatial memory in the Radial Arm Maze at multiple time points between 72 h and 90 days on the diet. Interestingly, the authors found impairment in spatial memory after only 72 h, which was well before any difference in body weight emerged. Impairment in nonspatial memory developed after 30 days on the diet, when the HF fed rats were significantly heavier than controls [57].

Further suggesting that specific components of a HF diet might contribute, at least in part, to deficits in learning and memory are findings from one of the first studies to assess the cognitive impact of HF diets in which the authors compared standard chow to 20% HF diets enriched with either saturated fat or PUFAs and found that, in male Long–Evans rats, neither HF diet affected body weight but a diet high in saturated fat impaired working memory in a baited Radial Arm Maze [58].

Finally, one interesting study in male C57BL/6J mice found impaired acquisition and working memory in the baited Radial Arm Maze after 8 weeks of exposure to 45% HF diet [59]. In this study, consumption of the HF diet was associated with increased weight gain in the absence of increased glucose, insulin, or triglycerides. While this study is not able to separate the effects of diet composition from the effects of obesity, it does suggest that a HF diet may have an impact on cognition that is independent of the effects of metabolic disorders often associated with HF consumption.

2.4. Y-Maze

The Y-Maze consists of a Y-shaped platform with three equally spaced, enclosed arms. Many variations of the test have been published but most rely on the tendency for rodents to explore novel environments and thus prefer entering a new arm rather than returning to an arm that has just been explored. Most commonly, the primary outcomes are the total number of arm entries and number of 'spontaneous alternations' or 'triads' which are defined as entering into each of the three arms without returning to a previously explored arm [60]. Alternatively, a single arm can be initially blocked, then unblocked in subsequent trials. In this case, the outcome can simply be whether or not the rodent first enters the previously blocked arm [60,61]. The precise brain regions associated with Y-Maze performance likely vary depending on the experimental set-up. Lesion studies (reviewed in [62,63]), morphological studies [64], computational modeling [65], selective induction of oxidative stress [66], and transgenic mice (reviewed in [62]) have suggested that networks including the hippocampus, septum, prefrontal cortex, basal forebrain, striatum, and cerebellum are involved.

At least two studies using the Y-Maze appear to support an association between cognitive impairment and HF diet exposure in the absence of obesity or other metabolic diseases. In one study of short-term exposure to 60% HF diet, juvenile C57BL/6 mice were found to have decreased spontaneous alternations after only 1 week on the HF diet, despite no differences in body weight [67]. In another long-term study, adult Long–Evans rats were found to have impairment in preference for the novel arm of a Y-Maze after 12 weeks of exposure to either a 'Western diet' or 60% HF diet despite the fact that only those rats consuming the 'Western diet' were heavier than controls [68]. A second study using a 21.2% HF diet in adult male mice did find increased body weight and impaired preference for the novel arm of a Y-Maze after 10 weeks on the diet [69].

In two negative studies in male rats, no difference in Y-Maze performance was found after 12 weeks on a combined 'HF/high fructose' diet [70] or after exposure to 60% HF diet for 10–12 weeks [71].

A single study focused mostly on the cognitive effects of diabetes found impairment in the Y-Maze and impaired insulin secretion despite normal body weight in the often used 60% HF diet + STZ mouse model of diabetes [32].

2.5. T-Maze

The T-Maze consists of an elevated, T-shaped platform with three enclosed arms. Like the Y-Maze, many variations of the T-Maze are in

common use. Also like the Y-Maze, the most common set-ups involve measuring tendency to enter a previously unexplored arm (i.e. 'spontaneous alternation'), tendency to enter a previously blocked arm, or latency to retrieval of a reward in a baited arm. In contrast to the Y-Maze, which measures 'spontaneous alternations' within a single trial, 'spontaneous alternations' in the T-Maze are usually measured in separate trials. That is, a cognitively intact rodent that choses to explore the left arm of a T-Maze in one trial is expected to explore the right arm on the next trial and doing so would be counted as a spontaneous alternation [72]. A much more complex 14-unit T-Maze has also been used in which a rodent is required to learn a series of right and left turns to reach a goal box. In the 14-unit T-Maze, rodents are motivated to find the escape by foot shocks that are administered upon failure to complete sections within a certain amount of time. Successful navigation of the 14-unit T-Maze is thought to rely more on procedural memory than spatial memory and thus may depend on striatal function with the hippocampus playing a subtler role [73,74]. Again like the Y-Maze, brain regions involved in T-Maze performance likely depend on the precise experimental set-up. Insights from many studies of brain lesions and transgenic mice indicate that the hippocampus, septum, prefrontal cortex, basal forebrain, thalamus, striatum, and cerebellum may all be involved (reviewed in [62,72]).

Among studies of HF diet effects on cognition, at least four have assessed performance in variations of the T-Maze. In the first, C57Bl/6 mice were given access to a 60% HF diet, a 41% fat 'Western diet', or standard chow beginning at 12 months of age. The authors found that mice on the HF, but not the 'Western' diet exhibited increased errors in the 14-unit T-Maze [75]. In another study using 60% and 45% HF diets, the authors found decreased spontaneous alternations in a T-Maze after only 17 days on the 60% HF diet and after 8 weeks on the 45% HF diet [76]. Interestingly, another study investigated the effects of a 45% HF diet or 10% fat standard diet on female APP/PS1 mice, a commonly used model of Alzheimer's disease. After 6 months of diet exposure, the authors found that while transgenic mice were impaired compared to WT, there was no additional effect of HF diet on T-Maze performance [77]. Finally, one study gave 12-month-old male CD-1 mice access to a diet containing either 10% or 5% fat and found impaired T-Maze performance among mice consuming the 10% fat diet [78]. While this study may suggest that fat exposure can have detrimental cognitive effects even at low concentration, the interpretation is complicated by the fact that the mice consuming the 10% fat diet were not included unless they were at least 30% heavier than the average of mice consuming the 5% fat diet.

2.6. Novel Object Recognition

Several variations of the Novel Object Recognition test are in common use. Generally, the test involves a memory acquisition phase and a recall phase. In the acquisition phase, a rodent is allowed to explore a chamber containing two identical objects. The recall phase then takes place after an interval (usually ranging from several hours to a few days), during which one object is either moved to a new location or replaced with a novel object and the rodent is again allowed to explore. The ratio of time spent exploring the novel versus familiar object is measured. Alternatively, rodents can be presented with a series of objects at different times during the acquisition phase, then, during the recall phase, the 'familiar' object is considered the one that was most recently seen. Cognitively intact animals are expected to discriminate between novel and familiar objects and preferentially interact with novel objects. Performance in the Novel Object Recognition test and similar tests of recognition memory are thought to involve function of the hippocampus as well as cortical areas. Taken together, the results of several different lesion studies indicate that the hippocampus appears to be involved when tests involve recall of an object's place or object recency, but the prefrontal and perirhinal cortex are more involved in novel object preference [79–82].

