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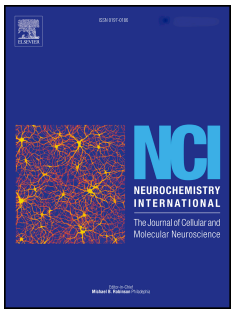

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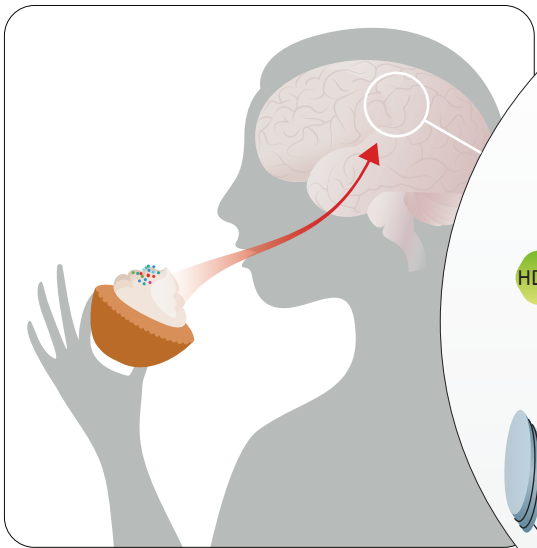
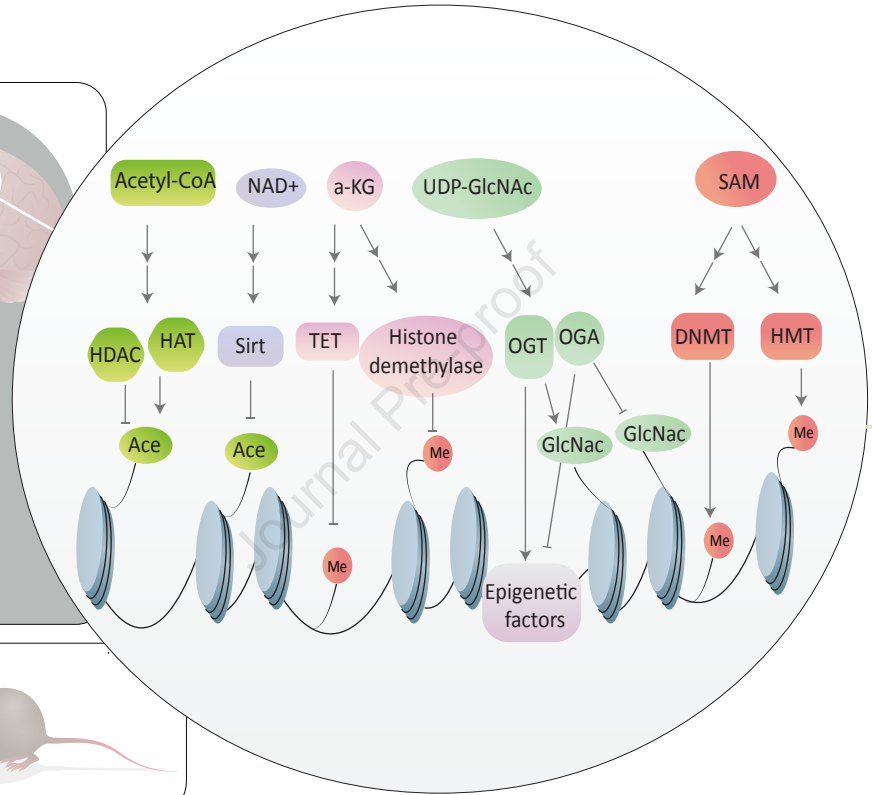
AV and MD discussed the studies and wrote the manuscript.





- Food Intake
- Food Choice
- Motor Defects
- Anxiety
- Sensory Plasticity
- Learning and Memory

Brain on Food: The Neuroepigenetics of Nutrition

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Abstract:

Humans have known for millennia that nutrition has a profound influence on health and disease, but it is only recently that we have begun mapping the mechanisms via which the dietary environment impacts brain physiology and behavior. Here we review recent evidence on the effects of high nutrient and methionine diets on neural epigenetic marks, gene expression, and behavior in invertebrate and vertebrate model organisms. We also discuss limitations, open questions, and future directions in the emerging field of the neuroepigenetics of nutrition.

Keywords:
Behavior, epigenetics, metabolism, high fat diet, high sugar diet, obesity, dietary methionine

"Let food be thy medicine and medicine be thy food"

-Hippocrates

1. Introduction

The connection between nutrition and health is ancient: philosophers like Hippocrates, Plutarch, Confucius, and Muhammad ibn Zakariya al-Razi wrote about it in books and religious texts, and oral traditions worldwide contain extensive references to diet, wellbeing, and disease. Philosophers and sages were not the only ones interested in this topic: the first printed gastronomy book, *De honesta voluptate et valetudine,* – authored in Latin by humanist Bartolomeo Platina in ~1465– was so successful that it was quickly translated into Italian, French, and German (Platina et al., 1998). In this light, today's public interest, and often obsession, with diet, lifestyle, and wellbeing is not surprising.

It is well established that the dietary environment influences health, life expectancy, and the risk for diseases such as diabetes, cancer, and neurodegeneration (Oleson et al., 2017; Zamroziewicz and Barbey, 2016). The molecular mechanisms through which diet affects physiology, however, are still under investigation. In the last decade, research in the emerging field of nutrigenetics has illuminated the cellular networks connecting diet with cell function, as well as shedding light on how individual genetic variation interacts with dietary nutrients to promote or protect from disease susceptibility (Müller and Kersten, 2003). In addition to identifying how metabolic pathways sense and respond to variations in the nutrient environment to acutely regulate cell physiology (Haro et al., 2019), these studies have also revealed that nutrients can produce long-lasting epigenetic effects (Bartke and Schneider, 2020; Haws et al., 2020; Janke et al., 2015).

The sensitivity of the epigenome to diet arises from the ability of nutrients and metabolites to function as substrates and cofactors for enzymes that covalently modify DNA, RNA, and histones proteins (Etchegaray and Mostoslavsky, 2016; Zhang and Kutateladze, 2018). By changing the activity of metabolic enzymes or the flux of metabolic pathways, diet composition alters the availability of the cofactors for these modifications, as well as regulates the binding of gene-regulatory complexes to their substrates (Haws et al., 2020; Zhang and Kutateladze, 2018). This discovery that diet-derived metabolites fuel the epigenetic machinery has reshaped our understanding of the interplay between nutrition, health, and disease and led to new avenues of investigation and treatment, especially for cancer and metabolic disease (Decourcelle et al., 2019; Kalea et al., 2018; Sapienza and Issa, 2016; Zeisel, 2017).

