The Role of Nutritional Status in Neuroepigenetic Modification

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Abstract The study of epigenetic has brought about a deeper understanding of developmental programming through a complex network of modifications involving the DNA. While the DNA sequence remains conservative throughout, the mechanism of epigenetic modification involves changes through histone modification, DNA methylation, and chromatin remodeling. The overall dynamic effect of epigenetic modification allows the gene expression to be altered leading to a diverse phenotypical expression; a functional change in the genome without affecting the DNA. The emergence of nutritional neuroepigenetic serves to bring into focus the impact of nutrition as an environmental agent in regulating gene expression patterns leading to phenotypical expression with profound neurological and cognitive implication in later life. This link is supported by evidence from animal models suggesting that epigenetic marks, which are formed following DNA methylation or histone modification, can induce changes leading to developmental diseases or persist into adulthood. The difficulty in understanding the intrinsic biomolecular correlation between 1) epigenetic modification, 2) nutritional imbalance, and 3) cognitive impairment in an animal based model provides a compelling question regarding the developmental origins of cognitive related diseases. There have been few animal model studies involving the molecular basis of neuroepigenetic dysfunction in the relation to overnutrition or under nutrition. The main criteria in this review will focus on the few animal based studies in nutrition based epigenetic reprogramming and its role in neuroepigenetic dysregulation and cognitive impairment.

Keywords: *cognition, autism, dementia, malnutrition, obesity, neuroepigenetic, memory*

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1. Introduction

The field of epigenetics has brought a wide ranging understanding into somatically heritable states of gene expression [1] through changes in the genome without altering the DNA sequence. The phenomena of epigenetic changes are brought about through various mechanisms such as DNA methylation, histone modifications, chromatin remodeling and miRNA. During the developmental process of the fetus, maternal environmental exposures such as nutritional deficiency can lead to susceptible epigenomic dysregulation [2] with strong implications in the phenotypical expressivity or in the development of later life diseases. The impact of maternal nutritional deficiency has been implicated in poor nervous system development as a result of heritable changes in DNA methylation state during cell division [2,3,4]. While it is well known that folate deficiency during the early gestational period can result in spinal dysraphism, some epigenetic processes involving DNA methylation and histone methylation causes inheritance process (genomic imprinting). In Beckwith-Wiedemann Syndrome results from an epigenetic mutation wherein a preferential or exclusive domain from either the paternal or maternal allele is expressed [5].

The phenomenon of epigenetic imprinting through the DNA methylation has been well studied. DNA methylation is stable and common throughout the human genome. It occurs within the CpG dinucleotides, which exists in methylated and unmethylated form. The establishment of DNA methylation patterns occurs through a complex enzymatic action of DNA methyltransferases (DNMT). During this reaction the methyl group of S-adenosylmethionine is donated to the 5' position of cytosine, resulting in the formation of 5-methylcytosine [6,7]. The CpG dinucleotide methylation process provides the mechanism in transmitting DNA methylation patterns to subsequent generations, a form of epigenetic inheritance.

In order to achieve the inheritance pattern, the enzyme DNA methyltransferase 1 (DNMT1) acts to keep the methylation mark on the cytosine on the nascent strand during DNA replication [6,8]. This is particularly important in epigenetic gene regulation since variations in this process have been associated with developmental abnormalities, particularly neurodegenerative disorders such as cerebellar ataxia, deafness and hereditary sensory neuropathy.

While DNA methylation provides a stable and well understood process, in contrast histone methylation is

more complex and difficult. And while DNA methylation of CpG islands in the gene promoter region is associated with repression of gene transcription [6,7], in contrast histone methylation results in gene transcription that is typically either activated or repressed, depending on the type of methylation and position of the methyl group attached.

Histone proteins are part of the fundamental unit of a nucleosome. Work on histone modification is associated with transcriptional activation or deactivation. Histone modifications undergo a post-translational process involving methylation, phosphorylation, acetylation, ubiquitination, and sumoylation. During this stage, chromosome packaging and transcription activation or deactivation can take place, which can alter the chromatin structure. Epigenetic mark provides basis for quantitative detection of misguided transcriptional states and increased susceptibility to diseases [2,9,10].

Methylation is involved in nearly every aspect of life. *S*-adenosyl methionine (SAM) is a substrate in the methyl-transfer reaction that serves as the sole methyl donor for a variety of reactions in DNA, proteins, phosphilipids, and neurotransmitters. In histone methylation, histone methyltransferases (HMT) act on lysine or arginine residues of the H3 and H4 histones by transferring the methyl group from SAM, which also requires dietary folate as methyl donors. Histone methylation results in different effects on gene activity. For instance, the enrichment at H3K9me, H3K20me, or H4K27me [11,12,16] will result in gene repression, whereas enrichment of histone methylation at H3K4me, H3K36me, or H3K79me [13,14,15] will result in active transcription. In adjusting the acetylation or methylation of histone modifying enzymes, dysregulation that occurs has been implicated in several types of cancer development.

Histone acetylation is generally more simplified. The acetylation of lysine residues in histone H3 and H4 involves the enzyme histone acetyltransferase (HAT), or deacetylation by histone deacetylases (HDACs). Histone acetylation can disrupt the chromatin structure by regulating the transcription activity. Actively transcribed regions of chromatin involve hyperacetylated histones, whereas transcriptionally silent regions involved hypoacetylated histones. This provides a more predictable correlation with activated transcribed genes, which is more often difficult to achieve in histone methylation [8,11,17]. Large number of studies provides evidence of the role of dietary histone deacetylase inhibitor (HDAC) in cancer [18] and neuro-cognitive diseases [19,20,21,22].

