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Do Diet and Obesity Reprogram the Hippocampus Via Epigenetic Mechanisms?

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Abstract

Obesity may be viewed as disease state in which both the body and mind have been inappropriately programmed.Cycles of weight loss and regain experienced by obese individuals emphasize the behavioral aspects of the problem.This article builds from the premise that diminished activities in the hippocampus contribute to hyperphagia and obesity, because this region of the brain normally exerts restraint on overeating.The hippocampus appears to control the memory of and the emotional response to a meal; its time, size, and duration; and is well connected to other brain structures known to have a direct influence on hunger and satiety. Preliminary analysis of research in this area suggested the working hypothesis that"Obesity and diet reinforce aberrant eating behavior in part by the epigenetic reprogramming of hippocampus functions."A synthesis of data from brain imaging, physiological, molecular, genetic, epigenetic, and behavioral studies in humans and/or rodent models was used herein to test this hypothesis. Similar to physical damage, high fat and high calorie diets and obesity induce changes gene expression in the hippocampus and maythey cause physical damage. The resulting changes in behavior support hyperphagia and/or alter metabolic function, resulting in weight gain and continued obesity. Initial experimental evidence, most of it indirect, suggests that neurons in this region of the brain have been epigenetically reprogrammed to produce these states of altered gene expression, but we currently only have a hint at the extent and quality of these changes. Limitations and approaches to the future dissection of this hypothesis and its relation to obesity research and therapeutics are discussed.

Gene Abbreviations:

BDNF	:	Brain-Derived Neurotrophic Factor
DAT	:	Dopamine Active Transporter
GR	:	Glucocorticoid Receptor
IKBA	:	Nuclear Factor of Kappa Light Polypeptide Gene Enhancer in B-Cells Inhibitor, Alpha
IL6	:	Interleukin 6
INSR	:	Insulin Receptor
MC4R	:	Melanocortin 4 Receptor
MKP1	:	Mitogen-Activated Protein Kinase Phosphatase-1
MOR	:	M-Opioid Receptor
MR	:	Mineral corticoid Receptor
NFKB	:	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NPY	:	Neuropeptide Y
POMC	:	Pro-Opiomelanocortin
SIRT1	:	Sirtuin 1
SYNI	:	Synapsin I
TH	:	Tyrosine Hydroxylase

Other Abbreviations:

5hmC	:	5-Hydroxymethylcytosine
5mC	:	5-Methylcytosine
APP	:	Amyloid Precursor Protein
BMI	:	Body Mass Index
CAMK2:		Calcium/Calmodulin-DependentProteinKinaseII
CNS	:	Central Nervous System
CREB	:	Camp Response Element Binding Protein
fMRI	:	Functional Magnetic Resonance Imaging
GM	:	Grey Matter
H3K9	:	Histone 3 Lysine 9 Position

HDAC	:	Histone Deacetylase
HED	:	High-Energy Diet
HFD	:	High-Fat Diet
HPA	:	Hypothalamic-Pituitary-Adrenal
INDELs:		Insertions and Deletions
LTP	:	Long-Term Potentiation
LPS	:	Lipopolysaccharide
MECP2	:	Methyl-Cpg-Binding Protein 2
MRI	:	Magnetic Resonance Imaging
NACC	:	Nucleus Accumbens
NSE	:	Neuron-Specific Enolase
PFC	:	Prefrontal Cortex
PTM	:	Post-Translational Modification
PVN	:	Par Ventricular Nucleus
SNP	:	Single Nucleotide Polymorphism
TET	:	Ten-Eleven Translocase Methyl Cytosine Dioxygenase
VTA	:	Ventral Tegmental Area
WM	:	White Matter

Introduction

There has been an epidemic increase in global rates of obesity over the last 30 years. For example, according to current United States current statistics, more than one-third of American adults have obesity[1]. Current efforts to prevent or reduce obesity by diet, exercise, education, surgery, and drug therapies are failing to provide effective long-term solutions to this epidemic suggesting we have much to learn about the disease.Without denying the importance of genetics, purely genetic models relying solely on genetic polymorphisms in the human population do not appear to account for the occurrence of the disease in such large diverse populations. There is also a growing awareness that the influence of alterations in the Central Nervous System(CNS) on eating behavior and metabolism further complicate the obesity problem.Epigenetic models better accommodate some of the influences of the environment, CNS-controlled behavior, and age on reprogramming gene expression and the seemingly stochastic display of obesity-related disease symptoms over time in the adult brain[2-5]. Our goal with this synthesis and review is to stimulate more research focused on altered epigenetic controls in the hippocampus in particular, hippocampal dysfunction, and obesity.