This new paradigm, however, has only recently reached neuroscience, and more specifically, the field of neuroepigenetics, which studies the molecular mechanisms bridging the environment, brain, and behavior. Understanding the role of diet on neural function is critical to advancing our fundamental knowledge of the brain, but also to uncovering the etiology of neural diseases linked to dietary exposure. Indeed, a diet high in processed foods– which contains high amounts of fat and sugar and is widely consumed because of its convenience and low-cost– has been linked with both mood and neurological disorders, such as depression and memory deficits (Gómez-Pinilla, 2008). *How does the dietary environment alter brain function and behavior? What are the molecular mechanisms that connect nutrition to neural physiology? And which metabolic and epigenetic pathways play a role in different neural diseases?* These are some of the questions that research in the neuroepigenetics of nutrition field is trying to answer. Here we review recent studies that examine how specific diets affect the brain epigenetic machinery and/or the epigenome to influence behavior and disease. To limit the scope of this review, we have focused on the effects of three main dietary nutrients– high sugar, high fat, and methionine– on brain DNA and histone methylation and acetylation, protein glcnacylation, as well as a handful of other nutrient responsive effector molecules in cognitive function, energy balance, and motivated behaviors. In the interest of space, we do not discuss research on RNA modifications and regulation (Jung and Goldman, 2018; Roundtree et al., 2017), caloric restriction (Gensous et al., 2019; Kapahi et al., 2017; López-Otín et al., 2013), aging (Finkel, 2015), or circadian clocks (Hawley et al., 2020) since these have been recently reviewed. We end the manuscript with challenges and open questions that, in our view, will define the next decade of research in this new and fascinating field.

Preview Box 1: An overview of the metabolites and pathways that fuel the brain epigenetic machinery

Here we summarized the connection between the diets covered in this manuscript and the epigenetic mechanisms involved (also see Table 1 and Fig. 1). For an in-depth treatment of these metabolic pathways in relation to gene regulation, refer to (Cavalli and Heard, 2019; Haws et al., 2020; Nieborak and Schneider, 2018).

DNA and Histone Methylation: Covalent methylation of DNA and histones leads to alterations in chromatin accessibility, transcription factor binding, and gene expression (Li et al., 2018).

Methylation is regulated by the abundance of S-Adenosylmethionine (SAM), the universal methyl donor for enzymes that methylate not just DNA and proteins, but also RNA and lipids. SAM is synthesized from methionine and ATP, depending on the availability of substrates and cofactors for 1-carbon metabolism, such as methionine, threonine, serine, glycine, choline, histidine, glucose, and folate (Ducker and Rabinowitz, 2017). The transfer of a methyl group from SAM to its substrate, produces S-adenosylhomocysteine (SAH), which negatively regulates this process by robustly inhibiting methyltransferases (Berger, 2007). Because of this, the intracellular SAM:SAH ratio, as well as other 1-carbon cycle metabolites, dynamically regulates the activity of methyltransferases (Mentch et al., 2015; Serefidou et al., 2019). Consumption of foods that are rich in methyl-donors (SAM, folic acid and vitamin B) increases these metabolites and can promote DNA and histone methylation and influence gene expression (Li et al., 2018). Enzymes that remove the methyl group from DNA and histones are also sensitive to metabolic cofactors. Specifically, both Jumonji-domain containing histone demethylases and Ten-Eleven Translocation proteins (TET), which catalyze the creation of 5-hydroxymethylation, an intermediate in the removal of cytosine methylation– use the TCA cycle intermediate α-Ketoglutarate (α-KG). High α-KG levels – maintained by glucose and glutamine catabolism– promote the demethylation of histones and DNA, while high levels of fumarate and succinate inhibit their removal (Tran et al., 2017).

Histone Acetylation: Histone acetylation is a dynamic and reversible process primarily regulated by the activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs acetylate conserved lysine residues on histone tails by transferring an acetyl group from acetyl-Coenzyme A. Acetyl-CoA is produced from acetate, citrate and pyruvate by Acetyl-CoA Synthetase Short-chain family member (ACSS), ATP citrate synthase (ACLY), and the pyruvate dehydrogenase complex (PDC); it can also be generated from fatty acid β-oxidation and amino acids and ketone bodies (Sivanand et al., 2018). The levels of acetyl-CoA are affected by the catabolic/anabolic state of the cell and affect global histone acetylation levels by serving as a cofactor for HATs (Sivanand et al., 2018). HDACs are sensitive to metabolites that are increased by catabolism. The Sirtuin 1 and 2 deacetylases (SIRT1 and SIRT2) require oxidized Nicotinamide adenine dinucleotide (NAD+) for their activity: high levels of NAD+ activate these enzymes while nicotinamide (NAM), a precursor of NAD+, inhibits them (Cantó et al., 2015). Class I histone deacetylases (HDACs) are inhibited by the major ketone body β-hydroxybutyrate (BHB), a byproduct of fatty acid breakdown during fasting (Newman and Verdin, 2017).

O-GlcNAcylation: O-GlcNAcylation (short for O-linked β-N-acetylglucosamine) is a type of glycosylation that involves the attachment of a single O-GlcNAc moiety to serine and threonine residues of cytoplasmic, nuclear, and mitochondrial proteins (Yang and Qian, 2017) (Fig. 1). The output of glucose, amino acid, fatty acid, and nucleotide metabolisms generate uridine diphosphate GlcNAc (UDP-GlcNAc), the donor substrate for O-GlcNAcylation (Olivier-Van Stichelen et al., 2017). A single pair of enzymes, O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA), add and remove O-GlcNAc groups to and from proteins, controlling the dynamic cycling of this post-translational protein modification in a nutrient-responsive and stress-responsive manner (Olivier-Van Stichelen and Hanover, 2015; Yang and Qian, 2017). O-Glcnacylation is also targeted to other epigenetic regulators besides histones, such as TET proteins, Polycomb Group Proteins, and transcription factors such as cyclic AMP response-element binding protein (CREB) (Altarejos and Montminy, 2011; Decourcelle et al., 2019; Yang and Qian, 2017).

3. The Effects of a Western-Type High Fat, High Sugar Diet on the Brain Epigenome

A western-type diet, also known as “cafeteria diet,” refers to diets with high levels of saturated fats and refined sugars, largely via the consumption of processed or ultra-processed foods (Sampey et al., 2011). In humans this diet is associated with the development of obesity, inflammation, neurodegeneration, and metabolic disease (Carrera-Bastos et al., 2011; Haddad et al., 2016; Hsu and Kanoski, 2014; Popkin et al., 2012); similar effects also occur in rodent (Singh et al., 2019) and invertebrate (Musselman and Kühnlein, 2018) models exposed to the Western diet or components of it. Across organisms, consumption of fatty and sugary foods has also been linked to alterations in behaviors such as reward signaling, learning and memory, taste sensation, food intake, and sleep (DiFeliceantonio and Small, 2019; Heyward et al., 2016, 2012; May et al., 2020, 2019; Stice and Yokum, 2016; St-Onge et al., 2016; Valladolid-Acebes et al., 2011). While studies have reported some of the neural changes that occur with diet-induced obesity (Haws et al., 2020; Nuthikattu et al., 2019; Rodriguez et al., 2017; Woodie et al., 2020), the molecular mechanisms linking high nutrient diets to behavioral changes are just now being uncovered.