2. Methods

The role of animal based studies is critically important in furthering our knowledge and understanding into the molecular basis of epigenetic modification and related environmental (nutrition) agents in disease causation. However, given the difficulty in designing protocols, knockout models, and techniques that are designed to look into nutritional epigenetics and developmental origins of cognitive impairment, it is not surprising that there a very few of these research studies undertaken. Furthermore,

there are perils in using these animal models. For instance, rats expressing transgenes in the study of dementia that are similar to those used in transgenic mouse models, have been shown that few of them have actually develop the plaques notable in Alzheimers dementia [23]. In addition, the problem of bias and randomization remains an inherent problem in the research community [24].

There are many studies in epigenetic programming looking at environmental (nutrition) influence and subsequent neuropsychological adverse outcome. However, there have been only a handful of animal studies looking at the causality and subsequent neural biology changes that occur following nutrition related epigenetic modifications. The scope of our journal search involved research articles. The main selection criterion was based on animal based studies with these 2 key factors: 1) nutritional epigenetic modification, and 2) the resultant neuropsychological cognitive impairment.

2.1. Nutritional Epigenetic Modification: DNA Methylation and Histone Acetylation

Even as we continue to gain insight and understanding in the mechanism of epigenetics the challenge in accurately predicting the outcome of a genome following DNA methylation or histone modification remains elusive. DNA methylation alone is involved in a wide array of tissue specific gene expression from differentiation, developmental programming, chromatin restructure and genomic imprinting resulting in phenotypic variance. Even though observations on the correlation between environment and epigenetic modification through DNA and histone methylation are well established, the specific, predictive function and outcome has yet to be elucidated. Environmental observation serves as a function of epigenetic modification that is necessary in the hierarchical understanding of how nutrition plays a critical role in a diverse range of biological processes involved in the regulation of gene expression. In turn these functional outcomes provide relevant understanding of disease programming and development.

Nutrition is a key environmental factor that has gained broad interest with its strong influence in epigenetic modification. The causal relationship between nutrition and DNA methylation has been clearly elucidated both in animal studies and clinical disease entities. The study of folic acid in DNA methylation process provides an invariable basis in nutritional epigenetic. It is a water soluble vitamin and a one-carbon source in the critical cellular pathway for DNA and protein methylation. The consumption of folic acid leads to its reduction into tetrahydrofolate (THF), which in the presence of Vitamin B6 dependent enzyme serine hydroxymethyltransferase is ultimately reduced to 5-methyltetrahydrofolate (5-methylTHF). This reaction provides the supply of methyl groups for the remethylation of homocysteine to methionine as well as DNA methylation.

The association between diet and DNA methylation can lead to corresponding metabolic alterations with profound implications. Studies involving animal models [25,26,27,28] reveal changes in the gene expression activity and subsequent enzyme activity. These metabolic changes in

turn can lead to increase susceptibility to chronic diseases such as diabetes, cardiovascular diseases, obesity and even cancer. The total burden of DNA hypermethylation and histone hypoacetylation is known to cause gene repression which can invariably lead to these diseases. For instance when DNA hypermethylation causes epigenetic control and suppression of adiponectin- a protein in humans that helps regulate glucose and fatty acid metabolism- there is a subsequent increase expression of DNA methyltransferase I (DNMT1) which acts to suppress the level of adiponectin activity. The result is a predictable exacerbation of obesity. Alternatively, when DNMT1 activity is suppressed, the level of adiponectin expression rises while decreasing obesity-induced glucose intolerance and insulin resistance [26]. This is particularly important as it suggests that the epigenetic modifications through DNA methylation can result in chromatin remodeling with adverse and deleterious effects on the metabolic outcome of individuals.

The epigenetic control of various metabolic processes is not limited to DNA methylation programs alone. Molecular mechanisms involving histone deacetylase inhibitor (HDAC) in mice [19,20,29] has led to further studies to determine possible therapeutic modalities. Histone deacetylases (HDACs) has been implicated in insulin resistance and subsequent development of cognitive impairment in dementia. When mice were subjected to a high fat diet (8 weeks), the results revealed a reduction of H3 acetylation and BDNF (brain derived neurotrophic factor) along with decrease memory and learning deficits [29]. These findings represent findings that notable in Alzheimer's disease. In contrast mice that were fed with high fat diet and given HDAC inhibitor (suberoylanilide hydroxamic acid, SAHA) revealed increased levels of H3 acetylation and BDNF, suggesting a neuroprotective role and potential disease modifying agent.

2.2. Maternal Nutrition & Fetal Programming

The honeybee model provides a unique example of the role of maternal diet in genomic imprinting that can affect the DNA methylation, resulting in a phenotypical different offspring. The caste determination in honeybees has been well studied in detail and represents an example of developmental programming in epigenetics. Even though female honeybee larvae possess identical gene sequences [30,31] they will develop either to become a worker or a queen bee, depending on the diet given to them. In this case, a female larvae fed with royal jelly will develop to become the queen bee, while other larvae fed with regular diet develops into worker bees. The difference in gene expression is primarily determined by DNA methylation. Studies have shown that silencing of the DNA methyltransferase 3 (DNMT3) induces the development of queen bees that are fed with royal jelly [31,32].