Overall, the effects of HF diets on Novel Object Recognition appear to be mixed. In rats, impairment has been found in male Sprague–Dawley rats fed a 'HF, high sucrose' diet for 8 weeks [27], or treated with 60% HF diet + streptozotocin in a model of diabetes [83]. Alternatively, no Novel Object Recognition deficits were found in male Long–Evans rats after consuming either a 'Western diet' or a 60% HF diet [68].

In mouse studies, all of which used the C57BL/6 strain, results are similarly mixed. No diet effects on Novel Object Recognition were found after exposure to 60% HF diet for 10–12 weeks [71] or 32% HF diet for 6 months [84]. In three reports that did find evidence of HF diet-related impairment, deficits were seen after 1 and 3 weeks on a 60% HF diet [67] as well as after 2, 3, and 4 months on a different 60% HF diet [24]. The most recent report found impairment after 21 weeks on 40% HF diet [85]. Another study using a 60% HF diet in male C57BL/6 mice did not find a diet effect on Novel Object Recognition, but did find impairment in the more hippocampal dependent object-in place variation of the test [86]. Finally, one study found deficits in the object-in place task among adolescent but not adult mice after 8 weeks on a 45% HF diet suggesting a potential critical period for hippocampal sensitivity to HF diet [87].

Interestingly, as with other tests of learning and memory, there does not appear to be a robust association between Novel Object Recognition and body weight. Among the studies finding an association between HF diet exposure and novel object performance, there are reports of no changes [27] and increased body weight [24,83,86,87] after HF diet consumption. Among the negative studies, there are reports of body weight increases [68,71,84,87], and decreases [68] upon exposure to various HF diets.

2.7. Conditioned inhibition

Several tests of learning and memory measure behavioral inhibition which may be particularly relevant in the maintenance of energy balance and body weight as it relates to an individual's ability to appropriately inhibit or suppress responses to food cues (reviewed in [88]). The tests of behavioral inhibition, including discrimination reversal, feature negative discrimination (FN), and the Variable Interval Delayed Alternation (VIDA) task, seem to be largely dependent on the ventral hippocampus with potential roles for the cortex and hypothalamic reward circuits (reviewed in [88]).

Both discrimination reversal and FN involve variations of classical conditioning. In discrimination reversal, rodents are first trained in a simple discrimination task such that one conditioned stimulus (CS1) is paired with an unconditioned stimulus (US), often a food or sucrose pellet, while another conditioned stimulus (CS2) is not. After asymptotic performance is reached, the pattern is reversed such that CS2 is paired with the US. Learning the pattern after reversal is related to hippocampal and prefrontal cortex function [89]. During FN, a CS1 is paired with an US, but no US is delivered when CS1 is preceded by CS2. Learning to preferentially respond to CS1 alone is thought to be hippocampal-dependent [90].

In one study that assessed discrimination reversal, male Sprague–Dawley rats were fed chow, or a high-saturated fat/high-glucose diet, or a high-saturated fat/high-sucrose diet. Additionally, half of the rats in each group were restricted to 85% baseline body weight. The authors found that only unrestricted access to the high-saturated fat/high-glucose diet impaired discrimination reversal learning suggesting that hippocampal function may be sensitive to interactions between diet composition and amount of access or body weight [89]. In three separate studies, adult male Sprague–Dawley rats were used to assess the effects of a 'high energy' diet that is high in both saturated fat and glucose on FN performance [90–92]. The first found that 90 days of access to the high-energy diet impaired performance in the FN task but, importantly, not in a separate discrimination based task that does not depend on hippocampal function [90]. The second found that the cognitive effects of high-energy diet were restricted to diet induced obesity (DIO) rats

while high-energy diet-resistant (DR) rats were indistinguishable from controls suggesting that weight gain or adiposity may mediate the dietary impact on hippocampal function [91]. The third study again found FN impairment among high-energy DIO rats, but differences in FN performance preceded differences in body weight. The authors also assessed the effects of a ketogenic diet that is high in saturated fat but low in carbohydrates. Interestingly, the authors found that the ketogenic DIO group performed better on the FN task than the ketogenic DR group despite increased body weight, adiposity, and glucose levels among DIO rats. Curiously, FN performance among rats fed the ketogenic diet but not the other diets was positively correlated with circulating ketone levels [92]. Together, these studies seem to support a clear, but complicated link between HF diet exposure and hippocampal-dependent cognitive impairment that is not simply related to obesity, blood glucose, or a specific diet composition.

Finally, a few of the first studies to assess cognition in response to HF diet consumption used the VIDA test, which is a modified go/no-go task. In the standard protocol, rodents are first trained to lever press for a food pellet using a continuous reinforcement schedule before introducing a simple alternating pattern between go and no-go trials. At first, the go and no-go trials are not separated by an intertrial interval and rodents quickly learn to lever press preferentially during go trials. After the rodents have successfully learned the alternating go/no-go pattern, a variable intertrial interval is introduced with longer intervals requiring more sustained memory of the previous trial. Memory can then be measured by comparing latency to lever press during go versus no-go trials with various intertrial intervals [3,93]. Learning the simple alternation rule is thought to principally involve the frontal cortex while performance in trials with longer intertrial intervals is thought to be more hippocampal dependent [94,95].

While many of the most recent papers have used other behavioral measures such as the Morris Water Maze or Novel Object Recognition, the VIDA test bears mentioning as it was used in several of the earliest studies to suggest an association between HF diet consumption and cognitive impairment. A series of several papers using young adult rats found that dietary saturated fat content is strongly negatively correlated with performance in the VIDA [58,93,96,97], though diets high in poly-unsaturated fats can still result in deficits [58,96].

Together, the behavioral studies summarized here suggest that consumption of essentially any HF diet, even for a short period of time, can negatively affect performance on a number of different tests of cognition. Interestingly, while individual studies may suggest that cognitive deficits are attributable to either adiposity or specific dietary components (i.e. glucose, saturated fat, or cholesterol), the current body of literature as a whole remains unclear and additional studies are certainly warranted.

In the next section we will discuss potential mechanisms underlying the link between HF diet exposure and cognitive impairment. Surprisingly, though behavioral data imply that several brain regions involved in learning and memory are likely impacted by HF exposure, the study of potential mechanisms has been largely limited to the hippocampus.

3. Potential mechanisms

3.1. Insulin, leptin & glucose regulation

As HF diet intake has been found to result in impaired performance across a number of tests of cognition, several potential mechanisms have been proposed. Directly connecting the effects of a HF diet on energy metabolism to its effects on cognition is a large body of evidence suggesting that the insulin receptor is highly expressed in the hippocampus and cortex, that synaptic insulin signaling is critical for learning and memory, and that peripheral insulin insensitivity can have dramatic effects in the CNS [98–104]. Consistent with insulin's potential role in learning and memory, a number of the studies reviewed here have found that HF diet-related cognitive impairment is also associated with impaired peripheral and central insulin signaling [16,19,20,22,23,76]. Interestingly, insulin sensitivity is thought to be largely related to adiposity and, as discussed previously, obesity is an inconsistent finding among studies of dietary effects on cognition. While it is possible that in some cases HF consumption is changing adiposity without affecting body weight, body composition analyses have not been routinely done.