Learning, Memory, and Synaptic Function: A growing body of evidence has shown that in rodents exposure to a high fat or high sugar diet is associated with cognitive impairments, shifts in DNA 5’ cytosine methylation (5mc), and the balance of histone acetylation and deacetylation

in the brain. In two studies, mice fed a high fat diet for 20 weeks had impairments in spatial memory and synaptic plasticity (Heyward et al., 2016, 2012). Consistent with these phenotypes, the authors found an increase in the promoter 5mc levels (Heyward et al., 2016), and a corresponding decrease in expression of genes previously associated with memory consolidation in the hippocampus, such as relin (Reln), protein phosphatase 1β (Ppc1b), and Sirtuin1 (Sirt1) (Heyward et al., 2016, 2012). In particular, removal of the NAD- dependent histone deacetylase Sirt1 (see Box 1, Fig. 1) from the forebrain recapitulated the learning and memory defects in control diet animals, while supplementation with the Sirt1-activator resveratrol for 10 weeks rescued memory deficits in animals on a high fat diet without enhancing that of control diet mice (Heyward et al., 2016). Together, these studies suggest that a high fat diet impairs hippocampal memory consolidation by altering the expression of genes important for synaptic plasticity, especially the histone deacetylase Sirt1. Variations in brain histone acetylation/deacetylation with diet-induced obesity have been described in other studies. (Wang et al., 2014) and colleagues reported an increase in the expression of Class IIa histone deacetylases in the brain of humans with type II diabetes and in the hippocampus of mice fed a high fat diet. These changes in mRNA levels of HDAC IIa proteins, such as HDAC9, were associated with lower levels of synaptic proteins such as PSD95 in humans and in lower evoked and basal synaptic transmission in mice (Wang et al., 2014). In female rats, consumption of a high fat diet for 8-10 resulted in lower levels of the of mineralocorticoid receptor and glucocorticoid receptor genes, as well as nuclear factor kappa beta gene expression the hippocampus, suggesting a dysregulation of the hypothalamic-pituitary axis that was reflected in higher anxiety behaviors as measured by the light/dark open field task (Sivanathan et al., 2015).

A reduction in learning and memory with corresponding alterations in DNA methylation and transcription in the hippocampus and hypothalamus have also been reported in rats fed a diet supplemented with 15% fructose for 6 weeks (Agrawal and Gomez-Pinilla, 2012; Meng et al., 2016). The authors identified differences in the methylation status and mRNA levels of transcription factors and epigenetic regulators which they hypothesized to be responsible for the complex alterations in networks of extracellular matrix, collagen, and transporter genes (Meng et al., 2016). Another study reported similar changes in the transcription of genes involved in metabolism, cell adhesion, and synaptic function and a small decrease in DNA methylation (measured by dot blot) in the frontal cortex of mice fed a high fat and high sugar diet for 12 weeks (Meng et al., 2016; Yokoyama et al., 2018). Collectively, these studies suggest a broad

link between high nutrient diets, DNA methylation, histone acetylation, and cognitive function, which may explain the comorbidity between diet-induced obesity and neurodegenerative diseases in humans (Fig. 2) (Agrawal and Gomez-Pinilla, 2012; Heyward et al., 2016; Meng et al., 2016; Wang et al., 2014; Yokoyama et al., 2018). They also hint that the balance of histone acetylation and deacetylation may be disrupted by Western-like diets and correlated with shifts in synaptic function (Fig 1 and 2). However, if and how this imbalance originates from alterations in the levels of metabolites that are used by HATs and HDACs, such as acetyl-CoA, NAD+, and ketone bodies, was not investigated in these studies (Box 1).

Energy balance, intake, and motivated behaviors: Consumption of high fat and sugar diets has also been associated with disrupted feeding behavior and weight gain, raising the possibility that neuroepiegentic mechanisms may affect the expression of genes that play a role in energy homeostasis, reward, and motivated behaviors. This question has been addressed by examining the mRNA levels and DNA methylation status of genes important for feeding behavior in the hypothalamus, which controls energy balance and food intake via dedicated circuits (Timper and Brüning, 2017). In the arcuate nucleus (ARC) of the hypothalamus an increase in the DNA methylation at the promoter of the Proopiomelanocortin (POMC) gene, an anorexigenic neuropeptide, was found in male rats fed a high fat diet for shorter (post weaning to 90 days) (Marco et al., 2016, 2013), longer (21 weeks) exposures (Cifani et al., 2015), and during neonatal development (Plagemann et al., 2010); interestingly, a positive correlation between POMC promoter hypermethylation and BMI has also been established in humans (Kühnen et al., 2016). However, higher POMC promoter methylation corresponded to a decrease in mRNA abundance only in (Cifani et al., 2015; Plagemann et al., 2010), but not in (Marco et al., 2013). Further, the mRNA and DNA methylation levels of other obesity-related ARC genes, such as Neuropeptide Y gene (NPY, orexigenic) was changed, but not that of the Agouti Related Peptide (AgRP, orexigenic) in male rats fed the HFD (Cifani et al., 2015), although a recent study using single cell sequencing of the ARC in male mice fed a HFD for 10 weeks found that both POMC and AgRP mRNAs were lower (Deng et al., 2020). Expression of both NPY (in other hypothalamic nuclei) and POMC (in the ARC) however, was higher in female rats fed a western type cafeteria diet for 20 weeks, with a corresponding decrease in DNA methylation (Lazzarino et al., 2017); in these animals the levels of steroid hormone receptors thought to play a role in obesity were also altered, suggesting that there may be sex specific differences in the regulation of these neuropeptide genes by diet. More recently, the single-cell transcriptome of the Lateral Hypothalamic Area, and especially of glutamatergic neurons in this

region, was found to be changed by a high fat diet in mice, but how these alterations in expression were connected to deficits in the responses of glutamatergic neurons to satiety in the diet-induced obesity animals was not investigated (Rossi et al., 2019). Importantly, connections between SAM, SAH, and α-KG levels in relation to changes in DNA methylation were not investigated in any of these studies.

In addition to the hypothalamus, dopamine and opioid-receptor expressing neurons in the Ventral Tegmental Area (VTA) and Nucleus Accumbens (NAcc) also play a critical role in food intake and weight gain (DiFeliceantonio and Small, 2019; Leigh and Morris, 2018). Indeed, dysfunctions in dopaminergic signaling and transduction have been described with a high fat diet (Décarie-Spain et al., 2016) and are thought to deregulate energy intake (DiFeliceantonio and Small, 2019; Geiger et al., 2009; May et al., 2020; Stice et al., 2011; Volkow et al., 2011). Studies in male mice fed a high fat diet for 20 weeks showed a decrease in expression and an increase in DNA methylation at the promoters of genes critical for dopaminergic transmission, such as the Tyrosine Hydroxylase and Dopamine Transporter (DAT) genes in the VTA, as well as an increase in food intake, meal number, and meal size (Vucetic et al., 2012). The same group also identified lower expression of the μ-opioid receptor in the VTA, NAcc, and prefrontal cortex with diet-induced obesity. They also uncovered higher 5mC, histone 3 lysine 9 methylation, and Methyl CpG Binding Protein 2 binding, and lower H3 K4 acetylation in the μ-opioid receptor promoter region (Vucetic et al., 2011). An association between changes in DNA methylation at genes involved in DA transmission and BMI have been observed in a study that measured the methylation patterns of white blood cells among ~400 adults in the Methyl Epigenome Network association (Ramos-Lopez et al., 2018). Of note, *SLC18A1(VMAT1)* and *SLC6A3* (DAT) DNA methylation signatures were also correlated with total energy and carbohydrate intakes (Ramos-Lopez et al., 2018); some alleles of the *SLC6A3* gene have been previously associated with obesity risk (Bieliński et al., 2017; González-Giraldo et al., 2018), suggesting that gene x environment effects could converge on this gene. Together, these findings in the midbrain and those in the hypothalamus suggest that calorically dense diets may enhance gene repression to promote feeding behavior and metabolic disease, but direct links between metabolite levels and these epigenetic modifications (Box1 and Fig. 1) were not established.

