A human milk perspective on the transmission of maternal factors to her child

Focus on stress, nutrition and immunity

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CHAPTER

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The potential role of nutrition in modulating the long-term consequences of early-life stress

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Abstract

Stress exposure during sensitive developmental periods lastingly affects brain function, cognition and increases vulnerability to psychopathology later in life, as established in various preclinical and clinical studies. Interestingly, similar patterns are seen in children who suffer from perinatal malnutrition. Stress and malnutrition can act closely aligned and stress and nutrition interact. There is emerging evidence that specific nutritional supplementation during various time windows may ameliorate the long-lasting effects of early-life stress, although possible mechanistic insights in this process are sparsely reported. Understanding how stress exposure in early-life influences brain development, and understanding the role of nutrition in this process, is essential for the development of effective (nutritional) therapies to improve long-term health in children exposed to early-life stress. This is especially important in the situation of preterm birth where both stress exposure and malnutrition are common. Here we will discuss the programming effects of early-life stress, the possible underlying mechanisms, how nutrients impact on this process and the promising role of nutrition in modulating (some of) the lasting consequences of early-life stress on brain function and health in adulthood.

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The importance of the early-life environment

The first 1,000 days of life, starting at conception up to approximately 2 years of age, form a critical window in which environmental factors may exert a powerful influence on later health outcomes. This concept is often referred to as the Developmental Origins of Health and Disease [1]. In particular, the first 1,000 days are a period of rapid central nervous system development, in which many processes take place, among myelination, neurogenesis, synaptogenesis, cortical layering and neural circuitry formation throughout various parts in the brain [2]. Environmental factors like stress, but also nutrition, can profoundly influence early brain development [3].

Early-life adversity includes a wide range of experiences, including malnutrition and different forms of stress, among physical stress (e.g. prematurity, prolonged hospital admission, pain) and emotional stress (e.g. parental neglect, physical or emotional abuse). Indeed, increasing evidence from preclinical and clinical studies shows that early-life adversity lastingly affects cognitive functions and increases vulnerability to psychopathology later in life [4]–[6], although the underlying mechanisms remain elusive.

During fetal and early postnatal life, the brain is the fastest growing organ, thus very high in energy and nutrient demand [7] and therefore very sensitive to malnutrition [8]. There is emerging evidence suggesting that nutrition might play a key role in modulating the effects of early-life stress [9]. Unraveling the important intersection between stress and nutrition in the context of early-life adversity is crucial, especially for premature infants, in which both high levels of stress and malnutrition are common.

First, we will briefly discuss how early-life stress and malnutrition impact on the brain and later life health. Secondly, we will discuss the possible mechanisms involved, with a focus on nutrition. Finally, we will discuss the promising preclinical evidence for nutritional interventions in the prevention of the detrimental effects of early-life stress.

Understanding how stress in early-life influences brain development and understanding how nutrition impacts on this process is essential for the development of effective nutritional therapies to improve long-term health in (preterm) children exposed to early-life stress.

Early-life stress and malnutrition: a long lasting mark

Over the past decades an increasing number of studies have identified associations between adverse early-life experiences and a broad range of later life health outcomes.

Indeed, early-life stress is associated with an increased risk of cardiovascular disease, cancer, obesity and type 2 diabetes mellitus [10]. It is also associated with adverse neurodevelopment and higher rates of mental illnesses like cognitive decline [11], anxiety and depression in adulthood [10].

The programming effects of early-life stress begin already at conception. Intrauterine life represents one of the most sensitive developmental periods, when the effects of stress are transmitted intergenerationally from a mother to her unborn child as described in many clinical [12], [13] and preclinical [14] studies. For example, high maternal pregnancy-specific anxiety was associated with impaired executive functioning in the children at 7 years of age [15].

Adverse experiences in early-life continue to affect an individual's long-term health after birth. Lower maternal affection in early-life predicts emotional distress in adulthood [16] and in (pre)term neonates, moderate touch reduced reactivity to stress at adult ages [17]. Animal studies show that adult offspring born to mothers engaging in low levels of licking and grooming behavior increased anxiety-like behavior and physical responses to stress [18], [19]. Interestingly, stroking (simulating of maternal tactile stimuli) reversed these effects [20].

