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System biology approach intersecting diet and cell metabolism with pathogenesis of brain disorders

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Abstract

The surge in meals high in calories has prompted an epidemic of metabolic disorders around the world such that the elevated incidence of obese and diabetic individuals is alarming. New research indicates that metabolic disorders pose a risk for neurological and psychiatric conditions including stroke, Alzheimer's disease, Huntington's disease, and depression, all of which have a metabolic component. These relationships are rooted to a dysfunctional interaction between molecular processes that regulate energy metabolism and synaptic plasticity. The strong adaptive force of dietary factors on shaping the brain during evolution can be manipulated to transform the interaction between cell bioenergetics and epigenome with the aptitude to promote long-lasting brain healthiness. A thorough understanding of the association between the broad action of nutrients and brain fitness requires high level data processing empowered with the capacity to integrate information from a multitude of molecular entities and pathways. Nutritional systems biology is emerging as a viable approach to elucidate the multiple molecular layers involved in information processing in cells, tissues, and organ systems in response to diet. Information about the wide range of cellular and molecular interactions elicited by foods on the brain and cognitive plasticity is crucial for the design of public health initiatives for curtailing the epidemic of metabolic and brain disorders.

Keywords

Neurotrophin; Bioenergetic; Metabolism; Brain disorders; Diet; Lifestyle; Systems biology; Systems nutrigenomics

1. Introduction

The advent of mechanization has dramatically changed peoples lifestyle in the last few decades. In particular, the surge in meals rich in caloric contents and adoption of a sedentary life style has triggered an epidemic of metabolic disorders (Haffner and Taegtmeyer, 2003; Lutsey et al., 2008; Trushnikova et al., 2014) with subsequent detriment of brain function.

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There is immense necessity to understand the action of diet on gene regulatory mechanisms, which are endowed with the capacity to direct all molecular and physiological processes governing brain function. The process of adjustment to environmental challenges has played an imperative role for species survival, and we are starting to understand the engagement of cellular, molecular, and ultimately gene regulatory events. In particular, it is becoming evident that diet influences the genome, and that epigenetic alterations enable the organism to elaborate complex multiorgan responses and behaviors that may extend throughout lifetime and across generations. The human genome comprises an entire collection of genes that are encoded and controlled by more than 3 billion DNA base pairs, which contain all of the information needed to maintain an organ system. Such information is subject to the effects of environmental modulations which determine the balance between health and disease.

We are starting to learn that adjustments in cell metabolism are the driving force for genomic adaptations and epigenomic alterations, and that reprogramming of the epigenome is a fundamental mechanism by which the effects of diet are saved in our genes (Albuquerque et al., 2015). Energy use and conservation are essential needs of all living organisms. The brain has tremendous dependency for energy, particularly in humans where the brain contributes to about 20% of resting metabolism while only accounting for 2% of the total body mass. Maintenance of caloric homeostasis has been a powerful driving force in evolution such that alterations in cell metabolism have a strong impact on gene regulatory mechanisms that determine cellular features and ultimately, the phenotypic identity of an individual throughout its life-course. Herein we discuss how bioenergetic operations driven by environmental challenges can reprogram genes resulting in alterations of cellular and phenotypic identity underlying brain function. The broad impact of dietary nutrients can engage the entire cascade of gene regulatory mechanisms including epigenomic (modifications of DNA elements) and transcrip-tomic (abundance and alternative splicing), and their functional protein and metabolite products. In addition, thousands of endogenous microbes (microbiome) that live in multiple tissues and organ systems are surfacing as important modulators of the action of ingested foods on body and brain (Org et al., 2015; Parks et al., 2013). Growing evidence indicates that alterations in these regulatory mechanisms are core aspects of wide-ranging pathogenesis and also amenable to the manipulation of scientifically-based lifestyle management (Gomez-Pinilla, 2008; Meng et al., 2016). Here, we explore how diet affects the interrelationship between cell metabolism and genetic/epigenetic regulation with the potential to impact cellular processes sub-serving cognitive function.

Given their broad spectrum of action, foods can act on a multitude of molecular interfaces that control cellular homeostasis. A thorough understanding of the molecular-level associations between nutrients and complex brain functions requires high-level integrative analysis. Recently, nutritional systems biology harnessing advances of diverse omics technologies has emerged with the merit to help assess the consequences of nutritional intake at several levels of molecular information processing at the cell and organismal levels. These associations range from the DNA elements composing the genome, modifications in the genome (epigenome), protein products of genes (proteome), metabolite products of metabolic pathways (metabolome), to the microbiome (Zhao et al., 2015). These genome-

wide approaches have the power to acquire multi-dimensional evidence to achieve a systems-level comprehension of the regulatory mechanisms governing the effects of foods on the brain. Information about these regulatory mechanisms can be used to guide public health programs to improve mental health and quality of life across lifespan, with particular relevance to the growing metabolic disease epidemic. Here we review the increasing evidence bonding metabolic dysregulation to brain disorders, the role of diet in this connection, and the mechanistic insights gained through both conventional and emerging systems biology approaches.

2. The threat of the new epidemic of metabolic disorders

2.1. Obesity and type-2 diabetes

The adoption of dietary habits abundant in calories and the lack of exercise in modern societies are perceived as main contributors to the mounting contemporary incidence of metabolic disorders. The metabolic syndrome (MetS), defined as a cluster of metabolic dysfunctions (triglycerides, abdominal fat, and blood pressure, and low HDL and insulin sensitivity) that predispose individuals to cardiometabolic disorders including obesity, diabetes, and cardiovascular disease, is attaining epidemic levels around the world. Type 2 diabetes (T2D) has significantly increased in recent decades in both the adult and child populations—a change in incidence rate that is documented to be escalating in association with the adoption of a sedentary lifestyle and excessive caloric-intake (Flegal et al., 1998; Mokdad et al., 2001; Ogden et al., 2002; Pinhas-Hamiel et al., 1996). Moreover, T2D ranks amongst the fastest growing health problems worldwide, and the number of diabetic individuals is predicted to increase to 350 million worldwide by the year 2020. It is appraised that the prevalence of obesity around the world has increased 41% between the years 1980 and 2013 (Ng et al., 2014). According to data from the National Health and Nutrition Examination Survey (Ogden et al., 2012) obesity in USA reached up to 36% in adult men and women and 17% in children between years 2009–2010. Currently, more than 2 billion people worldwide are overweight or obese (González-Muniesa et al., 2017), and projections predict that the density of obese individuals will keep increasing for the next three decades up to 60% in adult men, 40% in adult women, and 25% in children (CDC Report 2014, <http://www.cdc.gov/obesity/data/adult.html>). Obesity is also linked to an increased risk of T2D, cardiovascular disease, cancer, and mortality (Hedley et al., 2004). Clearly, MetS, obesity and associated metabolic diseases present a worldwide clinical and public health burden that needs to be urgently addressed.

2.2. Metabolic perturbations increase risk of neurological and psychiatric disorders

The threat posed by metabolic disorders on the brain, especially MetS, is particularly frightening on the face that most brain disorders have some malfunction in the capacity of brain cells to metabolize energy (Chan, 2005; Cheng et al., 2012; Du et al., 2013). The growing prevalence of metabolic disorders appears to have grave consequences for the maintenance of brain metabolic homeostasis and cognitive function. Both obesity and T2D are significant risk factors for neurodegenerative diseases such as Alzheimer's disease (AD) and dementia, which constitutively involve hippocampal atrophy. Diabetic individuals show impairments in multiple aspects of cognitive function. Moreover, a high body mass index

(BMI) in otherwise healthy adults has been associated with executive dysfunction. Insulin resistance associated with T2D is implicated in the pathogenesis of AD (Jiang et al., 2007) and may affect as high as 80% of the AD population (Janson et al., 2004). In fact, it appears that the cognitive dysfunction observed in many AD patients could be associated with impaired insulin signaling or sensitivity—a condition that has gained the recognition of being a type 3 diabetes. Animal models of diabetes further corroborate that cognitive impairment is a central characteristic of metabolic disorders, which entails a dysfunction in hippocampal synaptic plasticity (Stranahan et al., 2008). Similar to findings from human studies, obese mice exhibit memory impairments on multiple cognitive domains (Farr et al., 2008). At the molecular level, it has been shown that the brain-derived neurotrophic factor (BDNF) system, which is central to the regulation of both energy homeostasis and neurocognitive processes, is compromised in disorders of both energy metabolism such as obesity and insulin resistance (Kernie et al., 2000; Lyons et al., 1999) and cognitive function such as dementia, AD, Huntington's Disease, Parkinson's disease, and schizophrenia (Caraci et al., 2018; Zuccato and Cattaneo, 2009).

In addition to cognitive disorders, several lines of evidence have implicated abnormal metabolism in the pathophysiology of psychiatric disorders. An increased incidence rate of T2D, impaired glucose tolerance, and insulin resistance occur in the psychiatric population (Dixon et al., 2000; Lilliker, 1980; Mukherjee et al., 1996; Pasinetti et al., 2007; Rasgon et al., 2010; Regenold et al., 2002). In diabetics, the commonness of depression is 2–3 folds higher (Anderson et al., 2001; Gavard et al., 1993), and there is high risk of developing diabetes during the 13-year period following diagnosis of major depression (Eaton et al., 1996). Both lines of evidence highlight the co-occurrence of metabolic diseases and depression. A similar panorama exists for other psychiatric illnesses, including manic depression. For example, a 3-fold increase in the incidence of diabetes has been reported in a study of 203 manic-depressive subjects (Lilliker, 1980). The association between metabolism and long-term vulnerability to neurological disorders has received indirect support by several epidemiological studies. For example, people who were either conceived or in utero during the Dutch Famine of 1944–45 or the Chinese Famine of 1959–1961 had a two-fold greater risk of schizophrenia as adults (Brown and Susser, 2008; Susser and St Clair, 2013; Xu et al., 2009).