The precise role of epigenetic modification during fetal development is not yet fully understood. Strong evidence suggests that early life insult even during pregnancy can lead to fetal developmental programming by which epigenetic marks such as DNA methylation and histone modification could elicit lifelong effects on the health of the offspring. Observations made on the maternal nutritional state during pregnancy indicates that epigenetic changes in the fetus can in turn lead to susceptibility changes in the gene transcription process and later life diseases. Fetal overnutrition can have negative implications that can lead to neuro-metabolic syndrome of diabetes, obesity and adult onset dementia [25,27]. Recent epidemiological and animal studies have shown that patterns of obesity in later life is mediated by the early changes in gene expression starting from maternal nutrition to fetal programming leading to several transcription factor susceptibility changes.

2.3. The Epigenetics of Cognitive Disorders & Nutrition

Cognitive process implies the constructive ability to understand process information and create fund knowledge and store them through memory. The mechanism by which cognition takes place requires a series of refinement and cortical response by which the experience dependent neuroplasticity is altered and stored as memory. The regulation of synaptic plasticity and formation of memory is accomplished through epigenetic mechanisms of transcription regulation [33,34,35]. The role of DNA methylation on CpGs is an epigenetic activity that results in the silencing of transcription regulation through the catalytic activity of DNA methyltransferases (DNMTs). Besides the CpG methylation, DNA methyltransferase is also involved in the active demethylation of 5mCpGs through deamination process. The active inhibition of methylation will result in demethylation and subsequent transcriptional activation. The overall result of DNA methylation and DNMTs is the consolidation of memory. This molecular storage and consolidation of memory relies on the hippocampal methylation and cortical hypermethylation for long term memory. Conversely, DNMT inhibition leads to *de*methylation and transcriptional activation of the memory suppressing genes [34,36,37]. These epigenetic events create a memory of cell identity while their genomic functions remain conservative, stable and maintain its function.

The construct relationship of cognitive neurosciences and nutrition is predicated upon the epigenetic regulation which serves to modify gene expression without changing the DNA sequence. As we continue to advance our knowledge in the epigenetic of nutrition, the global impact of cognitive disorders continue to rise. The effect of nutrition in cognitive development and degenerative conditions is mediated thru multiple gene expressivity and variability. Various studies looking into the role of nutrition and cognition reveals a cause & effect through methylation and histone modifications. The silencing of transcription factors while activating other factors suggest that nutrition plays a critical role in shaping the development of neuro-cognitive conditions through gene modification.

There is strong evidence from animal and human studies that support the level of understanding related to the development of cognitive impairment following epigenetic alterations and its effect in cell specific and age related gene expression. These results suggest that the key

mechanism by which cognitive dysfunction occurs can be a long term effect of poor diet and nutrition which in turn mediate changes in the epigenome that can modify gene expression and enable the development of neurological diseases. This layer of regulation has important implications into the hypothesis of the "developmental origin of health and disease" (DOHaD). These epigenetic changes are theoretically potentially reversible which provides a critical concept in the role of nutrition in the prevention and treatment of diseases.

The effects of dietary factors in the brain have been well documented and elucidated in human and animal studies. The interaction between environmental factors such as nutrition, age, and physical activity is required for proper brain functioning. Alterations from this highly regulated interaction have been linked to cognitive decline such as dementia and Alzheimer's disease. One of the most widely investigated hypotheses has been the role of Vitamin B12 and folate can affect the methylation process by altering the one-carbon metabolism [3,7,38]. Altered cholesterol homeostasis in general has also been implicated in the development of late-onset Alzheimer's disease [39,40]. The elevated cholesterol level results in a pro-inflammatory environment in the brain which contributes to the development of cognitive impairment, but could also lead to enhanced amyloidogenesis by up-regulation of BACE-1 (the beta-secretase enzyme in Alzheimer's disease [39]. Studies on the role of polyunsaturated fatty acids in learning and behavioral impairment such as ADHD (attention deficit hyperactivity disorder) provide a potential treatment through nutritional supplement. Dietary supplementation of n-3 polyunsaturated fatty acid (PUFA) on patients with attention-deficit hyperactivity disorder (ADHD) [41,42] results in improvement of literacy and behavior.

2.4. Neuroepigenetic Dysregulation from Overnutrition

Overnutrition is a metabolic condition that predisposes an individual to obesity, diabetes and nutritional deficiencies. Overnutrition can not only result in insulin resistance and hyperglycemia but its long term outcome can lead to epigenetic reprogramming. There have only been a few in vivo and in vitro studies by which the dynamic relationship between the contribution of DNA methylation and overnutrition (obesity) in relation to the development of cognitive related diseases has been shown. Part of the inherent difficulty in methylation studies and overnutrition comes from the diverse epigenetic expression across the spectrum of cognitive dysfunction. For instance the DNA methylation expression in the neuropathological substrates of Alzheimer's disease can vary significantly across the spectrum of disease. Even beyond the spectrum of the disease, methylation studies performed in blood reveals a complete different expression done in the brain [43]. This observation is supported by studies showing that the higher the methylation is around the gene, the lower the expression.