Similar to early-life stress, early-life malnutrition is associated with long-term adverse effects on neurocognitive development, mental health and behavior. During the sensitive periods of fetal and early neonatal life, even minor nutritional insufficiencies can have adverse long-term effects, since they can permanently change brain structure and function [8]. Although all nutrients are necessary for brain growth, key nutrients that support neurodevelopment include macronutrients such as fatty acids and proteins, and micronutrients such as iron, choline, folate, iodine and vitamins [21]. The effects of undernutrition during pregnancy on adult outcomes have been studied in the Dutch and Chinese famine studies. Individuals exposed to famine prenatally showed poorer visual-motor skills, mental flexibility, and selective attention in a cognitive task in adulthood compared to a control group, furthermore, there were more mental health problems such as anxiety and depression, suggesting a long lasting negative effect of maternal undernutrition during pregnancy [22], [23].

After birth, the neonate derives its nutrients ideally through breast milk. Differences in breast milk nutrient composition have been associated with child development, for example a positive relation between DHA amounts in breast milk and neurodevelopment of the infants has been shown [24]. More research in this area is needed to better identify the key beneficial components of breast milk for optimal development.

An important condition in which both stress as well as nutritional deficiencies play an important role, is preterm birth. The last decades, neonatal care has been greatly improved, however, preterm born infants often suffer from long-term psychosocial and neurodevelopmental sequelae including impairments in language skills, memory [25] and executive functions [26]. Preterm infants are separated frequently from their mothers after birth, and, are exposed to a stressful environment with invasive procedures, interruption of sleep states, shifts in environmental temperature and noise. Also hits like infections, hypoxic-ischemic insults and bronchopulmonary dysplasia play a role in long-term detrimental effects. During this period, malnutrition is also playing an important role since administering the right amount of nutrients is still challenging in preterm born infants. One of the most important predicting factors in development after preterm birth is growth rate of the infant, which can be improved significantly by adequate nutrition [27]. Thus, understanding the contribution of the stress, nutrition and their intersect in the context of preterm care and optimizing this might lead to great advances in long-term health outcomes for preterm born infants.

The precise mechanisms underlying the detrimental and persistent impact of early-life stress on long-term health are currently unknown, even though some structural and functional changes in the brain following early-life stress have been identified. For example, human studies show that early-life stress is associated with a reduction in gray matter volume [28], decreased hippocampal volume [29] and functional and structural changes in cortical/limbic circuits, in particular the prefrontal cortex and the amygdala at different ages later in life [30]–[32]. Different kinds of abuse seem to be associated with cortical thinning in adulthood [33] and a smaller hippocampus [34], [35]. In line with the human evidence, preclinical models of early-life stress showed impairments of spatial and declarative memory [36] and showed associations with a number of alterations in hippocampal structure, neuronal plasticity [37] and age-dependent changes in adult hippocampal neurogenesis levels [38]. In addition, other experimental animal studies in a wide variety of species demonstrate similar links between early-life stress, brain anatomy/function and mental health throughout life.

Next to early-life stress, perinatal malnutrition shows lasting changes in the brain. For example, in humans, prenatal undernutrition is negatively correlated with total brain volumes at age 68 in men [39] and in animal models, pre- and postnatal iron deficiency is associated with structural and functional changes in the hippocampus [40].

When considering the lasting effects of early-life stress, it is interesting to consider them in an evolutionary perspective. The effects of early-life stress are mostly adaptive responses, to render an individual most fit to the predicted environment. In fact, there is initial evidence that early-life stress, rather than just exerting negative effects,

might prepare the offspring to respond optimally under stressful circumstances later in life. This concept is known as the match–mismatch theory [37], [41] and needs further investigation [42].

Considering the observed similarities in neurocognitive, mental and behavioral outcomes between children exposed to perinatal malnutrition and to early-life stress [43], and the converging mechanisms and interplay between the regulation of stress and the food system, it is interesting to further explore how we can exploit these features. In the next section, we will discuss the possible underlying mechanisms for the long lasting consequences of early-life stress and we will discuss how nutrition might be able to impact on these processes.

The impact of nutrition on the programming pathways of early-life stress

Some of the mechanistic pathways that have been suggested to underlie the programming effects of early-life stress, can also be influenced by nutrition, these include among others: 1). The hypothalamic–pituitary–adrenal (HPA) axis, 2). Epigenetic mechanisms, 3). Oxidative stress, 4). The immune system.