Nonetheless, the notion that some diets may enhance gene repression is interesting in the light of research that used transgenic animals to address the role of epigenetic modifiers in

diet-induced obesity. One study showed that pan-neuronal knockout of the DNA methyltransferase 1 (DNMT1) reduced obesity, food intake, and attenuated changes in gene expression in the ventromedial hypothalamus in mice fed a high fat diet (Bruggeman et al., 2018). However, in the paraventricular nucleus of the hypothalamus–which is sensitive to anorexigenic signals– (Kohno et al., 2014) showed that the expression of the de novo methyltransferase Dnmt3a was reduced with HFD treatment for 6 weeks, and that knockout of this gene led to hyperphagia and higher body weight and fat mass. Notably, knockout of MeCP2 in the same neurons also induced hyperphagia and obesity via upregulation of NPY levels. Interestingly, knockout of Sirt1 in the AgRP neurons promoted lower food intake and body weight (Dietrich et al., 2010); in the same light, loss of the transcriptional repressor PHD finger protein 6 (PHF6) from the orexigenic AgRP neurons protected mice from weight gain and obesity when they ate a high fat yo-yo diet (Gan et al., 2020). Specifically, the authors showed that binding of PHF6 at the promoters of immediate early genes– such as transcriptional regulators, signaling, and channels– shifted upon refeeding to alter the firing properties of the AgRP neurons and the levels of the AgRP neuropeptide (Gan et al., 2020). Together, these studies suggest that alterations in the DNA methylation patterns at the promoters of feeding and energy homeostasis genes in the hypothalamus and striatum, and more broadly an increase in repressive drive, may play an important role in the regulation of food intake and energy homeostasis. However, the exact mechanisms via which this epigenetic mark is altered by diet are still unknown; further, whether these effects are due to the direct action of metabolites on epigenetic modifiers, or are instead a consequence of overall higher caloric intake or weight gain, was not addressed in these studies.

The dissection of molecular mechanisms and, more specifically, the uncoupling of the effects of diet from those of higher caloric intake and/or weight gain, have been directly addressed in invertebrate models like the fly *Drosophila melanogaster.* Consumption of a high sugar or high fat diet promotes higher feeding (May et al., 2020, 2019) and leads to fat accumulation and the hallmarks of metabolic syndrome in this model (Beshel et al., 2017; Musselman and Kühnlein, 2018; Wilinski et al., 2019). Our group found that in flies chronic consumption of a high sugar diet desensitizes the taste cells to sweet stimuli to promote dopamine dysfunction, overeating, and obesity (May et al., 2020, 2019). This decrease in taste was due to the activation of the Hexosamine Biosynthesis Pathway (HBP) and the related metabolic enzyme O-GlcNAc Transferase (OGT) by a high sugar diet, independently of higher caloric intake and fat accumulation/weight gain (May et al., 2019; Wilinski et al., 2019). The HBP

is a cellular nutrient sensor that integrates different metabolic pathways to regulate many aspects of cellular physiology through post-translational protein modification (Olivier-Van Stichelen et al., 2017) (see Box1); many of the downstream targets are epigenetic modifiers and transcriptional regulators (Butler et al., 2019; Chu et al., 2014; Decourcelle et al., 2019; Olivier-Van Stichelen and Hanover, 2015). In a recent study our group discovered that high dietary sugar caused the redistribution of the Polycomb Repressive Complex 2 (PRC2) – on the chromatin of the sweet taste cells (Vaziri et al., 2020), and this shift depended on OGT (unpublished data). PRC2 is a conserved gene silencing complex that acts via histone 27 (H3K27) trimethylation, and others have shown a link between its repressive function and OGT (Decourcelle et al., 2019). In the fly study, changes in the chromatin occupancy repressed a neurodevelopmental transcriptional hub composed largely of homeobox genes (Nubbin, Ptx1, Caudal, Scarecrow, and GATAe), which in turn regulated the expression of a battery of ~600 genes required for the synaptic, connectivity, and metabolic properties of the sweet taste receptor expressing cells. Manipulations of the transcriptional hub or its downstream targets led to defects in chemosensory plasticy that recapitulated the effects of diet on taste and body weight. Notably, up to half of the diet-induced alterations in gene expression persisted even when the animals were returned to a control diet for up to 20 days, suggesting that PRC2 leaves a molecular memory of the dietary environment in these cells (Vaziri et al., 2020); this likely occurs via H3K27 methylation but the authors did not measure this modification. OGT also regulates the activity of the other important transcription factors involved in synaptic plasticity and neural physiology. Indeed, O-Glcnacylation of cAMP response element-binding protein (CREB) inhibits transcriptional activation by blocking its association with the cofactor CRTC, and preventing long term memory formation (Rexach et al., 2012). In hippocampal mouse tissue, CREB phosphorylation (Cavaliere et al., 2019) and CREB-mediated activation of Brain-derived neurotrophic factor (BDNF) (Kalivarathan et al., 2020) were decreased in mice fed a high fat diet; the chemosensory plasticity of the sensory neurons of flies on a high sugar diet was also dependent on CREB signaling (Wang et al., 2020). A recent study also found that the activity of OGT changes during memory consolidation to influence the binding of PRC2 and remodel chromatin (Butler et al., 2019). Interestingly, knockout of the histone acetyltransferase CREB Binding Protein (CBP) in the hypothalamus resulted in higher food intake and obesity (Moreno et al., 2016). Thus, modification of CREB by OGT may decrease signaling through this transcription factor and influence the expression of behaviors such as learning and memory and feeding. OGT has also been studied in the modulation of epilepsy, a neurological disease whose severity is influenced by diet (Sánchez et al., 2019). Moreover, manipulations of OGT

levels or its catalytic activity has been implicated in dopaminergic (Lee et al., 2020), hypothalamic (Lagerlöf et al., 2016; Ruan et al., 2014) and hippocampal circuits (Hwang and Rhim, 2019; Tallent et al., 2009; Taylor et al., 2014), gabaergic neurons (Giles et al., 2019), and sensory neurons (Su and Schwarz, 2017), in ways that alter DA neuron cell viability, food intake, energy balance, and synaptic maturity, plasticity, and function (Lagerlöf et al., 2017). This opens the possibility that the alterations in gene expression and DNA methylation described above may occur via this metabolic signaling pathway. However, a metabolomics study in flies showed that a high sugar diet reshaped not just the HBP, but also 1C metabolism and the TCA cycle (Wilinski et al. 2019), which could impact neural activity via other metabolite cofactors (see Box 1 and Fig.1). In particular, many studies have examined the effects of these metabolic pathways prenatally or across generations, which hints that these alterations could have long term consequences (Lempradl, 2020).