2.3. Diet as an escalator of MetS and brain dysfunction (Figs. 1 and 2)

Dietary factors high in caloric contents such as sugars and high saturated fat are considered important contributors to the epidemics of MetS (Gerrits and Tsalikian, 1993; Zivkovic et al., 2007). Rodents exposed to a fructose diet display physiological signs of MetS such as increased hepatic lipid and triglyceride level (Agrawal and Gomez-Pinilla, 2012; Kelley et al., 2004), and peripheral insulin resistance (Agrawal and Gomez-Pinilla, 2012; Dekker et al., 2010). Consumption of fructose has recently been recognized as a critical instigator of the current epidemic of metabolic disorders in humans (Dhingra et al., 2007; Ishimoto et al., 2013; Lanaspá et al., 2013; Lyssiotis and Cantley, 2013; Stanhope et al., 2009), and its effects on compromising neuronal function are becoming alarming (Farooqui et al., 2011; Newcomer, 2007; Raji et al., 2010; Zhang et al., 2009). We have adopted fructose in the drinking water as a rodent model to promote metabolic disturbances such as peripheral and

central insulin resistance, lipid dysregulation, and disrupted insulin signaling (Figs. 2 and 3) (Agrawal and Gomez-Pinilla, 2012). Our research has revealed the harmful impact of fructose on the brain (Agrawal and Gomez-Pinilla, 2012; Cisternas et al., 2015; Gomez-Pinilla, 2008) such that the animals on fructose show impaired memory and learning skills, as well as reductions in proteins related to brain plasticity and mitochondrial bioenergetics (Figs. 1–3) (Agrawal and Gomez-Pinilla, 2012). In addition, the capacity of the hippocampus to sustain synaptic plasticity in the forms of long-term potentiation (LTP) and long-term depression (LTD) was seriously compromised (Cisternas et al., 2015). Fructose exposure also reduced the number of contact zones and the size of postsynaptic densities (PSDs) in the hippocampus, which changes were concomitant to a decrease in hippocampal neurogenesis (Cisternas et al., 2015). The results of these studies challenge the current view that the effects of diet-induced metabolic abnormalities are restricted to the periphery. As discussed below, diet may also use epigenetic mechanisms to promote long-term alterations in the brain (Tyagi et al., 2015).

In addition to high fructose diet, high fat diet (HFD) composed by high contents of sugars and saturated fats is another established promotor of MetS and contributes significantly to harm brain function and plasticity (Buettner et al., 2007; Freeman et al., 2014; Zivkovic et al., 2007), disrupting signaling through insulin receptors which are abundant in brain areas associated with cognitive function such as the hippocampus (Agrawal et al., 2009). The effects of the HFD has also been allied to reduced cognitive capacity which is accompanied by impaired synaptic plasticity and elevated inflammatory parameters in the brain (Hao et al., 2016; Hsu et al., 1989; Molteni et al., 2002).

In turn, poor consumption of dietary omega-3-fatty acids poses a risk to disturbances in insulin signaling that are common in diabetes (Agrawal and Gomez-Pinilla, 2012). The necessary action of dietary omega-3 fatty acids is also observed in studies showing that their dietary deficiency during brain formation exacerbates the outcome of metabolic disorders in the adult brain (Bhatia et al., 2011). The omega-3 fatty acid docosahexaenoic (DHA), an important supporter of metabolic homeostasis, has been demonstrated to be instrumental to counteract the action of fructose (Agrawal and Gomez-Pinilla, 2012). We discuss below how diet can reprogram metabolic pathways in the brain and can determine lifelong predisposition to metabolic disorders.

2.4. Cell metabolic dysfunction disrupts brain plasticity (Fig. 3)

Energy efficiency and accumulation of high-quality structural materials provided by diet have been primordial elements for successful biological adaptation (Gomez-Pinilla, 2008), and new studies show that these properties are operational for the maintenance of proper brain function. Alterations in bioenergetics mechanisms likely contribute to the cellular and molecular abnormalities that characterize various metabolic and neurodegenerative diseases. The functional significance of a disturbance in cell energy metabolism becomes evident when we examine it in the context of neurocognitive deficits common to ageing and neurodegenerative diseases. It has been reported that both senile dementia of the Alzheimer's type (Schubert, 2005) and T2D (Wren and Garner, 2005) are characterized by a decrease in cerebral glucose metabolism and associated with disturbances in acetyl-CoA

synthesis and oxidative phosphorylation (Meier-Ruge et al., 1994). Multiple studies demonstrate that metabolic derangements, including oxidative stress and glucose dysregulation, accelerate brain ageing (Nunomura et al., 2006; Yaffe et al., 2004). Interestingly, a perturbed energy status related to a dysregulation in cellular energy transfer mechanisms (creatine synthesis and/or uptake) is implicated in the pathoetiology of AD (Nunomura et al., 2006). A mitochondrial deficit constitutes one of the main features in all major age-related neurodegenerative diseases and during normal ageing (see review (Reeve et al., 2008)). Notably, the incidence of T2D is increased in association with ageing (Kelley, 2002; Mootha et al., 2003; Patti et al., 2003). Moreover, the levels of BDNF, a key neurotrophin involved in both cell metabolism and neuroplasticity, decrease progressively during the ageing process (Cotman, 2005; Yamanaka et al., 2007), especially being prominent in hippocampal pyramidal and dentate granule cells. Conspicuously, the age-related BDNF decline in the hippocampus occurs in concert with neurocognitive impairments in both animals and humans (Cotman, 2005; Kramer et al., 1999; Laurin et al., 2001). Exemplative findings are encountered in human AD studies, in which AD brains exhibit decreased hippocampal BDNF levels (Phillips et al., 1991) and impairments in energy metabolism (Hoyer, 2004a, b) such as altered cytochrome c oxidase activity (Valla et al., 2001). Overexpression of BDNF and CREB has been shown to attenuate cognitive deficits in rodent models of AD (Caccamo et al., 2010; Nagahara et al., 2013).

Given the strong dependency of brain function and plasticity on proper regulation of cellular energy, they are highly amenable to fluctuations in the energy status of the cell occurring during development, in response to environmental challenges, and in disease states (Gomez-Pinilla and Tyagi, 2013; Mattson, 2012). Across many species, the energy demands of the central nervous system are directly related to the density of neuronal connectivity irrespective of brain mass (Herculano-Houzel, 2011). Cell energy metabolism is an important driving force of gene regulation and epigenetic mechanisms. As discussed above, this relationship is conspicuously revealed in conditions in which energy homeostasis is compromised in the pathoetiology of numerous metabolic and neurocognitive disorders including T2D, dementia, depression, addiction, and neurodegenerative diseases. Recent evidence demonstrates that diet have a powerful capacity to foster biological adaptability to support cognitive aptitude by engaging epigenetic mechanisms (Gomez-Pinilla and Tyagi, 2013).

3. Epigenetics bridging diet and long-term brain plasticity (Fig. 4)

3.1. Interaction between diet and epigenetics

Despite the association between diet and brain health supported by epidemiological and clinical evidence, we are just starting to understand mechanisms involved. Increasing evidence from the clinical, epidemiological, and experimental literature supports the idea that diet can promote stable modifications in the brain that can last for a long time up to the point to affect future generations. New research indicates that the powerful action of diet on cell metabolism is operational for reprogramming gene regulatory mechanisms underpinning brain function and plasticity, and disease susceptibility. As discussed below, cumulative evidence over the past decade shows the potential of select food components to alter the

functional program of genes using epigenetic modifications. Epigenetics denotes changes in the genome that can alter gene expression without involving alterations in DNA sequence (e.g., C to T nucleotide change on the DNA) as in the case of genetic variations. Exciting new information has revealed clues how the interaction between cell metabolism and epigenetics is significant for control of patho-physiological processes, which are amenable to dietary regulation.

3.2. Mechanisms of epigenetics

Unlike genetic variations that are relatively static, epigenetic alterations are dynamic and potentially reversible such that nutritional supplementation or pharmaceutical agents may be developed to counteract undesirable epigenomic profiles. DNA methylation and various histone modifications such as methylation, acetylation, phosphorylation, ribosylation, and ubiquitination are widely studied epigenetics modifications, although microRNAs and long noncoding RNAs (lncRNAs) are also considered epigenetic regulators (Cech and Steitz, 2014; Rivera and Ren, 2013). The idea behind is that accessibility of DNA to the transcriptional machinery is crucial to regulate gene expression and DNA transcription. Heterochromatin regions that are tightly wound-up tend to be expressionally repressed, whereas euchromatin regions are open and conducive to gene transcription. Therefore, agents that alter the structure of chromatin can change the transition between silent to transcriptionally permissive chromatin leading to changes in gene expression (Fischle et al., 2003; Sng et al., 2006).