Obesity and Diet Result in Physical and Functional Alterations in the Hippocampus

The hippocampus is a brain structure long recognized for its role in learning and memory.A critical function of the hippocampus is to form episodic memories, recording the "What, when, and where" of experiences and events.What does this mean in the context of food intake? Evidence shows that pharmacological disruption of hippocampus function affects the timing and size of subsequent meals [6,7](Figure 1).

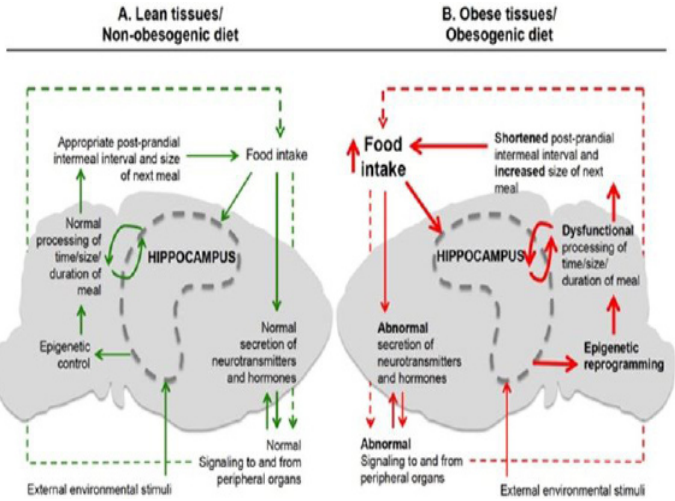

Figure 1: Involvement of the hippocampus in the cycle of food intake and the interplay of diet and obesity.

In one study, following bilateral excite toxic lessoning of the hippocampus, rats showed a marked increase in meal frequency and a decrease in meal size [6]. In a more recent study, infusion of the $GABA_A$ agonist muscimol into the hippocampus also increased meal frequency, but increased the size and duration of the next meal, in rats [7]. Both studies show that proper functioning of the hippocampus is required to maintain meal patterning in rodents, specifically to delay consumption of the next meal.Data from the historical patient H. M. and other humans suffering from temporal lobe damage reveals aberrant meal patterning in these individuals as well, who report altered perceptions of hunger and satiety and who cannot remember having just eaten and will eat another meal right away if offered [8,9]. It is clear that memories regardingpast and recent eating experiences play into our decisions about what and when to eat next, as well as how much, and so should provide insight into the etiology of overeating and obesity.

Human brain imaging studies provideinteresting evidence regarding how thebrain is activated in response to information about food as well as the effects of obesity on the human brain.1.After viewing high calorie food images, functional Magnetic Resonance Imaging (MRI) revealed that human subjects with largest waist measurements showed the most significant activation of the hippocampus [10]. 2. Human subjects that are told to simply imagine a food craving show increases in hippocampal Blood-Oxygen-Level Dependent (BOLD) signal relative to hippocampal activity, compared to when they are told to imagine a less appealing food [11].This hippocampal response was similar to that observed

in cravings for addictive drugs such as cocaine, making the obvious implication that overeating may be an addictive phenotype.In addition, a number of studies also suggest that obesity damages the hippocampus.3.Waist to hip ratio, a positive measure of obesity, negatively and significantly correlates with hippocampal volume [12]. 4. Morph metric measurements show that when obese, overweight, and normal-weight individuals are compared, increasing BMI negatively correlates with total Grey Matter (GM) volume and White Matter (WM) volume in the brain (p= 0.001) and this negative linear correlation is particularly strong for the hippocampus (r = -0.31)and orbital frontal cortex (r = -0.31) [13]. In other words, these two studies suggest that the hippocampus is reduced in size in most obese individuals. 5.Even studies on a more defined group, individuals with Type II Diabetes Mellitus, show that those with high levels of visceral adipose tissue and high BMI have a significant decrease in hippocampal volume relative to those with normal levels of visceral adipose tissue and lower BMI [14]. These first three MRI studies leave open the question of what mechanisms reduce the size of the hippocampus. 6.WhenMRI analysis of brain GM density is compared between the brains of overweight/obese subjects and those of normal BMI there is a negative correlation between BMI and hippocampal GM density and a positive correlation of BMI with serum levels of Neuron-Specific Enolase (NSE)[15], an enzyme normally present in neuronal cell cytoplasm and when found elsewhere, a marker that can be used as a proxy for neuronal cell death.Because reduced hippocampal GM density is significantly associated with increased serum NSE levels, these data suggest that loss of GM density could result from neuronal cell death.