Taken together, evidence from flies and rodents fed high nutrient diets suggest that the disruptions in memory, sweet taste detection, and feeding behavior are associated with epigenetic processes and alterations in gene expression in both the peripheral and central nervous system (Fig. 2). However, with a few exceptions, the link between changes in metabolite levels and epigenetic modifications was not established in most of these studies. In terms of conservation, the metabolic and epigenetic pathways identified show profound conservation in multicellular organisms such as in the case of the HBP or that of PcG proteins, although most studies to date have been carried out in rodents. Extending these investigations to genetic models like flies, worms, and zebrafish, as well as other eusocial model organisms, such as ants or bees, would catalyze our understanding of metabolic signaling in neural function.

4. The effects of Methyl Donor Diets on the Brain epigenome:

Methionine, folate, and vitamin B are essential amino acids and vitamins that are not synthesized in animals and are obtained from foods such as dairy, meats, and soy products (Mahmoud and Ali, 2019). Dietary methionine fuels one-carbon metabolism, a series of metabolic reactions that convert methionine to the universal methyl-donor SAM; donation of the methyl group from SAM to its substrate, creates SAH (Box.1, Fig. 1). These reactions are closely linked to the folate cycle, which is fueled in large part by serine and glycine, among other amino acids (Locasale, 2013). Together, these reactions transform nutrients such as folate, vitamin B12, vitamin B6, betaine, choline, and methionine into methyl group acceptors and

donors required for cellular processes such as DNA, RNA, and protein methylation and demethylation (Fig. 1) (Anderson et al., 2012; Ducker and Rabinowitz, 2017; Mahmoud and Ali, 2019). As such, the levels of methionine in the diet have a profound influence on cellular physiology and this topic has been studied in the context of lifespan extension, metabolic health, and cancer therapy (Gao et al., 2019; Lee et al., 2014; Malloy et al., 2013; Obata and Miura, 2015; Orentreich et al., 1993; Parkhitko et al., 2016).

Low methionine diets: The effects of dietary methionine also extends to neural signaling and behavior, where several studies have linked methionine levels to disruptions in long term memory formation (Fig. 2) (Ishii et al., 2014; Kalani et al., 2019; Muehlmann et al., 2020; Serafini et al., 1996; Tomizawa et al., 2015) and low methionine diets to brain hypermethylation in particular (Pogribny et al., 2008). Two studies from the same group suggest that lowering the amounts of methionine in the diet in juvenile mice disrupts memory consolidation by altering the expression of glutamate receptors genes, which are important for long term potentiation (Ishii et al., 2014; Tomizawa et al., 2015). In one study, young male mice consumed a folate-methionine-choline deficient diet (FMCD) for 6 weeks, followed by a control diet ad libitum for 6 more weeks. These animals showed a decrease in contextual fear conditioning and memory extinction, as well as increase in increased anxiety-like behaviors at both time points (Ishii et al., 2014). The authors also found a decrease in the expression of the N-methyl D-aspartate receptor subtype 2b (Grin2b) and Gamma-aminobutyric acid receptor subunit alpha-3 (Gabra3) at both timepoints; interestingly, the mRNA levels for the DNA methyltransferases Dnmt3a and Dnmt3b were also lower at 6 weeks, but returned to normal levels by 12 weeks if the control diet was supplemented with extra methionine. In a follow up study where 3 week old mice ate the FMCD diet for 3 weeks, the researchers measured an overall impairment in novel object recognition and fear extinction (Tomizawa et al., 2015) but found no differences in anxiety-like behavior. In the hippocampus of these mice the CpG island in the promoter of the Glutamate Receptor 1 gene (Gria1) was hypermethylated, and the expression levels of this gene lower. However, no changes in the levels of other glutamate receptors (Gria2, Gria3, Grin2a, and Grin2b) were observed (Tomizawa et al., 2015). Together, these studies suggest that a methyl depleted diet impairs hippocampal memory consolidation by altering the expression of genes important for long term potentiation, potentially through an increase in DNA methylation, as it has been shown (Fig. 2) (Pogribny et al., 2008) although the relationship between SAM/SAH and gene expression was not established in these studies.

High methionine diets: Impairments in memory have also been observed when animals were fed diets high in methionine, suggesting that the right balance of methyl donors is critical for the signaling and the synaptic plasticity that plays a role in memory formation. (Kalani et al., 2019) reported that male mice fed a high methionine, low folate, and low vitamins containing diet (HMLVD) exhibited a loss of fear-motivated long term memory starting at 4 weeks on the diet that was correlated with an overall increase in 5mc levels after 4, 5, and 6 weeks (Kalani et al., 2019). Specifically, the authors discovered that expression of the Netrin (Ntn1) protein– a major regulator of axon branching and guidance (Serafini et al. 1996) important for synaptic plasticity and the maintenance of spatial memory (Bayat et al. 2012)–was lower in HMLVD fed mice due to higher DNA methylation at the promoter region. Of note, administration of Ntn1 intracerebrally at 6 weeks restored long-term fear motivated memory, suggesting that the repression of Ntn1 via DNA hypermethylation is a potential mechanism linking methionine levels and memory consolidation (Kalani et al., 2019). The levels of dietary methionine also affect behaviors other than learning and memory. A recent study reported that supplementing the mice diet with a methyl, folate, and vitamin B12 rich diet, attenuated the development of repetitive motor behaviors indicative of Autism Spectrum Disorder (ASD) (Muehlmann et al., 2020). The authors observed an increase in 5mc levels in the cortex and cerebellum, but not the striatum after 9 weeks dietary exposure (Muehlmann et al., 2020). Together, these studies have begun to uncover the effects of dietary methionine on cognitive function by linking it to alterations in DNA methylation and gene expression in the hippocampus and a few other brain regions. Future studies on this topic will shed light on how exactly the balance of methyl donors in the brain shapes synaptic plasticity and signaling to influence behaviors such as learning and memory, exploration, and anxiety.