It is also now well established that the leptin receptor is highly expressed in several brain regions including the hippocampus [105,106] and recent evidence suggests that leptin signaling, like insulin, may have a critical role in hippocampal dependent learning through regulation of synaptic plasticity and trafficking of neurotransmitter receptors [104,107–109]. While several studies have found that leptin resistance is associated with cognitive deficits [3,110,111], and that administration of leptin into the hippocampus enhances LTP [112] while also modulating food-related learning [113], leptin levels do not appear to have been routinely measured in most studies of HF diet-related cognitive impairment.

3.2. Oxidative stress & inflammation

Fatty acids are also known to increase the burden of oxidative stress and increase inflammation [114], which may negatively affect cognition. In fact, chronic inflammation in adipose tissue is thought to heavily contribute to the effects of HF diet and obesity on insulin sensitivity [115,116] which, as discussed above, may additionally impact learning and memory. Among the studies that have been reviewed here, several have found a HF diet-related increase in oxidative stress in the hippocampus [15–17,22,26,53,69,83] and cortex [17] as well as increased inflammatory cytokines in the hippocampus [17,55,85] and cortex [17,75,85]. However, at least two reports have found no change in cytokines despite finding HF diet-induced cognitive impairment [67,86].

3.3. Blood–brain barrier (BBB) dysfunction

A number of studies have also found that consumption of a HF diet can result in BBB dysfunction by increasing permeability [90,91,92,117] while also decreasing the active transport of leptin [118] and ghrelin [119] across the BBB. In fact, several reports have also proposed that BBB impairment may serve as a critical link between HF diet consumption and Alzheimer's disease pathology [120,121]. A few papers have used rodent models to directly link HF diet consumption to BBB integrity and cognition [90,91,92]. In two of these studies, BBB dysfunction was found in high-energy diet fed DIO but not DR rats [91,92] suggesting a possible interaction between diet composition, body weight, and BBB permeability. While measures of BBB function were not often included in the studies reviewed here, as mentioned above, a large number of studies have found that HF consumption is associated with increased inflammation, which may modulate BBB permeability [122–124].

3.4. Brain-derived neurotrophic factor (BDNF)

Finally, multiple studies have found that HF diet intake is associated with decreased expression of BDNF in both the hippocampus [13,14,16,26,85,89] and cortex [15,67,75,85,89] suggesting that the negative effects of HF diet consumption on learning and memory may also be mediated in part by alteration of BDNF-related synaptic plasticity. This is further supported by at least three studies that have found HF diet-related loss of dendritic spines [14,56,76], though one study did find increased spine density in the hippocampus which the authors suggested may have been a compensatory mechanism [87].

4. Developmental programming by maternal diet

A growing body of evidence is suggesting that maternal diet during gestation and the postnatal period can have a profound and long lasting effect on the brain, behavior, and metabolism of the offspring [125]. For

example, maternal HF diet consumption has been found to result in increased body weight [126,127] and adiposity [127,128] of offspring during the early perinatal period. Additionally, maternal HF diet consumption has been shown to increase food intake and body weight [127] and preference for a HF diet [129] among adult offspring. Prior work in our lab using a rat model has found that maternal exposure to a 60% HF diet increases the offspring's risk of developing diet-induced obesity [130], while also altering leptin sensitivity [131], and ingestive behavior [132,133]. Further, several behavioral studies in mice and rats have found that maternal consumption of various HF diets can result in impairment in the Morris Water Maze [126,134] and Barnes Maze [135]. Two other studies in rats found Morris Water Maze impairment among offspring born to HF fed dams that were then continued on a HF diet after weaning [136,137]. Finally, while the specific contributions of prenatal versus early postnatal exposure to HF diet has not been well established, results from our own cross-fostering experiments suggest that exposure at either time is sufficient to induce impairment in both Novel Object Recognition and the Barnes Maze among adult offspring [138], which, in rats, is consistent with the trajectory of hippocampal development that spans both the prenatal and early postnatal periods [139–141]. Regarding potential mechanisms underlying these changes, maternal HF diet consumption has been found to increase hippocampal inflammation [126], increase plasma leptin [127], and decrease hippocampal BDNF [134,135], while alterations in placental transport of nutrients and hormones may also be involved [125]. In our own lab, we have found that maternal HF diet exposure results in offspring with decreased hippocampal gene expression of insulin receptor (*Insr*), leptin receptor (*Lepr*), and glucose transporter 1 (*Slc2a1*) at weaning. Interestingly, the decreased expression of *Insr* and *Lepr* persisted into adulthood suggesting potential underlying epigenetic mechanisms [138]. While a great deal of work remains to be done related to these and other potential mechanisms as well as critical periods of exposure that present the greatest risk to the developing offspring, and respective contributions from maternal versus paternal diets, all of the evidence to date suggests that exposure to HF diet early in life can have lasting impacts on cognition and metabolism.

5. Conclusions, implications & future directions

While use of varying diets, ages, and behavioral tests make comparison between individual experiments difficult, the overwhelming majority of studies support the conclusion that HF diet exposure can have a dramatic and long lasting impact on hippocampal dependent learning and memory. While there are clear suggestions that other brain regions (especially the prefrontal cortex) are likely to be affected, results from behavioral tests that assess more distributed neural networks or non-hippocampal learning are more mixed and warrant additional study.

Further, the rodent studies reviewed here provide evidence suggesting that consumption of any number of HF diets for even a brief period of time at any point across the lifespan can potentially result in impaired performance on a number of behavioral tests of learning and memory including the Morris Water Maze, Barnes Maze, Radial Arm Maze, T-Maze, Y-Maze, Novel Object Recognition test, and conditioned inhibition. However, comparison across studies is complicated by the various designs and much work remains to be done in order to determine if there are sensitive developmental periods of exposure, doses of HF, specific fatty acids, or sex differences that increase an individual's susceptibility to the adverse effects of a HF diet on cognition. Similarly, the specific interactions between HF diet consumption and normal cognitive aging or forms of dementia such as Alzheimer's disease remain largely unknown.

A great deal of work has also been done to understand what potential mechanism(s) might be driving the cognitive effects of HF diet. Among the most consistently reported are changes in peripheral and central insulin signaling, leptin signaling, and glucose tolerance, an increased burden of oxidative stress as well as inflammation, BBB dysfunction, and decreased expression of BDNF. Though studies of mech-anisms underlying the cognitive effects of HF diet have focused almost entirely on the hippocampus and cortex, it is likely that other brain regions are involved and few studies have attempted to determine the actual contributions of each proposed mechanism to impairment in learning and memory or how the various mechanisms may interact.

Finally, emerging evidence indicates that maternal consumption of a HF diet may have effects on the learning and memory of offspring. While critical periods and doses of exposure as well as respective contributions from maternal versus paternal diets remain largely unstudied, all of the findings to date imply that the cognitive impact of a HF diet may extend to future generations. Given the growing rates of diabetes, obesity, and the metabolic syndrome as well as expanding concerns for the burden of dementia in a rapidly aging population, it seems that the studies reviewed here suggest an increasingly urgent need to understand the effects of HF diet on cognition, further explore underlying mechanisms in the brain, and ultimately develop effective interventions.

