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Review

# Cognitive and neuronal systems underlying obesity

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ABSTRACT

Since the late 1970s obesity prevalence and per capita food intake in the USA have increased dramatically. Understanding the mechanisms underlying the hyperphagia that drives obesity requires focus on the cognitive processes and neuronal systems controlling feeding that occurs in the absence of metabolic need (i.e., "non-homeostatic" intake). Given that a portion of the increased caloric intake per capita since the late 1970s is attributed to increased meal and snack frequency, and given the increased pervasiveness of environmental cues associated with energy dense, yet nutritionally depleted foods, there's a need to examine the mechanisms through which food-related cues stimulate excessive energy intake. Here, learning and memory principles and their underlying neuronal substrates are discussed with regard to stimulus-driven food intake and excessive energy consumption. Particular focus is given to the hippocampus, a brain structure that utilizes interoceptive cues relevant to energy status (e.g., neurohormonal signals such as leptin) to modulate stimulus-driven food procurement and consumption. This type of hippocampal-dependent modulatory control of feeding behavior is compromised by consumption of foods common to Western diets, including saturated fats and simple carbohydrates. The development of more effective treatments for obesity will benefit from a more complete understanding of the complex interaction between dietary, environmental, cognitive, and neurophysiological mechanisms contributing to excessive food intake.



**Contents**



## 1. Introduction

The need to more fully understand the neuronal substrates underlying food intake control is highlighted by the profound increase in obesity prevalence that has emerged in the USA and other developed countries across the past few decades [1–3]. Food intake and energy balance are regulated, in part, by neuronal processing in the hypothalamus and the brainstem. A great deal of research has focused on neurohormonal and neurotransmitter systems in these brain regions that regulate what has been called "homeostatic", or energy deficit-driven feeding [4–6]. Much less is known, however, about the neurochemical and psychological factors that underlie food intake that

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occurs in the absence of metabolic need, or "non-homeostatic" food intake. Substantial progress in research aimed at treating obesity can be made through a deeper understanding of the neuronal systems that control non-homeostatic-driven feeding. This notion is highlighted by two important points: 1) the excessive energy intake that drives human obesity is clearly not based on metabolic need, and 2) decisions about eating or not eating, or how much food is consumed undoubtedly involves neuronal processing in higher-order (extrahypothalamic and extrahindbrain) brain regions that control cognitive processes.

Given the rarity of monogenetic causes of obesity [7] and the extreme unlikelihood that the human genome has changed substantially in the past 30 years, the exponential increase in obesity prevalence is largely attributed to environment factors present in modernized Western cultures [8,9]. While specific causal environmental factors are difficult to identify, it is likely that changes in diet composition in Western cultures (e.g., more energy dense and highly processed foods), the easy availability of these "Western" foods, as well as the abundance of cues in the modern environment associated with this type of food are contributing to the alarming increase in obesity. Increased feeding stimulated by exposure to these types of environmental food-related cues involves associative learning mechanisms. This review discusses learning principles and their underlying neuronal substrates in relation to excessive energy consumption, and considers the perspective that one antecedent fueling the hyperphagia driving obesity is dietary-induced disruption of the higher-order learned controls of feeding behavior.

## 2. Basic conditioning mechanisms and feeding

### 2.1. Learned associations

Learning about the relationships between food-related cues (e.g., visual, olfactory, and gustatory) and postingestive consequences undoubtedly influences feeding behavior. Powerful demonstrations of this are found in rodent models of conditioned taste aversion/avoidance (CTA) learning [10], in which animals will subsequently avoid or reject neutral or preferred flavor cues that have been paired with visceral malaise, commonly induced experimentally by noxious agents such as lithium chloride. Similarly, neutral flavors can be conditioned to be subsequently preferred through pairing with intragastric nutrient infusion [11–14]. Conditioned aversions and preferences involve the formation of learned associations between conditioned stimuli, or CSs (flavors), and unconditioned stimuli, or USs (postingestive malaise or nutrient absorption).