Nutrients and dietary factors can promote epigenetic functional changes by acting at various levels of chromatin regulation such as a source of methyl groups or as co-enzymes involved in methyl transfer for one-carbon metabolism (Kim et al., 2009). It has also been shown that select bioactive food components directly affect enzymes involved in the catalysis of DNA methylation and histone modifications (Choi 2010). Interestingly, the vitamin B9 or folate influences the epigenome, and in combination with vitamin B12, acts as a cofactor in generating the major source of methyl groups in the brain, namely S-adenosylmethionine (SAME). Folate is heavily involved in cell metabolism by interacting with the mitochondria such that folate dietary deprivation results in mitochondrial dysfunction (Ye et al., 2010). Though folate is a methyl donor in one-carbon metabolism (Luccock, 2000), high levels of folate during pregnancy cause both hyper and hypomethylation of offspring DNA in a gene-specific manner (Barua et al., 2014). It has been shown that doses of folate around those prescribed (4 mg/day) to women with a history of neural tube defect pregnancy, can alter the methylation status of candidate autism genes in the DNA of the offspring (Barua et al., 2014). It has also been shown that high folate supplementation during pregnancy promotes a reversible methylation of the promoter for the anorexigenic peptide pro-opiomelanocortin (POMC) in the hypothalamus of the offspring (Cho et al., 2013), reducing POMC expression, and ultimately causing hyperphagia and obesity in the offspring. The impact of foods on epigenetic mechanisms is additionally relevant on the face that epigenetic alterations are potentially reversible opening to the possibility to employ diet to offset unhealthy epigenetic marks. In these terms, epigenetic regulation is perceived as a fundamental tool used by evolution to ensure species adaptation to challenging

environmental conditions. The same property is under the scope of several pharmaceutical strategies to combat several diseases.

3.3. Epigenetic regulation of *Bdnf* transcription, and implications for brain disorders

DNA methylation is altered globally with age and neurological conditions (Teschendorff, 2013; Teschendorff et al., 2013). For example, methylation of histone 3 lysine 9 (H3K9), which has a repressive function (Lachner et al., 2001), has been found elevated in timing with cognitive deficits in an animal model of AD, causing reduced *Bdnf* expression (Walker et al., 2013). Several studies have reported the influences of foods on epigenetic regulation including DNA methylation and histone modifications, and are reviewed by Choi et al (Choi et al., 2013). In particular, it has been reported that *Bdnf* methylation in the human frontal cortex changes proportionally to age (Keleshian et al., 2013). In primary neuronal cultures, both ageing and a rodent model of AD like pathology reduced histone acetylation in hippocampal/cortical neurons. In the blood, DNA methylation on the CpG island of the promotor region for exon I, but not IV, was significantly associated with major depression (Fuchikami et al., 2011). The clustering of disorders related to impaired glucose metabolism, i.e., T2D, and psychiatric, i.e., dementia and depression are prominently associated with lowered levels of BDNF (Krabbe et al., 2007). Lowered levels of serum BDNF has been described in patients with major depression (Karege et al., 2002), and the protective action of BDNF against the pathogenesis of depressive disorders has received abundant experimental support (Filus and Rybakowski, 2005). Psychiatric disorders such as depression, bipolar, and in many instances, severe cognitive impairments have been coupled with epigenetic regulation of the *BDNF* gene (Ikegame et al., 2013; Kang et al., 2013). Though these studies were done in humans and therefore may only reflect peripheral changes in BDNF regulation, data suggest that methylation status of the *BDNF* promoter may be consistent across brain and peripheral tissues, reflecting the possibility that methylation of peripheral *Bdnf* gene may serve as a biomarker for *Bdnf* methylation status in the brain (Ikegame et al., 2013). Although low levels of BDNF and elevated methylation of the *BDNF* promoter are not correlated with the severity of symptoms (Birkenhäger et al., 2012; Molendijk et al., 2011), epigenetic changes may be related to the interaction between the disorder and antidepressant treatment (Carlberg et al., 2014; Lopez et al., 2013). The frontal cortex of patients with bipolar disorder and AD have been found hypermethylated in the CpG islands of the *BDNF* promoter region (Rao et al., 2012). Reduced levels of BDNF have been found in the hippocampus, prefrontal cortex (Dwivedi, 2009; Karege et al., 2005; Pandey et al., 2008) and plasma (Kim et al., 2007) of suicidal patient. One study found hypermethylation of the *BDNF* promoter region in Wernickes area in the brain of patients who had committed suicide (Keller et al., 2010).

3.4 Diet and epigenetic alterations (Fig. 4)

It has been reported in rodents (Tyagi et al., 2015) that the type of food consumed in early life can imprint the genome by promoting epigenetic alterations in the *Bdnf* gene. These studies showed that prior exposure to a diet with adequate levels of omega-3 fatty acids reduced the cognitive decay originated from subsequent exposure to a Western diet (WD) high in saturated fat and sugar. Abundant evidence indicates that dietary exposure to the omega 3 fatty acid docosahexaenoic or DHA promotes resilience against several types of

injuries and neuropsychiatric disorders. Interestingly, Tyagi et al (Tyagi et al., 2015) also reported that exposure either to WD or omega-3 fatty acids exerted opposite actions on the methylation of the *Bdnf* promoter exon IV. The metabolic sensor NAD/NADH and SIRT1 metabolic regulator appeared to act as an intermediate step between the diet and *Bdnf* methylation. The use of a DNA methyltransferase inhibitor counteracted the *Bdnf* hypermethylation and cognitive decay, and blocked the WD-reducing effects on the mitochondrial transcription regulator PGC-1 α suggesting that the PGC-1 α action is downstream to the *Bdnf* methylation. The results of this study support the possibility that the effects of the omega-3 fatty acid diet are saved in the epigenome as an epigenetic memory by interplaying with metabolic signals. This epigenetic memory could serve as an underlying mechanism for protecting the brain during periods of hardship. Exemplifying an association between cell metabolism and epigenetics, it has been shown that caloric intake regulates cell metabolic factors involved in chromatin modifications such as ATP, acetyl-CoA, s-adenosyl-L-methionine, and NADH (Ramsey et al., 2007; Wallace and Fan, 2010). In addition, glucose availability affects ATP- dependent histone acetylation (Wellen et al., 2009).

Another front for the action of foods on epigenetics is the control and temporal preservation of signals related to the hedonic reward system. Chronic administration of a WD has been shown to impact sensitivity to rewarding behaviors by increasing DNA methylation of the opioid receptor (Vucetic et al., 2011b). The decision to eat or not to eat is susceptible to epigenetic regulation of the POMC promoter region, which is affected by folate supplementation during pregnancy (Cho et al., 2013). Too much folate during pregnancy may lead to overconsumption of salient foods, which can cause epigenetic silencing of the μ -opioid receptor (Vucetic et al., 2011b), which has been suggested to increase susceptibility to over-indulging in rewarding behaviors such as consuming highly palatable foods (Vucetic et al., 2011a). Together, the results of these studies support the idea that this type of epigenetic alterations may result in overconsumption of foods and obesity, and increased vulnerability to cognitive disorders.

3.5 Transgenerational inheritance

An increasing number of epidemiological studies suggest the possibility that the epigenomic consequences of dietary habits can be inheritable with the intrinsic capacity to influence vulnerability to metabolic disorders such as diabetes in the posterity (reviewed in Ref. Wang et al., 2011). This capacity may extend to cognitive disorders, for example, both over and under nutrition during pregnancy increases susceptibility of the offspring to neurodegenerative diseases (Chouliaras et al., 2010). As discussed below, the propensity to metabolic disorders and obesity becomes even more alarming for public health in the context of transference of information across generations.

It is increasingly recognized that epigenetic variability can last for considerable time. Although still debatable, the concept of epigenetics brings in heritable changes in gene function that are not attributable to alterations in DNA sequence, that entails the transmission of epigenetic marks (e.g. the methylation pattern of certain genes) from parent to daughter. There is captivating evidence in the epidemiological literature that an

environmentally induced phenotype can be inherited (Ramsey et al., 2007). Edvinsson and colleagues examined the records of the 1890, 1905, and 1920 cohorts from Overkalix, an isolated community in Northern Sweden, resulting in the intriguing discovery that longevity (Bygren et al., 2001) and diabetic mortality (Kaati et al., 2002) are linked to ancestral food supply. Prominently, it was found that diabetes mortality in subsequent generations increased if the paternal grandfather was exposed to a surplus of food during his mid-childhood (the slow growth period occurring before the prepubertal growth peak) (Kaati et al., 2002). In a subsequent study, they found that the paternal grandfathers food supply during mid-childhood was linked to mortality risk in the grandsons, but not in the granddaughters. These results in humans support the existence of a sex-specific, male-line transgenerational inheritance system that records and utilizes nutritionally related information from previous generations, or rather, a system that enables the memory of an environmental event to be passed on to subsequent generations (Kaati et al., 2007). Genomic imprinting embraces the principle of transgenerational epigenetic inheritance in which an epigenetic signature in one-generation influences gene expression in subsequent generations (Ferguson-Smith and Surani, 2001). Additionally, complex diseases such as T2D, do not seem to have a gene that predetermines a person to develop the disease—only genes that influence predisposition to the disease (Edwards and Myers, 2007), which are likely subject to epigenetic modification. Therefore, Conrads Waddington's original definition is highly relevant when we consider the ability of the environment to impact the genome through experience-dependent epigenetic mechanisms.