5. The Next Decade of studies in the Neuroepigenetics of Nutrition: Approaches, Challenges, and Questions

The studies reviewed here examined the effects of high fat, high sugar, and methionine diets on brain DNA methylation, protein modifications, and chromatin binding and correlated them with changes in behaviors such as food intake, energy balance, and learning and memory (Fig. 1 and 2). The collective evidence from these findings is that diet influences brain function by altering signaling, neuropeptide and neuromodulator transmission, connectivity, and cell identity (Pizzorusso and Tognini, 2020). While the mechanisms are still unclear, the work presented here suggests that this occurs via variations in DNA methylation, histone acetylation,

and protein GlcNacylation in many brain regions, such as the hypothalamus, hippocampus, striatum, cortex, and sensory neurons. Among the metabolites that fuel the epigenome, SAM has been studied the most, because its levels are influenced by both high fat, sugar, and protein diet and can impact DNA, RNA, and histone methylation. However, there is evidence that the balance between histone acetylation/deacetylation is also important, and, as such, the levels of acetyl-CoA, α-KG, NAD+, and BHB could also underlie the effects observed in these studies (see Box 1, Fig. 1 and 2). Further, enhanced activity of the hexosamine biosynthesis pathway with calorically-dense diets promotes the GlcNacylation of Polycomb Group Proteins and transcription factors such as CREB, which remodel chromatin to modulate gene expression. Together, diet-dependent fluctuations in all of these pathways could contribute to behavioral differences, although no clear link between metabolism and epigenetic was established in most of the studies here, and this is the major challenge that future studies will have to address. Moreover, the field of epigenetics is continually expanding to include new factors and modifications, most of which have not been studied in the context of diet. For example, RNA modifications are also known to be dynamic and dependent on SAM catabolism (Pendleton et al., 2017; Tzelepis et al., 2019). Such modifications are essential for brain development in both invertebrate and vertebrate models, and contribute to gene expression mechanisms directly or indirectly, most notably by coordinating with epigenetic factors like Polycomb Group Proteins (Yao et al., 2018). Finally, numerous new types of histone modifications have recently been discovered, such as hydroxylation, poly (ADP) ribosylation, sumoylation and dopaminylation (Flotho and Melchior, 2013; Hou et al., 2019; Lepack et al., 2020; Unoki et al., 2013). Thus, research in the neuroepigenetics of nutrition field will need to tackle the role of diet on these newer aspects of gene regulation, and also continue studying connections between diet, microbiome, and the brain (Ezra-Nevo et al., 2020).

Challenges, Limitations, and Future Approaches: The major challenge for the next generation of studies in the neuroepigenetics of nutrition will be to address some of the limitations the current approaches present. First, most of the current investigations have focused on whole brain regions, such as the arcuate nucleus of the hypothalamus or the ventral tegmental area, but not on specific brain circuits. Although this approach identifies genes that act broadly across different types of neural and neuronal cells, it fails to pinpoint the specific mechanisms within a particular circuit. Indeed, uncovering how metabolic signaling acts at a circuit specific level to alter the biophysical, synaptic, and connectivity properties of neurons, is essential to link the effects of nutrition to behavior and understand the etiology of diet-related brain diseases. Most

of these initial studies have also prioritized specific genes, such as POMC or TH, rather than examine the effects of diet on the whole transcriptome and epigenome of the cell. This means that we have only scratched the surface and that a whole myriad of genes and pathways remain yet to be discovered; in particular, the application of bioinformatic tools to genome-wide datasets has the potential to identify the underlying regulatory and molecular mechanisms, which can then be studied using genetic and pharmacological interventions.

Another limitation of the current approach is the lack of a causal connection between dietary metabolites, behavioral effects, and epigenetic and transcriptional alterations. Indeed, in most of the studies there is no direct indication that the epigenetic and gene expression variations are the result of diet-dependent changes in metabolites, rather than a consequence of higher caloric intake and weight gain. In many of these studies, most animals were only tested at a later time when weight gain, insulin resistance, and obesity had already occurred and no interventions were taken to prevent weight gain or to balance caloric intake. Similarly, very few studies used pharmacology, mutants, or cell specific genetic manipulations to show that the epigenetic changes caused changes in the behavior of the animal. The availability of cell specific methodologies, from single cell sequencing to DAM-ID (Cheetham et al., 2018; Marshall et al., 2016; Vogel et al., 2007) and ribosomal profiling (Chen and Dickman, 2017; Gonzalez et al., 2014), together with the use of transgenic animals will allow researchers to dissect the epigenetic mechanisms acting in specific circuits and test their role in diet-dependent behavior. The use of functional neuroscience tools, such as in vivo imaging, electrophysiology, optogenetics, and imaging, will also lay the foundation to link metabolic-epigenetic signaling to underlying differences in neural physiology and morphology. For example, in (Gan et al., 2020; Vaziri et al., 2020) the authors used cell specific measurements of chromatin binding, gene expression, in combination with mutants and functional neuroscience assays such as imaging and electrophysiology to link diet and epigenetic changes to variations in neural physiology and behavioral phenotypes in flies and mice. Applying these intersectional strategies will help advance our understanding of the causal connection between metabolism, epigenetics, and neural physiology. Of note, all but two of the studies reviewed here used female animals, and so one of the important goals of the neuroepigenetics of nutrition field will be to study both sexes to understand the sex-specific effects of nutrition on disease.

Perhaps, the biggest challenge of the next decade will be to understand how metabolism senses environmental variation and orchestrates a coordinated response in neurons. This will

require mapping how diet alters metabolites in the body and the brain and how this affects metabolic signalling in specific neural cell types, as studies in the fields of development and cancer are accomplishing (Miyazawa and Aulehla, 2018; Pavlova and Thompson, 2016; Pearce and Pearce, 2018). While it is true that metabolomics studies can be costly and hard to do in small numbers of cells or in intact tissues, new techniques are emerging to measure brain metabolites and their effects on neurotransmitters (Perry et al., 2009; Qi et al., 2018; Rinschen et al., 2019). This step will be essential to link diet composition to variations in metabolite levels and epigenetic modifications. Another important aspect will be to integrate metabolomic analysis with cell specific assays for gene expression and epigenetic marks, to better understand how the network of metabolites and pathways is changed in the brain. In this context, the development of software to visualize these complex shifts based on the metabolic pathways of specific organisms will also be important (Karnovsky et al., 2012); for example our group recently published an open access tool called Flyscape for nutrigenetics analysis in *D. melanogaster* (Wilinski et al., 2019) and a similar tool is available for human studies (Karnovsky et al., 2012).

Open Questions and Future Directions: The studies discussed here highlight potential interactions between metabolites and epigenetic/gene regulatory pathways and their role in brain physiology and behavior. However, how exactly metabolic-epigenetic signaling contributes to neural function, neurotransmitter balance, and synaptic plasticity are still unanswered questions. Metabolic gene regulation plays a critical role during development (Miyazawa and Aulehla, 2018) and neuronal cells must continue to express their terminal differentiators to maintain their identity (Hobert, 2011). Thus, it is possible that modulation of synaptic plasticity and connectivity by environmental factors such as diet may be achieved by altering the expression of neuronal identity/developmental programs, as recently suggested in (Vaziri et al., 2020). This possibility raises the question of specificity in the action of metabolic signaling pathways. Are different pathways engaged across brain regions or do they change depending on the cell type? If the same pathways are activated in different cell types, does the outcome of their activity depend on the transcriptional programs specific to each neuron type? And since neural cells such as glia and neurons have fundamentally different metabolic profiles (Magistretti and Allaman, 2015), will fluctuations in dietary nutrients be read in unique ways among these two broad cell types ? These studies also raise the intriguing question of whether the informational role of metabolites is limited to functioning as cofactors or substrates for modifications, or whether metabolic enzymes and complexes are associated with epigenetic

complexes at neural genomic loci (Egervari et al., 2020; Haws et al., 2020). More broadly, thinking about the whole host of alterations that could occur with diet composition, it will be interesting to study whether areas of convergence between different brain metabolic-epigenetic signaling pathways and whether these reinforce the effects of environmental variation. Along these lines, there could also be convergence between individual genomic variation at specific loci, such as the DAT gene, and diet-induced effects. This could give rise to gene x environment interactions that are often observed in the context of neuroepigenetics and vulnerability to disease, such as with the case of abuse/trauma and naturally occurring variation in the BDNF and Serotonin Transporter genes (Gutiérrez et al., 2015). In this light, therapeutics that target metabolic regulatory and signaling pathways could potentially be used to treat neurological and psychiatric conditions (Kuehner et al., 2019).

