Nutrition, the Brain and Epigenomics: A Lifelong Approach to Optimal Cognition

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Abstract

Nutrition affects the brain throughout life, with profound implications for optimal cognition. Advances in epigenomics are helping to elucidate the underlying mechanisms involved. Nutrition is one of many epigenetic regulators that modify gene expression without changes in DNA sequence. Although epigenetic modifications can be stable and heritable, they can be reversible, emphasizing critical roles for nutrition in both prevention and treatment of cognitive impairment. Insights into nutritional regulation of gene expression, involving a One Health strategy across species, should provide novel lifelong approaches to optimal cognition and mental well-being in companion animals.

Glossary of Abbreviations
BDNF: Brain-Derived Neurotrophic Factor
DHA: Docosahexaenoic Acid
IGF: Insulin-Like Growth Factor
miRNA: MicroRNA
ncRNA: Nonprotein-Coding RNA
SIRT1: Sirtuin Silent Information Regulator 1

Introduction

Optimal brain development, structure and function result from complex interactions between numerous factors, including food intake, physical activity, microbiota, social interactions, stress, infections, and genetics. Advances in epigenomics, genomics, and brain imaging are providing insights into the molecular mechanisms involved.[1-9] They suggest novel approaches to optimization of cognition and prevention of cognitive decline and dementia.

Nutrition has a highly complex role in neurological function. Effects can be beneficial or detrimental, as well as immediate or long term. The concern is not with the impact of a single chemical on the brain, but with multiple nutritional components and other interacting environmental and genetic factors.[10-14] Changes in expression of multiple genes and associated regulatory networks play a key role in mediating these effects, and responses to nutrition are, in turn, affected by genetic variability.[1,4] A critical layer of regulation is provided by the epigenome. Nutrition is one of many epigenetic regulators that modify gene expression without changes in DNA sequence. Epigenetic modifications affect gene expression in multiple brain processes and are an integral part of brain development and function. Nutrition could, thus, be used throughout life to optimize cognition and alleviate adverse effects of early-life experiences on the brain.

This review focuses on interactions between nutrition, the brain, and cognition, and the underlying mechanisms involved. Three interrelated topics are discussed:

1. The role of nutrition in brain health and cognition
2. Underlying mechanisms in relation to gene expression and epigenetics
3. Interactions between nutrition and epigenomics and their relevance to nutritional optimization of cognition throughout life

1. Nutrition, the Brain and Cognition

One Health Approach: Comparative Biology

The One Health approach aims to optimize health in humans, other animals, and the environment.[15-18] Studies in comparative biology and medicine are increasing understanding of mechanisms underlying many aspects of health and disease, including growth, development, metabolism, and neuroscience.[1,4,19-21]

Numerous advantages come from studies across species, with findings in humans being relevant to companion animals and vice versa. Moreover, the ability to closely control parameters such as diet, environmental temperature, and physical activity can be easier in one species than in another. However, biological differences among species need to be acknowledged, including stage of development at birth, body size, life span, nutritional requirements, and gastrointestinal, thermoregulatory, hormonal, metabolic, and neurological systems. In relation to nutrition and cognitive neuroscience, findings from a wide range of species are advancing knowledge of nutrition-gene interactions in brain health, dysfunction, and disease.

Definitions of cognition tend to be broad and imprecise and vary across species.[4,10,22,23] In general, it refers to the mental processes involved in acquiring knowledge and the integration of these processes into responses such as learning, attention, concentration, and memory. Cognitive decline is often associated with aging.[2,24] It involves an inability to reason, understand, and interpret, and can lead to dysfunctional behaviors and dementia. There are considerable

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opportunities and challenges related to characterizing cognitive aging across species.[25] This review focuses on human studies, which often are highly relevant to nutritional strategies for optimal cognition and treatment of cognitive decline in companion animals.

Multiple Nutritional Components Affect Brain Function and Cognition

Numerous aspects of neuroscience are affected by nutrition including neurodevelopment, neurogenesis, myelinogenesis, and functions of neurons, synapses, and neural networks in specific brain regions.[4,26,27] Multiple nutritional components are implicated in a wide range of cognitive functions and disorders including memory, mental health, depression, anxiety, dementia, schizophrenia, and Alzheimer's disease. These range from specific nutrients to dietary pattern, the microbiome, and energy status.[4,10,12-14,23,28-38]

Energy status has a critical role in cognition and mental well-being.[2,4,12] The term is used here to include energy intake, physical activity, energy metabolism, and related changes in body composition. This broader, less-precise term than energy balance reflects the multifaceted influence of a key component of nutritional status. Complex interactions occur between energy status and cognition. Physical activity, aerobic fitness and optimal energy intake in adults are beneficial to mental health and well-being. They decrease the risk of depression and improve mood and self-esteem. In older adults, regular aerobic exercise increases brain volume and reduces the risk of cognitive impairment, dementia, and Alzheimer's disease. By contrast, obesity is linked with cognitive dysfunction, cognitive decline, and dementia. In children, aerobic fitness benefits learning and memory, while inactivity is linked with poor cognitive health.