A growing line of evidence in rodents has provided experimental support to the possibility that epigenetic traits can be transmitted from one generation to others. Maternal-pup licking behavior, which seems to be coded in experience-dependent epigenetic modifications, can be transmitted to her offspring and persist over many generations (Weaver et al., 2004). The quality of maternal care may “program” the genome through epigenetic mechanisms to modulate the stress response in the offspring (Weaver et al., 2004). Through epigenetic modifications, acquired traits such as maternal and paternal conditions (Champagne, 2016; Peter et al., 2016) (Ng et al., 2010), hormonal (Stolzenberg and Champagne, 2016) may be transmitted to offspring. In support of a link between cell metabolism and epigenetics, it has been shown that chronic consumption of a caloric diet can program pancreatic β -cell dysfunction, impaired insulin secretion and glucose tolerance in the female rat offspring (Ng et al., 2010).

4. Challenges posed by the multiple effects of diet on brain can be met by the new science of nutritional system biology (Fig. 5)

4.1. Challenges: the need for multiple events consideration and big data processing

As discussed above, a growing body of evidence denotes that diet influences brain function and plasticity by engaging epigenetic regulation of genes that can extend the effects of diet for considerable time up to the point to determine vulnerability to neurological disorders. However, the greater part of previous studies focus on individual candidate genes, pathways, and molecular events, offering limited mechanistic insights. A thorough understanding of the association between nutrients and disease requires the use of approaches to integrate

information derived from a multitude of molecular entities and pathways involved. Recently, nutritional systems biology has emerged as a powerful approach to address challenges in nutritional research using advanced omics technologies (de Graaf et al., 2009; Kaput and Morine, 2012; Panagiotou and Nielsen, 2009; van Ommen et al., 2008; Zhao et al., 2015). In principle, nutritional systems biology purposes to assess the interactions and influences of nutritional intake at multiple molecular layers involved in information processing in cells, tissues, and organ systems. The molecular level information involves the genome (DNA sequence), transcriptome (gene expression, particularly mRNAs) epigenome (DNA and chromatin modifications), proteome (protein products of coding genes), metabolome (metabolic products), and the gut microbiome interacting with the host.

The various levels of molecular entities carry intrinsic relationships. According to the central dogma, all instructions for protein synthesis are encoded in the DNA (genome) which is transcribed into mRNA (transcriptome), and subsequently translated into proteins (proteome). However, recent studies have revealed the critical role of epigenetic mechanisms (epigenome) as an additional dimension in gene regulation through DNA and histone modifications, chromatin remodeling, or noncoding RNAs in the absence of alterations of the DNA coding information (Cech and Steitz, 2014; Rivera and Ren, 2013). Coding genes in the transcriptome, in turn, produce a wide range of proteins (pro-teome) which are the basic functional units of cellular structures as well as metabolic, biochemical and signaling pathways. Proteins involved in metabolic reactions are responsible for producing various metabolites (metabolome). Many proteins, such as DNA/RNA binding proteins, transcription factors, splicing factors, DNA methyltransferases, and histone deacetylases, are also essential regulators of transcriptional and translational processes. In addition to these molecular entities belong to the host, gut microbiome residing in host digestive tract has recently been recognized as our second genome. Gut microbiome has been found to modulate host metabolism and influence the metabolome, which can in turn modify the epigenome to regulate gene expression.

Genome-wide approaches enabling the capturing of multi-dimensional signals involved with the action of diet can help derive a systems-level landscape of the molecular underpinnings of the broad effects of diet on the brain. We define such diet or nutrition related omics studies “nutri-omics”. However, most of current dietary studies involving omics have targeted peripheral tissues such as liver, adipose, pancreas, and muscle, and very few studies have investigated the effects of foods on the brain (Zhao et al., 2015). In the sections below, we introduce the concepts of individual nutri-omics and highlight the corresponding recent application examples that utilize these concepts to study the dietary effect on the brain.

4.2. Nutrigenetics

Individuals can respond to nutrients or diets differently depending on the genetic background. Nutrigenetics investigates how nutrients or diets interact with genetic variations in individual genomes to impose personalized dietary response (Ioannidis et al., 2011). The term genetic variation is generally used to describe DNA sequence differences between individuals in a population. DNA sequence variations include single nucleotide polymorphisms (SNPs), insertions, deletions, copy number variations (CNVs), and

inversions, with the most common be-DNA variations can be correlated with dietary responses across individuals to identify which genetic variants are associated with differential response to a diet across the population. For instance, individuals with the ApoE-ε4 genetic polymorphism, an established genetic risk for Alzheimer's disease, show little protection against AD when consuming fish (Plourde et al., 2009) based on decreased half-life and enhanced β- oxidation of ingested DHA (Chouinard-Watkins et al., 2013).

Of note, when genome-wide analysis is conducted, that is, examining the interactions between millions of genetic variants with a particular diet or nutrient, the term “nutrigenomics” is more appropriate because strictly speaking, “genomics” is used to define studies of DNA sequences at global scale. However, the term “nutrigenomics” has been traditionally reserved to describe studies of the nutritional effect on gene expression at messenger RNA level (see next section). In addition, the majority of the genetic studies of nutritional response are candidate gene based, rather than genome-wide, and replication of findings has been difficult (Ioannidis et al., 2011). For these reasons, we retain the use of “nutrigenetics” in the current review as traditionally referred to. Future global nutrigenetic studies examining the relationship between the larger numbers of genetic variations with dietary response are warranted to offer a more comprehensive understanding regarding how gene by diet interactions modulate the balance between health and disease. The information on which genetic variants determine beneficial or deleterious dietary responses in terms of disease risks from such studies are critical for designing personalized nutritional remedies to prevent or reverse diseases.

4.3. Nutritranscriptomics (Fig. 6)

Diets or nutrients can also alter the transcriptional activities of genes, that is, the conversion of DNA to messenger RNAs (mRNAs), by modulating the expression levels of genes or alternative splicing, which can then further induce physiological or pathophysiological effects. Transcriptomics studies that measure >20,000 expressed genes or transcripts in response to nutritional or dietary challenges are the most abundant type of omics studies in nutritional systems biology (Capozzi and Bordoni, 2013). Such studies have been termed “nutrigenomics” in the past. Here we adopt the term “nutritranscriptomics” to more accurately describe the molecular entities under investigation being mRNA transcription, rather than DNA sequences as examined in a genetic or genomic study. In a nutritranscriptomic study, the transcriptional activities of individual genes and transcripts can be measured with either microarray technologies or more recently RNA sequencing approaches, and then correlated with dietary information to identify all genes whose activities are influenced by a diet.

One of the first demonstrations about the contribution of nutritranscriptomics to nutritional neuroscience is highlighted by a recent study showing the influence of fructose and DHA on gene regulatory mechanisms in the brain (Fig. 6) (Meng et al., 2016). Fructose consumption has become a major risk factor for a broad spectrum of complex metabolic disorders such as obesity, diabetes, and cardiovascular diseases, and its impact on the pathology of neurological and psychiatric disorders is starting to be recognized. The application of nutritranscriptomics revealed that fructose and DHA each affects hundreds of genes by

altering expression levels or modulating alternative splicing and elicit opposite actions on gene regulatory mechanisms in the hypothalamus and hippocampus brain regions in rodents. The transcriptional alterations carried by fructose were shown to converge with genes posing genetic risks of metabolic and neuropsychiatric disorders uncovered by human genome-wide association studies. More interestingly, fructose and DHA elicit opposite actions on gene regulatory mechanisms, posing the potential to engage DHA supplementation to counteract the deleterious effects of fructose on the brain.

4.4 Nutriepigenomics (Fig. 6)

As discussed previously, there has been tremendous progress in the last few years about the mechanisms through which environmental exposures are “remembered”, and how they may be accountable for dysfunctions observed in various brain disorders (Nestler, 2009; Nestler et al., 2016; Tshala-Katumbay et al., 2015). The epigenome is dynamic and responsive to environmental stimuli, such that it is becoming known as a main intermediate mechanism by which dietary factors can affect long-term gene expression. As discussed earlier, various epigenetic mechanisms including DNA methylation, histone modification, chromatin remodeling, and noncoding RNAs are all critical transcriptional regulators (Holoch and Moazed, 2015). Recent technological progresses have enabled global epigenetic measurements using array- or sequencing-based methodologies (Morozova and Marra, 2008; Pritchard et al., 2012; Telese et al., 2013; Zhao et al., 2015). The individual epigenomic signals can be associated with dietary treatment information to detect which epigenetic events are perturbed by a particular diet.

Our recent nutriepigenomics study strongly implicated extensive epigenetic reprogramming, far beyond what was explored before based on individual genes such as *Bdnf* to be involved in the dietary effects on the brain (Meng et al., 2016). Based on DNA methylome profiling of millions of methylation sites via next generation sequencing, fructose diet was found to perturb thousands of DNA methylation sites in both the hypothalamus and hippocampus of rodent brain, which was normalized by the omega-3 fatty acid DHA supplementation. Many of the differentially methylated DNA sites by fructose and DHA co-localized with a subset of genes whose expression was affected by fructose, indicating the cis-regulatory role of DNA methylation in gene transcription. In addition, transregulatory mechanism of DNA methylation was supported by the co-localization of differential methylation sites with a number of transcriptional regulators such as transcription factors and splicing factors and microRNAs (e.g., rno-miR-421, rno-miR-143) whose predicted target genes were amongst the fructose-affected genes. As an increasing body of evidence indicates that neurological and psychiatric disorders have an epigenetic component, these results support that diet has the capacity to regulate the susceptibility to disease by modulating the global epigenetic regulatory machinery, rather than a limited number of epigenetic sites.