Table 1. Neuroepigenetic Dysregulation from Overnutrition

Title	Author	Cognitive Disorder	Epigenetic Mechanism	Neuro-Epigenetic Modification
1) Obesity Weighs down Memory through a Mechanism Involving the Neuroepigenetic Dysregulation of Sirt1.	Heyward F.D., et al.	Memory-impairing effect	DNA methylation	Effects of diet-induced obesity may potentially be mediated by neuro-epigenetic alteration of Sirtuin 1 (Sirt1) via DNA methylation within the hippocampus.
2) Epigenetic Modification in Metabolic Syndrome/Induced Brain Energy Impairment	Varghese M., et al.	Dementia, Alzheimer's disease	Histone deacetylase 5 (HDAC5)	Diet induced metabolic syndrome (obesity) might induce epigenetic modification of DNA that controls energy metabolism, while modulation of HDAC activity may improve mitochondrial function in neurons.
3) Childhood and adolescent obesity and long-term cognitive consequences during aging	Wang J., et al.	Synaptic dysfunction	Histone deacetylase 5 (HDAC5)	Obesity and insulin resistance during childhood/adolescence induces irreversible epigenetic modifications leading to increased expression of histone deacetylases 5, accompanied by reduced expression of brain-derived neurotrophic factor (BDNF)
4) Epigenetic dysregulation of the dopamine system in diet-induced obesity.	Vucetic Z., et al.	Dopamine homeostatic control of central reward circuitry	DNA methylation	High fat diet led to altered DNA methylation within the promoter regions of tyrosine hydroxylase (TH) and dopamine transporter (DAT), thereby affecting Ventral tegmental area (VTA), Nucleus accumbens (NAc), & Pre-frontal cortex (PFC).
5) Chronic High-Fat Diet Drives Postnatal Epigenetic Regulation of μ-Opioid Receptor in the Brain.	Vucetic Z., et al.	μ-Opioid receptor (MOR) homeostatic control	DNA methylation	Increase DNA methylation led to increase binding of MeCP2 at the MOR promoter region (Ventral tegmental area (VTA), Nucleus accumbens (NAc), Prefrontal cortex (PFC), & hypothalamus). Subsequently increased H3K9 methylation and decreased H3 acetylation.

Childhood and adolescent overnutrition is causally related to obesity and juvenile onset diabetes. Early onset of obesity can lead to cognitive changes such as memory impairment and learning difficulties. Memory is a cognitive function that relies on the hippocampus part of the brain for storage and later retrieval. Damage to the hippocampus can lead to memory impairment and difficulty in establishing new memories. Recent studies suggest that the loss of memory in the state of obesity results from alterations in DNA methylation involving Sirtuin 1 (Sirt1) protein within the hippocampus. In vitro studies suggest that Sirtuin proteins are known to regulate epigenetic gene silencing and suppress recombination of rDNA. Experimental animal models on obesity induced memory impairment [44] *(Table 1: Heyward, et al.)* revealed that the effects of memory impairment from reduced hippocampal Sirt1 in knockout mice can be mitigated by dietary supplement of epigenetic based Sirt1 activating molecule (resveratrol). The result shows that the memory response mechanism improved following supplementation.

The epigenetic modification involved in obesity induced memory impairment is not restricted to DNA methylation alterations. Cognitive memory impairment can also result from alterations in histone deacetylase activity (HDAC). Obesity induced cognitive impairment can result from impaired glucose tolerance and epigenetic changes in the DNA which controls energy metabolism. Mice fed with high fat diet resulted in changes in the mitochondrial activity in the neuronal cells, leading to energy deficit [45] *(Table 1: Varghese, et al.)*. The addition of HDAC inhibitor trichostatin A proved to be beneficial in mediating an improved cognitive activity based on fMRI findings and isolated mitochondrial oxygen consumption. Nonetheless, the understanding of role of histone deacetylase (HDAC) in mitigating or reversing the effects of cognitive impairment induced by obesity remains incomplete. In a similar obesity induced mice model study, an increased expression of histone deacetylases 5 along with the reduced expression of brain-derived neurotrophic factor in the brain was observed following high-fat diet [46] *(Table 1: Wang, Freire, et al.)*. The findings of synaptic dysfunction in the hippocampus even after putting the mice on a regular diet suggest a more permanent and possibly irreversible epigenetic change in the brain that can persists following restoration of normal diet.

Obesity induced cognitive impairment is not limited to memory changes often linked to Alzheimer's disease, vascular dementia or learning disorders such ADHD. There are, however, exceptionally few studies linking obesity induced homeostatic dysregulation and cognitive impairment. Homeostatic regulation in the brain is a coordinated interaction involving the neurotransmitters, hormones, and peripheral metabolic organs. The homeostatic regulation impart by the brain is critical in the maintenance of energy and glucose metabolism. Dopamine is a neurotransmitter with a highly important role in regulating several metabolic processes. It serves a key role in the reward related brain regions, primarily involving prefrontal cortex, hypothalamus, ventral tegmental area (VTA), and nucleus accumbens (NAc). Using a mouse model of diet induced obesity [47] *(Table 1: Vucetic,*

Carlin, et al.), alterations in the hypothalamic dopamine expression was observed, while decrease expression was noted in the prefrontal cortex, VTA and NAc circuitry. High-fat diet (HFD)-induced models of obesity has also been observed in the opioid system dysregulation [48] *(Table 1: Vucetic, Kimmel, et al.)*. Similar results of increase opioid expression in the hypothalamus while decrease expression in the other circuitry was also observed. Taken together the results suggest that the epigenetic mechanism of DNA methylation linking the chronic intake of high fat diet led to altered dopamine or opioid related gene expression. Homeostasis was also altered with changes in either the dopamine or opioid expression in the reward related circuitry in the brain. These observations improves on further assumptions regarding the multiple, complex interaction between diet and the epigenetic modifications at various levels of involvement by which neuroepigenetic impairment can result in cognitive dysfunctions.

