Effects of Early Malnutrition on Mental System, Metabolic Syndrome, Immunity and the Gastrointestinal Tract

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ABSTRACT. The notion of how malnutrition early in life affects ontogenesis has evolved considerably since the mid-1960s. Since then, there have been many studies on the effects of early malnutrition. Nutritional and metabolic exposure during critical periods in early human and animal development may have long-term programming effects in adulthood. This is supported by evidence from epidemiological studies, numerous animal models and clinical intervention trials. In this paper, we review the effects of early malnutrition on cognitive function, metabolic syndrome, immunity and the gastrointestinal tract, as well as possible underlying mechanisms, and consider diarrheal disease and poor cognitive function as examples for understanding the interrelation of the harmful effects caused by early malnutrition. Previous studies on early malnutrition have mainly concentrated on humans and rats. Therefore, the main aim of the present review was to give animal scientists a clear understanding of the harmful effects of early malnutrition on animal growth and animal production, and to help identify appropriate feeding techniques to prevent early malnutrition.

KEY WORDS: early malnutrition, gastrointestinal development, immunity, metabolic syndrome.

Important nutrients during fetal and neonatal development

While all nutrients are important for cell growth and body development, some appear to have more important effects especially during the last trimester and early neonatal period. These nutrients include protein, zinc, iron, copper, selenium, iodine, folate, vitamin A, choline and long-chain polyunsaturated fatty acids (LC-PUFA) [32]. The importance of these nutrients has been investigated primarily through nutrient-deficiency studies and through knowledge of their possibly specific biochemical pathways that affect growth and function.

Protein-energy malnutrition is the most common cause of early stunting and later chronic disease. A severe state of protein-energy malnutrition has been shown to significantly diminish body weight, body length, and intestine length of rats compared with control animals [64, 77]. Intestinal weight and total DNA were similarly diminished in malnourished rats [37]. Fetal and early postnatal protein malnutrition had a long-term negative impact on rat liver and muscle mitochondria of rat [60]. Protein malnutrition in weanling murine systems elicited early elevations in blood glucocorticoid levels to a magnitude reminiscent of critical illness of multiple trauma [52].

Micronutrients including zinc, iron, copper, iodine and selenium are essential in fetal and neonatal development. With zinc deficiency, the individual of rat is more susceptible to toxin-producing bacteria or pathogens that activate guanylate and adenylate cyclases, which stimulate chloride secretion, to produce diarrhea disease and reduce the absorption of nutrients [88]. The zinc concentration might regulate insulin-like growth factor 1 and growth hormone receptor gene expression [78, 79, 82]. Severe protein deficiency produced an altered neurochemical profile of the developing hippocampus in children [68] and significantly altered the development of myelination around the hippocampus in rat [92]. Fetal and neonatal iron deficiency resulted in diminished oxidative metabolism in the hippocampus and frontal cortex in rat [20], increased intracellular neuronal glutamate concentrations in rat [70], and reduced striatal dopamine concentrations [6, 89]. Copper is an essential divalent cation for proteins involved in brain energy metabolism, dopamine metabolism, antioxidant activity, and iron accretion in the fetal and neonatal brain [32]. Gestational copper deficiency appeared to affect the developing fetal cerebellum in rat, which would have long-term effects on motor function, balance and coordination [61]. Iodine deficiency reduced the size of the thyroid in rat [10]. Selenium has been shown to be essential for optimal thyroid hormone metabolism [84].

Other nutrients such as LC-PUFA and vitamins also have important effects on growth and physiological function in animals and humans. Fats, particularly docosahexaenoic acid, have been shown to be potent neurobiological agents that affect neuronal membrane structure, synaptogenesis and myelination [86]. Low maternal vitamin B12 and high folate status could contribute to the epidemic of adiposity and type 2 diabetes in India [93].

All of these studies showed that an individual nutrient deficiency resulted in the impairment of multiple systems and the development of the organism was influenced by vari-
ious nutrients simultaneously.

