Chapter 12
Maternal Protein Restriction and Effects on Behavior and Memory in Offspring

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Key Points

- Exposure to an adverse intrauterine environment promotes intrauterine growth restriction.
- Nutritional changes during the fetal period result in adaptations that can permanently change the structure and physiology of several organs.
- Early postnatal dietary restrictions influence cognitive performance and can lead to behavioral abnormalities and disorders in memory and learning.
- High stimulation results in changes of glucocorticoid receptors expression in the hippocampus.
- Chronic exposure to glucocorticoid caused by maternal protein restriction alters the morphological structure of the hippocampus, and these changes have been linked to impaired learning and memory ability and with altered long-term behavior.

Keywords Fetal programming • Behavior and memory • Maternal protein restriction • Hippocampal formation • Hippocampus and memory

Abbreviations

$5HT_1A$	Serotonin-specific receptors
$5HT_2A$	Serotonin-specific receptors
ACTH	Adrenocorticotrophic hormone
AT_1	Type 1 angiotensin II receptor
CNS	Central nervous system
CRH	Corticotrophin-releasing hormone

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DEX   Dexamethasone
DOHaD   Developmental origins of health and disease
GR   Glucocorticoid receptor
HHPA   Hippocampus-hypothalamic-pituitary-adrenal axis
HPA   Hypothalamic-pituitary-adrenal axis
IUGR   Intrauterine growth restriction
LP   Low protein
MRs   Mineralocorticoid receptors
MWM   Morris water maze
NP   Normal protein

Introduction

The implications of events that occurred in early periods of life and its relationship to health in the long term are of great interest for public health in both developed and underdeveloped countries and have resulted in a number of studies to elucidate underlying biological mechanisms. It is well established that the disturbances at critical periods of fetal development may cause permanent changes in the physiology and morphology of organs [1]. Epidemiological evidence suggests that exposure to an adverse intrauterine environment promotes intrauterine growth restriction (IUGR) which has been associated with decreased supply of substrates for the fetus affecting their growth and development [2–4].

Maternal Protein Restriction and Brain

The central nervous system (CNS) is very sensitive to modifications in the environment. Its development is dependent on internal and external factors to the system itself. However external factors have been receiving increasing attention due to their influence on neuroplasticity. There is a strong association between IUGR, low birth weight and maternal low-protein intake. Maternal low nutritional levels decrease the supply of nutrients to the fetus. Thus, maternal nutrition plays a critical role in the growth and development of offspring. Nutritional changes during the fetal period result in adaptations that can permanently change the structure and physiology of organs, predisposing the individual to metabolic and endocrine diseases in adulthood and several cognitive disorders.