4.5 Nutriproteomics and nutrimetabolomics

The functional products of transcriptomic and epigenomic alterations in response to nutrients are reflected in proteins and metabolites. The past few years have seen major progresses in high throughput proteomics and metabolomics technologies (Breker and Schuldiner, 2014; Gibbons et al., 2015; Sauer and Luge, 2015), greatly expanding the

informative molecular dimensions when monitoring the effects of nutrition. Now it is possible to measure the abundance and post-translational modifications of hundreds of proteins as well as hundreds or thousands of metabolites to capture key pathways affected by nutritional or dietary modulation (Gibbons et al., 2015).

Recent applications of nutriproteomics in neuroscience have revealed that proteins involved in mitochondrial complex, tricarboxylic acid cycle, heat shock, fatty acid utilization are altered in diabetic sensory neurons (Akude et al., 2011), and are associated mitochondrial activity in mouse neurons (Chowdhury et al., 2011). Whole brain proteomics analysis of rats receiving a HFD revealed proteins involved in mitochondria function, oxidative phosphorylation, calcium homeostasis hypoxia inducible factor (HIF) signaling, glycolysis/gluconeogenesis, and cytoskeleton to be affected by HFD (Smine et al., 2017). Interestingly, supplementation with a grape seed and skin extract (GSSE) in the HFD animals reversed the changes in many proteins involved in oxidative phosphorylation, calcium signaling, HIF signaling and glycolysis/gluconeogenesis pathways, supporting a protective role of GSSE in counteracting the HFD effects (Smine et al., 2017). Other processes affected by GSSE included FOXO signaling pathway, chemokine immunity signaling and platelet activation signals. In terms of the nutrimentalomics, existing applications are largely limited to the peripheral such as plasma, urine, and liver tissues (Llorach et al., 2012; Vasilopoulou et al., 2016; Zhao et al., 2015), and future brain-specific profiling are warranted to increase comprehension of the effects of diet on brain metabolism.

4.6. Nutrimicrobiomics

The intestinal microbiome has profound effects on whole body physiology by regulating metabolism of fatty acids and vitamins and by contributing to host immune homeostasis. As such, it has the capacity to serve as an essential mediator of the effects of nutrients on the pathophysiology of various organ systems. An increasing number of studies indicate that the microbiome acts as a pivotal station for the interaction between gut, immune system, and brain (Fung et al., 2017). It is starting to be understood that the action of the microbiome is important for the regulation of important aspects of brain development, adult plasticity, and resistance to disease via modulation of the immune systems (Sandhu et al., 2017). As the immune system is an important regulator of brain function including inflammation, response to damage, and behavior, the fact that gut microbes influence peripheral immune cells and whole immune response has provided the mechanistic link between the action of microbiome and several aspects of brain function. It is now understood that the microbiota affects the maturation and function of brain cells such as microglia and astrocytes and their sub-products actions on inflammation, neuronal function and signaling (Fung et al., 2017). Dietary composition, and caloric intake appear to strongly and swiftly regulate microbial composition and function, making the microbiota-gut-brain communication a crucial element to understand the action of nutrition and diet on brain function and resistance to diseases.

As with the cases of other omics, microbiome sequencing technologies including 16S rDNA sequencing and metagenomics are enabling high throughput studies of dietary effects on gut microbiota as well as metabolic and brain functions. In particular, high caloric diets, high

fiber diets, and food additives have shown profound impact on the gut microbiota. For instance, protein and fat were found to promote *Bacteroides*, *Alistipes* and *Parabacteroides*, while long-term carbohydrate consumption favors *Prevotella*, *Paraprevotella* and *Catenibacterium* in human subjects (Wu et al., 2011). The specific microbiota altered by diets, in turn, can influence food digestion and nutrient absorption and metabolism, such that obesity-associated bacteria promote energy harvest and inflammation (Hartstra et al., 2015). Butyrate-producing bacteria which produce small chain fatty acids such as butyrate appear to have protective effects on metabolic and brain disorders. Butyrate can enhance mitochondrial activity, prevent metabolic endotoxemia, activate intestinal gluconeogenesis, activate G protein coupled receptors, interact with histone deacetylases to regulate gene expression, and promote microbiome homeostasis (Bourassa et al., 2016; Hartstra et al., 2015). The ability of diets to influence gut microbiota composition and metabolites can be harnessed to explore potential therapeutic avenues. Indeed, gut bacteria and metabolite modulations through oral administration of butyrate or fecal transplantation can reverse metabolic perturbations seen in metabolic syndrome (Chassaing et al., 2015; Gao et al., 2009; Suez et al., 2014; Vrieze et al., 2012) and enhance brain plasticity in neurological disease models ranging from depression and autism to neurodegenerative diseases and cognitive impairment (Bourassa et al., 2016; Stilling et al., 2016). High fiber diet, which promotes butyrate-producing bacteria, has been proposed as a potential remedy to promote mental health (Bourassa et al., 2016).

4.7. Application of nutritional systems biology to clinical neuroscience (Fig. 7)

It is becoming an alarming concern that metabolic disorders can compromise brain function and precipitate to neurological disorders. Most of the existing approaches to understanding the impact of metabolism on the brain have been focused on the action of a few genes and proteins or examining individual types of molecular information in individual tissues one at a time, which hardly explain the whole dimension of the pathology. Our group has recently applied the nutritional system biology concepts described above to combine dietary treatment, genome-wide transcriptome, and DNA methylome analyses to extract information about crucial gene regulatory mechanisms (expression level, alternative splicing, epigenetic regulation) underlying the action of nutrients on multiple brain regions, setting the start of the systems nutrigenomics field in neuroscience (Meng et al., 2016).

Information about the intersection between rodent modeling with human genome-wide association studies (GWAS) of brain disorders is useful to infer translatability to human pathophysiology. For example, the system biology approach allows to compare signature genes activated by fructose as well as the key driver genes (KDs) identified from hypothalamus and hippocampus to large-scale human GWAS of metabolic disorders and brain related diseases or traits (Meng et al., 2016). Numerous overlapping genes between fructose signature genes and top GWAS hits were found for a broad range of brain disorders (e.g., Alzheimer's disease, attention deficient hyperactive disorder, depression, addiction, Parkinsons disease) and metabolic-related diseases or traits (e.g., blood pressure, cardiovascular disease, lipids, obesity, and T2D). We found that human orthologs of the fructose signature genes from the hypothalamus and the hippocampus are highly enriched for genetic polymorphisms associated with many of these diseases or traits (Fig. 7). As the

human GWAS genes are based on genetic evidence and imply causal information, these results support that the hypothalamus and hippocampus genes perturbed by metabolic fructose treatment in the rodent model likely play causal roles in both metabolic and brain disorders in humans. As human GWAS studies identify causal genes for a variety of human diseases, the convergence between human disease causal genes and those affected by nutrition or diet has raised the exciting possibility that the effects of foods and metabolic alterations can be saved in the organism in the form of genomic and epigenomic modifications that can predict disease susceptibility. Of course, comprehensive characterization of additional layers of molecular information such as genetic variations, proteins, metabolites, and gut microbiome are needed to further complement the existing studies.

5. Consequences and considerations

5.1. Changes in environmental conditions: the need for lifestyle intervention

Globally, the prevalence of obesity in adults is now estimated to be about 36%, which is an 8% increase from 1980 (Trushnikova et al., 2014). Metabolic disorders such as T2D rank amongst the fastest growing health problems worldwide (Padwal, 2014; Verma and Hussain, 2017). In recent years, metabolic disorders have demonstrated a tendency to manifest earlier and earlier in life and interestingly, at a higher rate in women (Attig et al., 2013). Particularly disconcerting is the rise of T2D in the child/adolescent population, even in children as young as 8 years of age (Libman and Arslanian, 1999). These findings have critical implications in light of the growing body of evidence demonstrating the establishment of the epigenome can be affected during critical developmental periods (Attig et al., 2013). In particular, studies have shown that the quality of a mother's nutrition during her childhood years can influence her children's risk for developing cardiovascular disease, T2D, and hypertension in adulthood (Attig et al., 2010, 2013; Dyer and Rosenfeld, 2011). Moreover, the nutritional condition of the grandmother during her pregnancy can influence the mother's nutrition in utero, which in turn can influence the grandchild's birth weight (Heijmans et al., 2008). Particularly, epigenetic modifications during the perinatal period may have a powerful ability to induce persistent changes in behavioral adaptations related to energy metabolism and the availability of dietary methyl donors (Attig et al., 2013; Dominguez-Salas et al., 2014; Tyagi et al., 2015; Waterland, 2014). Increasing evidence for epigenetic effects at the level of the cell, organism, and family lineage, warrant considering the implications and consequences of the metabolic epidemic, i.e., that the increased rate of metabolic diseases in women may have detrimental and long-lasting consequences in their offspring and possibly function to perpetuate the prevalence of metabolic syndromes worldwide.