2.5. Malnutrition and Cognitive Impairment

The effects of malnutrition on DNA methylation during the vulnerable stages of development in children affect the health and behavioral outcomes in later life. The role of either DNA or histone modification is central to the understanding of epigenetic inheritance, while the role of chromatin remodeling remains less clearly understood since not all epigenetic inheritance involves the chromatin modification. Histone modification enzymes include a variety of post-translational processes and often do not provide a straightforward outcome in relation to the environmental insult in malnutrition. The influence of diet to DNA methylation is direct which comes specifically from SAM donor feedstock. Methionine, choline, and folic acid in the diet provide a major source of methyl group during DNA methylation. Significant reduction in their supply has a direct effect on the DNA methylation and gene expression, resulting in the alteration of protein transcription.

While nutritional status of an individual from birth to adulthood is strongly correlated to intellectual and cognitive development, the Dutch famine at the end of World War II provides an example of how nutritional deprivation can impact the neurodevelopment and cognitive outcomes in adults following prenatal famine. The results of prenatal famine were associated to cognitive outcomes in the following condition: (1) congenital anomalies of the central nervous system, (2) schizophrenia, and (3) schizophrenia spectrum personality disorders [49].

The longitudinal studies from the great famines (Dutch, Chinese, Barbados) [49,50,51] provide an analysis into the extent of cognitive dysfunction with a wide range of phenotypical expression. The long term impact on behavioral and learning processing disorders as a result of profound malnutrition showed persisting effects into adulthood even independent from nutrition rehabilitation. Research into the biomolecular effects of childhood nutritional deficiency in brain pathology suggests significant and potentially irreversible changes in the cortex, hippocampus, midbrain and brainstem [52,53,54]. Multiple regression analysis reveals problems related to focus, attention span, memory, and mood disorders were

commonly observed in these studies [54]. These areas are crucial throughout the lifespan but even more significant during early cognitive development.

In the Barbados Nutrition Study [55] (Table 2: *Peter, Fischer, et al.*), DNA methylation study was conducted on 168 individuals exposed to severe malnutrition revealed long lasting epigenetic changes in the prefrontal cortex that are associated with increase susceptibility to attention and cognitive disorders. The study identified 134 nutrition sensitive, differentially methylated genomic regions. Further identification of specific neuropsychiatric risk genes (including COMT, IFNG, MIR200B, SYNGAP1, and VIPR2) revealed the association of specific methyl-CpGs with attention and IQ. The lack of proper nutrition during maternal pregnancy can similarly lead to learning and behavioral disabilities (ADHD), autism spectrum disorder and even neuropsychiatric conditions [56] (Table 2: *Udagawa, Hino*). The study suggests the role of maternal reprogramming of the hypothalamic-pituitary-adrenal axis which can then possibly lead to neuro-epigenetic modification and later cognitive susceptibility in the offspring.

The association of micronutrient deficiency in the development of neuro-epigenetic dysfunction has been elucidated in a few studies. For instance, the presentation of dementia in animal studies can be reduced by increasing the DNA methylation in conjunction with increased S-adenosylmethionine (SAM) expression [57] (Table 2: *Fuso, Seminara, et al.*). The epigenetic modification that takes place in this process is highly regulated by the availability of folic acid and vitamin b micronutrients. A significant micronutrient dysregulation would therefore lead to neuroepigenetic changes and subsequent neuropsychiatric development.

Severe nutritional micronutrient deficiency (iodine, iron, zinc and vitamin B-12) can result in poor neuro-cognitive development. Iodine deficiency during the prenatal stage can result in devastating clinical outcomes resulting in congenital hypothyroid and related cognitive dysfunction. In many parts of the world, iron deficiency continues to be a significant cause of morbidity. Iron deficiency anemia can lead to reduced oxygen carrying capacity especially to the brain. Children are highly susceptible to learning and behavioral disorder due to low levels of focus and attention as the brain requires increased amount of oxygen from which the blood cannot sustain adequately. Various animal models involving the relationship between iron [58,59] and zinc [60] deficiency reveals how the hippocampus-mediated spatial recognition learning is affected which ultimately leads to reduced memory and learning response. Observational studies link early life iron deficiency with the reduced expression of brain-derived neurotrophic factor (BDNF) [58], a gene critical for long-term memory and normal neuronal development, in the hippocampus and prefrontal cortex in the brain which ultimately affects the cognitive function into adulthood. The influence of zinc deficiency in neuropsychiatric pathology is better understood than its role in neuronal plasticity. Animal studies [50,60] suggest that zinc is essential in cognitive development specifically involving sensory skills, thinking, memory, learning and attention. The exact mechanism in relation to epigenetic modification is not clear and evidence is limited. Neuronal zinc is widely distributed throughout the cortex, amygdala and hippocampus, which subserve mood regulation and cognitive functions. Studies reveal that zinc deficiency leads to increase histone acetylation and decrease in deacetylation, methylation and phosphorylation in post-translational modification of H3 [61]. These findings suggest that zinc deficiency can play a role in altering hippocampal DNA methylation in the development of neuropsychopathology.