Concluding Remarks:

Converging evidence from animal models and human studies suggests that the dietary environment influences the brain epigenome to change neural physiology and behavior in ways that promote or protect from disease. While so much still remains to be defined about the molecular mechanisms through which dietary metabolites can shape the brain epigenome, a multidisciplinary approach that integrates tools at the intersection of neuroscience, epigenetics, and metabolism will pave the way for the next decade of research in this field. In particular, the development of new tools and the establishment of shared experimental approaches across model organisms will be essential to tackle the many open questions. Together, these will propel our understanding of the mechanisms that underlie the profound link between nutrition, brain health, and disease. This question has been with us for thousands of years, and it's exciting to know that in the not too distant future, we may finally be able to answer it.

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FIGURES and LEGENDS

Figure 1: The influence of diets on metabolites and the epigenetic machinery.

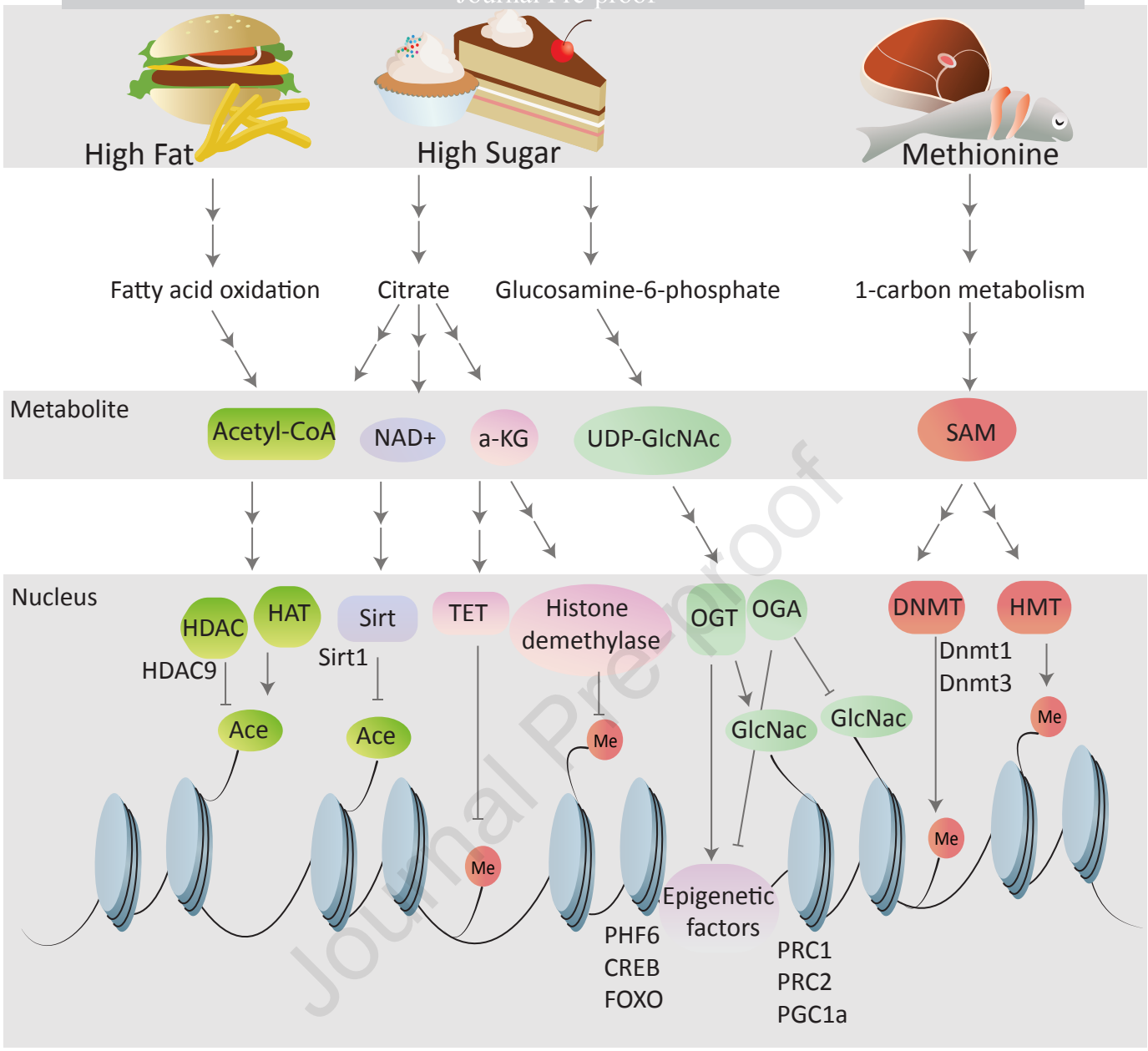
Diets high in fat and sugar alter the levels of acetyl-coA through fatty acid oxidation and citrate metabolism. Changes in acetyl-coenzyme A (acetyl-coA) levels impact the activity of Histone Acetyl Transferases (HAT) and Histone Deacetylases (HDAC) leading to changes in histone acetylation and subsequently gene expression. Diets high in sugar influence the levels of Nicotinamide adenine dinucleotide (NAD+) and α-Ketoglutarate (a-KG) that change the activity of NAD-dependent histone deacetylases (Sirtuins), and DNA and histone demethylases, respectively to influence gene expression. 1-3% of sugar enters the Hexosamine Biosynthesis Pathway (HBP) and leads to the production of uridine diphosphate GlcNAc (UDP-GlcNAc) from the intermediate metabolite glucosamine-6-phosphate. UDP-GlcNac is added to the Serine/Threonine residues of target proteins and histones by O-GlcNAc Transferase (OGT). UDP-GlcNAc can be dynamically removed by O-GlcNAcase (OGA). Dietary methionine fuels one-carbon metabolism and leads to the production of S-Adenosylmethionine (SAM), a cofactor to DNA methyltransferases (DNMT) and Histone methyltransferases (HMT), to mediate gene expression. The studies covered implicate the epigenetic modifiers Histone deacetylase 9 (HDAC9), Sirtuin 1 (Sirt1), DNA methyltransferase 1 and 3 (Dnmt1 and Dnmt3, respectively), PHD finger protein 6 (PHF6), cAMP response element-binding protein (CREB), FOXO, Polycomb Repressive Complex 1 and 2 (PRC1 and PRC2, respectively), and the Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1a).