Rodent studies addressing the topic of diet-induced obesity and consumption of aHigh-Fat Diet (HFD) or High-Energy Diet (HED, defined as high fat/high sugar) provide further evidence of hippocampal dysfunction in this state.In tests designed to study hippocampal-dependent memory, such as the Morris water maze, the radial arm maze, novel object recognition test, tests of spontaneous or variable-interval delayed alternation, and contextual conditioning, rodents fed HFDs or HEDs perform worse than their chow, or low-fat-fed, counterparts [16-28]. Several of these studies point to specific diet- or obesity-inducedmolecular perturbations to explain the observed deficits, such as leptin signaling deficiency [27], insulin resistance [22,26], reduced dendritic spine density and reduced Long-Term Potentiating (LTP) [23,26], reductions inmolecules positively associated with LTP and neuronal plasticity such asBrain-Derived Neurotrophic Factor (BDNF)[20,26] and reline [24], detrimental effects on the blood-brain barrier in the vicinity of the hippocampus [17,21], and high levels of lipid in the plasma and liver [16,25]. Results from these studies suggest that HFDs, HEDs, and obesity diminish hippocampal function.

Within the brain the hippocampus is well poised for being responsive to and influencing food intake. The hippocampus formation lies in the brain's temporal lobe and includes the dentate gyros; the CA3, CA2, and CA1 fields; and the cubiculum.The hippocampus is richly connected with other areas of the brain involved in food intake, such as the hypothalamus, bed nucleus of the strainterminals, amygdale, ventral striatum, lateral septum, amygdale, and the olfactory and insular cortices [29]. In addition, the hippocampus contains receptors for numerous feeding-related hormones and adipose tissue-derived signaling molecules such as lepton [30], insulin [22], and gherkin [31]. These data further support that the hippocampus plays a role in injective behavior and should be considered a major player in the study of obesity.See the reviews by Davidson, Kano ski, Parent, and Bassinette for more evidence to support this point [17,32-34].

Epigeneticat Play in the Hippocampus

Not only is the hippocampus critically involved in food intake, it is a central player in the study of epigenetic reprogramming in the brain.Modification of the epigenome occurs at a level above the basic genetic code and involves chromatin modifications such as DNA methylation, histone methylation and/or acetylation, nucleosome repositioning, and RNA interference.Environmental inputs and experiences modify the epigenome to allow the expression or repression of certain genes.Many recent publications in the field of epigenetic have focused on the role of epigenetic in learning and memory.Sir Francis Crick first proposed an epigenetic mechanism for memory in a letter to Naturein 1984 [35] and more than 30 years later, we are beginning to realize the truths in his hypothesis [36]. The remainder of this section will focus on the interactions between environmental stimuli and how these events are recorded by changes to chromatin in the hippocampus, but for some nice reviews on the epigenetics of learning and memory [5,36-39].

A variety of environmental stimuli are able to induce epigenetic events in the hippocampus.1.Stressors such as social defeat or physical restraint activate the sympathetic nervous system and the Hypothalamic-Pituitary-Adrenal (HPA) axisto produce behavioral alterations, such as enhancing social avoidance and anhedonia and changing eating patterns[40,41].Rats exposed to a social defeat stress exhibited increased depressive-like behavior and had different hippocampal histone acetylation profiles when compared to their unstressed peers[42].Just 30 minutes following the social defeat stress, histone H3 became hyperacetylated in the hippocampus, an effect that increased during the 24 hours following the stress and then returned to baseline levels after 72 hours.No effects of stress were seen in the amygdala or Prefrontal Cortex (PFC) in this study.Psychosocial stress has been shown to differentially affect BDNF methylation in functional poles of the hippocampus, increasing methylation in the dorsal CA1 (with a concurrent reduction in BDNF mRNA) and decreasing methylation in the ventral CA3[43], while restraint stress increased hydroxymethylation in the Glucocorticoid Receptor (GR) gene in the hippocampus[44].2.Enriching the living environments of rodents by theaddition of tunnels, running wheels, or differently colored or textured toys to their home cages [45] or by exposure

to these stimuli during defined sessions [46], can also affect the hippocampal epigenome, altering histone lysine methylation at BDNF promoters (and increasing BDNF mRNA levels) [45] and preventing aging-induced hydroxymethylation in genes important in axon guidance, learning, and memory [46]. 3. Along similar lines, voluntary exercise induced several epigenetic changes in the hippocampi of rats.These data are presented in Section D.