Disclosures

The authors have no conflicts of interest to declare.

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References

[1] M.H. Eskelinen, T. Ngandu, E.L. Helkala, J. Tuomilehto, A. Nissinen, H. Soininen, M. Kivipelto, Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study, International Journal of Geriatric Psychiatry 23 (7) (2008) 741–747.
[2] G.M. Pasinetti, J.A. Eberstein, Metabolic syndrome and the role of dietary lifestyles in Alzheimer's disease, J. Neurochem. 106 (4) (2008) 1503–1514.
[3] G. Winocur, C.E. Greenwood, G.G. Piroli, C.A. Grillo, L.R. Reznikov, L.P. Reagan, B.S. McEwen, Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity, Behav. Neurosci. 119 (5) (2005) 1389.
[4] R.G.M. Morris, P. Garrud, J.N.P. Rawlins, J. O'Keefe, Place navigation impaired in rats with hippocampal lesions, Nature 297 (5868) (1982) 681–683.
[5] R. Morris, Developments of a water-maze procedure for studying spatial learning in the rat, J. Neurosci. Methods 11 (1) (1984) 47–60.
[6] C.V. Vorhees, M.T. Williams, Morris water maze: procedures for assessing spatial and related forms of learning and memory, Nat. Protoc. 1 (2) (2006) 848–858.
[7] R.G.M. Morris, E. Anderson, G.S. Lynch, M. Baudryl, Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5, Nature 319 (1986) 27.
[8] Morris, R. G. (1989). Synaptic plasticity and learning: selective impairment of learning rats and blockade of long-term potentiation in vivo by the N-methyl-D-aspartate receptor antagonist AP5. The Journal of Neuroscience, 9(9), 3040–3057.
[9] K.J. Jeffery, R.G. Morris, Cumulative long-term potentiation in the rat dentate gyrus correlates with, but does not modify, performance in the water maze, Hippocampus 3 (2) (1993) 133–140.
[10] J.P. de Bruin, F. Sànchez-Santed, R.P. Heinsbroek, A. Donker, P. Postmes, A behavioural analysis of rats with damage to the medial prefrontal cortex using the Morris water maze: evidence for behavioural flexibility, but not for impaired spatial navigation, Brain Res. 652 (2) (1994) 323–333.
[11] R. D'Hooge, P.P. De Deyn, Applications of the Morris water maze in the study of learning and memory, Brain Res. Rev. 36 (1) (2001) 60–90.
[12] S.E. Kanoski, T.L. Davidson, Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity, Physiol. Behav. 103 (1) (2011) 59–68.
[13] R. Molteni, R.J. Barnard, Z. Ying, C.K. Roberts, F. Gomez-Pinilla, A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning, Neuroscience 112 (4) (2002) 803–814.
[14] A.M. Stranahan, E.D. Norman, K. Lee, R.G. Cutler, R.S. Telljohann, J.M. Egan, M.P. Mattson, Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats, Hippocampus 18 (11) (2008) 1085–1088.

[15] S.F. Xia, Z.X. Xie, Y. Qiao, L.R. Li, X.R. Cheng, X. Tang, et al., Differential effects of quercetin on hippocampus-dependent learning and memory in mice fed with different diets related with oxidative stress, Physiol. Behav. 138 (2015) 325–331.

[16] T. Kishi, Y. Hirooka, T. Nagayama, K. Isegawa, M. Katsuki, K. Takesue, K. Sunagawa, Calorie restriction improves cognitive decline via up-regulation of brain-derived neurotrophic factor, Int. Heart J. 56 (1) (2014) 110–115.

[17] Y. Liu, X. Fu, N. Lan, S. Li, J. Zhang, S. Wang, et al., Luteolin protects against high fat diet-induced cognitive deficits in obesity mice, Behav. Brain Res. 267 (2014) 178–188.

[18] A.R. Pathan, A.B. Gaikwad, B. Viswanad, P. Ramarao, Rosiglitazone attenuates the cognitive deficits induced by high fat diet feeding in rats, Eur. J. Pharmacol. 589 (1) (2008) 176–179.

[19] H. Pintana, N. Apaijai, W. Pratchayasakul, N. Chattipakorn, S.C. Chattipakorn, Effects of metformin on learning and memory behaviors and brain mitochondrial functions in high fat diet induced insulin resistant rats, Life Sci. 91 (11) (2012) 409–414.

[20] Pintana, H., Apaijai, N., Chattipakorn, N., & Chattipakorn, S.C. (2013). DPP-4 inhibitors improve cognition and brain mitochondrial function of insulin-resistant rats. J. Endocrinol., 218(1), 1–11.

[21] N. Pipatpiboon, H. Pintana, W. Pratchayasakul, N. Chattipakorn, S.C. Chattipakorn, DPP4-inhibitor improves neuronal insulin receptor function, brain mitochondrial function and cognitive function in rats with insulin resistance induced by high-fat diet consumption, Eur. J. Neurosci. 37 (5) (2013) 839–849.

[22] J. Lu, D.M. Wu, Y.L. Zheng, B. Hu, W. Cheng, Z.F. Zhang, Q. Shan, Ursolic acid improves high fat diet-induced cognitive impairments by blocking endoplasmic reticulum stress and IκB kinase β/nuclear factor-κB-mediated inflammatory pathways in mice, Brain Behav. Immun. 25 (8) (2011) 1658–1667.

[23] B.T. Jeon, E.A. Jeong, H.J. Shin, Y. Lee, D.H. Lee, H.J. Kim, et al., Resveratrol attenuates obesity-associated peripheral and central inflammation and improves memory deficit in mice fed a high-fat diet, Diabetes 61 (6) (2012) 1444–1454.

[24] A.N. Carey, S.M. Gomes, B. Shukitt-Hale, Blueberry supplementation improves memory in middle-aged mice fed a high-fat diet, J. Agric. Food Chem. 62 (18) (2014) 3972–3978.

[25] J. Wang, D. Freire, L. Knable, W. Zhao, B. Gong, P. Mazzola, et al., Childhood and adolescent obesity and long-term cognitive consequences during aging, J. Comp. Neurol. 523 (5) (2015) 757–768.

[26] R. Molteni, A. Wu, S. Vaynman, Z. Ying, R.J. Barnard, F. Gomez-Pinilla, Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor, Neuroscience 123 (2) (2004) 429–440.

[27] H.M. Francis, M. Mirzaei, M.C. Pardey, P.A. Haynes, J.L. Cornish, Proteomic analysis of the dorsal and ventral hippocampus of rats maintained on a high fat and refined sugar diet, Proteomics 13 (20) (2013) 3076–3091.

[28] J.G. Mielke, K. Nicolitch, V. Avellaneda, K. Earlam, T. Ahuja, G. Mealing, C. Messier, Longitudinal study of the effects of a high-fat diet on glucose regulation, hippocampal function, and cerebral insulin sensitivity in C57BL/6 mice, Behav. Brain Res. 175 (2) (2006) 374–382.