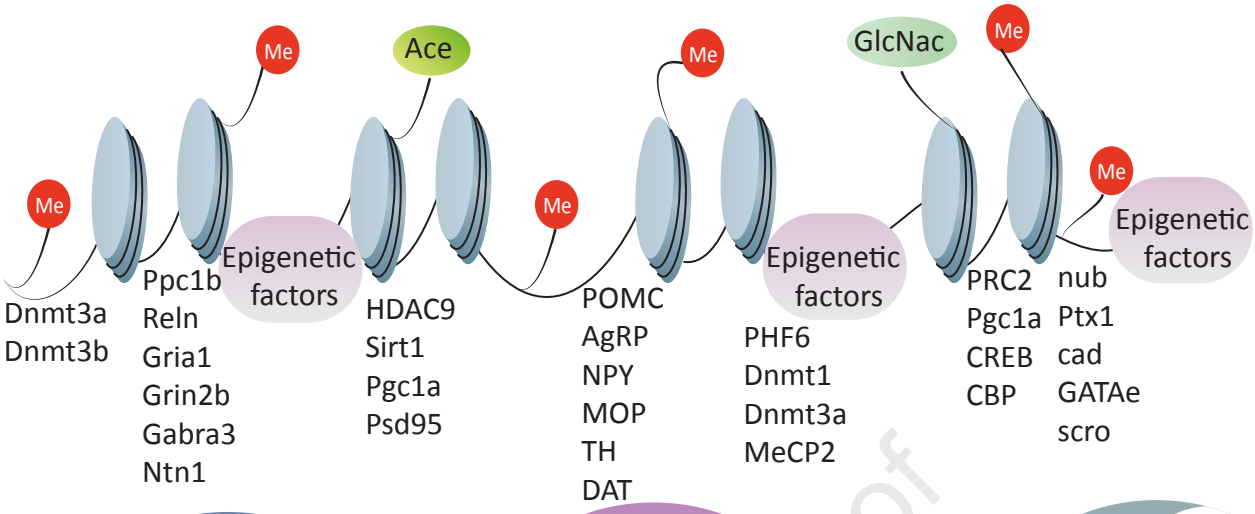
Figure 2: Dietary regulation of the epigenetic machinery and its effects on gene expression and behavior.

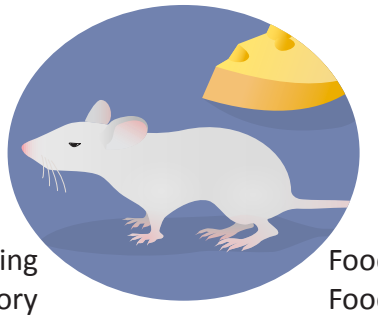
(Left) Diets high in fat and sugar and with different amounts of methionine change the expression of neural genes such as the DNA methyltransferases (Dnmt3a and Dnmt3b), Netrin-1 (Ntn1), Phosphatidic acid phosphatase 1b (Ppc1b), Reelin (Reln), Glutamate Ionotropic Receptor AMPA Type Subunit 1 (Gria1), N-methyl D-aspartate receptor subtype 2B (Grin2b), Gamma-aminobutyric acid receptor subunit alpha-3 (Gabra3), Histone deacetylase 9 (HDAC9), Sirtuin1 (Sirt1), Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Pgc1a), and postsynaptic density protein 95 (Psd95) in the hippocampus. These changes in expression are associated with alterations in behaviors like learning and memory, repetitive motor behavior, and anxiety. (Middle) Diets high in fat alter genes such as Pro-opiomelanocortin (POMC), Agouti-related protein (AgRP), Neuropeptide Y (NPY), mu-opioid (MOP) receptor, Tyrosine hydroxylase (TH), Dopamine transporter (DAT), PHD finger protein 6 (PHF6), DNA methyltransferases 1 and 3a (Dnmt1 and Dnmt3a), and methyl CpG binding protein 2 (MeCP2) in the striatum and hypothalamus of rodents. These shifts in expression influence food intake to promote weight gain and obesity. (Right), diets high in sugar affect the activity of nutrient-dependent transcription factors and epigenetic modifiers such as the Polycomb Repressive Complex 2 (PRC2), Pgc1a, cAMP response element-binding protein (CREB) and the CREB binding protein (CBP), which in turn can mediate the expression of homeobox genes (nubbin, Ptx1, caudal, GATAe, and scarecrow). These variations in chromatin binding and gene expression underlie changes in neural and behavioral phenotypes such as chemosensory plasticity, food intake, and choice, promoting weight gain and obesity.

Table 1: Mechanisms of the Neuroepigenetics of Nutrition

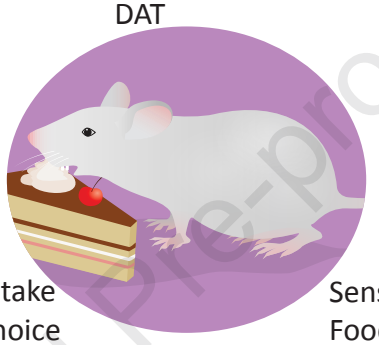
Epigenetic mechanisms	**Covered in this review?**	**Mechanism reviewed in**
DNA modifications	Yes	(Bannister and Kouzarides, 2011; Li et al., 2018)
RNA modifications	No	(Jung and Goldman, 2018; Roundtree et al., 2017; Tzelepis et al., 2019)
Post-translational protein modifications	Yes	(Olivier-Van Stichelen et al., 2017; Yang and Qian, 2017)
Chromatin remodeling	No	(Morrison, 2020; Reid et al., 2017; Suganuma and Workman, 2018)
Noncoding RNAs	No	(Yao et al., 2019; Zhao and Lin, 2015)
Transposons	No	(Fedoroff, 2012; Slotkin and Martienssen, 2007)
Histone modifications	Yes	(Berger, 2007; Berger and Sassone-Corsi, 2016; Sivanand et al., 2018)



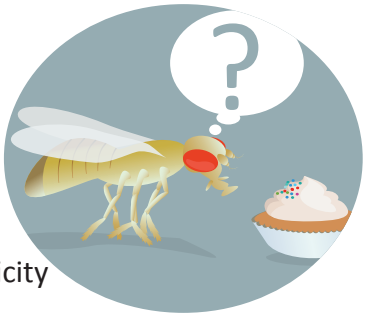




Learning
Memory
Motor defects (ASD)
Anxiety



Food intake
Food choice



Sensory plasticity
Food intake
Food choice

Highlights

- The dietary environment is associated with changes in the brain epigenome, such as histone modifications, DNA methylation, and chromatin occupancy.

- These changes are correlated or causally linked to alterations in learning and memory, food intake and energy balance, motivated behaviors, anxiety and depression.

- Nutrients can directly fuel the epigenetic machinery, but which metabolic pathways remodel the brain epigenome in different dietary environments is still under investigation

- The next decade of studies in this field will have to surmount a number of challenges to answer the many open and exciting questions about the role of metabolic-epigenetic signaling in the brain

Conflict of Interests: The authors declare no conflict of interest.