The modern environment in Western industrialized countries is flooded with food-related cues such as fast food signs, television commercials, catchy logos and images on food packaging, vending machines, etc. Human studies show that food intake can be elevated by experimentally manipulating food-relevant external cues, including the time/clock [15] and meal vs. snack-related cues (e.g., ceramic vs. paper plates) [16,17]. Evidence from animal models also shows that the presence of conditioned food-associated cues can stimulate feeding. Weingarten demonstrated that discrete stimuli (e.g., tones, lights) previously paired with access to a meal when rats were food restricted would later stimulate increased eating even when the rats were food-sated and would not otherwise eat [18]. Petrovich et al. developed a similar "cue-potentiated eating" paradigm in which food-deprived rats were trained in conditioning boxes with discrete cues that signal either food access (CS+) or no food access (CS−) [19]. When the rats were later tested in a nondeprived (food-sated) state, presentation of the CS+ evoked elevated feeding compared to the CS−. In a series of studies this lab elucidated part of the neuronal circuitry that mediates this phenomenon [19–22], which includes neuronal communication between the basolateral amygdala (BLA) and lateral hypothalamus (LH) [see [23,24] for reviews]. It is unclear whether this type of cue-driven feeding phenomenon is augmented in obese and obesity-prone individuals, as has been suggested by Schachter [25] and others [26,27], and whether pharmacological treatments targeting specific neurohormonal systems have the potential to alleviate obesity and hyperphagia by reducing the ability of conditioned cues to drive excessive food intake.

### 2.2. "Reward"-driven feeding

It is clear that some foods are more sought after and enjoyable than other foods, and are hence more likely to be consumed independent of need or hunger. Which foods are more reinforcing/rewarding than others is a dynamic individual-specific state modulated by physiological status (e.g., hunger, overall health), recent consumption history (e.g., sensory specific satiety), previous experience (e.g., CTA), and various other factors [28]. The neuronal system mediating the hedonic aspects of consumption begins in the brainstem, as illustrated by pioneering work from Grill and Norgren showing that the isolated brainstem is capable of eliciting basic appetitive (e.g., ingestion) and aversive (e.g., rejection) facial expressions to sweet and bitter tastes [29]. Hedonic "liking" of certain tastes and foods is thought to be largely mediated by opioid peptide signaling in a distributed CNS network including hindbrain, midbrain, and forebrain regions, such as the nucleus tractus solitarius (NTS) [30], the nucleus accumbens (NAcc) [31–33], the amygdala [34,35], the ventral tegmental area (VTA) [36], and hypothalamic nuclei [LH, paraventricular hypothalamus(PVH)] [34,35]. Activation or blockade of CNS opioid receptor signaling can increase or decrease feeding even for foods that are considered bland and not palatable (standard lab chow) [37–39]. However, for the most part, results support the hypothesis that opioid effects on feeding are larger with preferred foods [40–45], which for both humans and animal models are typically foods that contain fats and/or simple (mono- and di-saccharides), sweet carbohydrates.

A related construct associated with feeding that is linked with brain "reward" circuitry is incentive motivation (i.e., wanting) in which cues associated with rewarding foods can act as incentive motivators for food independent of basic homeostatic drive (e.g., hunger) [46,47]. The neurotransmitter dopamine (DA) is a critical player in the neurochemical controls of incentive motivation. The mesolimbic/mesocortical DA neurons originate in the midbrain (substantia nigra and VTA) and project to the NAcc, prefrontal cortex (PFC), hypothalamus, and amygdala (see [48] for review). The mesolimbic DA system regulates neuronal processing of natural rewards such as feeding and sex, as well as pharmacological stimuli (addictive drugs) that hijack this system [49,50]. Intake of a preferred food increases DA levels in the NAcc [51,52]. Further, pharmacological manipulations that increase DA signaling in the NAcc (e.g., dopamine receptor agonists, amphetamine, etc.) increase the extent to which an animal will work for food in operant lever pressing paradigms [53,54], yet typically do not alter total food intake in a free-feeding situation [53]. According to Berridge [48], environmental cues associated with appetitive reinforcement induce burst-firing and phasic DA release in the mesolimbic DA system, which in turn increase goal-directed behavior. Interestingly, the mesolimbic DA control of incentive motivation for food reinforcement is modulated by an array of neurohormonal signals relevant to energy balance, particularly leptin and ghrelin, a topic reviewed in detail elsewhere [55–57].