HPA-axis and glucose homeostasis: The HPA-axis, with glucocorticoids as its end product, is the main neuroendocrine stress system and regulates many body processes, including glucose homeostasis. Early-life stress induces alterations in HPA-axis dynamics [44]. Such changes are considered to be instrumental in the link between early-life stress and subsequent brain development. In fact, early-life activation of the HPA-axis programs behavioral responses to stress for life, which, in turn, may be a trigger for psychopathology [45]. Studies show that increased cortisol levels in infants are associated with adverse neurodevelopment in childhood [46]. Glucocorticoids are key regulators of glucose homeostasis. During fasting concentrations of glucocorticoids rise, allowing the release of stored glucose. Moreover, nutritional stimuli, such as the metabolic hormone leptin, have shown to dampen the stress system. Chronic leptin treatment early in life leads to lifelong altered stress-induced HPA-axis activity and changes in the hippocampus of rats [47]. In addition, imbalanced perinatal protein and fat intakes have shown to affect HPA-axis dynamics [44]. How nutrients interact with glucocorticoids and metabolic hormones is not yet clear, and warrants more research.

Epigenetic mechanisms and micronutrients: Epigenetic mechanisms determine whether a gene is transcribed or repressed without changing the DNA sequence. In contrast to the genome, the epigenome is dynamic, allowing adaptation to the environment. Over the past few years, a growing body of evidence has implicated epigenetic mechanisms in mediating persistent effects of early-life stress [48]. There is evidence

that the epigenome is also affected more globally. For example, whole genome DHA methylation is different between children who were institutionalized and children that were raised by their biological parents [49]. Differences in the amount of perinatal nutrition, including periconceptional nutrition availability [50] are able to cause lasting modifications in DNA methylation and chromatin structure as well [19]. Early-life stress and malnutrition have been shown to both affect acetylation of histones [51]. Thereby, methylation pathways are regulated by dietary factors, both directly but also through provision of methyl groups (vitamin B12, methionine and choline). Pregnant animals lacking methylation levels in specific gene regions that were fed a methyl-rich diet, produced healthy offspring with high methylation levels in this gene regions [52].

Oxidative stress and dietary antioxidants: Early-life stressful experiences can generate oxidative stress. Oxidative molecules can have impact on key transcription factors that influence cell signaling pathways involved in proliferation, differentiation, and apoptosis. Therefore, oxidative stress can alter many important reactions that affect development and subsequently influence later life health. The developing brain is particularly sensitive to injury to oxidant molecules [53]. For example, Prado et al. found oxidative damage in adolescents who were exposed to maltreatment in early-life. Antioxidants provided by the diet, such as polyphenol and certain vitamins and minerals, can counteract the detrimental effects of oxidative molecules [54]. Providing adequate nutrition to premature infants can also boost the anti-oxidant defense mechanisms [55].

Immune system and fatty acids: Early-life stress can activate the neuroimmune system via inflammatory pathways within the central nervous system (CNS). Early-life stress induces an immediate immunosuppressive state, but in the long-term this changes to a pro-inflammatory state, which triggers secretion of inflammatory molecules [56]. Inflammatory molecules can interact with all of the above described mechanisms and are known to impact on the brain. Moreover, the primary immunocompetent cells of the CNS itself, microglia and astrocytes, are involved in several aspect of brain development and function [57]. Activation of the immune system in early-life is associated with (neuro)psychopathologies in adulthood, including cognitive dysfunction [58]. For instance, inflammation during pregnancy is associated with lower IQ in adult men [59]. In addition, pre- and postnatal activation of the immune system have been associated with anxiety-like and depressive-like behavior and cognitive impairments in adulthood [60]. Next to early-life stress, also early-life nutritional insults can affect the neuroimmune system. There are indications for an association between circulating leptin levels and a reduced lymphoproliferative response and pro-inflammatory cytokine secretion in protein malnourished infants [61]. Moreover, some specific nutrients have shown to have anti-inflammatory effects, either by directly influencing the immune system or by diminishing oxidative stress, such as fatty acids, polyphenols and carotenoids [62]. For

example, dietary fatty acids have been shown to have a protective effect against many immune related diseases [63].