Table 2. Malnutrition and Cognitive Impairment

Title	Author	Cognitive Disorder	Epigenetic Mechanism Involved	Neuro-Epigenetic Modification
1) Impact of Maternal Stress in Pregnancy on Brain Function of the Offspring.	Udagawa J., et al.	Increased risks schizophrenia, autism spectrum dis-order (ASD), & attention-deficit hyperactivity dis-order (ADHD)	DNA methylation	Maternal stress reprograms the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the stress response in the offspring.
2) S-adenosylmethionine reduces the progress of the Alzheimer-like features induced by B-vitamin deficiency in mice	Fuso A., et al.	Alzheimer /Dementia	DNA methylation	Presenilin1 (PS1) & BACE (beta-secretase) regulated thru DNA methylation and that the reduction of folate and vitamin B12 in culture medium can cause a reduction of SAM levels
3) Folic acid, neurodegenerative and neuropsychiatric disease	Kronenberg G., et al.	Cerebral ischemia, Alzheimer's dementia and depression	DNA methylation	Low folate status and elevated homocysteine lead to induction of DNA damage, uracil mis-incorporation into DNA and altered patterns of DNA methylation and contribute to neurodegenerative and neuropsychiatric disease.

3. Conclusion

In elucidating the interrelationship between nutrition and cognitive neuroscience, thru its epigenetic modification, our understanding of the developmental programming in later life diseases continue to unfold. The specific role of overnutrition or malnutrition in creating a chronic stress environment represents a state of unmitigated, repeated stress resulting in various neuroepigenetic reprogramming. This neuroepigenetic reprogramming represents a dysfunctional state by which a lack of recovery phase and loss of transcription regulation can lead to the development of cognitive impairment and other neuropsychological conditions. The burden of epigenetic misprogramming is affected by the degree of environmental (nutrition) insult, although the critical temporal process remains undefined.

Unfortunately the specific molecular basis and mechanism by which nutritional status (either overnutrition or malnutrition) can cause neuroepigenetic modification, in relation to cognitive dysfunction, is not yet fully understood. There are few human and animal molecular studies looking into the association and causal effects of diet and nutrition in mediating the programming leading to neuroepigenetic dysregulation. Majority of studies nutritional cognitive studies are based on clinical observations, although these generally lack the molecular basis and hierarchical mechanisms to further expand our understanding. While basic science research is needed to properly elucidate these mechanisms, the lack of animal models specifically focused on neuroepigenetic and cognitive related disorder are also few and requires further development to advanced the breadth of our understanding.

The need to understand the interrelationship between the epigenetic of nutrition and cognitive dysfunction is critical in part due to the growing worldwide burden of metabolic disorders, malnutrition, dementia and psychiatric disorders. With the lack of understanding into the molecular mechanism of cognitive impairment as it relates to nutritional epigenetic modification, the role of proper diet and nutrition will remain the cornerstone in improving the clinical outcome of cognitive related diseases. The need to improve our understanding in relation to nutritional epigenetics can be best achieved through increase animal based studies and its cognitive neurological outcomes. Animal based protocols should also be improved by creating new knockout models and techniques. And without these objectives in place, our knowledge based understanding will remain unperturbed and remote.

References

[1] Choi, SW., & and Friso, S. (2010). Epigenetics: A New Bridge between Nutrition and Health. *American Society for Nutrition*, *1*, 8-16.

[2] Perera, F., Herbstman, J. (2011). Prenatal environmental exposures, epigenetics and diseases. *Reproductive Toxicology*, *31*(3), 363-373.

[3] Pogribny, I., Karpf, A., James, S., et al. (2008). Epigenetic alterations in the brains of fisher 344 rats induced by long-term administration of folate/ methyl-deficient diet. *Brain Research*, *1237*, 25-34.

[4] Radford, EJ., Ito, M., Shi, H., et al. (2014). In utero undernourishment perturbs the adult sperm methylome and is linked to metabolic disease transmission. *Science*. 2014; 345(6198): 1255903.

[5] Weksberg, R., Smith, AC.. (2003). Beckwith-Wiedemann syndrome demonstrates a role for epigenetic control of normal development. *Human Molecular Genetics*. 1, 12 Spec No 1: R61-8.

[6] Tammen, SA., Friso, S., Choi, SW. (2013). Epigenetics: the link between nature and nurture. *Molecular Aspects of Medicine*, *34*(4): 753-764.

[7] Crider, KS., Yang, TP., Berry, RJ. (2012). Folate and DNA Methylation: A Review of Molecular Mechanisms and the Evidence for Folate's Role. *Advances in Nutrition*, *3*: 21-38.

[8] Margueron, R., Reinberg, D. (2010). Chromatin Structure and the Inheritance of Epigenetic Information. *Nature Reviews Genetics*, 11, 285-296.

[9] Vickers, MH. (2014). Early Life Nutrition, Epigenetics and Programming of Later Life Disease. *Nutrients, 6*, 2165-2178.

[10] Dauncey, MJ. (2014). Nutrition, the brain and cognitive decline: insights from epigenetics. *European Journal of Clinical Nutrition*, 68(11):1179-85.