Considering the fact that the structural brain development begins in the early days of the embryonic period and extends to the first years of life, changes in prenatal and early postnatal development can be highly detrimental to the neurodevelopment [5]. The brain maturation happens through a series of temporally overlapping phases (Fig. 12.1). The final structure of the brain arises during ontogenesis phase, in which there is a migration of postmitotic cells in germinal zones, which differentiate and interact with other nonneural tissues nearby in a highly ordered sequence. However, the normal brain development is dependent not only of this exact sequence but also of many metabolic reactions that regulate these cellular events. These sequences are determined mainly by the genome, but the genetic regulation of brain development is highly influenced by environmental factors such as stress, smoking, infections, and nutritional changes. Thus, protein-restricted intake during the prenatal period followed by the low birth weight of the offspring acts as a risk factor for the development of neurological and psychiatric diseases. Substantial evidence from studies in animals and in humans shows that gestational as well as early postnatal dietary restrictions influence cognitive performance and can lead to behavioral abnormalities and disorders in memory and learning [6–8].
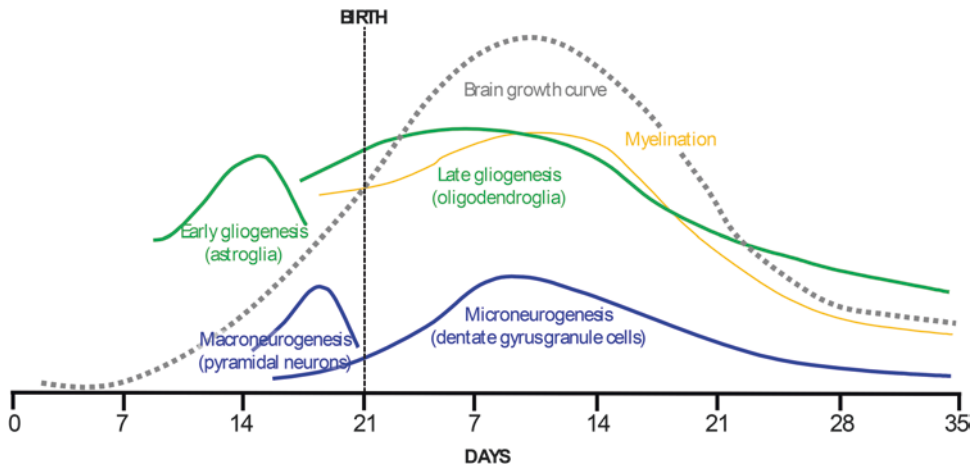
Fig. 12.1 Rat brain growth curve showing the time of cell types differentiation. The rat brain at birth has approximately 12% of adult brain weight, while that found in humans is about 27% of the adult brain weight (Adapted from Morgane et al. [5])

Critical Period of the Brain Development

The life evolution is integrated, cumulative, and continuous and not episodic, static, or discrete. Behavioral researchers rarely forget this, but medicine doctors and biologists often do. Developmental biology is the one domain of the life sciences where the organism as a progressively unfolding phenomenon is a central concept. The reemergence of developmental biology as a vigorous discipline, intersecting in important ways with genetics [9], evolution [10], and epidemiology [11–13], has injected new ideas into all those fields. Within epidemiology a seminal impact of this new attention to developmental biology has been in the formulation of the "fetal programming hypothesis," also known as the *fetal origins hypothesis* or, more generally, as the *developmental origins of health and disease* (DOHaD). Simply put, this hypothesis suggests that conditions very early in development, even in utero, can leave lasting imprints of an organism's physiology, imprints that may affect susceptibility to diseases with onsets that may occur many decades later [14, 15].

The concept of fetal programming is, of course, not new. Behavioral endocrinologists and neuroscientists, for example, have long recognized organizational effects of prenatal androgen hormones in *programming* certain aspects of reproductive axis function and reproductive behavior that emerges later in an animal's life [16]. The ontogenetic critical periods, including fetal development, are familiar concepts in psychology even as they are in biology. So, rather than being a radically new concept, the ascendancy of the fetal programming hypothesis should be seen as representing a new appreciation for these kinds of effects together with a deeper understanding of the mechanisms that produce them and the significance they may play for individuals and species. The question of the potential adaptive significance of fetal programming is an important one, both theoretically and practically. It affects the way in which the phenomena clustered under the DOHaD aegis are integrated in a broader context of evolutionary biology and the practical responses and interventions that might be made to affect health outcomes. It is a question that is still keenly debated, however.

As stated above, there are periods during the development in which the organism is highly vulnerable. Such periods are known as critical period, which represents a stage of development that cannot be reversed or repeated later, and in which organizational processes are more easily modified. If the progression of morphological, physiological, and biochemical development does not occur at the correct time, there will be a permanent functional deficits being determined by severity of the insult

and the duration of the development period and which is imposed. In animals and human beings, the period of greatest vulnerability of the CNS occurs from the second third of pregnancy to early week or year of life (in humans); however, the peak of the curve brain growth occurs during pregnancy. At this stage occurs the genesis of glial and pyramidal neurons cells, resulting in the birth in 27% of brain weight. Already in rodents, this phase comprises from birth until about third week of life, when there is a development of the hippocampus and cerebellum. Thus, the impact on brain development of the fetus by maternal nutritional deficiency can be irreversible (Fig. 12.1).