Overweight and obesity/hyperadiposity are the most common forms of malnutrition in dogs and cats in developed countries.[24] These conditions are associated with multiple health disorders. The probability is that in companion animals, optimal energy status is linked with optimal cognition, while overnutrition and lack of exercise are detrimental to cognitive function.

Nutrition Has Immediate and Long-Term Effects on the Brain

Optimal nutrition is essential for optimal brain function throughout life, especially during early development.[4,26,39] Programming is the phenomenon whereby an insult, such as malnutrition, during a critical period of development has long-term or permanent effects on structure and function. Both timing and type of insult are important to later brain function.

Critical periods of neurodevelopment occur prenatally and postnatally. Intrauterine growth restriction reflects a reduction in nutrient supply to the fetus, and infants born small for gestational age and preterm are at major risk of impaired neurodevelopment and multiple cognitive deficits. This may be relevant to cognitive outcomes in the runt of the litter, often a favored and much-loved animal companion. Marked changes in brain structure and function occur in children, especially during the first two years after birth, and malnutrition during this period carries significant risk for long-term cognition.

Adolescence is a critical time during which the brain continues to be plastic to environmental modulation. During this period, when the brain is developing, there are marked changes in motor and cognitive abilities, and many psychiatric disorders are first manifest.[40]

Parental nutrition has both immediate and long-term effects on brain function and cognition in the offspring.[10,41] Prenatally, maternal intake of micronutrients including folate, vitamin B12, and omega-3 polyunsaturated fatty acids is positively associated with cognitive outcomes in children. Postnatally, breast milk is linked with enhanced neurodevelopment due, in part, to the beneficial effects of long-chain fatty acids and insulin-like growth factors (IGFs). Of additional critical importance is the realization that the father's nutritional status can affect development of the offspring.[42]

In mature adults and the elderly, the brain remains remarkably plastic to nutritional intervention. This indicates that the effects of early nutritional programming could be mitigated by optimal nutrition later in life. Insights into mechanisms underlying nutritional regulation of brain function are suggesting new approaches to optimization of cognition at all life stages.

2. Underlying Mechanisms

Nutrition and Gene Expression

Nutrition-gene interactions play a major role in brain development and function, with effects on cell membranes, enzymes, neurotransmitters, metabolism, neurogenesis, and synaptic plasticity.[4,26] Nutritional regulation of gene expression is central to this response. Changes can be dynamic and short term, stable and long term, and even heritable among cell divisions and across generations. Moreover, gene variability significantly modifies the effects of nutrition on gene expression.

Nutrition has direct and indirect effects on gene expression.[20,43] Many nutrients and metabolites act directly as ligands for nuclear receptors/transcription factors, e.g., vitamin A and retinoic acid receptor, vitamin D and its receptor, calcium and calcineurin, and fatty acids and peroxisome proliferator-activated receptors. By contrast, energy status acts indirectly by influencing numerous hormones and growth factors that act as nutritional sensors to influence expression of multiple genes. These include growth hormone, IGFs, insulin, brain-derived neurotrophic factor (BDNF), thyroid hormones, and glucocorticoids. Epigenetic mechanisms play a central role in many of these

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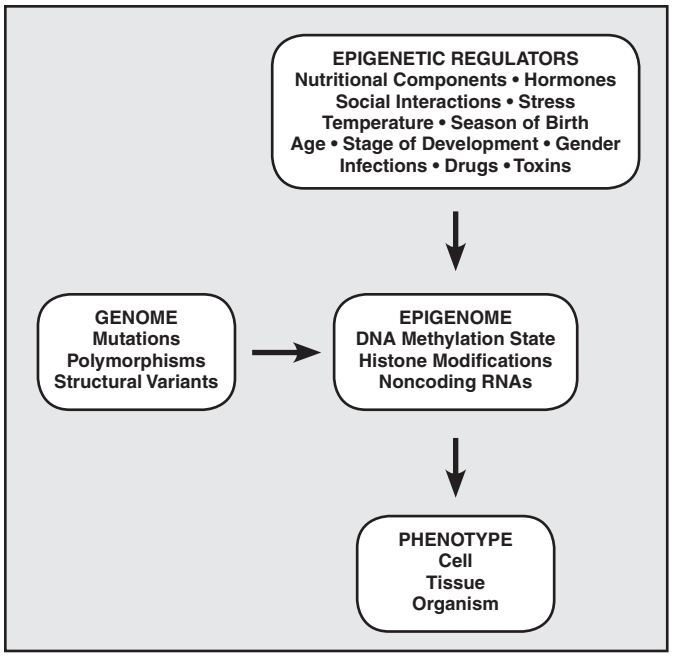