**Nutrition and mental system development**

In the mid-1960s, the relationship between nutrition and mental system development had become a focus of research. The evidence is quite clear that nutrients are vital to mental system development, especially during the late fetal and early neonatal life period. During this period, regions such as the hippocampus, the visual and auditory cortices, and the striatum undergo rapid development characterized by the morphogenesis and synaptogenesis that make them functional [54, 83]. For any given region, early malnutrition have a greater effect on cell proliferation, thereby affecting cell number [81, 91].

The harmful impact of early malnutrition on morphological development of the nervous system has been confirmed in previous studies. Early malnutrition obviously reduced the size of the brain [29, 23]. The cerebral cortex, which is the brain region that is most closely linked to cognitive and intellectual functioning, showed reductions in volume [7] and width [29] after neonatal malnutrition. Neuroanatomical studies using Golgi staining techniques showed that malnutrition caused a significant disruption in pyramidal cells of the cerebral cortex, a reduction in the density of cortical dendritic spines, and a decrease in both the width of cortical cells and the complexity of the dendritic branching of the cortex [44]. For any given region, early malnutrition reduced the speed of cell proliferation and the total cell number in rat [81].

Some studies showed that morphologic and neurological parameters of the brain could recover with nutritional rehabilitation after malnutrition. The smaller volume and width of cerebral cortex of rat were normalized after later nutritional rehabilitation [23]. The increase in cell packing and dendritic branching observed in the cortex in rat during early malnutrition was reversed by subsequent nutritional rehabilitation [15].

However, the reduced number of cortical dendrites in synaptic spines, as a neural aberration in the cortex, failed to recover with later nutritional rehabilitation [44]. Moreover, the reduction in brain myelin in rat, which might be indicative of a reduction in the number of myelinated axons in the brain, was not normalized after nutritional rehabilitation [90]. Recently, there was also a suggestion that chronic protein malnutrition in rat induced abnormalities in the density and morphology of the soma of vasopressive and vasoactive intestinal polypeptide neurons [75].

Nutrients can affect not only morphological development, but also neurochemistry and neurophysiology. Neurochemical alterations include changes in neurotransmitter synthesis, receptor synthesis, and neurotransmitter reuptake mechanisms [6, 70]. Neurophysiologic changes reflect changes in metabolism and signal propagation. The changes across all 3 venues ultimately result in altered neuronal behavior. Early malnutrition reduced the number of large fibers in the adult corticospinal tract of rat [66]. Learning and memory in early postnatal protein-malnourished rats were investigated in the Morris water maze. The results showed no impairment of learning or memory in malnourished rats, but did show an increased latency and distance traveled to find the submerged platform [30]. Early iron deficiency also affected locomotor behavior and water maze performance of rat [12]. With regard to behavioral self-selection, rats could choose an adaptive form when recovering from protein malnutrition [14].

In human studies, malnourished children have been described as having less activity, more anxiety, and less imagination in solving a problem than well-nourished children [5], and exhibit decreased exploration of the environment, as well as decreased verbal activity [31]. Malnourished children have been reported to be deficient in arithmetic, standardized reading and vocabulary, as well as literacy and general knowledge compared to controls [13, 46]. Furthermore, it has been shown that low-birth-weight children born to malnourished women might have deficits in mental and psychomotor development indexes [11, 33].

From above, it is quite clear that malnutrition limited to the prenatal period is not only sufficient to have a permanent effect on brain structure but also causes enduring changes in behavior, while postnatal malnutrition produces temporary morphological effects and permanent alterations in behavior. Therefore, the effects of early malnutrition on behavior can not be recovered. The conclusion was also supported by the evidence as followed. Early malnutrition could relatively directly predispose to externalizing behavior problems by impairing brain mechanisms such as those in the prefrontal cortex that are thought to regulate emotion and inhibit impulsive aggressive behavior [67], malnutrition could also predispose to externalizing behavior problems more indirectly by impairing cognitive functioning, which in turn predisposes to externalizing behavior problems [47]. Poor cognitive ability has been found consistently to predispose to externalizing behavior problems [24].