[29] C. Boitard, A. Cavaroc, J. Sauvant, A. Aubert, N. Castanon, S. Layé, G. Ferreira, Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is associated with enhanced hippocampal inflammation in rats, Brain Behav. Immun. 40 (2014) 9–17.

[30] P.E. Wainwright, H.C. Xing, G.R. Ward, Y.S. Huang, E. Bobik, N. Auestad, M. Montalto, Water maze performance is unaffected in artificially reared rats fed diets supplemented with arachidonic acid and docosahexaenoic acid, The Journal of Nutrition 129 (5) (1999) 1079–1089.

[31] M.C. de Wilde, E. Farkas, M. Gerrits, A.J. Kiliaan, P.G. Luiten, The effect of n − 3 polyunsaturated fatty acid-rich diets on cognitive and cerebrovascular parameters in chronic cerebral hypoperfusion, Brain Res. 947 (2) (2002) 166–173.

[32] L.Y. Jiang, S.S. Tang, X.Y. Wang, L.P. Liu, Y. Long, M. Hu, et al., PPARγ agonist pioglitazone reverses memory impairment and biochemical changes in a mouse model of type 2 diabetes mellitus, CNS Neurosci. Ther. 18 (8) (2012) 659–666.

[33] D. Peng, X. Pan, J. Cui, Y. Ren, J. Zhang, Hyperphosphorylation of tau protein in hippocampus of central insulin-resistant rats is associated with cognitive impairment, Cellular physiology and biochemistry: international journal of experimental cellular physiology, biochemistry, and pharmacology 32 (5) (2012) 1417–1425.

[34] J. Liu, L. Feng, D. Ma, M. Zhang, J. Gu, S. Wang, et al., Neuroprotective effect of paeonol on cognition deficits of diabetic encephalopathy in streptozotocin-induced diabetic rat, Neurosci. Lett. 549 (2013) 63–68.

[35] X.H. Chang, L.N. Liang, L.B. Zhan, X.G. Lu, X. Shi, X. Qi, et al., The effect of Chinese Jinzhida recipe on the hippocampus in a rat model of diabetes-associated cognitive decline, BMC Complementary and Alternative Medicine 13 (1) (2013) 161.

[36] A.D. Goldbart, B.W. Row, L. Kheirandish-Gozal, Y. Cheng, K.R. Brittian, D. Gozal, High fat/refined carbohydrate diet enhances the susceptibility to spatial learning deficits in rats exposed to intermittent hypoxia, Brain Res. 1090 (1) (2006) 190–196.

[37] T. Zhang, B.S. Pan, B. Zhao, L.M. Zhang, Y.L. Huang, F.Y. Sun, Exacerbation of poststroke dementia by type 2 diabetes is associated with synergistic increases of β-secretase activation and β-amyloid generation in rat brains, Neuroscience 161 (4) (2009) 1045–1056.

[38] A. Wu, R. Molteni, Z. Ying, F. Gomez-Pinilla, A saturated-fat diet aggravates the outcome of traumatic brain injury on hippocampal plasticity and cognitive function by reducing brain-derived neurotrophic factor, Neuroscience 119 (2) (2003) 365–375.

[39] M.R. Hoane, A.A. Swan, S.E. Heck, The effects of a high-fat sucrose diet on functional outcome following cortical contusion injury in the rat, Behav. Brain Res. 223 (1) (2011) 119–124.

[40] N.F. Fitz, A. Cronican, T. Pham, A. Fogg, A.H. Fauq, R. Chapman, et al., Liver X receptor agonist treatment ameliorates amyloid pathology and memory deficits caused by high-fat diet in APP23 mice, The Journal of Neuroscience 30 (20) (2010) 6862–6872.

[41] C.A. Barnes, Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat, J. Comp. Physiol. Psychol. 93 (1) (1979) 74.

[42] F.E. Harrison, A.H. Hosseini, M.P. McDonald, Endogenous anxiety and stress responses in water maze and Barnes maze spatial memory tasks, Behav. Brain Res. 198 (1) (2009) 247–251.

[43] N.J. Anderson, M.R. King, L. Delbruck, C.G. Jolivalt, Role of insulin signaling impairment, adiponectin and dyslipidemia in peripheral and central neuropathy in mice, Disease Models & Mechanisms 7 (6) (2014) 625–633.

[44] C.L. Ohland, L. Kish, H. Bell, A. Thiesen, N. Hotte, E. Pankiv, K.L. Madsen, Effects of *Lactobacillus helveticus* on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome, Psychoneuroendocrinology 38 (9) (2013) 1738–1747.

[45] L. Li, Z. Wang, Z. Zuo, Chronic intermittent fasting improves cognitive functions and brain structures in mice, PLoS One 8 (6) (2013) e66069.

[46] Olton, D.S., & Samuelson, R.J. (1976) Remembrance of places passed: spatial memory in rats. J. Exp. Psychol. Anim. Behav. Process., 2(2), 97.

[47] Hodges, H. (1996). Maze procedures: the radial-arm and water maze compared. Cogn. Brain Res., 3(3), 167–181.

[48] D.M. Diamond, C.R. Park, K.L. Heman, G.M. Rose, Exposing rats to a predator impairs spatial working memory in the radial arm water maze, Hippocampus 9 (5) (1999) 542–552.

[49] L. Ward, S.E. Mason, W.C. Abraham, Effects of the NMDA antagonists CPP and MK-801 on radial arm maze performance in rats, Pharmacol. Biochem. Behav. 35 (4) (1990) 785–790.

[50] S.B. Floresco, J.K. Seamans, A.G. Phillips, Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay, The Journal of Neuroscience 17 (5) (1997) 1880–1890.

[51] S.B. Floresco, D.N. Braaksma, A.G. Phillips, Thalamic–cortical–striatal circuitry subserves working memory during delayed responding on a radial arm maze, The Journal of Neuroscience 19 (24) (1999) 11061–11071.

[52] K.H. Alzoubi, K.K. Abdul-Razzak, O.F. Khabour, G.M. Al-Tuweiq, M.A. Alzubi, K.A. Alkadhi, Adverse effect of combination of chronic psychosocial stress and high fat diet on hippocampus-dependent memory in rats, Behav. Brain Res. 204 (1) (2009) 117–123.

[53] K.H. Alzoubi, O.F. Khabour, H.A. Salah, Z. Hasan, Vitamin E prevents high-fat high-carbohydrates diet-induced memory impairment: the role of oxidative stress, Physiol. Behav. 119 (2013) 72–78.

[54] K.H. Alzoubi, K.K. Abdul-Razzak, O.F. Khabour, G.M. Al-Tuweiq, M.A. Alzubi, K.A. Alkadhi, Caffeine prevents cognitive impairment induced by chronic psychosocial stress and/or high fat–high carbohydrate diet, Behav. Brain Res. 237 (2013) 7–14.

