

Role of Brain Derived Neurotrophic Factor in Inducing Childhood Obesity: Impact in Maternal Opioid Addiction



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Submission: August 08, 2017; **Published:** August 28, 2017

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Abstract

Pregnant females consuming drugs of abuse is becoming an adverse social problem. In these subjects increases the risk of complications during pregnancy, may permanently harm the infants cognitive functions. Obesity in children and adolescents is a worldwide health problem, linked to a variety of somatic, psychosocial and psychiatric complications. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays an important role in control of feeding behavior, food intake regulation, energy metabolism and weight control. A common polymorphism of the BDNF genotype (Val66Met) has been associated with a range of forms of eating disorders, alterations in body mass index (BMI) values and obesity in adult populations. Its presence in the arcuate, ventro medial and para ventricular nuclei indicates its vital role in regulation of feeding and body weight. Obesity is presently so common within the world's population that it is beginning to replace under nutrition and infectious diseases as the most crucial contributor to ill health. In particular, obesity is linked with diabetes mellitus, coronary heart disease, certain forms of cancer and sleep-breathing disorders. The worldwide epidemic of obesity results from a grouping of genetic vulnerability, increased accessibility of high-energy foods and decrease requirement for physical activity in current society. Obesity should no longer be observed simply as anaesthetic problem disturbing certain individuals, but an epidemic that threatens global well being.

Keywords: Obesity; Opiate addiction; BDNF

Introduction

Obesity is an excessive storage of energy as fat, which has adverse effects on health. Obesity can be define by a body-mass index (weight divided by square of the height) of 30kg m⁻² or greater, but this does not take into account the morbidity and mortality related with more modest degrees of overweight, nor the harmful effect of intra-abdominal fat. Obese people suffer increased mortality and morbidity from cardiovascular, gastroenterological and malignant disorders beside with many other conditions [1,2]. It is one of the fastest-growing health problems globally. A current national health survey reported that approximately 16% of children in the United States are obese [3].

A number of susceptibility genes that results in common childhood obesity were recently identified and compiled base on

GWAS and some mouse model studies reported [4]. Childhood obesity being a complex metabolic disorder resulting from genetic and epigenetic interactions with environmental factors such as dietary molecules, prior exposure to risk factors contained in maternal blood may also contribute to the pathogenesis of this disorder. The objective of this article is to provide a review on the pathophysiology of BDNF dependent cognitive dysfunction in childhood obesity as it relates to maternal opioid addiction. It is believed that increased knowledge of the interrelationship between BDNF and maternal opioid consumption will provide valuable insight for community preventative lifestyle intervention and eventually develop therapies for memory and learning complications that accompany childhood obesity.

Childhood obesity did approximately doubled in the past three decades and adolescent obesity has more than tripled

during the same period in US and some developing nations [5]. National Household Survey on Drug Abuse (NHS) suggests that 10% of children residing in US have at least one drug or alcohol addicted parent, 6% have at least one parent who is in need of treatment for addiction to drugs and that 3.7% of pregnant women indulge in the use of illicit drugs [6,7]. As awareness of the extent of substance abuse problems among mothers has increased, so has concern about the health and development of children of addicted mothers. More importantly, much attention has been given to the effects of prenatal exposure to drugs on child's health and development [8].

Opioids are one of the most frequently abused drugs [9,10]. The rate of increase in the number of people abusing prescription drugs such as opioids is alarmingly high [11]. As was reported, 32% increase in persons abusing pain relievers was recorded at the interval of 2005 to 2006 in US (from 4.7 million to 5.2 million) [10]. In line with this, opioid use during pregnancy was estimated to range between 1% and 21% in several populations [12]. Opioids cross the placenta easily, this may result in a number of complications especially in addicted women, for example low birth weight, meconium aspiration, preeclampsia, puerperal morbidity, third-trimester bleeding and fetal intolerance to labor. Neonatal complications may include narcotic withdrawal, microcephaly, neurobehavioral anomalies, increased neonatal mortality and significant increase in sudden infant death syndrome [13]. Nevertheless, it can be suggested that, the pathogenesis of neurobehavioral anomalies observed in childhood obesity with a history of maternal opioids addiction may be as a result of coexistence of both morbidities.

Mechanism involved in pathology of obesity

The pathology of obesity is complex due to several genetic and ecological factors and their interactions [14]. BDNF, one member of the neurotrophin family of proteins, contributes to a specific type of memory inhibition function and suppresses food intake through hippocampal signaling [15,16]. It has been found that Plasma BDNF is lower in humans with obesity and type 2 diabetes [17]. The mutation in TrkB, the receptor for BDNF was shown to be associated with an obese phenotype [18]. Decreased hippocampal BDNF and TrkB expression increased the risk of high-fat diet-induced obesity [19]. Collectively these findings support an important role for BDNF in energy metabolism and food intake regulation. Brain-derived neurotrophic factor (BDNF) is a protein that is significant in nervous system development and function. According to National Institutes of Health Clinical Center BDNF also appears to function downstream of the leptin-melanocortin signaling pathway to control hunger. In both animals and humans, diminished BDNF function is associated with hyperphagia, obesity, and neurocognitive deficits.

Role of BDNF in obesity

Studies in animal models suggest that brain-derived neurotrophic factor (BDNF) plays a key role in energy homeostasis [20]. Heterozygous BDNF \pm mice with decreased

BDNF expression and increased food intake exhibited hyperplastic behavior and obese phenotypes [21], while mice with BDNF knockout in the postnatal brain showed increased glucose and cholesterol concentrations [22]. Furthermore, hypothalamic over expression of BDNF is one kind of genetic regulator, converting white fat into brown fat in adipose tissue, leading to energy dissipation and a lean phenotype [23]. BDNF is believed to act primarily within the ventromedial hypothalamus to regulate energy intake downstream of the leptin-proopiomelanocortin signaling pathway [20]. In mice, genetic BDNF haploinsufficiency leads to obesity [22,24].