Figure 1. Interactions between extrinsic epigenetic regulators, genomics and epigenomics in specifying phenotype. Note that a single genome leads to multiple cell-specific epigenomes in different organs and tissues. Modified from Dauncey, 2013.[1]

responses and enable nutrition to regulate expression of multiple genes linked with brain function and cognition. It should be stressed that nutrition is one of many environmental epigenetic regulators that play a highly complex interacting role in regulating gene expression (Figure 1). The epigenetic mechanisms involved are discussed in the next section.

Epigenetics and Epigenomics: Definitions, Mechanisms, Regulation

The term epigenetics means "above genetics" and includes mechanisms that alter gene expression without changes in DNA sequence. The epigenome is the overall sum of epigenetic modifications in the cell or tissue. Epigenetic modifications enable cell-specific and age-related differences in gene expression. They are fundamental to normal development and play a major role in health and disease.[1-4,9,44-46]

Epigenetic mechanisms include DNA methylation, histone modifications, nonprotein-coding RNAs (ncRNAs), RNA editing, telomere control, and chromosomal position effects. Recent advances highlight the variety and complexity of these mechanisms. They often involve chemical modifications to chromatin — the form in which DNA is packaged with histone proteins in the cell nucleus. Induction of chromatin remodelling then results in altered gene expression, e.g., DNA methylation can reduce gene activity, whereas histone acetylation can increase gene activity. Although protein-coding genes are the focus of many functional studies, most of the genome gives rise to ncRNAs that play key roles in development, health, and disease. For example, microRNAs (miRNAs) are a class of short ncRNAs that can act by translational control of transcription factors or via direct action on chromatin, and thus contribute to nongenetic control of environment-gene interactions.

Epigenetics explains the phenotypic diversity of adult-differentiated cells that arise from identical genomes. A single genome gives rise to multiple cell-specific epigenomes in different organs and tissues. Epigenetic modifications can be transient or stable, and may involve heritable effects between generations. However, epigenetic changes are not necessarily irreversible or one way but can be plastic and reversible. Indeed, reversible epigenetic memories are essential for normal development. In germ cells and early embryos, there is striking genomewide removal and subsequent re-establishment of epigenetic information.[47]

Both intrinsic and extrinsic signals shape the epigenome. In very early development, retinol and ascorbic acid act synergistically to enhance the erasure of epigenetic memory and reprogramming of epiblast stem cells.[48] Occurrence of errors in the removal of epigenetic memory makes very early prenatal development an especially critical period that can impact long-term health and may extend to future generations. Environmental factors, including nutrition, have a major role in epigenetic regulation throughout life.[1,3,4,6,12,49-52] The role of nutrition as a neuroepigenetic regulator is discussed in Section 3 of this review.

Neuroepigenetics in Health and Disease

Advances in neuroepigenetics have had a major impact on the understanding of brain function in health and disease.[1-4,8,53] Epigenetic mechanisms in the brain impact proximally on gene transcription, protein synthesis, and synaptic plasticity and distally on cognitive functions including memory formation and impairment.[3,54] These mechanisms are essential for the development of specific brain-cell types and regions, with marked influences on early development and age-related change.[55-57] Epigenetic mechanisms are implicated in aging effects on brain DNA repair, cognitive decline, dementia, and Alzheimer's disease.[58-60]

Numerous disorders of neurodevelopment, mental health, and neurology are linked with interactions between multiple genetic and environmental factors, including nutrition. It is now appreciated that epigenetic mechanisms are involved in many of these responses. Particular interest focuses on the potential roles of nutritional and pharmacological interventions in prevention and treatment of cognitive dysfunction.