[55] L. Thirumangalakudi, A. Prakasam, R. Zhang, H. Bimonte-Nelson, K. Sambamurti, M.S. Kindy, N.R. Bhat, High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with loss of working memory in mice, J. Neurochem. 106 (1) (2008) 475–485.

[56] A.C. Granholm, H.A. Bimonte-Nelson, A.B. Moore, M.E. Nelson, L.R. Freeman, K. Sambamurti, Effects of a saturated fat and high cholesterol diet on memory and hippocampal morphology in the middle-aged rat, J. Alzheimers Dis. 14 (2) (2008) 133–145.

[57] S.E. Kanoski, T.L. Davidson, Different patterns of memory impairments accompany short- and longer-term maintenance on a high-energy diet, J. Exp. Psychol. Anim. Behav. Process. 36 (2) (2010) 313.

[58] C.E. Greenwood, G. Winocur, Cognitive impairment in rats fed high-fat diets: a specific effect of saturated fatty-acid intake, Behav. Neurosci. 110 (3) (1996) 451.

[59] I. Valladolid-Acebes, P. Stucchi, V. Cano, M.S. Fernández-Alfonso, B. Merino, M. Gil-Ortega, et al., High-fat diets impair spatial learning in the radial-arm maze in mice, Neurobiol. Learn. Mem. 95 (1) (2011) 80–85.

[60] K.R. Bailey, J.N. Crawley, Methods of Behavior Analysis in Neuroscience, CRC Press, Augusta, Boca Raton (FL), 2009.

[61] F. Dellu, W. Mayo, J. Cherkaoui, M. Le Moal, H. Simon, A two-trial memory task with automated recording: study in young and aged rats, Brain Res. 588 (1) (1992) 132–139.

[62] R. Lalonde, The neurobiological basis of spontaneous alternation, Neurosci. Biobehav. Rev. 26 (1) (2002) 91–104.

[63] S.L. Biggan, R.J. Beninger, J. Cockhill, K. Jhamandas, R.J. Boegman, Quisqualate lesions of rat NBM: selective effects on working memory in a double Y-maze, Brain Res. Bull. 26 (4) (1991) 613–616.

[64] J.W. Koo, C.H. Park, S.H. Choi, N.J. Kim, H.S. Kim, J.C. Choe, Y.H. Suh, The postnatal environment can counteract prenatal effects on cognitive ability, cell proliferation, and synaptic protein expression, FASEB J. 17 (11) (2003) 1556–1558.

[65] H.E. Atallah, M.J. Frank, R.C. O'Reilly, Hippocampus, cortex, and basal ganglia: insights from computational models of complementary learning systems, Neurobiol. Learn. Mem. 82 (3) (2004) 253–267.

[66] O. Dean, A.I. Bush, M. Berk, D.L. Copolov, M. van den Buuse, Glutathione depletion in the brain disrupts short-term spatial memory in the Y-maze in rats and mice, Behav. Brain Res. 198 (1) (2009) 258–262.

[67] M.M. Kaczmarczyk, A.S. Machaj, G.S. Chiu, M.A. Lawson, S.J. Gainey, J.M. York, et al., Methylphenidate prevents high-fat diet (HFD)-induced learning/memory impairment in juvenile mice, Psychoneuroendocrinology 38 (9) (2013) 1553–1564.

[68] S. Kosari, E. Badoer, J.C. Nguyen, A.S. Killcross, T.A. Jenkins, Effect of western and high fat diets on memory and cholinergic measures in the rat, Behav. Brain Res. 235 (1) (2012) 98–103.

