Adolescent Brain Vulnerability and Psychopathology Through the Generations: Role of Diet and Dopamine

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Early neurodevelopment in utero and in the early adolescence is a key stage during maturation with various structural, neurochemical, and molecular changes taking place in response to genetic and environmental cues (1). These include synaptic pruning, where "redundant" synapses are eliminated, resulting in decreased levels of cortical gray matter as the brain matures. Coinciding with this is the formation of new neuronal connections producing a phase of high plasticity throughout much of the brain. Of note is a key role for dopamine signaling in regulating the formation of appropriate synaptic connections in an age-dependent manner (2). A consequence of this major neuronal rewiring during adolescence is a high level of vulnerability to pathologic insults ranging from stress to drugs of abuse to dietary deficiencies (1). This developmental time point is also the peak time for the onset of numerous psychiatric disorders including schizophrenia, substance abuse disorders, and mood disorders (1), all of which are associated with aberrant dopamine signaling. Thus, pathologic vulnerability of the adolescent brain makes it uniquely susceptible to neurochemical changes that presage the onset of mental illness.

The Role of Nutrition in Neuronal Development

The concept of nutritional status as a key environmental factor influencing the onset and severity of psychiatric disorders is gaining credence (3), with adequate concentrations of the essential fatty acids, mainly the omega-3 (n-3) and the omega-6 (n-6) polyunsaturated fatty acids (PUFAs), being critical for normal brain development (3). Furthermore, nutritional status can have a great impact on the levels and severity of psychiatric disorders that emerge in later generations (4). Considering the enormous shift in dietary habits that have taken place in developed nations over the past 50 to 100 years, including a diminution of the intake of n-3 PUFA consumption, the implications emerging from this are profound. Furthermore, increased proportions of urban living and high stress levels of modern life are two additional factors that can predispose individuals to psychiatric disorders (5). A scenario thus emerges in which a dramatic increase to the levels of mental illness could emerge in the coming generations. If we are to effectively combat this insidious epidemic, we must improve our mechanistic understanding of how the various factors can have an impact on mental health. Moreover, there is a growing desire for dietary interventions that promote health in the form of medical foods. Interestingly fatty acids, methylfolate, and microbiota-based strategies are among those now being heavily investigated in this regard (6).

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Poor Nutrition Can Have a Negative Impact on Cognitive Processes

As described in the current issue of *Biological Psychiatry*, Bondi and colleagues have made some interesting headway in addressing the impact of dietary deficiencies in adolescent animals. They present an elegant model that allows for the detailed behavioral and molecular evaluation of the deficits arising from PUFA dietary deficiency across generations (7) (Figure 1). Interestingly, the authors show that animals kept on a PUFA-deficient diet had only modest behavioral changes compared with those on a control diet. However, and of marked interest, they found that second-generation adolescent animals (i.e., those whose mothers were subjected to a PUFA-deficient diet during throughout their life span) had greatly exacerbated deficits in behaviors linked to dopamine neurotransmission. Specifically, they spent less time exploring the center of a novel arena, coupled with a general increase in locomotion. Furthermore, these animals also presented short-term memory deficits in a novel object recognition task and displayed poorer acquisition in an operant instrumental learning task. Moreover, increased impulsive-like behavior was observed in adolescence only. The relationship of this adolescent phenotype to the susceptibility of adult behavioral deficits is currently unclear, but it is worth noting that impulsivity is a risk factor for the development of many psychiatric disorders including substance abuse and anxiety disorders (8). Importantly, although many studies have investigated the role of PUFA deficiency on behavior in adulthood, the focus on adolescent-related behaviors in this study is particularly notable.

PUFA Deficiency Leads to Altered Brain Neurochemistry: Implications for Transgenerational Effects

Perhaps unsurprisingly, the authors found levels of various fatty acids were dramatically altered in the brains of animals fed a PUFA-deficient diet. However, this led to an even more dramatic alteration to the PUFA profile in the offspring of these animals that were themselves fed a PUFA-deficient diet with significantly lower levels of docosahexaenoic acid coupled with elevated concentrations of docosapentaenoic acid. At both a neurochemical and behavioral level, deficiencies were exacerbated in the second generation; this is in line with an ever-growing corpus of data detailing transgenerational effects on brain function that influence the onset of psychiatric disorders (9). Indeed, the interactions between dietary status and transgenerational effects have been studied in the elevated levels of metabolic and mental illnesses that followed the Dutch famine in the 1940s (10).