[11] Handy, DE., Castro, R, Loscalzo, J. (2011). Epigenetic Modifications: Basic Mechanisms and Role in Cardiovascular Disease. *Circulation*, *123*(19): 2145-2156.

[12] Ruthenburg, AJ., Li, H., Patel, DJ., Allis CD. (2007). Multivalent engagement of chromatin modifications by linked binding modules. *Nature Reviews Molecular Cell Biology, 8*(12): 983-94.

[13] Wang, Z., Zang, C., Rosenfeld, JA., et al. (2008). Combinatorial patterns of histone acetylations and methylations in the human genome. *Nature Genetics, 40*(7):897-903.

[14] Krivtsov, AV., Feng Z., Lemieux, ME., et al. (2008). H3K79 methylation profiles define murine and human MLL-AF4 leukemias. *Cancer Cell, 14*(5): 355-68.

[15] Guenther, MG., Levine SS., et al. (2007). A chromatin landmark and transcription initiation at most promoters in human cells. *Cell, 130*(1):77-88.

[16] The AACR Human Epigenome Task Force & EUNE. (2008). Scientific Advisory Board, *Nature, 454*, 711-15.

[17] Feinberg, AP., Tycko B. (2004). The history of cancer epigenetics. *Nature Reviews Cancer, 4*(2):143-53.

[18] Dashwood RH. & Ho, E. (2007). Dietary histone deacetylase inhibitors: from cells to mice to man. *Seminars in Cancer Biology, 17*(5), 363-369.

[19] Bassett, SA., Barnett, MPG. (2014). The Role of Dietary Histone Deacetylases (HDACs) Inhibitors in Health and Disease. *Nutrients, 6*(10): 4273-4301.

[20] Volmar, CH. & Wahlestedt, C. (2015). Histone deacetylases (HDACs) and brain function. *Neuroepigenetics, 1*, 20-27.

[21] Sun, H., Kennedy, PJ., Nestler, EJ. (2013). Epigenetics of the Depressed Brain: Role of Histone Acetylation and Methylation. *Neuropsychopharmacology*, *38*(1):124-137.

[22] Gold, PW. & Chrousos, GP. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Molecular Psychiatry, 7*(3): 254-275.

[23] Cavanaugh, SE., Pippin, JJ., Barnard, N. (2014). Animal Models of Alzheimer Disease: Historical Pitfalls and a Path Forward. *Altex*, 31(3):279-302.

[24] Andrea Gawrylewsk. (2007). The Trouble with Animal Models. The Scientist, Volume 21(7).

[25] Ge, ZJ., Luo, SM., Lin, F., et al. (2014). DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet–induced obesity. *Environmental Health Perspective*, 122:159-164.

[26] Kim, AY., Park, YJ., Pan, X., et al. (2015). Obesity-induced DNA hypermethylation of the adiponectin gene mediates insulin resistance. *Nature Communications*, 6: 7585.

[27] Zhang, N. (2015). Epigenetic modulation of DNA methylation by nutrition and its mechanisms in animals. *Animal Nutrition, 1*(3): 144-151.

[28] Zhang, P., Chu, T., Dedousis, N., et al. (2017). DNA methylation alters transcriptional rates of differentially expressed genes and contributes to pathophysiology in mice fed a high fat diet. *Molecular Metabolism*, 1-13.

[29] Sharma, S., Taliyan, R. (2016). Epigenetic modifications by inhibiting histone deacetylases reverse memory impairment in insulin resistance induced cognitive deficit in mice. *Neuropharmacology, 105*: 285-97.

[30] Barchuk, AR., Cristino, AS., Kucharski, R., et al. (2007). Molecular determinants of caste differentiation in the highly eusocial honeybee Apismellifera. *BMC Developmental Biology*, 7(70).

[31] Evans, JD., Wheeler, DE. (1999). Differential gene expression between developing queens and workers in the honey bee, Apismellifera. *Proceedings National Academy Science USA*, 96(10): 5575-80.

[32] Kucharski, R., Maleszka, J., et al. (2008). Nutritional control of reproductive status in honeybees via DNA methylation. *Science*, *319*(5871): 1827-30.

[33] Kangaspeska, S., Stride, B., Metivier, R., et al. (2008). Transient cyclical methylation of promoter DNA. *Nature 452*, 112-115.

[34] Courtney, A., Miller, J., Sweatt, D. (2007). Covalent Modification of DNA Regulates Memory Formation. *Neuron, 53*(6), 857-869.

[35] Métivier, R., Gallais, R., Tiffoche, C., et al. (2010). Cyclical DNA methylation of a transcriptionally active promoter. *Nature, 463*(7279): 384.

[36] Miller, CA., Campbell, SL., Sweatt, JD. (2008). DNA methylation and histone acetylation work in concert to regulate memory formation and synaptic plasticity. *Neurobiology of Learning and Memory, 89*, 599-603.

[37] Lubin, FD., Roth, TL., Sweatt, JD., (2008). Epigenetic regulation of BDNF gene transcription in the consolidation of fear memory. *Journal of Neuroscience*, 28, 10576-10586.

[38] Brunaud, Alberto, Ayav, et al. (2003). Effects of vitamin B12 and folate deficiencies on DNA methylation and carcinogenesis in rat liver. *Clinical Chemistry and Laboratory Medicine*, 41(8):1012-9.