Fetal Programming of Behavioral Outcomes

The most elegant example of epigenetic modification of behavior by early environments is not strictly an example of fetal programming but offers clear documentation of the epigenetic processes that determine the effect. Meaney and his colleagues have focused on maternal behavior in rats, describing individual variation in the pattern of arch-backed nursing intense licking and grooming of pups [17, 18]. Pups who receive greater degrees of maternal stimulation show less anxiety in open field tests and other indices as adults. Females who receive greater stimulation as pups give greater amounts of stimulation to their own pups, inducing the same low-anxiety behavioral phenotype in their own off-spring. The entire effect appears to be mediated by epigenetic alterations in histone acetylation and methylation of the promoter region of the glucocorticoid receptor (GR) gene in the hippocampus of the rat pups depending on the type of maternal behavior they receive [19, 20]. High stimulation results in changes of glucocorticoid receptors expression in the hippocampus, which is in turn associated with modification in sensitivity to corticosteroid feedback, a pattern that persists into adulthood [21]. In hippocampus, the effect of standard glucocorticoid signaling is to suppress hypothalamic release of corticotrophin-releasing hormone (CRH), leading to lower pituitary release of adrenocorticotrophic hormone (ACTH) and lower secretion of glucocorticoid from the adrenal cortex. Adults who receive high levels of maternal stimulation as pups thus show relatively low HHPA axis reactivity to stress, while the reverse is true in those who receive less stimulation as pups. This appears to correlate with their behavior in open field and other tests and with the maternal style that females may display toward their own pups. In this way a stable difference in HPA axis sensitivity is transferred across generations through females based on an *inherited* epigenetic pattern. Interestingly, the epigenetic pattern is passed through first being translated into a behavioral pattern in the mothers and then back into an epigenetic pattern in the offspring. Prior studies have documented the effect of maternal behavior to similarly program reproductive axis activity through epigenetic effects on steroid receptor expression [22]. Although this example of rat maternal behavior is not an example of "fetal" program-ming, it is an elegant demonstration of the potential for programming of the HHPA axis to have behavioral consequences [23, 24]. Furthermore, one of the most impressive studies to implicate fetal programming in psychiatric outcomes is the work of Susser and colleagues on the follow-up of indi-viduals conceived during the Nazi occupation of Holland at the end of World War II [25]. The so-called Dutch hunger winter provides a rather gruesome natural experiment in which pregnant women, along with the rest of the civilian population, were subject to extreme food deprivation during a rela-tively discrete period [25]. Susser's parents conducted seminal studies of the effects of this famine resulting in the recognition of the importance of folate nutrition in pregnancy in avoiding neural tube defects [26]. The younger Susser undertook to determine whether less debilitating effects on nervous system development as a consequence of famine exposure in utero might have consequences for psy-chiatric risk after birth. He found a significant increase of risk of schizophrenia and related disorders among those whose mothers went through the peak of the famine during their second trimester of pregnancy [25, 27]. Subsequent work with individuals born during discrete famines in China has yielded similar results [28]. Whether the mechanisms mediating these effects are epigenetic in nature remains to be determined [29].

Costello and colleagues provide a second example of prenatal influences on psychiatric outcomes [30]. They assessed a population-based sample of over 1400 boys and girls in North Carolina between at the ages of 9 and 16 for psychiatric symptoms. They found that the rates of adolescent depression were over four times higher (38.1%) in girls who were low birth weight compared to normal weight girls at birth (8.4%) and seven times higher than in boys of any birth weight (4.9%). The well-known sex difference in adolescent depression was thus almost entirely accounted for by the higher risk in low birth weight girls. However, there was an interesting interaction. Low and normal birth weight girls who experienced no subsequent adversities showed no incidence of depression. But with each additional adverse circumstance, the rate of depression in low birth weight girls, but not normal ones, increased significantly. The authors suggest that low birth weight girls are more sensitive to adverse circumstances later in life in terms of their risk of depression, a result that suggests possible alteration of physiological responses to stress, perhaps involving the HPA axis.