Obesity and Diet Reprogram the Brain Via Epigenetic

Much of the epigenetic machinery requires certain dietary nutrients for activity and there is clear evidence that diet and obesity have the ability to epigenetically reprogram many cell types [4,47-49]. Specifically, in the brain, most of the current literature on HFD intake and epigenetic focuses on the hypothalamus and on brain reward pathways, understandably, due to their long-recognized role in consumptive behaviors.1.In the hypothalamus, HFD intake has been associated with altered DNA methylation patterns in the genes for Neuropeptide Y (NPY)[50,51], Pro-Opiomelanocortin (POMC)[50-52], Dopamine Active Transporter (DAT)[51,53], and the precursor for dopamine, Tyrosine Hydroxylase (TH)[53]. These changes are negatively correlated with transcription of these genes where tested.Interestingly, animals consuming HFD exhibit hyperphagia despite elevated levels of the anorexigenic POMC and reduced levels of the orexigenic NPY.This discrepancy could be the result of ineffective response of downstream targets. From the accurate nucleus of the hypothalamus, NPY and POMC neurons synapse with neurons in the Para Ventricular Nucleus (PVN) and these peptides can specifically act on Melanocortin 4 Receptors (MCR4s).A study by Widiker and colleagues examined changes in methylation and expression of MCR4 in whole brain following HFD intake and found the gene to be significantly hypo ethylated, however they only detected a marginal increase in MCR4 expression [54].In these animals, increased caloric intake is likely ramping up anorexigenic pathwaysin an effort to maintain energy homeostasis, decreasing NPY and increasing POMC; however, despite these efforts, hyperphagia continues to eventually produce and maintain a state of obesity.

Funato, et al.[55] explored the idea that diet might epigenetically modify normal eating behavior via changes in HDAC (histone deacetylase) expression.Feeding a HFD to mice for four weeks results in the 40% to 60% increase in hypothalamic HDAC5, 8, and 10 expressions and a 40% decrease in HADC4 expression, relative to mice fed a normal diet.Fasting results in 2-fold increases in HDAC3 and 4 expressions and 2-fold decreases in HDAC10 and 11 expressions.These data strongly suggest that a HFD influences epigenetic reprogramming in the hypothalamus.The obesity-related effects on gene expression are not described, but their data on the differences in the direction of HDAC expression changes suggests their role in relevant gene regulation is highly complex. This article goes on to show that for the ventromedial hypothalamus fasting reduces the number of cells that are positive for Histone H3 Lysine 14 Acetylation (H3K14Ac), a Post-Translational Modification (PTM) associated with gene expression that supports memory formation.They did not yet examine these changes when a HFD obese mouse was shifted to fasting, which might be quite interesting in relation to the weight loss/regain paradigm.

Maternal or neonatal overfeeding increases the tendency toward adult obesity, diabetes, and CD, but how is this new metabolic program transmitted to offspring?There is initial support for the idea that overfeeding alters hypothalamic DNA methylation to reprogram gene expression [56]Overfed rats show hypothalamic hypermethylation and silencing of POMC promoter regions necessary for the control of POMC expression by leptin and insulin. As a result, in overfed rats, the POMC epiallele is not appropriately upregulated in the presence of increased leptin and insulin. In other words, these animals are epigenetically reprogrammed to be leptin and insulin resistant.These data from the hypothalamus underscore the need to extend the study of food intake,as well as the search for answers to the problem of obesity, to brain regions with a different set of executive and behavioral controls.

Several studies have looked at the impact of HFD intake on brain reward pathways, focusing on structures such as the Ventral Tegmental Area (VTA), Nucleus Acumens (NACC), and PFC.Data on the epigenetic effects of HFD on DAT in the VTA show a sex-specific response, with HFD resulting in increased methylation/decreased expression in male mice [53,57] and decreased methylation/increased expression in females [57]. Other data show increased methylation/decreased expression of TH in the VTA of male mice [53] as well as increased methylation/decreased expression of the μ-Opioid Receptor (MOR) in the VTA, NAC, PFC, and hypothalamus of male offspring of mice exposed to HFD [58].If we take into account the results from males, it appears that HFD dampens dopamine and opioid signaling.Behavioral reports show consistency with this finding as HFD-exposed animals reduced preference for sucrose over water, a behavior consistent with reward hypofunction [53,57,58]. This section and the previous make clear that environment and experience alter the hippocampal epigenome, and that diet and obesity alter epigenetic marks in the brain.The remainder of this review will address how these activities might interact.