**Early malnutrition and metabolic syndrome**

Metabolic syndrome, a cluster of cardiovascular risk factors that includes diabetes, hypertension, and obesity, is now recognized as a major health problem in Western countries. Extensive logical and laboratory evidence has indicated that a suboptimal maternal environment such as malnutrition during fetal and neonatal development in both humans and experimental animals affects the offspring’s susceptibility to the later development of altered carbohydrate metabolism [63, 94]. Furthermore, many studies have suggested that a low birth weight was associated with an increased risk of the metabolic syndrome in adulthood [65, 68], although it has also been reported that neither prenatal exposure to famine nor reduced birth weight was associated with a greater prevalence of the metabolic syndrome [21].

Studies have indicated that impaired glucose tolerance and insulin resistance are the two major causes of diabetes [36]. A decrease in the mtDNA level in peripheral blood preceded the development of diabetes [42]. In addition to qualitative changes, quantitative changes in plasma insulin
concentrations and mitochondrial DNA (mtDNA) seem to be associated with insulin resistance and type 2 diabetes. When children were protein-malnourished, in early life (6 weeks-3 months) glucose tolerance was increased and plasma insulin concentrations were reduced, indicating increased insulin sensitivity [45, 59]. While there was no difference in glucose tolerance at age 1 year, glucose tolerance was impaired at 15 months and at 17 months in male rats, which may reflect the emergence of diabetes [35]. Insulin concentrations in male rat at 17 months were approximately doubled, clearly indicating insulin resistance at this stage [62]. In addition, the mtDNA content of the liver and skeletal muscle in rat were reduced in fetal and early postnatal malnourished rats even when they were provided nutritional rehabilitation after weaning [60]. This result indicated that early malnutrition causes long-lasting changes in mitochondria that might contribute to the development of alterations in insulin action in later life. The hypothesis that several mechanisms including genomic imprinting that change mtDNA content according to the nutritional status of fetal or early development was stated (Fig. 1) [43].

What is the link between nutrition and metabolic syndrome? According to the “thrifty phenotype” hypothesis, a poor nutritional condition in early life programs a phenotype in later life, in a way that is beneficial to survival under poor nutritional conditions but detrimental when nutrition is abundant [34]. If we also consider insulin resistance and glucose tolerance, three major themes have been proposed: effects of mild to moderate hyperglycemia, effects of compensatory hyperinsulinemia, and effects of unbalanced pathways of insulin action [51].

Hyperglycemia, largely below the diabetic threshold, may lead to a variety of effects that are usually associated with diabetes. For example, a moderate controlled hyperglycemia can lead to an increased non-oxidative glucose disposal rate that contributes to glucose tolerance after oral glucose ingestion [74].

A more important mechanism may be compensatory hyperinsulinemia. The maintenance of normal glucose homeostasis after a meal requires the stimulation of glucose uptake by muscle, which is responsible for the disposal of 80% to 90% of the ingested glucose load, and the suppression of endogenous glucose production, over 80% of which is derived from the liver. Moreover, compensatory hyperinsulinemia refers to an insulin-resistant condition in which the ability of insulin to augment glucose uptake and inhibit hepatic glucose production is impaired. The resultant hyperglycemia stimulates beta cells, which secrete large amounts of insulin after meals [71]. In addition, experimental evidence has substantiated that insulin resistance and compensatory hyperinsulinemia are increased in patients with essential hypertension [72].

Metabolic syndrome is associated with insulin resistance, but is neither a consequence of insulin resistance alone nor a direct consequence of the lack of insulin action. Low birth weight has been associated with specific changes in muscle insulin-signaling protein expression [58]. Recently, great progress has been made in understanding the signal transduction pathways that control the classical metabolic actions of insulin to promote glucose uptake in skeletal muscle and adipose tissue through translocation of the insulin-responsive glucose transporter [17]. The two major pathways for insulin signaling are the phosphatidylinositol 3-
kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways. The balance between the NO-dependent vasodilatory actions and endothelin-1-dependent vasoconstrictive actions of insulin is regulated by PI3K- and MAPK-dependent signaling in vascular endothelium, respectively. Under insulin-resistant conditions, pathway-specific impairment of PI3K-dependent signaling and enhanced MAPK-dependent signaling in vascular endothelium might contribute to reciprocal relationships between endothelial dysfunction and insulin resistance that underlie the close associations between metabolic and cardiovascular diseases [53]. Thus, insulin resistance which may be the result of early malnutrition could lead not only to severe diabetes but also hypertension, obesity and other cardiovascular diseases [50, 60, 73].