The neuronal systems and neurochemical players mediating the overconsumption of palatable foods are well-investigated, yet the underlying cognitive mechanisms remain poorly understood. Given that previous experience with food undoubtedly influences which types of foods are more preferred, most clearly illustrated by the fact that saccharine and sucrose can easily be conditioned to be aversive [58,59], learning and memory principles may offer some insight regarding the cognitive/psychological mechanisms underlying overconsumption of

palatable foods. From a learning theory perspective, the magnitude of the reinforcer (e.g., US magnitude) is one of the most important determinants of learning, influencing the rate at which learning occurs as well as the asymptote, or maximum level of conditioning possible [60–62]. Some foods (e.g., sweeter foods) appear to inherently have a greater reinforcing capacity than others, supported by findings from Sclafani's lab showing a direct relationship between sucrose concentration and the amount of operant licks to obtain sucrose in a progressive ratio reinforcement schedule [63]. Consumption of these more reinforcing foods represents a stronger US, perhaps due in part to greater elevations in endogenous CNS opioid signaling and altered mesolimbic DA neuronal firing during or following consumption. Compared with bland foods, which represent a weaker US, these palatable foods are more easily and strongly conditioned to environmental cues (increased learning rate and asymptote). Based on this stronger learned 'CS–US' association, exposure to environmental cues linked with palatable food therefore evokes a more powerful US memory and triggers greater procurement and consumption of these foods relative to cues linked with bland foods. Within this framework, environmental stimuli associated with palatable, preferred foods are particularly adept at having stimulus control over feeding behavior based on more powerful learned associations (e.g., golden arches of McDonald's).

These learning principles can account for how some foods (preferred foods) acquire and maintain greater stimulus control over food-directed behavior compared to less preferred foods; yet, reinforcement principles do not offer insight into the mechanisms underlying why/how some foods are *initially* more preferred (i.e., more reinforcing) than others. Unfortunately constructs such as reinforcement, reward, motivation, and palatability offer no real explanatory potential regarding psychological principles underlying the phenomenon that some foods are over-consumed to a greater extent than others. Further complicating our understanding of reward-based feeding and overconsumption is the fact that which specific foods are preferred relative to others is individual-specific and extremely dynamic.

## 3. Higher-order learning processes and feeding

### 3.1. Modulatory control of learned associations

While the learned CS–US associations produced from conditioned flavor aversion/preference and cue-potentiated feeding training yield powerful alterations in feeding behavior, animals encountering food in the natural environment are not allowed the luxury of making decisions about feeding behavior based solely on approach vs. avoidance of preferred or nonpreferred foods. Rather, decisions about whether to feed or not to feed, or about the continuation vs. cessation of an ongoing meal are made within the framework of a larger context. Contextual factors that influence feeding decisions include *external* environmental context cues, such as the presence or absence of predators and the location and accessibility of food, etc. In addition to these types of physical background cues, feeding behavior is also modulated by *internal* contextual cues, which can include interoceptive signals informing about general health, overall energy balance status (e.g., circulating nutrients, adipose reserves), and those that relate to ongoing and recent nutrient consumption and absorption (i.e., satiation and satiety cues) [64,65].

Contextual stimuli play a modulatory role in influencing conditioned behavior in the sense that contexts do not always have a direct stimulatory (or inhibitory) influence on responding, but rather modulate the ability of other cues (e.g., discrete cues) to evoke conditioned responding [66–69]. One manner in which internal contextual cues influence *feeding* behavior is by modulating the mnemonic strength of learned CS–US food-related associations, or put differently, by modulating how effectively food-associated cues (CS) evoke food memory and subsequent food-directed responding (conditioned response, or CR) [64,65]. Within this framework, the presence of neurohormonal signals that inform about sufficient long-term energy status, such as the adipostat hormone leptin [70], and signals informing about recent or ongoing nutrient ingestion, including the gastrointestinally-derived hormones cholecystokinin (CCK) [71] and glucagon-like peptide-1 (GLP-1) [72], will reduce the effectiveness of food-associated cues to evoke food procurement and consumption. On the other hand, ghrelin, a gut peptide which increases food intake via activation of CNS growth hormone secretagogue receptor (GHSR) [73], will presumably *increase* the strength of food-related CS–US associations. Thus, the internal milieu of hormonal and metabolic signals informing about energy status modulates how effectively environmental cues associated with food reinforcement (e.g., fast food sign) will trigger the procurement of food.