[69] Y. Cui, Y. Shu, Y. Zhu, Y. Shi, G. Le, High-fat diets impair spatial learning of mice in the Y-maze paradigm: ameliorative potential of α-lipoic acid, J. Med. Food 15 (8) (2012) 713–717.
[70] R.A. Anderson, B. Qin, F. Canini, L. Poulet, A.M. Roussel, Cinnamon counteracts the negative effects of a high fat/high fructose diet on behavior, brain insulin signaling and Alzheimer-associated changes, PLoS One 8 (12) (2013) e83243.
[71] D.N. Lavin, J.J. Joesting, G.S. Chiu, M.L. Moon, J. Meng, R.N. Dilger, G.G. Freund, Fasting induces an anti-inflammatory effect on the neuroimmune system which a high-fat diet prevents, Obesity 19 (8) (2011) 1586–1594.
[72] R.M. Deacon, J.N.P. Rawlins, T-maze alternation in the rodent, Nat. Protoc. 1 (2006) 7–12.
[73] C.L. Goodrick, Learning, retention, and extinction of a complex maze habit for mature-young and senescent Wistar albino rats, J. Gerontol. 23 (3) (1968) 298–304.
[74] P.J. Pistell, C.M. Nelson, M.G. Miller, E.L. Spangler, D.K. Ingram, B.D. Devan, Striatal lesions interfere with acquisition of a complex maze task in rats, Behav. Brain Res. 197 (1) (2009) 138–143.
[75] P.J. Pistell, C.D. Morrison, S. Gupta, A.G. Knight, J.N. Keller, D.K. Ingram, A.J. Bruce-Keller, Cognitive impairment following high fat diet consumption is associated with brain inflammation, J. Neuroimmunol. 219 (1) (2010) 25–32.
[76] S.E. Arnold, I. Lucki, B.R. Brookshire, G.C. Carlson, C.A. Browne, H. Kazi, et al., High fat diet produces brain insulin resistance, synaptodendritic abnormalities and altered behavior in mice, Neurobiol. Dis. 67 (2014) 79–87.
[77] Y. Peng, J. Liu, Y. Tang, J. Liu, T. Han, S. Han, et al., High-fat-diet-induced weight gain ameliorates bone loss without exacerbating AβPP processing and cognition in female APP/PS1 mice, Front. Cell. Neurosci. 8 (2014).
[78] S.A. Farr, K.A. Yamada, D.A. Butterfield, H.M. Abdul, L. Xu, N.E. Miller, et al., Obesity and hypertriglyceridemia produce cognitive impairment, Endocrinology 149 (5) (2008) 2628–2636.
[79] D.G. Mumby, J.P. Pinel, Rhinal cortex lesions and object recognition in rats, Behav. Neurosci. 108 (1) (1994) 11.
[80] T.J. Bussey, J.L. Muir, J.P. Aggleton, Functionally dissociating aspects of event memory: the effects of combined perirhinal and postrhinal cortex lesions on object and place memory in the rat, The Journal of Neuroscience 19 (1) (1999) 495–502.
[81] T.J. Bussey, J. Duck, J.L. Muir, J.P. Aggleton, Distinct patterns of behavioural impairments resulting from fornix transection or neurotoxic lesions of the perirhinal and postrhinal cortices in the rat, Behav. Brain Res. 111 (1) (2000) 187–202.
[82] G.R. Barker, E.C. Warburton, When is the hippocampus involved in recognition memory? The Journal of Neuroscience 31 (29) (2011) 10721–10731.
[83] A. Rahigude, P. Bhutada, S. Kaulaskar, M. Aswar, K. Otari, Participation of antioxidant and cholinergic system in protective effect of naringenin against type-2 diabetes-induced memory dysfunction in rats, Neuroscience 226 (2012) 62–72.
[84] K.R. Tucker, S.J. Godbey, N. Thiebaud, D.A. Fadool, Olfactory ability and object memory in three mouse models of varying body weight, metabolic hormones, and adiposity, Physiol. Behav. 107 (3) (2012) 424–432.
[85] D. Camer, Y. Yu, A. Szabo, F. Fernandez, C.H. Dinh, X.F. Huang, Bardoxolone methyl prevents high-fat diet-induced alterations in prefrontal cortex signalling molecules involved in recognition memory, Prog. Neuro-Psychopharmacol. Biol. Psychiatry (2015).
[86] F.D. Heyward, R.G. Walton, M.S. Carle, M.A. Coleman, W.T. Garvey, J.D. Sweatt, Adult mice maintained on a high-fat diet exhibit object location memory deficits and reduced hippocampal SIRT1 gene expression, Neurobiol. Learn. Mem. 98 (1) (2012) 25–32.
[87] I. Valladolid-Acebes, A. Fole, M. Martín, L. Morales, M.V. Cano, M. Ruiz-Gayo, N. Del Olmo, Spatial memory impairment and changes in hippocampal morphology are triggered by high-fat diets in adolescent mice. Is there a role of leptin? Neurobiol. Learn. Mem. 106 (2013) 18–25.
[88] T.L. Davidson, S.E. Kanoski, E.K. Walls, L.E. Jarrard, Memory inhibition and energy regulation, Physiol. Behav. 86 (5) (2005) 731–746.
[89] S.E. Kanoski, R.L. Meisel, A.J. Mullins, T.L. Davidson, The effects of energy-rich diets on discrimination reversal learning and on BDNF in the hippocampus and prefrontal cortex of the rat, Behav. Brain Res. 182 (1) (2007) 57–66.
[90] S.E. Kanoski, Y. Zhang, W. Zheng, T.L. Davidson, The effects of a high-energy diet on hippocampal function and blood–brain barrier integrity in the rat, J. Alzheimers Dis. 21 (1) (2010) 207–219.
[91] T.L. Davidson, A. Monnot, A.U. Neal, A.A. Martin, J.J. Horton, W. Zheng, The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood–brain barrier integrity differ for diet-induced obese and diet-resistant rats, Physiol. Behav. 107 (1) (2012) 26–33.
[92] T.L. Davidson, S.L. Hargrave, S.E. Swithers, C.H. Sample, X. Fu, K.P. Kinzig, W. Zheng, Inter-relationships among diet, obesity and hippocampal-dependent cognitive function, Neuroscience 253 (2013) 110–122.
[93] C.E. Greenwood, G. Winocur, Glucose treatment reduces memory deficits in young adult rats fed high-fat diets, Neurobiol. Learn. Mem. 75 (2) (2001) 179–189.
[94] G. Winocur, Functional dissociation of the hippocampus and prefrontal cortex in learning and memory, Psychobiology 19 (1) (1991) 11–20.
[95] G. Winocur, Conditional learning in aged rats: evidence of hippocampal and prefrontal cortex impairment, Neurobiol. Aging 13 (1) (1992) 131–135.
[96] C.E. Greenwood, G. Winocur, Learning and memory impairment in rats fed a high saturated fat diet, Behav. Neural Biol. 53 (1) (1990) 74–87.
[97] G. Winocur, C.E. Greenwood, The effects of high fat diets and environmental influences on cognitive performance in rats, Behav. Brain Res. 101 (2) (1999) 153–161.
[98] M.A. Abbott, D.G. Wells, J.R. Fallon, The insulin receptor tyrosine kinase substrate p58/53 and the insulin receptor are components of CNS synapses, The Journal of Neuroscience 19 (17) (1999) 7300–7308.
[99] W. Zhao, H. Chen, H. Xu, E. Moore, N. Meiri, M.J. Quon, D.L. Alkon, Brain insulin receptors and spatial memory correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats, J. Biol. Chem. 274 (49) (1999) 34893–34902.
[100] W.Q. Zhao, D.L. Alkon, Role of insulin and insulin receptor in learning and memory, Mol. Cell. Endocrinol. 177 (1) (2001) 125–134.
[101] S.C. Woods, R.J. Seeley, D.G. Baskin, M.W. Schwartz, Insulin and the blood–brain barrier, Curr. Pharm. Des. 9 (10) (2003) 795–800.
[102] C.A. Grillo, G.G. Piroli, R.M. Hendry, L.P. Reagan, Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent, Brain Res. 1296 (2009) 35–45.
[103] L.P. Reagan, Insulin signaling effects on memory and mood, Curr. Opin. Pharmacol. 7 (6) (2007) 633–637.
[104] J.R. Fadel, C.G. Jolivalt, L.P. Reagan, Food for thought: the role of appetitive peptides in age-related cognitive decline, Ageing Res. Rev. 12 (3) (2013) 764–776.
[105] J.G. Mercer, N. Hoggard, L.M. Williams, C.B. Lawrence, L.T. Hannah, P. Trayhurn, Localization of leptin receptor mRNA and the long form splice variant (Ob-Rb) in mouse hypothalamus and adjacent brain regions by in situ hybridization, FEBS Lett. 387 (2) (1996) 113–116.
[106] X.F. Huang, I. Koutcherov, S. Lin, H.Q. Wang, L. Storlien, Localization of leptin receptor mRNA expression in mouse brain, Neuroreport 7 (15–17) (1996) 2635–2638.
[107] C.A. Grillo, G.G. Piroli, A.N. Evans, V.A. Macht, S.P. Wilson, K.A. Scott, et al., Obesity/hyperleptinemic phenotype adversely affects hippocampal plasticity: effects of dietary restriction, Physiol. Behav. 104 (2) (2011) 235–241.
[108] C.A. Grillo, G.G. Piroli, L. Junor, S.P. Wilson, D.D. Mott, M.A. Wilson, L.P. Reagan, Obesity/hyperleptinemic phenotype impairs structural and functional plasticity in the rat hippocampus, Physiol. Behav. 105 (1) (2011) 138–144.
[109] G. McGregor, Y. Malekizadeh, J. Harvey, Minireview: food for thought: regulation of synaptic function by metabolic hormones, Mol. Endocrinol. 29 (1) (2015) 3–13.
[110] S.A. Farr, W.A. Banks, J.E. Morley, Effects of leptin on memory processing, Peptides 27 (6) (2006) 1420–1425.
[111] X.L. Li, S. Aou, Y. Oomura, N. Hori, K. Fukunaga, T. Hori, Impairment of long-term potentiation and spatial memory in leptin receptor-deficient rodents, Neuroscience 113 (3) (2002) 607–615.
[112] M.J. Wayner, D.L. Armstrong, C.F. Phelix, Y. Oomura, Orexin-A (hypocretin-1) and leptin enhance LTP in the dentate gyrus of rats in vivo, Peptides 25 (6) (2004) 991–996.
[113] S.E. Kanoski, M.R. Hayes, H.S. Greenwald, S.M. Fortin, C.A. Gianessi, J.R. Gilbert, H.J. Grill, Hippocampal leptin signaling reduces food intake and modulates food-related memory processing, Neuropsychopharmacology 36 (9) (2011) 1859–1870.
[114] S. Furukawa, T. Fujita, M. Shimabukuro, M. Iwaki, Y. Yamada, Y. Nakajima, et al., Increased oxidative stress in obesity and its impact on metabolic syndrome, J. Clin. Investig. 114 (12) (2004) 1752.
[115] H. Xu, G.T. Barnes, Q. Yang, G. Tan, D. Yang, C.J. Chou, et al., Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance, J. Clin. Investig. 112 (12) (2003) 1821.
[116] G.S. Hotamisligil, Inflammation and metabolic disorders, Nature 444 (7121) (2006) 860–867.
[117] L.R. Freeman, A.C.E. Granholm, Vascular changes in rat hippocampus following a high saturated fat and cholesterol diet, J. Cereb. Blood Flow Metab. 32 (4) (2012) 643–653.
[118] W.A. Banks, A.B. Coon, S.M. Robinson, A. Moinuddin, J.M. Shultz, R. Nakaoke, J.E. Morley, Triglycerides induce leptin resistance at the blood–brain barrier, Diabetes 53 (5) (2004) 1253–1260.
[119] W.A. Banks, B.O. Burney, S.M. Robinson, Effects of triglycerides, obesity, and starvation on ghrelin transport across the blood–brain barrier, Peptides 29 (11) (2008) 2061–2065.
[120] T.M. Hsu, S.E. Kanoski, Blood–brain barrier disruption: mechanistic links between Western diet consumption and dementia, Front. Aging Neurosci. 6 (2014).
[121] Mulder, M., Blokland, A., van den Berg, D. J., Schulten, H., Bakker, A. H., Terwel, et al. (2001). Apolipoprotein E protects against neuropathology induced by a high-fat diet and maintains the integrity of the blood–brain barrier during aging. Lab. Investig., 81(7), 953–960.
[122] N.J. Abbott, Inflammatory mediators and modulation of blood–brain barrier permeability, Cell. Mol. Neurobiol. 20 (2) (2000) 131–147.
[123] N.J. Abbott, L. Rönnbäck, E. Hansson, Astrocyte–endothelial interactions at the blood–brain barrier, Nat. Rev. Neurosci. 7 (1) (2006) 41–53.
[124] M. Ek, D. Engblom, S. Saha, A. Blomqvist, P.J. Jakobsson, A. Ericsson-Dahlstrand, Inflammatory response: pathway across the blood–brain barrier, Nature 410 (6827) (2001) 430–431.
[125] E.L. Sullivan, E.K. Nousen, K.A. Chamlou, Maternal high fat diet consumption during the perinatal period programs offspring behavior, Physiol. Behav. 123 (2014) 236–242.
[126] S.D. Bilbo, V. Tsang, Enduring consequences of maternal obesity for brain inflammation and behavior of offspring, FASEB J. 24 (6) (2010) 2104–2115.
[127] C.D. Walker, L. Naef, E. d'Asti, H. Long, Z. Xu, A. Moreau, B. Azeddine, Perinatal maternal fat intake affects metabolism and hippocampal function in the offspring, Ann. N. Y. Acad. Sci. 1144 (1) (2008) 189–202.
[128] T. Wright, S.C. Langley-Evans, J.P. Voigt, The impact of maternal cafeteria diet on anxiety-related behaviour and exploration in the offspring, Physiol. Behav. 103 (2) (2011) 164–172.
[129] S.A. Bayol, S.J. Farrington, N.C. Stickland, A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring, Br. J. Nutr. 98 (04) (2007) 843–851.
[130] K.L. Tamashiro, C.E. Terrillion, J. Hyun, J.I. Koenig, T.H. Moran, Prenatal stress or high-fat diet increases susceptibility to diet-induced obesity in rat offspring, Diabetes 58 (5) (2009) 1116–1125.