Early malnutrition and immunity

Nutrition is a critical determinant of the immune response, and malnutrition is the most common cause of immunodeficiency worldwide. Malnutrition in early life, particularly in the perinatal period, is critical for the immune competency of animals because it affects the immune system not only with regard to immediate function but also a long-term modulation [22]. Malnutrition usually permanently stunts the development of lymphoid organs. In rats, for example, malnutrition in dams caused impairment in the thymus [77]. Secondary to thymic atrophy, the production of thymic hormones that are critical for the differentiation of T lymphocytes was reduced, especially in protein-calorie malnutrition and zinc deficiency [49]. Rats from dams on a protein-deficient diet during gestation showed a permanent negative impact on growth and the size of organs including the thymus and spleen, even though they were given a well-balanced diet after weaning [48].

Immune responses were also influenced by early malnutrition. In protein-energy malnutrition, extensive dysfunction of the macrophage proinflammatory cytokine network and nuclear factor-κB (κB) regulation, which mediates innate immunity, was discovered in mouse [3]. Other studies have shown a loss of corticomedullary differentiation, fewer lymphoid cells, and enlarged, degenerated, and occasionally calcified Hassall bodies [16]. In addition, protein-energy malnutrition was associated with a significant impairment of cell-mediated immunity, phagocyte function, complement system, secretory immunoglobulin A antibody concentration, and cytokine production in children [27]. Dietary deficiencies in specific nutrients profoundly weak-ened cell-mediated immune responses in humans [76] and low-birth-weight infants showed a prolonged impairment of cell-mediated immunity [16]. Protein malnutrition also reduced antioxidant levels, impaired immune functions and increased sensitivity to opportunistic infections and septic shock [8, 19]. Malnutrition resulted in lower inducible nitric oxide synthase activity in the spleen and liver of malnourished mice and a failure of lymph node barrier function, which led to the development of visceral leishmaniasis after *L. donovani* infection that may have been related to the excessive production of prostaglandin E2 and decreased levels of interleukin-10 and nitric oxide [4]. Therefore, host-defense mechanisms influenced by the immune system are impaired.

Early malnutrition on development of the gastrointestinal tract

After birth, the neonate must quickly adapt to transition from intrauterine umbilical nourishment to oral nutrient assimilation. Consequently, the rapid growth and functional development of the gastrointestinal tract during the neonatal period are critical for optimal somatic growth and survival [26]. This increased functional demand on the infantile gastrointestinal tract has been associated with a disproportionately high rate of metabolic activity: the gastrointestinal tract represents only 5–7% of body mass, yet consumes roughly 15–20% of the neonate’s oxygen needs [28]. In addition to the absolute nutrient requirements, the functional demands of the gastrointestinal tract might also significantly affect the availability of nutrients to peripheral tissues [26]. In addition, the ontogeny of the intestine is critically influenced by the mother’s diet during gestation as well as during the nursing period. Some of the diet-associated changes in nutrient uptake resulting from the mother’s diet during pregnancy could be corrected by dietary interventions introduced after birth [38]. Therefore, early nutrition including during the fetal and early postnatal period is particularly important, and the lack of any nutrient may delay the growth of the intestine and other tissues.