3. Nutrition and Cognition: Role of Epigenomics

Nutrition Affects Epigenetic Regulation of Multiple Genes

Many nutritional components act as epigenetic regulators of numerous cell types. These include energy status and micronutrients involved in DNA methylation, e.g., folate, vitamins B6 and B12, choline, and methionine. Nutrition

also significantly affects ncRNAs and their functions in the gene regulation of multiple cells, tissues, and organs.

There is a close link between energy metabolism and epigenetic events, and BDNF plays a key role in mediating the effects of energy status on the brain.[1,11,12 61] This molecule is involved in prenatal and adult neurogenesis; in the growth, differentiation and metabolism of neurons and synapses; and in synaptic plasticity. Optimal energy status improves mental health and cognition, in part, by epigenetic remodelling of chromatin containing the BDNF gene. This results in BDNF-induced plasticity in the hippocampus, an important region for cognitive function. By contrast, suboptimal energy status including very strenuous exercise or high-energy intake are related to an increase in reactive oxygen species, decrease in BDNF, and impaired cognition. Moreover, omega-3 fatty acids add to the effects of exercise on BDNF gene expression. It is now also apparent that the beneficial effects of high-flavonoid intake on cognition are linked with changes in BDNF.[62]

Many other signalling molecules also are involved.[4,20,27,43] For example, IGF1 mediates the actions of BDNF, and the histone deacetylase sirtuin silent information regulator 1 (SIRT1) is modified by energy metabolism. The key actions of glucocorticoids, thyroid hormones, vitamins A and D, polyunsaturated fatty acids, and other ligands of the nuclear receptor super family mediate the effects of nutrition on the brain, in part, via epigenetic events. Their receptors act as transcription factors to affect multiple genes via changes in histone acetylation and chromatin remodelling.

Advances in epigenetics provide the basis for anti-aging nutritional strategies that may prevent or alleviate cognitive decline and dementia.[2,4,63-67] The limitations and advantages of these strategies are the subject of considerable current interest. Obesity is a major risk factor for cognitive decline, and many age-related changes in gene expression can be partially or completely prevented by a reduction in energy intake combined with adequate nutrient supply. Epigenetic mechanisms, including DNA methylation and histone modifications, are frequently involved in this response. Other anti-aging diets involve supplementation with nutrients in one-carbon metabolism and concomitant provision of methyl groups for DNA methylation. Diet also affects ncRNAs, and vitamin D supplements may have a beneficial effect on Alzheimer's disease, in part, via actions on miRNAs.

Nutrition Affects Cognition Throughout Life Via the Epigenome

Prenatal and postnatal nutrition can cause lifelong, persisting epigenetic changes in the brain.[2,4,45,68,69] Early childhood malnutrition also is linked with long-lasting effects on DNA methylation patterns in multiple neuropsychiatric genes, including those linked with cognition.[70] In adolescence, methyl donor deficiency affects epigenetic status and memory in the hippocampus.[71] Moreover, epigenetic responses to nutritional factors persist into old age.

The extent to which neuroepigenetic changes can propagate through the germline and affect neurological function in subsequent generations is of considerable interest. It was originally thought that after the dramatic epigenetic reprogramming that occurs in very early development, DNA methylation marks were permanent. However, it is now clear that they can be modified by environmental factors, emphasizing the importance of nutrition to immediate and long-term health. Not only do reversible epigenetic memories play a key role in development, they also are a mechanism by which nutrition could be used to ameliorate adverse effects of early life environment.

Prenatal environment has a major effect on the newborn's epigenome. Both preterm birth and birthweight-for-gestational age are linked with DNA methylation changes in the newborn and during childhood.[72,73] Nutritional status of both parents is implicated in this response and may have long-term consequences for cognition.[42,74,75] A supply of methyl donors is essential for epigenetic regulation of brain function, as is the relative intake of specific nutrients. Maternal folate intake is linked with improved birth outcomes of human infants,[76] and supplements of docosahexaenoic acid (DHA) have small but relevant effects on DNA methylation in newborns.[77] Maternal vitamin D status also affects DNA methylation in the young that may persist in multiple generations[78] and have an impact on brain function and Alzheimer's disease.[2]

Nutrient-nutrient interactions play a complex and critical role in long-term neuroprotection and cognition via effects on the epigenome.[4,14,79,80] For example, maternal folate depletion combined with high-fat feeding from weaning affects DNA methylation and DNA repair in the brain of adult mouse offspring. Moreover, maternal imbalance of folate and vitamin B12 causes DNA hypomethylation in neonatal offspring. This is not normalized by postnatal nutrition, whereas prenatal maternal omega-3 fatty acid supplementation can normalize DNA methylation postnatally.