The notion that neurohormonal signals provide an internal context that modulates food-directed responding is supported by studies employing the deprivation intensity discrimination paradigm developed by Davidson [69,74]. In this paradigm rats are trained to use a high (24 h) or low (0 h) level of food deprivation as discriminative internal cues for a food reward. Rats receive one of two contingencies: 1) a food reward is given on 24 h but not 0 h food-deprived training days (24+ contingency), or 2) the opposite contingency (0+; food only on 0 h deprived days). Discrimination learning is shown as heightened anticipatory appetitive responding (e.g., food cup approach) on rewarded compared to nonrewarded deprivation state conditions. In rats trained in this paradigm, peripheral CCK or leptin administration produced internal contextual cues that generalized to an energy replete state [75], whereas peripheral and ICV ghrelin [76], but not ICV administration of the orexigenic hormone, neuropeptide Y (NPY) [77] produced internal context cues that generalized to an energy deprived state. An important point derived from these studies is that exogenous administration of these peptides does not simply drive appetitive responding in a general direction consistent with known anorectic/orexigenic properties (e.g., leptin reduces appetitive responding, ghrelin increases). Rather, the ability of leptin or ghrelin to influence appetitive behavior depends on previous learned relationships between internal context cues and food access. This notion is best exemplified by the fact that leptin *increased* appetitive responding in rats trained with the 0+ contingency, yet it decreased responding for 24+ trained rats [75], whereas ghrelin produced the opposite pattern [76]. In other words, leptin and ghrelin modulate food procurement based on conditioned/learned mechanisms rather than simple unconditioned approach vs. avoidance of food. The idea that learning has a profound influence on the nature through which energy status cues guide feeding behavior is further supported by work from Dickinson and Balleine (e.g., [47,78,79]) showing that the ability of a food deprivation or repletion state to influence operant responding for food reinforcement is highly dependent on whether the animals had previously consumed the specific food reinforcer under that deprivation (or repletion) state.

In a free-feeding situation, the internal hunger or satiation/satiety context influences feeding by increasing or decreasing, respectively, how effectively environmental food-associated cues trigger food procurement and consumption. This occurs through mechanisms akin to a type of modulatory associative learning process known as occasion setting, in which stimuli (discrete or contextual) modulate the strength of CS–US learned associations. This model of food intake control has been presented in detail elsewhere [64, 65, 80, 81]. The take-home point is that the internal energy status context, which is largely derived from vagally mediated, as well as circulating meal and adiposity-related neurohormonal signals, controls feeding based on learned relationships between environmental food cues and food-based reinforcement, rather than *unconditionally* influencing approach vs. avoidance of feeding relevant behaviors.

### 3.2. The Hippocampus and modulatory control of feeding

The hippocampus is a brain structure that is strongly linked with contextual learning and memory processes [82]. Regarding external contextual cues, an abundance of data demonstrate that the hippocampus is critical for integrating learned information with representations of the spatial external environment [83–85]. All regions of the hippocampus contain populations of place-modulated neurons with distinct firing fields depending on an animal's precise location within a larger contextual realm [86,87]. Further, selective damage to the hippocampus in animals produces profound impairments in spatial learning and memory task such as the Morris water maze, and in paradigms such as contextual fear conditioning that involve incorporating external contextual information into learned associations (see [88,89] for reviews). This type of spatial/external contextual hippocampal-dependent learning has relevance to food procurement, which is evident from lesion studies showing that selective hippocampal damage either increases or decreases (depending on which subregion is lesioned) learning a "place preference" for a context paired with food access [90]. Further, hippocampal lesions impair learning and retention of spatial food location in a radial arm maze paradigm [91], in which rats learn which of various arms in an elevated maze are consistently baited with food based on external visuospatial cues located outside the maze.