Obesity and Diet Reinforce Aberrant Eating Behavior by Epigenetic Reprogramming of Hippocampal Functions

In spite of the evidence that epigenetic controls hippocampal learning and memory formation and that hippocampal function is essential for normal eating behavior, the current literature only indirectly addresses how epigenetic controls in the hippocampus might oppose or support obesity.Several studies have examined epigenetic events following a contrary treatment:caloric restriction. In one study by Chouliarasand colleagues, male mice were fed 85% or 50% of normal ad libitum consumption of standard mouse chow for 1 or 2 years [59]. As observed previously in whole

brain [60], levels of 5-hydroxymethylcytosine (5hmC) increased in the hippocampus with aging but this increase wassignificantly suppressed by 50% caloric restriction.5hmC, produced by the oxidation of 5-Methylcytosine (5mC) by the enzyme ten-eleven Transcocase methyl cytosinedeoxygenize(TET), is thought to be astable intermediate in the cycle of DNA demethylation. Supporting this theory is evidence that 5hmC is positively correlated with transcription and chromatin accessibility and is enriched in gene bodies of highly expressed genes.Age-associated increases in 5hmC have been specifically linked to genes implicated in neurodegenerative disorders [61,62] and, in one study, a Single Nucleotide Polymorphism (SNP) in CXXC6, the gene that codes for TET1, was associated with the late-onset form of Alzheimer's disease [63]. These findings agree with other evidence of the beneficial effects of caloric restriction on aging-associated diseases [64,65]. Though effects on specific epigenetic marks were not examined, caloric restriction has been shown to induce expression of Sirtuin 1 (SIRT1), an NAD-dependent protein deacetylase involved in the epigenetic-based gene silencing.In addition, there is evidence that diet and obesity rapidly alter the levels or activity of known epigenetic enzymes.In a recent study, we showed that after just 72 hours of consuming a HFD (45% fat by kcal), transcript levels of HDAC4 were increased in the ventral hippocampus of male rats [65]. HDAC4 is co localized with neurons containing orexin, serotonin, oxytocin, and vasopressin, to name a few;is known to play a role in synaptic plasticity;and has been investigated for its role in neurodegenerative disease [66]. Though regulation of HDAC4 is thought to occur via shuttling this protein between the cytoplasm and the nucleus of the cell, the protein itself can be degraded by the activity of Lip Polysaccharide (LPS) or by apoptosis (both of which are upregulated by HFD) [66-68]

A large portion of the current epigenetic literature focuses on the second generation and early life effects of dietary manipulations. There are a number of studies looking at the epigenetic consequences of variations in maternal care, stress, and drugs of abuse in the offspring.Here we sought to focus on direct effects of particular stimuli on epigenetic markers in the adult brain; however, there are a few maternal studies of note that address our hypothesis that "Obesity and diet reinforce aberrant eating behavior by physically damaging and/or by the epigenetic reprogramming of hippocampal functions."In a study by Langie, et al. young mice fed a HFD had differences in the methylation of genes involved in the base excision repair pathway in the hippocampus and decreased activity of this pathway when compared to their low-fat-fed peers [69]. Their data suggest that HFD reduces the ability to carry out efficient repair, with obvious implications for other studies showing HFD is linked to cognitive deficiencies.Changes to the micronutrient profile of the maternal diet also affects in the hippocampi of offspring:a low choline maternal diet resulted in hypo methylation of CpG islands near the promoter region of genes involved in angiogenesis [70], a methyl donor-deficient maternal diet was associated with changes in methylation status at a variety of CpG sites in the neuron tin gene [71], vitamin B_{12}deficiency and omega-3 supplementation both resulted in global hypermethylation in the hippocampus [72], and a maternal diet high in fat soluble vitamins (A, D, E, and K) increased methylation in the gene for dopamine receptor 1 [73], all as measured in the offspring.These studies demonstrate the ability of dietary nutrients to alter chromatin structure in the hippocampus.