Human habits are deeply rooted to culture and society such that the increase in automation in the contemporary society is strongly linked to deviations in traditional dietary habits in conjunction with a paucity of the practice of physical activity. In particular, conventional dietary routines based on the feasting of fish, lean meat, vegetables, fruits, and whole grains have become gradually superseded by processed foods including refined grains and sugars, fried meals, and fatty meats. The increased pace of life secondary to industrialization has

resulted in the rise of fast food restaurants and consumption of “junk food.” Excessive energy intake conjoint with a sedentary lifestyle poses a risk for developing late-life cognitive impairment, including AD (Janson et al., 2004; Malek-Ahmadi et al., 2013; Stranahan et al., 2008). Moreover, studies in humans show a strong association between western diet and the risk of mood disorders such as depression and anxiety (Jacka et al., 2010).

5.2 Advances in technologies: the need for nutritional systems biology

There is an urgent need for nutritional systems biology to delineate the effects of dietary manipulations at the various levels of information processing from gene transcripts, proteins, and metabolites, to the microbiome and epigenomics (responsible for mediating environmental responses). The remarkable technological advances we are experiencing today offer the ideal incubator for such systems level mechanistic studies to better understand the actions of diet and nutrition on diverse molecules and pathways in individual cells and tissues in a dynamic manner. When coupled with similar systems biology studies which delineate key disease causal molecular events and pathways, as implemented in the iPOP project (Li-Pook-Than and Snyder, 2013), it is possible to predict the consequences of various lifestyle and dietary conditions for early diagnosis and disease prevention. An added advantage is that the system biology information processing is based on molecular mechanistic information rather than traditional symptom-based approaches. Emerging evidence from gene-lifestyle interaction studies of brain disorders supports that life style modifications can counteract the biological effects of genetic predisposition (Temelkova-Kurktschiev and Stefanov, 2012). Nutritional systems biology promises comprehensive molecular signature maps of dietary components posing neurological and psychiatric risks as well as those with the potential to normalize disease risks.

6. Concluding remarks

The rise in consumption of high caloric foods has triggered an epidemic of metabolic disorders (Haffner and Taegtmeyer, 2003; Lutsey et al., 2008) such that the number of obese, diabetic and pre-diabetic persons in the U.S. is now estimated at over 40% of the population (Cowie et al., 2009). Epidemiological studies have attributed a majority of obesity, T2D, and MetS cases to major lifestyle factors such as unhealthy diet and physical inactivity and subsequent toll in brain function (Gomez-Pinilla, 2008). T2D is more prevalent in populations consuming the so-called western or conservative diet, which is high in carbohydrates (from refined grains and sugar), red meat, and saturated fat. On the other hand, dietary interventions involving increased polyunsaturated fat and fiber reduce T2D risk (Agrawal and Gomez-Pinilla, 2012; Gomez-Pinilla and Tyagi, 2013; Lim et al., 2005; Meng et al., 2016). It is becoming understood that diabetes and other metabolic disorders such as obesity increase the vulnerability to neurological disorders (Gomez-Pinilla, 2008; Newcomer, 2007). These associations are not surprising given that brain operation is heavily dependent on accuracy of mechanisms that manage supply of functional energy to cells. Metabolic syndrome is a risk factor for several neurological disorders such as brain trauma, stroke, Alzheimer's disease, and Huntington's disease, all of which have a metabolic component (Farooqui et al., 2011; Freiherr et al., 2013; Malek-Ahmadi et al., 2013).

Accumulating evidence points out that the remarkable capacity of the brain for cognitive plasticity is heavily rooted in a working connection between the gene regulation and cell metabolism. The advent of nutritional system biology offers the unique opportunity to integrate a multitude of molecular variables to have a thorough view of the broad impact of diet on the brain. The results from system nutrigenomic research is starting to reveal the power of diet and cell metabolism to modify the program of genes with subsequent implications for brain pathogenesis. Lifestyle factors that intrinsically alter cell energy metabolism, such as exercise and diet, are particularly influential on the epigenome. Diet and exercise engage epigenetic mechanisms to promote stable modifications of the broader realm of molecular systems that regulate synaptic plasticity and behavior. Epigenetic information which is potentially heritable has many implications for evolution and the etiology of diseases, including coping behaviors and psychological disturbances. In harmony with their strong adaptive force, dietary factors and exercise are surfacing as critical promoters of biological adjustments that can tip the balance between health and disease. Procurement of system level information concerning the action of diet on brain is insightful for the design of public health initiatives to prevent or redirect the course of the epidemic of metabolic and brain disorders.

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Abbreviations:

BDNF	brain-derived neurotrophic factor
DHA	docosahexaenoic
HFD	high fat diet
HIF	hypoxia inducible factor
MetS	metabolic syndrome
POMC	pro-opiomelanocortin
T2D	type 2 diabetes

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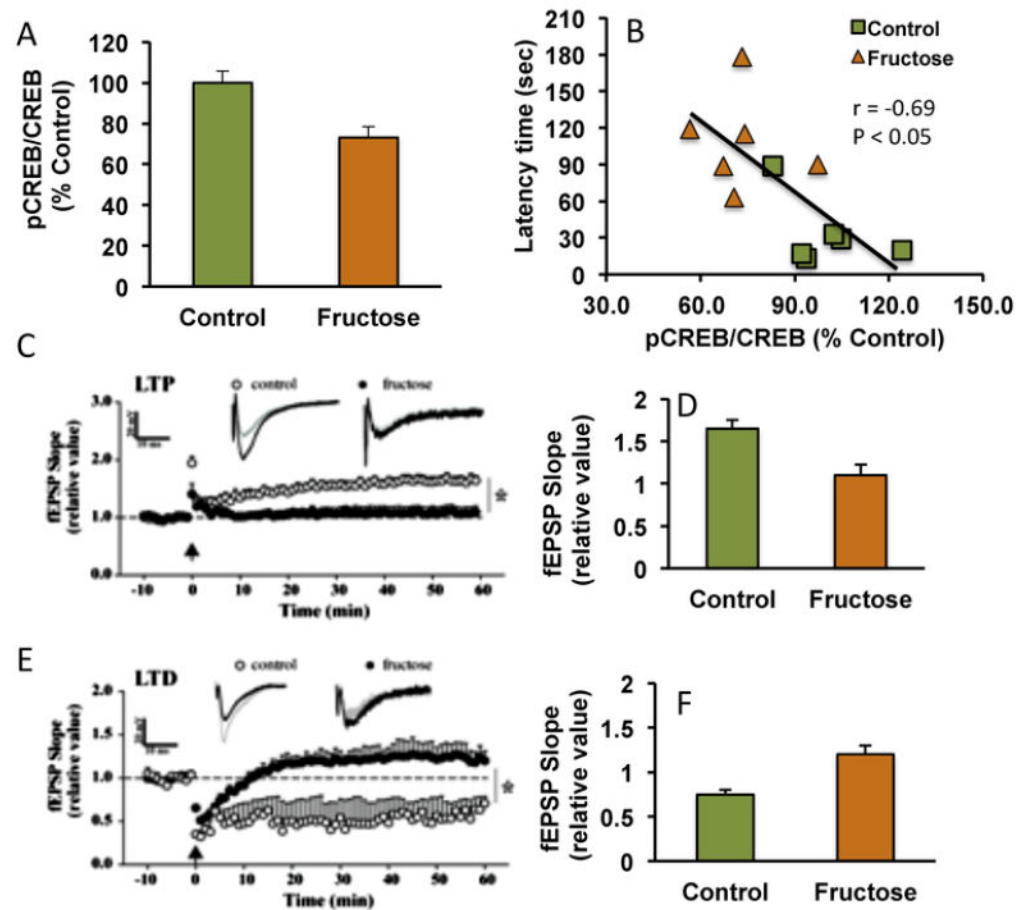


Fig. 1.

Influence of metabolic perturbation on brain plasticity and behavior. High fructose consumption for a period longer than six weeks promotes metabolic syndrome in rodents. (A) The effects of fructose on the brain are evidenced by reductions in the activation of molecular systems important for synaptic plasticity such as cAMP-response element binding (pCREB/CREB) in the hippocampus; for reviews see (Agrawal and Gomez-Pinilla, 2012). CREB belongs to a family of transcription factors that play a major role in synaptic plasticity and learning and memory (Benito and Barco, 2010). (B) Fructose treatment also results in memory deficit in the Barnes maze as evidenced by a decrease in latency time to find the escape hole, in proportion to an increase in CREB activation. (C, D) Fructose exposure also reduces hippocampal excitability in the form of long-term potentiation (LTP), and (E, F) synaptic strength or long-term depression (LTD); for reviews see (Cisternas et al., 2015). This information highlights the deleterious effects of metabolic perturbations on the substrates for synaptic plasticity and cognitive function in the brain.