The hippocampus is also critical for memory processes involving the utilization of internal contextual information. For instance, selective neurotoxic hippocampal lesions impair the ability of rats to use interoceptive cues arising from different levels of food deprivation to guide food-directed behavior in the deprivation intensity discrimination paradigm described above [92–94]. Similarly, Kennedy and Shapiro observed that the pattern of hippocampal (CA1 cell field) neuronal firing is dependent upon previous learned relationships between external and internal (food or water deprivation) contextual cues [95]. In humans, amnesic patients with hippocampal damage will consume a second meal immediately after consuming a full meal, and do not appropriately adjust hunger/satiety ratings following a meal [96–98]. This suggests that these amnesic patients are impaired in detecting and utilizing internal satiation cues (including stomach distention, changes in circulating nutrient and hormone concentrations, etc.) arising from recently consumed nutrients. Higgs and colleagues provided data indicating that this phenomenon may also be based on impaired episodic memory for recent eating episodes [99,100].

Evidence has been quickly amassing over the past decade that hippocampal-dependent processes involving the integration of internal energy status relevant signals with learned information is critical for the normal control of feeding behavior (see [64,65,80,81] for reviews). Human and rodent imaging studies show that the hippocampus is activated following food consumption [101–103] and by experimental manipulations that mimic aspects of nutrient intake, including gastric distention [104] and gastric electrical stimulation of the vagus nerve [105], the primary sensory conduit of information communicated from the gastrointestinal tract to the brain. Studies from rodents employing selective neurotoxic hippocampal lesions also support a role for this structure in food intake control. Relative to intact controls, hippocampal-lesioned rats show increased appetitive responding (e.g., lever pressing for food, food cup approach) when they are food-sated [106–108], increased meal frequency [109], and increased overall energy intake and body weight gain [65,92,110]. Thus, one role of the hippocampus in the control of food intake appears to involve anorectic/inhibitory control. Given that the hippocampus integrates and utilizes interoceptive signals relevant to energy status, it stands to reason that neurohormonal players involved in feeding behavior may signal in the hippocampus to influence food-directed behavior and energy intake.

### 3.3. Neurohormonal signaling in the hippocampus and feeding

The hippocampus contains receptors for several hormonal signals of relevance to energy status, including leptin [111,112], ghrelin [113,114], GLP-1 [115], and insulin [116,117]. Previous work has shown that all of these hormones improve hippocampal-dependent spatial or contextual learning (using nonappetitive memory paradigms), and also facilitate molecular and cellular processes that are thought to underlie memory formation (e.g., long-term potentiation, neurogenesis) [118–126]. However, these reports did not address the possibility that these energy balance relevant signals influence *feeding* behavior through signaling in the hippocampus. In a recent study our lab examined the role of leptin signaling in the hippocampus in food intake and in memory processes related to food procurement [127]. Results showed that doses of leptin that are without intake effects when given ICV reduced 24 h food intake and body weight in rats when administered directly to either the dorsal region of the hippocampus (DHPC), which is most strongly linked with spatial learning, or the ventral hippocampus (VHPC), which is most strongly linked with learning processes that have a motivational or emotional component (see [128] for review of dorsal/ventral hippocampal function). Intake suppression was notably larger following VHPC relative to DHPC leptin delivery, ranging between ~11–15% compared to 6–10% suppression, respectively. Other findings from this study demonstrated that VHPC (but not DHPC) leptin administration reduced the expression of a conditioned place preference for a location/context previously associated with food reinforcement, and reduced latency to run for food in a runway paradigm. These results suggest that leptin signaling in the VHPC may be reducing food intake via downstream signaling in brain regions associated with reward/motivational processing. This, notion is consistent with neuroanatomical data showing that the VHPC projects directly to, and in some cases receives direct projections from nuclei embedded within the brain reward circuit, including the VTA [129,130], NAcc [131,132], LH [133], amygdala [134,135], and PFC [136].

VHPC leptin signaling may also reduce appetitive and consummatory behavior by modulating which types of environmental cues are learned about and remembered. Leptin administered to the VHPC after rats learned the spatial location of food in an elevated plus maze paradigm blocked memory consolidation for the spatial location of food (assessed 7-days later in a retention test), whereas VHPC leptin had no effect on memory consolidation of an appetitive nonspatial response task [127]. However, Farr et al. [120] using a comparable dose of leptin demonstrated that post-training dorsal hippocampal leptin administration *improved* memory consolidation for a task that requires animals to associate a context with an aversive US (foot shock). That leptin can both decrease and increase memory consolidation depending on the type of reinforcement and the hippocampal subregion suggests that leptin signaling in this brain structure modulates what types of environmental cues are learned about and remembered, reducing resources invested into learning about food-relevant cues in favor of other cues when energy reserves are sufficient and endogenous leptin levels are elevated.