Mice that are heterozygous for inactivated BDNF have a 50% reduction in hypothalamic expression of BDNF, and they have hyperphagia and obesity, which are reversed by intracerebroventricular infusions of BDNF [25]. Although studies in animals provide support for a role of BDNF in energy homeostasis, data in humans are relatively limited. Some studies have shown an inverse association between the peripheral BDNF concentration and the body-mass index (BMI) (the weight in kilograms divided by the square of the height in meters) in children and adults [26].

A common BDNF polymorphism, Val66Met, has been inconclusively associated with altered body weight [26]. The most relevant data are from two case reports. One described an obese child with hyperphagia and a heterozygous 11p13p15.3 inversion that resulted in what has been termed "functional" BDNF haplo insufficiency (as determined from measurements performed in a lymphoblastoid cell line [27]; the other, more convincingly, described an obese child with hyperphagia and a heterozygous missense substitution resulting in impaired signaling of the cognate receptor of BDNF, TrkB [28]. Thus, the available data suggest the importance of BDNF in energy homeostasis in humans, but the evidence is not definitive.

Childhood obesity risk estimation by BDNF measurement

Brain derived neurotrophic factor (BDNF) play a significant role in the growth and pathophysiology of childhood obesity. In a study of Japanese children aged a mean of 10.3 years, the team found that plasma BDNF levels were considerably lower in morbidly obese children than in obese and non-obese children. Interestingly, plasma BDNF was associated with the children's birth weight. Shunsuke Araki and colleagues from University of Occupational and Environmental Health, Kitakyushu, Japan suggested that weight at birth could affect the plasma BDNF levels in obese children. Using national statistics for Japanese school children as reference, the team calculated body mass index (BMI), BMI-percentile, and BMI Z-score (a measure of their relative weight adjusted for age and gender) for 66 obese Japanese children and 32 age-matched obese children who underwent assessment of BDNF levels and anthropometric parameters. As reported in Obesity Research and Clinical Practice, the mean BMI-Z score was significantly higher among

the morbidly obese (BMI \geq 99th percentile) children than among those who were obese (\geq 90th BMI percentile, <99th BMI percentile) and non-obese (<90th percentile), at 3.39, 2.15, and -0.67, respectively. The mean plasma BDNF level among the morbidly obese children was significantly lower than in the obese and non-obese children, at 507pg/mL versus 626pg/mL and 621pg/mL, respectively [29].

The researchers also found that 10 of the children were diagnosed with the metabolic syndrome (eight morbidly obese and two obese) and that the mean BDNF level among these children was significantly lower than among children who did not have the metabolic syndrome, at 476pg/mL versus 611pg/mL. As some studies have also shown that a small size for gestational age at birth might be a risk factor for Type 2 diabetes and the metabolic syndrome, the team also assessed the relationship between birth weight and plasma BDNF levels in the obese children. Among the obese and morbidly obese children the plasma levels of BDNF were positively correlated with birth weight and inversely correlated with BMI-Z score [29]. Furthermore, multivariate analysis showed that BMI Z-score and birth weight were independent predictors of the plasma BDNF levels.

The hippocampus is part of the temporal lobe of the brain and has long been known to be involved in learning and memory. It has been shown that the hippocampus is especially important for converting short-term memory into long-term or permanently encoded memories. The hippocampus does not generally store memory, but is involved in the maintaining of the memories until they are transferred to more permanent storage in different areas of cerebral cortex [30]. Information is projected to hippocampus through neurons from the brain stem with common neurotransmitters such as norepinephrine (NE), acetylcholine (ACh) and serotonin (5HT, 5-hydroxytryptamine). The main excitatory projection from the hippocampus is, however, the glutamateric neurons, which connect the hippocampus with structures such as the cortex and the amygdala [29]. Glutamateric neurons are also projected to the nucleus accumbens (NAc) an important structure for the rewarding and reinforcing properties associated with drug consumption [31].

There is a growing body of evidence revealing the long lasting neurobehavioral and/or cognitive disturbances due to prenatal opiates exposure [32]. Animal studies have shown that learning and memory processes can be impaired by prenatal morphine exposure [33]. It has been demonstrated that in the uterus, morphine exposure impairs hippocampal long-term potentiation or depression due to decreased expression of NMDAR subunits (NR1, NR2A, and NR2B), postsynaptic density protein 95 and neuronal nitric oxide synthase, reduced phosphorylation of CREBSerine-133, and also decreased GABAergic inhibition. To show the early mechanisms responsible for the long lasting neurobiological changes, it was previously demonstrated that prenatal morphine exposure delays the neural tube closure and

increases the rate of neuroblast apoptosis in developing neural system. This prenatal imbalanced apoptosis may persist even after birth, as in a recent study the memory deficits resulted from prenatal heroin exposure is attributed to the increased neuronal apoptosis in the hippocampus of young offspring.

Conclusion

Opiate use during pregnancy is a risk factor for mother and child in relation to the possible complications during pregnancy and presentation of neonatal withdrawal symptoms and sudden death. Obesity should no longer be regarded simply as a cosmetic problem affecting certain individuals, but an epidemic that threatens global wellbeing. "The impact of birth weight on the circulation of BDNF levels in obese individuals needs to be investigated in further studies".

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DOI: [10.19080/CTBEB.2017.08.555727](https://doi.org/10.19080/CTBEB.2017.08.555727)

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