Aerobic exercise counters many of the negative health outcomes of obesity. A few studies relevant to our working hypothesis suggest that aerobic exercise enhances hippocampal neuronal plasticity and learning and memory performance in laboratory animals via epigenetic reprogramming. 1. Gomez-Piniella and colleagues found that free access to a running wheel reduced DNA cytosine methylation of the BDNF promoter and increased BDNF mRNA and protein in the hippocampus [74]. This study also reported exercise effects on molecules known to regulate the transcription of BDNF, where voluntary running elevated levels of phosphorylated Methyl-CpG-Binding Protein 2 (MECP2) and reduced levels of Histone Deacetylase 5 (HDAC5) mRNA and protein.In addition, exercise increased acetylation of histone 3 and elevated the phosphorylated forms of calcium/Calmodulin-Dependent Protein Kinase II (CAMK2) and cAMP Response Element Binding Protein (CREB), both of which are known to be involved in the epigenetic regulation of transcription in the brain [75]. 2.One week of exercise significantly increases the hippocampal expression of proteins essential to learning and memory such as BDNFand SynapsinI (SYNI) [75]. In rats, one week of exercise is sufficient to induce DNA cytosine demethylation at one of the four BDNF promoters, which results in increased BDNF transcription in the hippocampus [76]. Treating rats with inhibitors of DNA methylation such as 5-aza-2-deoxycytidine also results in increases in BDNF activity and improved performance in a forced swim test [77]. Hence, it appears that exercise improves hippocampal activity via epigenetic mechanism acting on an important neurotrophic factor, BDNF. SYNI expression is also downregulated by promoter DNA methylation [78], but no published evidence was found demonstrating that exercise de-represses SYNI by DNA demethylation. 3.The ratio of histone acetylation activity to histone deacetylation activity (HAT/HDAC) is believed to correlate with increased neuronal gene expression. When 3-month-old rats are given a single exercise session of 20 minutes on a motorized running wheel there is a 2-fold increase in hippocampal histone 4 lysine acetylation activities (HAT) and a 5-fold decrease Histone Deacetylase (HDAC) activity as assayed immediately or 1 hour after exercise [79]. The HAT/HDAC ratio increased 7- to 10-fold. No change from the control was measured by 18 hours after exercise, nor was there a change in HAT or

HDAC levels when measured after two weeks of chronic exercise (20 minutes/day). The speed of this initial response suggests exercise stimulates extremely rapid changes in histone acetylation and its return to normal levels suggests that this acetylation turns over with a short half-life.4. Hippocampal nucleosomalHistone 3 Lysine 9 Methylation (H3K9Me) levels are positively associated with neuronal gene silencing and reduced memory performance [80,81]. A single exercise session of 20 minutes or a chronic exercise protocol (2 weeks, 20 minutes daily) produces a significant 2- to 4-fold reduction in hippocampal H3K9Me levels in young 3-month-old rats 1hour and 18 hours after exercise [82]. The results were quite different for 18-month-old rats, where exercise produced increases in H3K9Me. These results have not yet been directly connected to expected exercise-induced increases and decreases in neuronal gene expression in young and old rats, respectively.

Appetite disturbances are core symptoms of Alzheimer's disease (AD) patients and AD model mice. Loss of memory and physical damage to the frontal cortex and hippocampus are among the first changes detected in the AD brain.Considering the data presented earlier, it is easy to imagine the connection between hippocampal damage and appetite disturbances. Controlled and quantified data from AD model mice lend the strongest support to the argument that AD contributes to eating and weight control disorders and that an early obese phenotype is due toepigenetic disorders of the hippocampus(Figure 1).Over expression of wild type APP (amyloid precursor protein), and particularly the double missense mutant forms of APPswe ($APP_{K595N,\ M596L}$),are correlated with AD in humans and transgenic model mice. APP and APPswe are both processed into secreted Aamyloid plaque that accumulates in the AD brain, a signature symptom of AD. However, APP is also a transcription factor that associates with the histone acetyltransferees Tip60 to promote histone acetylation in the brain. If fed ad libitum various transgenic AD-model mice that overexpress the human amyloid precursor protein APP_{Swe}tend toward early obesity, with or without other AD-inducing genetic defects[83-94]. In a study directly addressing obesity, the 3xTg mice carrying the APPswe mutation are obese by 2 months of age and this persists until 5 months, but by 12 months they are underweight[91-93].These mice are obese from 2 to 5 months (e.g., 36% heavier than controls) because they eat 17% more chow, but burn less energy, having significantly lower O_2consumption and lower CO_2 expiration than controls. By 12 months of age they are consuming 30% more calories than controls, but they weigh 15% less. This later weight loss appears due the fact that they are burning more calories as evidenced by their consuming 21% more O_2 and expiring 29% more CO_2 than controls. Evidence that overexpressed APPswe may be acting via a dominant inhibitory effect on Tip60's role as a histone acetyltransferee comes from studies with the histone deacetylase inhibitor phenylbutyric acid (PBA)[95]. Sixteen-month-old mice with the APPswe mutation are extremely defective in hippocampal-based spatial memory and learning potential as evidenced by their inability to efficiently learn to solve the Morris water maze. Remarkably, treating these mice with PBA restored their ability to solve the maze to the levels of wild type controls. There was a concomitant restoration of histone H3 and H4 acetylation levels in hippocampal neurons back up to the levelso wild type. PBA treatment did not reduce Ab plaque formation in the hippocampus of these APPswe mice. In a parallel study by the same group, treating APPswe mice with PBA also restored the abnormally low levels of dendritic spines in AD hippocampal neurons up to normal levels, an increase of 18% [96]. The obvious implication here is that PBA restored hippocampal neuronal histone acetylation, neuronal gene expression, and neuron development to APPswe mice, thereby reestablishing more normal memory performance and that this phenotype was not related to plaque formation. The impact of PBA treatment on hippocampal controlled eating behavior, obesity, and metabolism in APPswe mice has not been reported.In summary, from these indirect data it is againreasonable to propose that epigenetic reprogramming of hippocampal neurons will alter the learning and memory processeswith the potential to regulate temporal meal onset and food consumption, but the direct measurements of such relationships to obesity have not been made.