[131] B. Sun, R.H. Purcell, C.E. Terrillion, J. Yan, T.H. Moran, K.L. Tamashiro, Maternal high-fat diet during gestation or suckling differentially affects offspring leptin sensitivity and obesity, Diabetes 61 (11) (2012) 2833–2841.
[132] R.H. Purcell, B. Sun, L.L. Pass, M.L. Power, T.H. Moran, K.L. Tamashiro, Maternal stress and high-fat diet effect on maternal behavior, milk composition, and pup ingestive behavior, Physiol. Behav. 104 (3) (2011) 474–479.
[133] Y. Treesukosol, B. Sun, A.A. Moghadam, N.C. Liang, K.L. Tamashiro, T.H. Moran, Maternal high-fat diet during pregnancy and lactation reduces the appetitive behavioral component in female offspring tested in a brief-access taste procedure, Am. J. Physiol. Regul. Integr. Comp. Physiol. 306 (7) (2014) R499–R509.
[134] K.C. Page, E.K. Jones, E.K. Anday, Maternal and postweaning high-fat diets disturb hippocampal gene expression, learning, and memory function, Am. J. Physiol. Regul. Integr. Comp. Physiol. 306 (8) (2014) R527–R537.
[135] Y. Tozuka, M. Kumon, E. Wada, M. Onodera, H. Mochizuki, K. Wada, Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring, Neurochem. Int. 57 (3) (2010) 235–247.
[136] C.L. White, P.J. Pistell, M.N. Purpera, S. Gupta, S.O. Fernandez-Kim, T.L. Hise, et al., Effects of high fat diet on Morris maze performance, oxidative stress, and inflammation in rats: contributions of maternal diet, Neurobiol. Dis. 35 (1) (2009) 3–13.
[137] Ö.D. Can, E. Ulupinar, Ü.D. Özkay, B. Yegin, Y. Öztürk, The effect of simvastatin treatment on behavioral parameters, cognitive performance, and hippocampal morphology in rats fed a standard or a high-fat diet, Behav. Pharmacol. 23 (5 and 6) (2012) 582–592.
[138] Z.A. Cordner, T. Summers, G.J. Boersma, L. Song, T.H. Moran, K.L. Tamashiro, Maternal high-fat diet results in cognitive impairment and hippocampal gene expression changes in rat offspring, Presented at: 22nd Annual Meeting of the Society for the Study of Ingestive Behavior; July 29–August 2, 2014, WA, Seattle, 2014.
[139] S.A. Bayer, J. Altman, Hippocampal development in the rat: cytogenesis and morphogenesis examined with autoradiography and low-level-X-irradiation, J. Comp. Neurol. 158 (1) (1974) 57–79.
[140] P.D. Martin, A. Berthoz, Development of spatial firing in the hippocampus of young rats, Hippocampus 12 (4) (2002) 465–480.
[141] T.J. Wills, F. Cacucci, N. Burgess, J. O'Keefe, Development of the hippocampal cognitive map in preweanling rats, Science 328 (5985) (2010) 1573–1576.