To date, mechanistic investigations into this phenomenon focused mainly on DNA methylation and histone modifications; Bondi and colleagues demonstrate perturbations to the dopaminergic machinery in the second generation of animals fed a PUFA-deficient diet. These alterations may represent molecular

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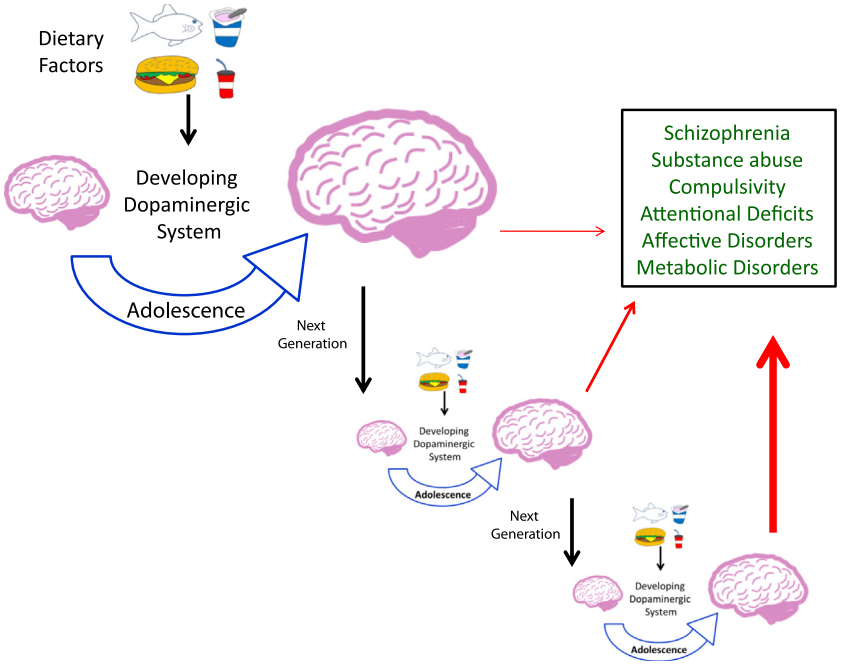

Figure 1. Schematic depicting the transgenerational effects of diet on the dopaminergic system in the developing adolescent brain and subsequent impact on disease progression. Diet can have both a protective or detrimental effect on the adolescent developing brain. Evidence for protective effects have been found for foods such as polyunsaturated fatty acids and probiotic dietary supplements. Nutritionally deficient diets and unhealthy foods high in sugar and fat content can have pathologic effects on the developing brain influencing disease progression. Diet-induced synergistic effects occur with the susceptibility to disease onset increasing with each generation.

pathologies that can be passed through generations. It will be of interest to elucidate whether these pathologies are mediated through mechanisms that have been the focus of epigenetic research to date or perhaps represent a novel means through which pathology may pass through generations. However, it should be noted that the exacerbated pathology seen in second-generation animals results from nutritional deficits present in the parents, which could affect the production of germline cells and/or in utero development of various aspects of physiology.

In addition to the marked sensitization of behavioral deficits across generations, Bondi and colleagues also show phenotypic differences in the dopaminergic system in PUFA-deficient adolescent animals compared with controls as shown by increased levels of tyrosine hydroxylase (TH) in the dorsal striatum. Interestingly, these alterations were different in adulthood where reduced levels of TH coupled with increases in the levels of the vesicular monoamine transporter 2 (VMAT2) levels in the dorsal striatum were observed. Dopamine plays a key role in governing motivation and reward processing, and alterations to dopamine levels have been linked to the onset of various psychiatric disorders including schizophrenia, substance abuse disorders, attention-deficit/hyperactivity disorder, and depression (Figure 1). Indeed, clinical evidence has linked disruptions to TH functioning in the form of polymorphisms to the onset of various psychiatric disorders including schizophrenia. As mentioned, emerging evidence suggests regulation of dopamine function to be highly age-dependent and important for regulating the formation of appropriate synaptic connections (2). As such, the transgenerational diet-induced increase in dopamine availability in the dorsal striatum of adolescent animals could result in developmental behavioral abnormalities, the impact of which may not emerge until adulthood. Interestingly, in the study by Bondi *et al.*, this phenomenon was reversed with decreased levels of TH in the dorsal striatum and increased levels of VMAT2 in adulthood. This might represent adaptive changes in which levels of TH gradually decrease throughout maturity, resulting in a compensatory increase in VMAT2. Increased VMAT2 would increase the packaging of dopamine into vesicles for subsequent release into dopaminergic synapses. However, this remains speculative, and further studies are warranted to unravel the temporal effects of such dopaminergic manipulations.

Public Health Implications

This research may have serious implications for public health. Given that behavioral and neurochemical deficiencies arise most significantly in the second generation of animals subjected to a PUFA-deficient diet, one can hypothesize this could continue and even lead to sensitization into subsequent generations. If one considers this experimental construct as a model of assessing the marked dietary changes that have been occurring in Western societies for the last few decades, these findings indicate an epidemic of mental illnesses lurking beneath the surface that may emerge in the coming years. Future studies will need to examine additional mechanisms of pathology resulting from nutritional deficiency; only once these neurochemical and molecular deficits have been established will we be able to devise suitable interventions to combat the potential epidemic of mental illness. Diets formulated with health-improving properties are increasingly being investigated as a means to improve the health of society as a whole and may represent low-cost prophylactic interventions possessing ease of implementation. Moreover, elucidation of the molecular and cellular basis of how pathologic insults taking place during periods of vulnerability such as adolescence will allow for targeted interventions to take place in at-risk populations. With changes in health care policies in many countries trending toward an appreciation of the importance of preventative interventions, augmentation of diets with evidence-based strategies including PUFAs, probiotics, or nutrients such as zinc and other micronutrients may eventually reduce rates of mental illness and thus having knock-on effects

in terms of health benefits to individuals and economic savings to society as a whole.

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