[39] Chen, X., Hui, L., Geiger, JD. (2014). Role of LDL cholesterol and endolysosomes in amyloidogenesis and Alzheimer's disease. *Journal of Neurology & Neurophysiology, 5*(5):236.

[40] Fiorenza, MT., Dardis, A., Canterini, S., Erickson, RP. (2013). Cholesterol metabolism-associated molecules in late onset Alzheimer's disease. *Journal of Biological Regulators & Homeostatic Agents*, 27(2 Suppl): 23-35.

[41] Milte, Parletta, Buckley, et al. (2012). Eicosapentaenoic and docosahexaenoic acids, cognition, and behavior in children with attention-deficit/hyperactivity disorder: a randomized controlled trial. *Nutrition*, 28(6): 670-7.

[42] Bélanger, SA., Vanasse, M., Spahis, S., et al. (2009). Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: A randomized, double-blind, placebo-controlled study. *Paediatrics & Child Health*, 14(2):89-98.

[43] Bryan, J., Traynor, AE. (2015). Renton Exploring the Epigenetics of Alzheimer Disease, *JAMA Neurology*, 72(1): 8-9.

[44] Heyward FD., Gilliam D., Coleman MA., et al. (2016). Obesity Weighs down Memory through a Mechanism Involving the Neuroepigenetic Dysregulation of Sirt1. *The Journal of Neuroscience* 36(4): 1324-1335.

[45] Varghese M., Wang J., Cheng A., et al. (2012). Epigenetic modification in metabolic syndrome-induced brain energy impairment. Alzheimer's & Dementia: *The Journal of the Alzheimer's Association* 8:4, 253-55.

[46] Wang J., Freire D., Knable L., et al. (2015) Childhood and adolescent obesity and long-term cognitive consequences during aging. *Journal of Comparative Neurology* 523:5, 757-768.

[47] Vucetic Z., Carlin JL., Totoki K., Reyes TM. (2012). Epigenetic dysregulation of the dopamine system in diet-induced obesity. *J Neurochem*. 120(6): 891-8.

[48] Vucetic Z., Kimmel J., Reyes TM. (2011). Chronic High-Fat Diet Drives Postnatal Epigenetic Regulation of μ-Opioid Receptor in the Brain. *Neuropsychopharmacology*. 36(6): 1199-1206.

[49] Hoek, HW., Brown, AS., Susser, E. (1998). The Dutch famine and schizophrenia spectrum disorders. *Social Psychiatry and Psychiatric Epidemiology*, 33(8): 373-9.

[50] Liu, J., Zhao, SR., Reyes, T. (2015). Neurological and Epigenetic Implications of Nutritional Deficiencies on Psychopathology: Conceptualization and Review of Evidence. *International Journal of Molecular Sciences*, 16(8): 18129-18148.

[51] Galler, JR., Bryce, CP., Zichlin, ML., et al. (2012). Infant Malnutrition Is Associated with Persisting Attention Deficits in Middle Adulthood. *The Journal of Nutrition*,142(4): 788-794.

[52] Schmidt, AT., Alvarez, GC., Grove, WM., et al. (2012). Early iron deficiency enhances stimulus-response learning of adult rats in the context of competing spatial information. *Developmental Cognitive Neuroscience*, 2(1): 174-80.

[53] Penido, AB., Rezende, GH., Abreu, RV., et al. (2012). Malnutrition during central nervous system growth and development impairs permanently the subcortical auditory pathway. *Nutritional Neuroscience*, 15(1): 31-6.

[54] Rocinholi, LF., de Oliveira, LM., Colafêmina, JF. (2001). Malnutrition and environmental stimulation in rats: wave latencies of the brainstem auditory evoked potentials. *Nutritional Neuroscience, 4*(3): 199-212.

[55] Udagawa J., Hino K. (2016). Impact of Maternal Stress in Pregnancy on Brain Function of the Offspring. *Nihon Eiseigaku Zasshi* 71(3):188-194.

[56] Fuso A., Seminara L., Cavallaro RA., et al. (2005). S-adenosylmethionine/homocysteine cycle alterations modify DNA methylation status with consequent deregulation of PS1 and BACE and beta-amyloid production. *Molecular and Cellular Neurosciences* 28(1): 195-204.

[57] Kronenberg G., Colla M., Endres M. (2009). Folic acid, neurodegenerative and neuropsychiatric disease. *Current Molecular Medicine* 9(3): 315-23.

[58] Blegen, MB., Kennedy, BC., Thibert, KA., et al. (2013). Multigenerational effects of fetal-neonatal iron deficiency on hippocampal BDNF signaling. *Physiological Reports*, 1(5):e00096.

[59] Schmidt, AT., Alvarez, GC., Grove, WM., et al. (2012). Early iron deficiency enhances stimulus-response learning of adult rats in the context of competing spatial information. *Developmental Cognitive Neuroscience*, 2(1): 174-80.

[60] Hagmeyer, S., Haderspeck, JC., Grabrucker, AM. (2014). Behavioral impairments in animal models for zinc deficiency. *Frontiers in Behavioral Neuroscience*, 8: 443.

[61] Sadli, N., Ackland, ML., De Mel, D., et al. (2012). Effects of zinc and DHA on the epigenetic regulation of human neuronal cells. *Cellular Physiology & Biochemistry*, 29(1-2): 87-98.