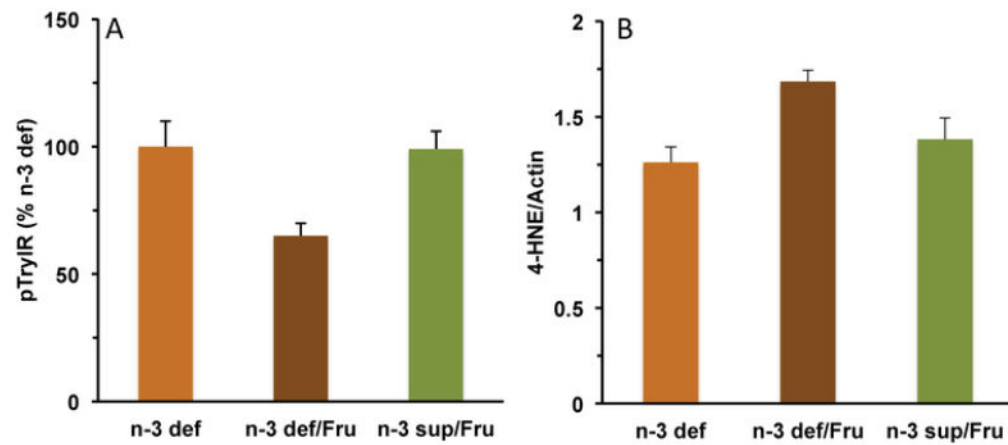


Fig. 2.

Interactive actions of fructose and omega-3 fatty acids consumption on the management of metabolic dysfunction in the hippocampus. (A) Although deficiency of omega-3 fatty acids (n-3 def) does not alter insulin receptor signaling, concurrent fructose administration reduces insulin signaling (n-3 def/Fru). N-3 supplementation provides protection against the effects of fructose (n-3 sup/Fru); see for reviews (Agrawal and Gomez-Pinilla, 2012). The results highlight the importance of dietary omega-3 fatty acids for maintaining proper insulin signaling in brain, particularly under the metabolic challenges posed by metabolic dysfunction carried by fructose consumption. (B) Deficiency in omega-3 fatty acids also makes the brain vulnerable to lipid peroxidation carried by fructose exposure. N-3 supplementation appears to protect against the lipid peroxidation driven by fructose. A failure in cell metabolism can result in lipid peroxidation of the plasma membrane by engaging membrane bound the omega-3 fatty acid DHA, and the omega-6 arachidonic acid (AA) resulting in the generation of 4-HNE and 4HHE, respectively (see Fig. 3). Insulin receptor activation examined by immunoprecipitation of phosphotyrosine (pTyr) followed by immunoblotting with insulin receptor.

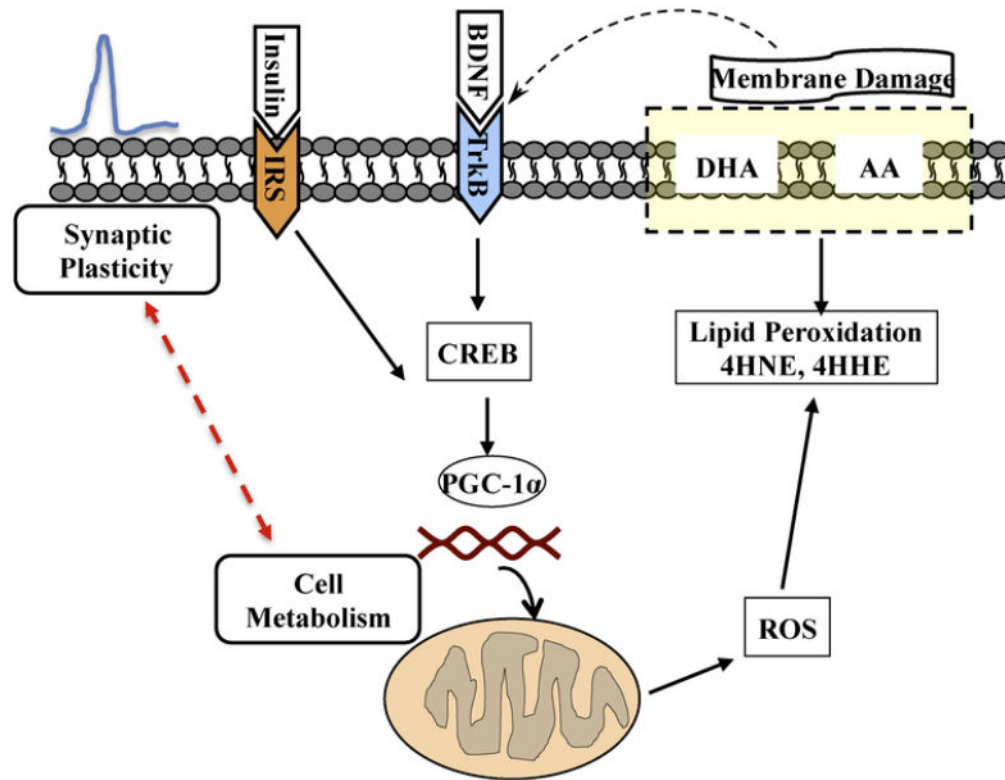


Fig. 3.

The diagram illustrates the working association between cell metabolism and synaptic plasticity, which is a target of dietary interventions. Most signaling receptors are embedded in the plasma membrane such that the functionality of the membrane is crucial for regulation of neuronal excitability and communication. In this hypothetical model, activation of the BDNF receptor (TrkB) or insulin receptor (IRS) signal a molecular cascade that regulates synaptic plasticity and cell metabolism. Insulin activates regulators of mitochondrial biogenesis, such as the peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1 α), a member of a family of transcription co-activators (Ventura-Clapier et al., 2008), using downstream systems overlapping with those of BDNF. A failure in cell metabolism involving the mitochondria can result in overproduction of reactive oxygen species (ROS), lipid peroxidation of the plasma membrane by engaging membrane bound omega-3 fatty acid docosahexaenoic (DHA), and the omega-6 arachidonic acid (AA) resulting in the generation of 4-HNE and 4HHE, respectively. Peroxidation of membrane produces alterations in the function of key membrane proteins including glucose transporter, glutamate transporter, and sodium potassium ATPases (Lauderback et al., 2001); (Mark et al., 1997). The DHA is an important component of the membrane and crucial to maintain membrane function. Both BDNF/trkB (Chen et al., 2009) and insulin receptor (Lee et al., 2005) pathways convergence on signaling pathways regulating synaptic activity and learning and memory (Alonso et al., 2002). Through TrkB receptor, BDNF leads to the activation of CREB, which is a potent activator of PGC-1 α (Herzig et al., 2001). Therefore, the effects of fructose on CREB activation in rats (Figs. 1 and 2) emphasize the interactive actions of metabolic and plasticity signals. As discussed in the text, metabolic dysfunction involving

mitochondrial abnormalities is getting recognition as a common feature in the pathogenesis of neurological disorders.