Mechanism of Genesis Changes

Although some nutritional effects are the result of direct change in substrate availability, part of these results is due to hormonal mediation, which can alter the development of specific fetal tissues at critical periods of development and lead to permanent changes in hormone secretion (Fig. 12.2). Animal evidences have suggested that a maternal nutritional or emotional stress during pregnancy is associated with behavioral outcomes in offspring [31, 32] . The nature of the stressing event applied may differ, but it is often assumed that the mother's HPA axis responds with higher levels of glucocorticoid hormones. It is unlikely that higher levels of maternal cortisol affect fetal physiology in humans, however, since the placenta is rich in type 2 11-ß-steroid-dehydrogenase, which converts cortisol to inactive cortisone, thus buffering the fetus from maternal cortisol levels [33]. The glucocorticoid secretion is made by the adrenal cortex and controlled by HHPA, a classic endocrine regulator of negative feedback. Glucocorticoids exert their effects by binding to GRs, a member of the family of nuclear steroid receptors. Additionally, in some tissues, glucocorticoid has higher affinity to mineralocorticoid receptors (MRs), also deeply related to the modulation of hippocampus function.
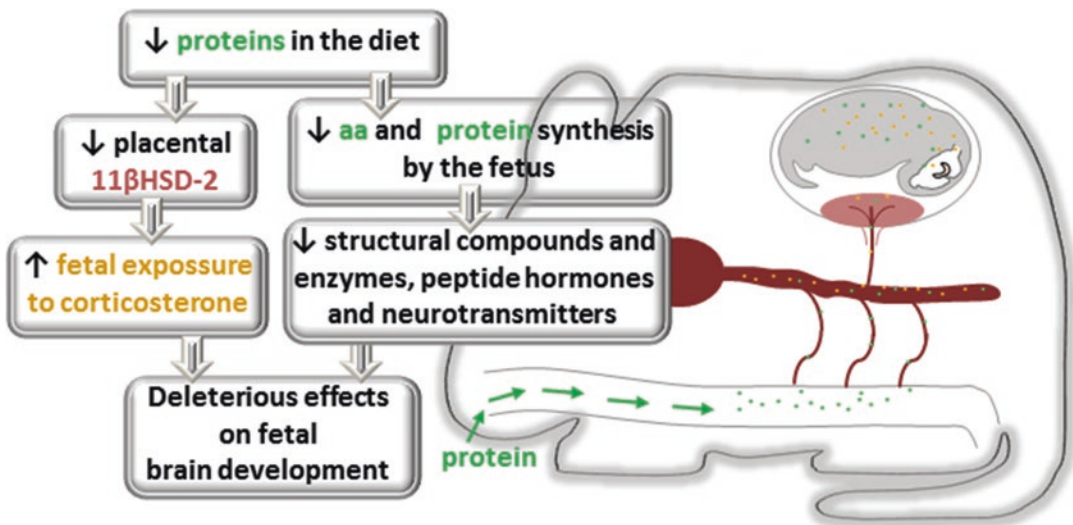

Fig. 12.2 A reduction in diet protein content lead to alterations on structural, physiological, biochemical, and psychological maturation of the brain

Although positive correlations between baseline levels of maternal and fetal cortisol have been observed [34] which in turn increases the concentration of glucocorticoids to the fetus, thereby promoting growth retardation of offspring and a possible programming of response related to cardiovascular diseases metabolic and psychiatric, evidence of changes in maternal and fetal cortisol responses to stress are independent [34]. Such buffering makes physiological sense since in late pregnancy the mother is essentially in a catabolic state, while the fetus is in an anabolic state with transient suppression of HHPA axis. In fetal programming context, cross talk between the energy metabolism of mother and fetus would be disastrous.