The food intake-stimulatory gut peptide ghrelin also appears to influence food intake through signaling on its receptor (growth-hormone secretagogue receptor, or GHSR) in the hippocampus. Preliminary unpublished data from our lab show that ghrelin administered to the VHPC, but not DHPC stimulates food intake in rats during a period when rats normally are not eating (during the light cycle). The mechanisms through which hippocampal ghrelin signaling stimulates feeding remain to be established. Data from both humans [137,138] and animal models [126,139,140] are consistent with the notion that ghrelin increases food intake by acting as a signal for meal initiation. Given that the hippocampus is necessary for utilizing interoceptive energy status cues to modulate food-directed/appetitive responding, and given that hippocampal damage profoundly increases meal frequency [109],

GHSR signaling in the hippocampus may modulate feeding by increasing how effectively environmental cues trigger food-related memories and stimulate meal initiation.

## 4. Obesity: A learning and memory problem

### 4.1. Environmental food cues and obesity

As discussed above, exposure to external food-associated cues can increase feeding in both human and animal models under experimental conditions. This phenomenon may also contribute to hyperphagia and obesity in the normal environment by either, 1) stimulating extra meals or snacks, and/or 2) directing meals and snacks towards foods that are more energy dense and reinforcing. A recent study from Duffey and Popkin suggests that the former possibility may be a contributing factor [141]. They reported that since the late 1970s, which is approximately when the slope of obesity prevalence began to dramatically shift upwards [142], average per capita energy intake in the USA has risen by approximately 570 kcal/day. To elucidate what is driving the increased intake, the authors utilized cross-sectional survey data to evaluate the contribution of changes in energy density, portion size, and number of eating occasions (meals or snacks). They reported that the increase in overall energy intake observed between the late 1970s and mid 1990s was attributable to both increased portion size and increased number of eating occasions. However, from the mid 1990s to 2006, portion size no longer contributed to increased overall energy intake, whereas increased number of eating occasions continued to have a large contribution (+ ~39 kcal/day). While this type of cross-sectional national survey analysis is limited in regard to establishing direct causal factors, their findings highlight increased number of meals and snacks as being an important variable correlated with the sharp rise in obesity prevalence seen across the past few decades. The increase in meal and snack frequency observed since the late 1970s (+ ~1.1 eating occasions [141]) is likely based, in part, on the heightened prevalence of cues in Western cultures that are associated with energy dense foods. In fact, the number of fast-food restaurants [143] and money spent on fast-food advertising [144] in the USA have more than doubled since this time, as has the number of television commercials that advertise foods with minimal nutritional value (e.g., candy, cereal, and fast-food) [145].

The greater prevalence of environmental cues linked with rewarding foods does not necessarily predict increased hyperphagia and meal/snack frequency, as higher-order brain regions involved with learning and cognitive function, including the hippocampus, should exert inhibitory control over the ability of these cues to stimulate feeding at inappropriate times and/or when energy reserves are sufficient. However, recent studies show that dietary factors that are particularly prevalent in modern Western diets, including simple carbohydrates (mono and disaccharides) and saturated fatty acids (SFA), disrupt hippocampal function, which in turn may reduce the effectiveness of anorectic neurohormonal signals (e.g., leptin) to negatively modulate food procurement and consumption.

### 4.2. Western diets impair learned controls of feeding

Obesity and Type II diabetes mellitus are both strongly linked with cognitive impairment and dementia (see [146,147] for reviews). Recent findings show that specific dietary factors can also produce cognitive impairment, in some cases independent of their effects on body weight gain and obesity. Human population-based prospective studies show that high intakes of SFA, but not total fat, over several years leads to a greater risk for the development of Alzheimer's disease and mild cognitive impairment [148–150]. A recent study reported that human subjects with high self-reported levels of saturated fat and refined sugar intake are impaired in memory problems (particularly hippocampal-dependent memory) relative to subjects reporting less saturated fat and refined sugar intake [151]. These findings are corroborated by reports in rats, showing that maintenance on a high SFA diet, but not a diet high in unsaturated fatty acids, impairs learning and memory function [152]. Research from rodent models also shows that long-term intake of fructose, a simple monosaccharide common in Western diets, can produce hippocampal insulin resistance and impair hippocampal-dependent memory function [153,154]. Further, excessive sucrose intake in rats disrupts hippocampal function independent of dietary fat intake [155].