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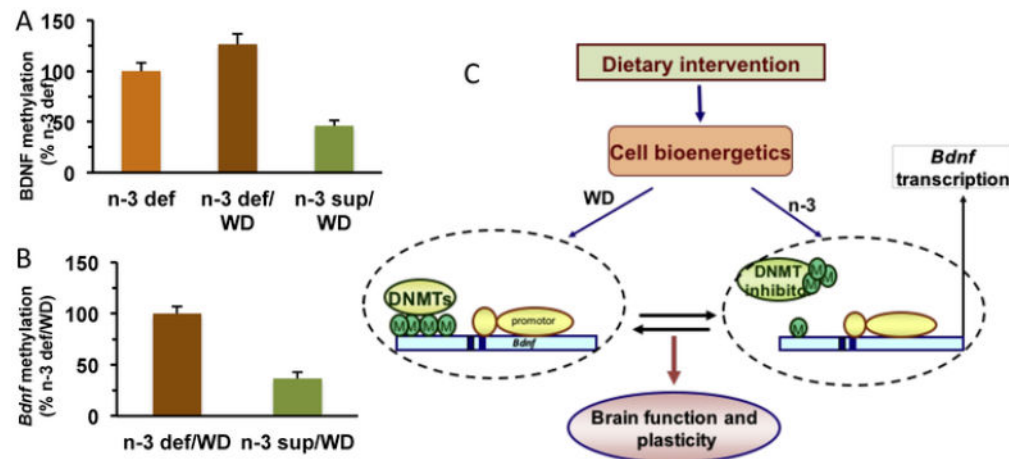
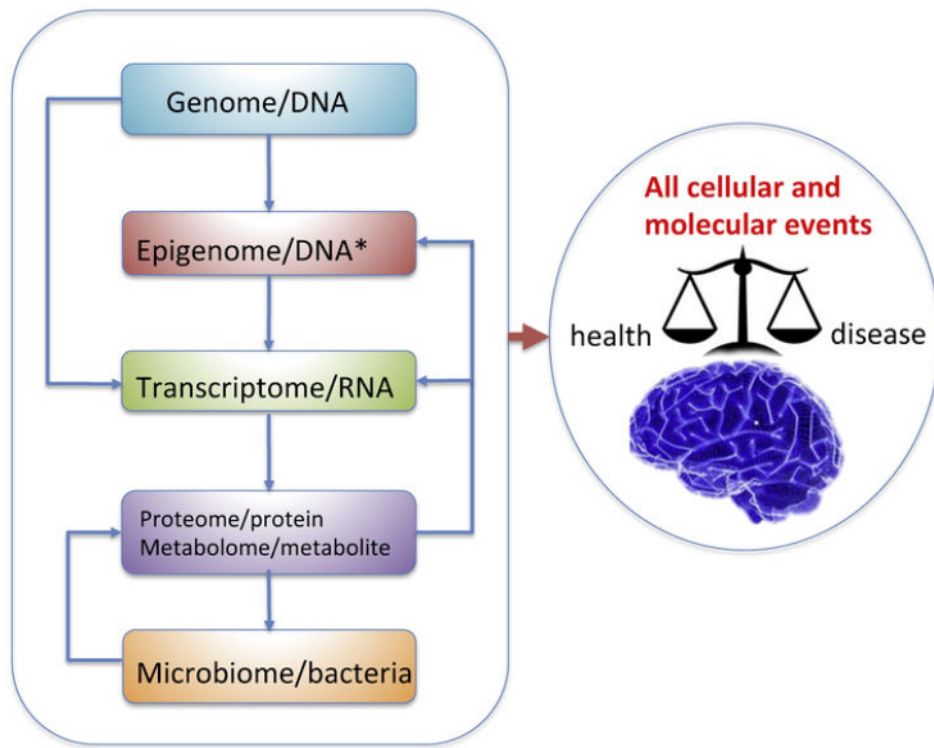
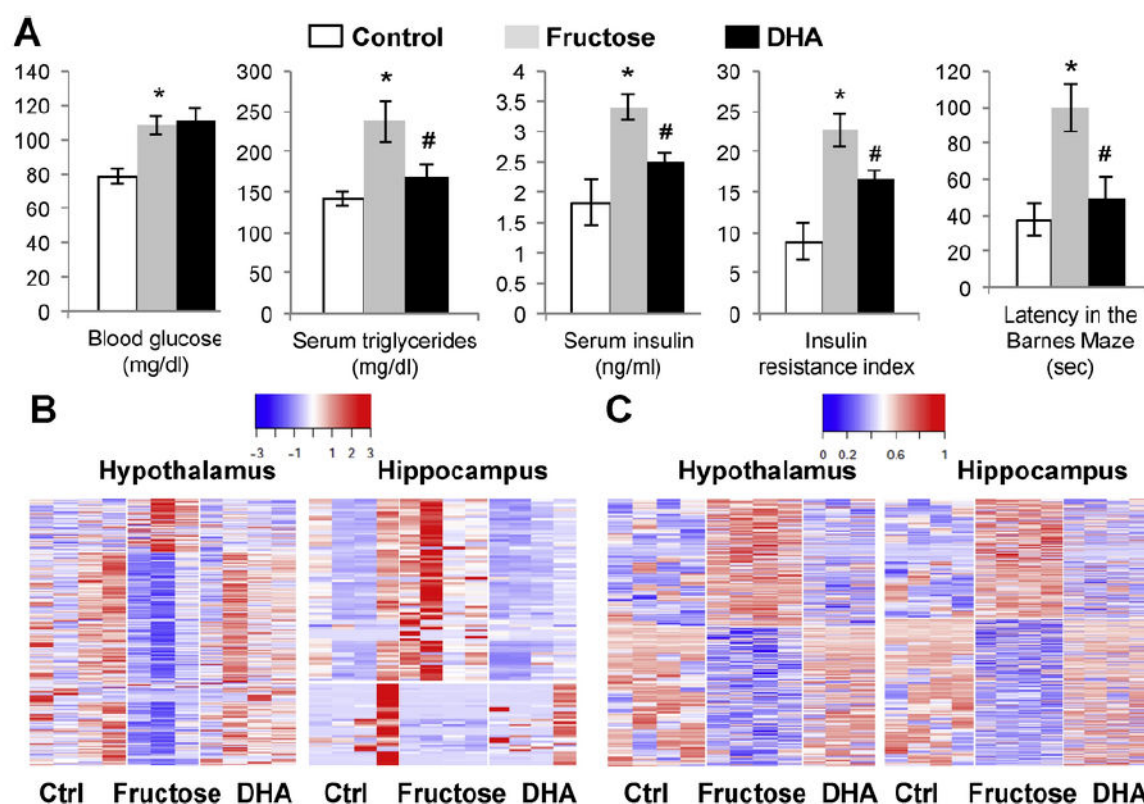


Fig. 4.

Dietary exposure is operational for building an “epigenetic memory” influencing long-term brain function and plasticity. Methylation of DNA occurs in about 80% of all CpG in mammals (about 80% of CpG are methylated). Methylation impacts transcription of genes by impeding binding of proteins or attracting binding of methyl-CpG-binding proteins such that reduction of methylation stimulate transcription of *Bdnf* gene. (A) Prior exposure to a diet rich in omega-3 fatty acids protects against the effects of switching to a western diet (WD) high in calories. Animals that had been exposed to a diet rich in omega 3 fatty acids (n-3 sup) show reduced methylation of the *Bdnf* promoter IV after switching to a WD, relative to animals that had been exposed to a diet deficient in omega-3 fatty acids (n-3 def/WD). The methylation was blocked using the methylation inhibitor decitabine (DEC). See for reviews (Tyagi et al., 2015). (C) Potential mechanism by which cell metabolism influenced by diet can serve to regulate methylation (M) of the *Bdnf* gene based on (Tyagi et al., 2015). Dietary interventions affect cell energy regulators such as NAD/NADH, SIRT1, and PGC-1 α , which in turn act on DNA methyltransferase (DNMT) to regulate *Bdnf* methylation and transcription. The pre-exposure to dietary n-3 fatty acid (n-3 diet) may act as a determining factor for the outcome of WD exposure. Omega-3 fatty acids and WD can have opposite actions on DNMTs by promoting hypomethylation and hypermethylation of the *Bdnf* exon IV, respectively.

**Fig. 5.**

Nutritional system biology provides a thorough representation of the multitude of molecular interactions affected by diet to ultimately regulate brain homeostasis and disease. The heritable genome has the program to direct all cellular and molecular events, and determines the expression of genes in the transcriptome of individual cells, which in turn instruct the proteome to synthesize functional protein products that are critical for cell to cell communication and processing of higher order information. Lifestyle factors such as diet can interact with the genome and modify the epigenome to affect the transcriptome. Byproducts of the gut microbiota can modulate the host immune system as well as enzymes that assist in metabolism to influence metabolite diversity and quantity. Metabolites, in turn, play important roles in gene expression regulation by contributing to modifications of the epigenome that subsequently change the transcriptional regulatory machinery. These complex cascades and interactions are critical elements for consideration in multidimensional data integration that can provide meaningful information about brain function and pathogenesis.

**Fig. 6.**

Changes in metabolic and behavior phenotypes, transcriptome, DNA methylome, and biological pathways in response to fructose treatment and supplementation with the omega-3 fatty acid DHA, according to (Meng et al., 2016). (A) Metabolic and behavior phenotypes. From left to right: blood glucose, serum triglycerides, serum insulin, insulin resistance index, latency time in the Barnes Maze test. Fructose group was compared with the control group, and the DHA + fructose group (DHA) was compared to the fructose only group. * $p < 0.01$ and # $p < 0.05$ by 2-sided Student's t-test. Error bars in the plots are standard errors ($n = 8$ /group). (B) Heatmap of gene expression changes in hypothalamus and hippocampus. Blue to red colors indicate low to high expression values. (C) Heatmap of DNA methylation changes in hypothalamus and hippocampus. Blue to red colors indicate low to high methylation levels.

Tissue	GWAS Disease/Trait	GWAS study ^a	p-value (ks) ^b	p-value (Fisher) ^b
Hypothalamus	HDL cholesterol	GLGC	4.35E-05	1.25E-12
	LDL cholesterol	GLGC	1.05E-03	1.90E-05
	Total cholesterol	GLGC	8.51E-06	3.65E-14
	Triglycerides	GLGC	5.88E-04	3.09E-09
	Diastolic blood pressure	ICBP	2.40E-05	7.55E-05
	Systolic blood pressure	ICBP	3.06E-03	1.16E-02
	Type 2 diabetes	DIAGRAM+	2.07E-02	3.39E-02
	Cognitive function	FHS	1.78E-02	3.18E-03
	Bipolar disorder	WTCCC	3.06E-02	4.04E-02
Hippocampus	HDL cholesterol	GLGC	6.48E-05	2.02E-07
	LDL cholesterol	GLGC	2.98E-05	2.16E-04
	Total cholesterol	GLGC	2.37E-05	4.19E-13
	Triglycerides	GLGC	1.34E-02	6.55E-06
	Diastolic blood pressure	ICBP	4.52E-01	4.59E-03
	Cognitive function	FHS	9.43E-03	4.28E-02
	Schizophrenia	CATIE	2.26E-02	3.02E-01
^a . GLGC: Global Lipids Genetics Consortium; ICBP: The International Consortium for Blood Pressure; DIAGRAM+: The Diabetes Genetics Replication And Meta-analysis Consortium; FHS: Framingham Heart Study; WTCCC: Wellcome Trust Case Control Consortium				
^b . numbers in bold indicate Bonferroni-corrected p-value < 0.05				

Fig. 7.

Relevance of fructose signatures and key driver genes (KDs) to human diseases, according to (Meng et al., 2016). To assess the relevance of nutrigenomic signals from the rodent model to human pathophysiology, the fructose signature genes as well as the KDs were compared to human GWAS of metabolic disorders and brain related diseases or traits. Numerous overlapping genes were found between fructose signature genes and top GWAS hits for a broad range of brain disorders (e.g., Alzheimer's disease, attention deficient hyperactive disorder, depression, addiction, Parkinsons disease) and MetDs-related diseases or traits (e.g., blood pressure, cardiovascular disease, lipids).