Maternal obesity affects expression of multiple genes in the developing brain and can alter the developmental program of fetal brain cell networks linked with neurological function in later life.[81] Moreover, maternal and paternal obesity before conception are associated with altered DNA methylation in newborns.[82] Paternal obesity is linked, in part, with altered epigenetic differences in sperm.[6,74] This has important implications for neurological function. Paternal obesity is an independent risk factor for autism in offspring.[83]

Conclusions

Advances in understanding nutrition-epigenome interactions are providing insights into mechanisms underlying brain health and disease (Figure 2). Effects can be beneficial or harmful, and consequences can be immediate or long term, with major consequences for cognitive function.

A lifelong approach to nutritional optimization of cognition and prevention of cognitive decline and dementia is of

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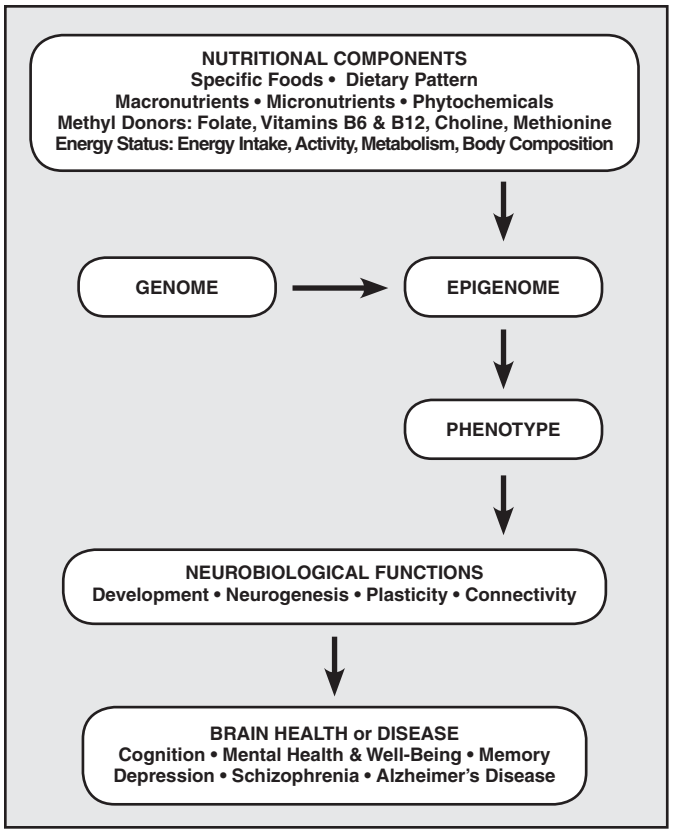

Figure 2. Impact of interactions between nutrition, genome, and epigenome on brain health and disease. Note that epigenome and phenotype are cell-type specific. Modified from Dauncey, 2013, 2015.[1,4]

critical importance. Understanding that parental, infant, childhood, adolescent, and adult environment profoundly impacts neuroepigenetic mechanisms should help in the development of strategies for optimizing nutritional status of humans and their animal companions throughout life.

Ideally, the focus should be on optimal energy status in relation to overall food intake, activity, and body composition. However, if it is impossible to improve food intake and activity, as may occur in the elderly, then the focus should be on key nutrients linked with epigenomics and cognition, including those involved in DNA methylation, DNA repair, histone modifications, and ncRNA function. Considerably more research is needed in this area, including study of nutrient-nutrient interactions and of individual gene variability that will affect responses to nutrition.

Moreover, significant interactions occur between nutrition and other extrinsic factors such as stress, social interactions, living conditions, temperature, infections, age, stage of development, and gender.[1,2,4,69,84,85] Understanding how multiple inputs from nutrition, other epigenetic regulators, and genetic variability affect the brain should help in the development of novel preventive and therapeutic approaches to cognitive decline. Future progress will result from increased links between nutrition studies and advances in epigenomics, genomics, and neuroscience.[1,2 7,9,86-89]

The companion animal-human bond is highly relevant to a One Health strategy for understanding links between nutrition, epigenomics, and cognition. There are clear advantages from studies of pets and their owners. For example, the relationship between obesity in people and their pet animals is closer and more complex than often acknowledged.[15,17,90,91] A fundamental understanding of epigenetic mechanisms involved in responses to nutrition is essential for future advances. Moreover, a two-way scientific approach linking humans and companion animals is critically important in relation to optimal brain health, mental well-being, and prevention/alleviation of devastating conditions such as cognitive decline and dementia.

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