A series of studies by Kanoski et al. examined the effects of Western diet (one containing high SFA and glucose) intake in rats on learning and memory processes that differ in sensitivity to hippocampal damage. Results show that simple conditioning processes (e.g., formation of CS–US associations) that do not require an intact hippocampus are minimally affected by long-term (> 90 days) maintenance on a Western diet. However, higher-order modulatory learning processes that do rely on the hippocampus, such as a negative occasion setting task where a discrete stimulus signals when another stimulus will not be followed by food reinforcement, are profoundly impaired by Western diet maintenance [156,157]. Importantly, the impairment was expressed as *increased* appetitive responding to conditioned cues on nonreinforced trials, suggesting that the Western diet consumption disrupted learned inhibitory/anorectic control of appetitive responding. Another study demonstrated that hippocampal-dependent spatial memory function, assessed in an appetitive radial arm maze task, is impaired after as little as three days of consuming a Western diet, whereas for the same rats it took a much longer-term maintenance period (more than 60-days) to disrupt nonspatial memory processes that do not rely on the hippocampus [158]. Thus, hippocampal-dependent learning and memory processes, including those involving modulation of feeding behavior, are particularly susceptible to disruption by intake of SFA and simple sugars, a finding that is consistent with the notion that this brain region is especially vulnerable to various disease and age-related insults [159]. Disruption of hippocampal inhibitory control over behaviors directed at obtaining food can yield further overconsumption of the same foods that contributed to hippocampal dysfunction in the first place, a "vicious circle" model of energy dysregulation that has also been discussed elsewhere [64,65,81,110,156,160].

The neurophysiological mechanisms underlying diet-induced impairment in hippocampal function include (but are not limited to) reductions in hippocampal levels of brain-derived neurotrophic factor (BDNF) [156,161], impaired blood–brain barrier integrity (increased permeability, reduced expression of tight junction proteins, impaired BBB leptin transport) [157,162], elevated levels of circulating triglycerides and cholesterol [163,164], and neuronal insulin resistance in the hippocampus [165,166] (see [160] for review). Western diet-induced hippocampal dysfunction may also involve impaired leptin (LepRb) and ghrelin (GHSR) receptor signaling in this brain region. LepRb "resistance" occurs in the hypothalamus in diet-induced obese rodents, which is evident from behavioral (reduced anorectic effects of CNS leptin delivery) and molecular (reduced leptin-induced activation of phosphorylation of the signal transducer and activator or transcription, or PSTAT-3) measures (see [167,168] for reviews). Obese rodents also show GHSR resistance, illustrated by a blunted food intake increase following peripheral ghrelin administration [169] and reduced CNS ghrelin-induced activation of NPY/AgRP neurons in the hypothalamus [170]. Yet unknown is whether Western diet-induced impairments in hippocampal-dependent modulatory control over appetitive behavior is based, in part, on LepRb and/or GHSR resistance in this brain region.

## 5. Conclusions

The hyperphagia driving obesity undoubtedly involves neuronal processing in extra hypothalamic and extra hindbrain "higher-order" brain regions that control learning and cognitive processes.

The dramatic elevations in food intake and obesity prevalence in the USA since the late 1970s are partially attributed to increased per capita daily number of meals and snacks consumed since that time [141]. This phenomenon may be based on increased pervasiveness of environmental cues associated with energy dense, yet nutritionally depleted foods. The hippocampus is a brain region that functions to modulate the effectiveness of food-related cues to stimulate food procurement and consumption via the detection and utilization of neurohormonal signals of relevance to energy balance. This type of modulatory control is disrupted by dietary factors common in modern Western diets, including simple carbohydrates (mono- and disaccharides) and saturated fatty acids. Thus, consumption of these dietary factors can have a detrimental impact on modulatory learning processes that normally function to curb excessive energy consumption. Research targeting obesity treatment will benefit from deeper understanding of the influence of dietary and environmental factors on the neuronal systems that control non-homeostatic food intake control.

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