Discussion

Early and continuing studies support the premise that "Diminished activities in the hippocampus generally produce hyperphagia and obesity."It appears that on the whole, the hippocampus exerts restraint over appetite and when damaged thisresults in orexigenic behavior and obesity. MRI data suggest that the hippocampus is involved in the emotional and visual responses to food that again are altered in obese or formerly obese individuals to support overeating. Preliminary interpretations of MRI data on the response of obese individuals to images or thoughts of food also suggest that hyperphagia and obesity parallel addictive behaviors like those for alcohol or other drugs of abuse, such as cocaine.In support of this tantalizing view of obesity, the most effective weight loss programs, which overcome the weight-loss and regain paradigm for obese individuals, appear to involve not only diet and exercise, but long-term meetings and social activities with a continuous focus on behavioral modification, programs similar those treating alcohol and drug addiction [97-104].This and other MRI-based studies point out the power of imaging the living brain to enhance obesity research.

Independent physiological, live imaging, molecular genetics, epigenetic,cognitive disease, and behavioral studies suggest diet and obesity may damage hippocampal function and reduce normal restraint from hyperphagia, leading to obesity(Figure 1). Thus, there is reasonable support for most aspects of the working

hypothesis addressed herein, "Obesity and diet reinforce aberrant eating behavior by physically damaging andor by the epigenetic reprogramming of hippocampal functions,"with one weakness.The epigenetic reprogramming of the hippocampus in relation to diet and obesity is not yet well tested. By contrast, there is substantial evidence that the brain is in some way reprogrammed by diet and obesity, and that this reprogramming is likely to be epigenetic in nature.Finally, there are data demonstrating that diet and obesity stimulate epigenetic changes in the hypothalamus and brain reward pathways that may alter behavior.The fusion of diverse arguments presented herein also makes clear that interdisciplinary information from experimental science is needed to understand the role of hippocampal functions in obesity.Taking together thesevarious research results, there is strong support for a cyclic relationship, where high fat diets and obesity cause dysfunction of the hippocampus, which in turn reinforces hyperphagia and continued obesity.

The way forward: Accepting a strong role for the hippocampus in obesity, there is a real need for more comprehensive analyses of changes to its epigenetic controls as model animals respond to changes in diet, diet-induced changes in weight, and exercise. Comprehensive epigenetic studies of post-mortem human hippocampal samples comparing the molecular genetics and epigenetic changes among lean and obese individuals should help pinpoint epialleles or groups of interacting epialleles with relevance to obesity.Only a few epitypes, primarily DNA methylation and three classes of PTMs, histone acetylation, methylations, and phosphorylation, have been studied in any detail in relation to epigenetic programming in the hippocampus [81]. However, there are several dozen other histone PTMs and a few additional modifications of cytosine, adenine, and thymidine counted among the known epigenetic marks. It is likely that many of these changes in the epigenome are also involved in neuronal reprogramming in the response to stimuli such as diet, exercise, and obesity. Nucleosome position is determined in part by histone variant composition and in part by the nucleotide composition of certain base-pair repeats in the DNA sequence with the potential to make contact with each nucleosome [105,106]. This relationship of DNA sequence to nucleosome position likely connects some allelic changes in DNA sequence (e.g., SNPs, Small Insertions and Deletions (INDELs)) associated with obesity [107,108] with epigenome-induced pathologies. Such DNA sequence polymorphisms are the likely cause of some multigenerationally inherited epigenome-induced risks for obesity [105]. Neither nucleosome position nor histone variant composition has yet been reported in any detail for particular regions of the brain or for their relationship to obesity.Neither have there been genome-wide correlations of SNPs nor INDELs associated with risk to changes in the epigenome.Clearly, the epigenetic analysis of neuronal reprogramming is in its infancy, particularly as it impacts hippocampal controls over eating behavior.