The neonate is immunologically naive and very susceptible to infection and damage from harmful antigens. Early nutrition plays an important role in protecting the developing intestine from harmful agents and in modulating immune responses following antigenic challenge [40]. In addition, the intestine and its associated cells require nutrients to support their proliferation and differentiation as well as the secretion of enzymes, proteins, and other materials [41]. The rates of enterocyte proliferation and migration are affected by a variety of factors. An overt nutrient deficiency, most notably for zinc [80], vitamin A [85], and cyanocobalamin (B12) [95], will affect intestinal physiology. Glutathione is a crucial antioxidant in the gastrointestinal mucosa that is also formed from glutamine [55, 72]. Dietary glutamine probably contributes significantly to intestinal glutathione synthesis [25]. It has been shown that dietary fatty acids directly affect the profile of fatty acids in the gastrointestinal tract of rat [57].

Abnormalities in gastrointestinal function [malabsorption, maldigestion, pancreatic dysfunction, and protein-losing enteropathy] have been shown to be associated with malnutrition [1]. A severe state of protein-energy malnutrition significantly diminished the intestine length of rats compared with control animals [77]. Intestinal weight and total DNA were similarly diminished in the malnourished rats [37]. In humans, the prevalence of micronutrient deficiencies, including zinc, folate, and the B vitamins, is especially high in Southeast Asia and sub-Saharan Africa [69], it
might indicate that malnourished people in less-developed areas may show the poor absorption and retention of macronutrients and minerals, including zinc. Experimentally, malnourished rats absorbed less zinc than well-fed controls [88]. Alterations in the ratio of polyunsaturated to saturated fatty acids in the diet modified the age-associated changes in the intestinal uptake of glucose, and these changes occurred rapidly, progressively, and irreversibly, suggesting that the intestinal uptake of glucose was subject to critical period programming [39]. However, another study suggested that the growth, metabolism, and perhaps absorptive function of the neonatal gastrointestinal tract were not significantly affected by a short period of protein malnutrition, and protein malnutrition significantly reduced the growth of the skeletal muscle [26]. The resultant repartitioning of lean body mass in protein-malnourished neonates might manifest itself in increased basal energy and protein requirements. These might result from a reduced insulin response to feeding which would lead to chronic reduction in amino acid absorption in protein-malnourished pigs, which presumably limits substrate availability and the anabolic stimulus for skeletal muscle protein accretion [26]. Since the mechanism is unclear, further studies are needed to explain why and how early malnutrition affects the gastrointestinal tract and the growth of other tissues.

Relation between malnutrition, diarrhea and cognitive function

In developing countries, diarrhea, which is one of main results of malnutrition, is a leading cause of child morbidity and mortality. Diarrhea is caused by the interrelated effects of immunodeficiency and gastrointestinal abnormalities.

Protein-energy malnutrition has been shown to be associated with a decrease in the immunologic defense mechanisms that lead to a greater susceptibility to infection and certain infectious diseases caused by malnutrition [2]. One of the consequences of protein-energy malnutrition has been shown to be impairment of the small intestinal mucosal absorptive capacity for zink [87]. In addition, the injection of IL-1α produced diarrhea in 66% of zinc-deficient rats, but not in any well-fed animals [18]. These results might explain the susceptibility of individuals with a compromised zinc status to infectious diarrhea. The alterations seen in the gastrointestinal tract during severe food restriction can lead to malabsorption, diarrhea, electrolyte depletion and even death [87].

Diarrhea is associated with cognitive function, in addition to immunodeficiency and gastrointestinal function abnormalities. Stunting, diarrheal disease, and parasitic infections caused mostly by malnutrition were also related to poor mental function [9]. In addition, a follow-up study that specifically addressed the possible long-term impact of early childhood diarrhea on cognitive function in later childhood suggested that childhood diarrhea was linked to deficits in cognitive abilities several years later [9, 56].

Conclusion

Early malnutrition can have harmful effects on the development of mental system, immune function and the gastrointestinal tract, and can cause metabolic syndrome. Thus, the harmful effects of early malnutrition are interconnected with other harmful effects.

It is well known that the development of mental system, immune function and the gastrointestinal tract are associated with animal growth and animal production. Therefore, we should give more attention to the harmful effects of early malnutrition. The key is to identify specific early malnutrition and harmful effects especial on gastrointestinal tract development under specific animal feeding mode, and find appropriate remedial feeding techniques to reduce the harmful effects of early malnutrition.

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