Above a few examples of programming mechanistic pathways for the long lasting effects of early-life stress, via which nutrients may impact, are mentioned. By no means this is meant as exhaustive as clearly many other factors and mechanisms have been suggested to play a role in this complex programming of early-life stress such as the microbiome [64].

Importantly, in most studies the above described elements (stress and nutrition), and the mechanisms underlying early-life programming, are addressed individually. These studies mostly focus on a specific brain region or even cell type. Considering that these mechanisms may have interactions with one another, it is likely that the final effect will be determined by the synergistic action of the different pathways, as depicted in Figure 1. The effects of nutrition on the programming of early-life adversity is complex, but may open a window of opportunity for intervention.

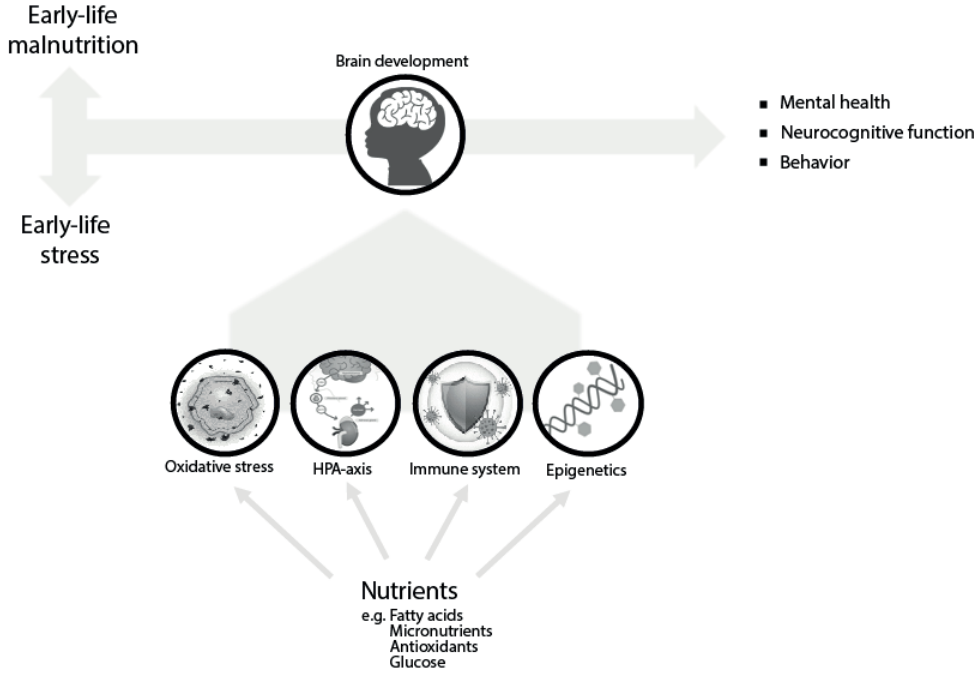

Figure 1. The long-term consequences of early-life adversity, some of its programming pathways and the potential role of nutrition in modulating the effects.

The interplay between early-life factors: nutritional interventions

In this paragraph, we will describe some of the evidence for nutritional interventions to mitigate the long lasting detrimental effects of early-life stress [9], which is largely based on pre-clinical evidence. For example, supplementation of macronutrients in the form of fat and fatty acids has been shown to prevent the lasting neurocognitive consequences of early-life adversity [65]– [67]. For example, the offspring of prenatally stressed rats had improved neurocognitive and behavioral outcomes (i.e. protective effect on hippocampus, reduced anxiety and improved social behavior) if fed a high fat diet throughout pregnancy and lactation compared with a regular diet [65], [66]. In addition, Yam et al. found that increasing the availability of omega-3 fatty acid in the early-life diet prevents the early-life stress-induced cognitive impairments associated with a rescue of the early-life stress-induced changes in microglia and neurogenesis [67]. Similarly, early dietary supplementation with essential micronutrients protected against early stress-induced cognitive impairments associated with the blunting of the early-life stress induced HPA-axis hyperactivation [68]. Additionally, choline supplementation to dams during pregnancy and lactation mitigates the effects of in utero stress exposure on adult anxiety-related behaviors [69]. Lastly, Yajima et al. showed that neuronal abnormalities induced by early-life stress in both offspring and mothers may be partially ameliorated by dietary lutein supplementation [70].