Cause-and-effect relationships will continue to be difficult to assign from studies correlating epigenetic changes with phenotypes. This problem mayhave addressed in at least two ways. First, by applying inhibitors of chromatin modifying machinery to problems of obesity such as histone deacetylase inhibitors (e.g., tri Chastain A, butyrate, phenyl butyric acid), or acetylated histone mimics that inhibit broom domain chromatin remodelers (e.g., I-BETs, benzodiazepines, phenyl is ox azoles, DNA methyl transferees inhibitors (5-azacytidine), or TET inhibitors; Second, mutational or RNA-mediated silencing of chromatin remodeling machinery has not been used to directly examine problems of obesity and the epigenetic response to high fat diet. For example, because butyrate and phenylbutyrate restore some aspects of hippocampal based spatial learning, these drugs may, for example, also impact the eating behavior of diet-induced obesity in rodents fed ad lib on a HFD. Benzodiazepine increases the expression of APO-A1, which negatively regulates the inflammatory response and expression of bacterial pathogen-induced gene promoters in mouse macrophages [109,110]. These inhibitors of epigenetic function may be used to dissect neuronal epigenetic regulation in relation to problems of obesity.

Epigenetic from its dual inception by David Nanny and Conrad Waddington has been focused on organ, tissue and cell-type specific differences [111-113]. In blood, genome wide analysis of the human methyl me among seven types of leukocytes, showed that all pair wise comparisons of cell type differed in a remarkable 8% to 40% of their DNA cytosine methylation sites [114]. The hippocampus is comprised of many cell types including neurons, glia, vascular cells and nucleated white blood cells. Each is likely to have its own epigenome for any one epictype and is as likely to haveas much difference as that among classes of leukocytes. The brains of mice, rats, and humans are estimated to contain 71, 200, and 86,000 million neuronal cells, respectively [115,116] and no one doubts that there is much diversity in types and subclasses of neurons. Considering that DNA cytosine methylation and the hundreds of different nucleosomal histone side chain modifications can be differentially positioned in the genome it is theoretically possible that most individual neuronal cells are distinct in their epigenome. Thus, the problem of performing cell-type specific epigenetic analysis in the brain will be daunting. Although many of the epigenetic studies described herein were performed on sub-regions of the hippocampus or other brain regions, none examined purified neurons. A number of technical approaches have been applied to increase the cell type specificity of brain research, including immune fluorescence microscopy used to examine changes in the levels of particular PTMs within layers of neurons, neuron-specific electrophysiology in brain slice preparations [117], laser capture micro-dissection of neurons [118], culture of immortalized neuronal cells[119,120], and fluorescence activated nuclear sorting of neuronal nuclei [121,122], but of these approaches only brain slice electrophysiologyhas been applied to

epigenetic analysis of obesity related problems.Cell-type specific studies would greatly increase the statistical significance for epigenetic data on neuronal cells as it does for peripheral blood, allowing us to pinpoint how diet and obesity are reprogramming cells in the hippocampus, other regions of the brain, and other organs, and providing a wealth of new targets for the prevention and treatment of obesity.

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A. In the normal weight or lean state the hippocampus records information about food intake including the time, size, and duration of a meal.Signals are sent from the hippocampus to other brain structures and to and from peripheral organs to delay consumption of the next meal.This normal/lean state is associated with specific chromatin modifications that play a role in the management and consistency of these signaling pathways.B. In the obese state, obesogenic tissues and increased food intake give rise to altered signaling cascades between brain structures and to and from peripheral organs.These changes in synaptic and hormonal signaling, along with the information being processed by the hippocampus, result in epigenetic reprogramming that promotes food intake in the absence of physiological necessity and perpetuates the cycle of obesity.In both scenarios, information regarding external environmental stimuli such as stress, living conditions, and exercise, are also recognized by the hippocampus and influence chromatin modifications.Pathways are superimposed on a cartoon image of the rodent brain with the hippocampus represented by a dotted outline.

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