In humans, studies that particularly focus on the effect of nutrition in case of early-life stress are scarce as studying the nutrition-stress interaction in the human setting is difficult, as so many other factors impact on child outcomes. A growing body of evidence found beneficial effects of supplementation with different macro- and micronutrients in developing countries where early-life stress and malnutrition are common. These suggest that several nutrients have a potential beneficial effect on the lasting consequences of early-life adversity, even though stress was not specifically assessed in these studies. An observational study in humans suggests that adequate dietary intakes of the minerals zinc and selenium protects against the adverse effects of prenatal stress exposure on child neurodevelopment [71]. In addition, a low omega-3 to omega-6 ratio in the prenatal diet combined with high prenatal stress resulted in a lower score for orientation and regulation at age 6 months, but only among the children of Afro-American women [72]. Furthermore, prenatal dietary insufficiency of key antioxidant micro-nutrients was found to exacerbate the effects of prenatal stress on offspring affective behavior [71]. Lastly, Barker et al., demonstrated that a broadly “unhealthy” prenatal and postnatal maternal dietary pattern mediated the adverse effects of prenatal maternal depression on child cognitive function at 8 years of age [73].

With greater survival rates in premature infants, behavioral and neurocognitive outcomes have become more relevant. Nutritional supplementation studies in preterm

infants have shown beneficial effects on neurocognitive development, even after adjusting for confounding factors (i.e. gestational age at delivery, birth weight and comorbidities). Increased cumulative intakes of energy, protein [74], and lipids [75] have been associated with better developmental outcomes, while the effect of micronutrient supplementation on neurocognitive, mental and behavioral outcomes in preterm infants, show varying results [76], [77].

In conclusion, early-life nutrition appears to be an appealing candidate for modulating, at least partially, the lasting consequences of early-life stress on adult brain function and health.

Future perspectives

Early-life stress and perinatal malnutrition lastingly alter brain, behavior and mental health. This review discussed the rich complexity of the mechanisms underlying its programming effects and emphasizes that still little is known about the exact working and interplay of these pathways.

Over the last years, there has been increased attention for the prevention of the detrimental consequences of stressful experiences in early-life. Stress reduction programs for both parents and (preterm) children have been developed [78], [79] and the advantages of family integrated care are being acknowledged increasingly [80]– [82].

Specific nutritional support may act as a powerful tool to modify the adverse effects of early-life stress. In animal studies, nutritional supplementations under stressful conditions have shown promising results and seem to be able to modulate the lasting consequences of the early-life stress. In humans, nutritional supplementation in early-life has shown beneficial effects, however, up to date, no studies have taken the stress aspects into account within this context. Of note, no studies have been performed to try to counteract or reverse the pathways that lead to the adverse effects of early-life stress in humans. Thereby, the existing evidence is limited by the number of available studies, the heterogeneity of the study designs and the inability to control for confounding variables. Future studies should focus on collecting longitudinal data, unraveling underlying mechanisms in humans and translate this knowledge into the development of early targeted (nutritional) interventions.

Some of the animal studies show that a nutritional supplement to the lactating dam helps to prevent the lasting effects of early-life stress in her offspring. This raises the question whether breastfeeding also plays a role in the modulation of early-life stress effects in humans. There is initial evidence that maternal stress levels are related to the immunological properties [83] and the microbiome [84] of human milk, but given the

above, it could be hypothesized that stress also changes the nutrient composition of breast milk and subsequently the nutrient availability for the infant, which both could be normalized by maternal supplementation. Nutritional supplementation to the mother may be an effective tool in improving the outcome of the offspring. Our ongoing prospective cohort study in the Netherlands is currently investigating the impact of maternal stress on breast milk nutritional composition.

Next to stress reduction programs like family integrated care, the development of nutritional interventions to reduce the adverse effects of early-life stress is promising as nutritional interventions are relatively safe, cheap and easy to implement. To be able to develop nutritional interventions for humans (pregnant/lactating mothers and infant), understanding the timing of critical developmental periods and the mechanisms and interactions involved in the programming of early-life adversity is crucial. Combining these factors may significantly improve short- and long-term child health with subsequently economic and societal benefits in children exposed to early life stress.

Conclusion

Stress and malnutrition in early-life have a major impact on the well-being of the infant, which exerts its effect into adulthood. Stress reducing programs and targeted nutritional interventions for both mother and child may alleviate the long term consequences of early-life adversity.

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