In addition, the exogenous administration of glucocorticoids in the mother or fetus, results in low birth weight plus several long-term diseases such as hypertension, hyperglycemia, and behavioral disorders in the offspring. Indeed, these effects are transmitted over generations without reexposure to glucocorticoids, suggesting the involvement of epigenetic mechanisms. However, dexamethasone (DEX) has been administered to mothers known to be carrying fetuses deficient in 21-hydroxylase and therefore at risk of congenital adrenal hyperplasia [35]. A secondary consequence is overproduction of adrenal androgens that can lead to varying degrees of genital androgenization [36]. Some studies have indicated potential effects on childhood and adult behavior, including sexual orientation, as well [37, 38]. DEX is often administered to head off these consequences, since it readily crosses the placenta; is not metabolized by 11-ß-steroid-dehydrogenase; and interacts with glucocorticoid receptors in the fetal hypothalamus to suppress excess production of ACTH and its corollary effects [39]. In animal studies using prenatal administration of DEX as a treatment alterations of offspring behavior and HHPA axis reactivity is observed. This suggests that the feedback sensitivity of the HHPA axis may be partially regulated through the level of activation of the axis during fetal development.

Hippocampal Formation

Given their prominent role in brain plasticity and in the regulation of cognitive processes, the hippocampal formation has been the focus of many studies designed to identify the morphological, biochemical, and physiological substrates' long-term disability of brain functions associated with dietary restrictions in the beginning of life. The hippocampus is a structure located in the medial temporal lobe. Anatomically, the hippocampus of mammals is divided into different subfields: CA1, CA2, CA3, CA4, and dentate gyrus. Functionally, it can be divided into two different regions: the ventral and dorsal hippocampus. While the ventral portion is involved primarily the *emotional processing*, the dorsal is mainly linked to *memory and learning*. It is a widely studied region for its importance in the acquisition and memory consolidation, but highly vulnerable to various environmental stresses due to plasticity of hippocampal circuits necessary for their functions in learning and memory. The hippocampal formation is a different target structure changes from the maternal environment. Studies have shown that changes during the prenatal period had influence on neurogenesis in the hippocampus immaturity and remodeling of dendrites of CA3 region, with possible cognitive changes. Furthermore, it is a preferred target region of the action of stress hormones, and through this brain area, it is part of a negative feedback mechanism in HPA axis.

Morphological studies in the hippocampus in animals that experienced maternal protein restriction showed that the pyramidal cells of CA1 and CA3 and granule cells of the dentate gyrus regions showed reduction in cell size in dendritic branching and a decrease in the number of synaptic spines in mice of various ages. However, chemical inhibitors, suggesting that hormones HHPA axis can modulate dendritic morphology in the hippocampus, can suppress these effects. Additionally, changes in the regulation of HHPA axis are consistent components in various types of affective disorders such as depression, panic disorders, and obsessive-compulsive disorder. Thus, adrenal steroids appear to be crucial factor in the structural remodeling of the hippocampus.

Fetal Programming of Psychological and Psychiatric Outcomes

Animal evidence has long suggested that maternal emotional and nutritional stress during pregnancy is associated with behavioral outcomes in offspring [31, 32]. The nature of the stresses applied may differ, but it is often assumed that the mother's HHPA axis respond releases higher levels of glucocorticoid hormones. It is unlikely that higher levels of maternal cortisol/corticosterone affect fetal physiology in humans and rodents, however, since the placenta is rich in type 2 11-β-steroid-dehydrogenase, which converts cortisol to inactive cortisone, thus buffering the fetus from maternal cortisol levels [33]. Such buffering makes physiological sense since in late pregnancy the mother is essentially in a catabolic state, while the fetus is in an anabolic state. Cross talk between the energy metabolism of mother and fetus would be disastrous.

However, dexamethasone, a synthetic glucocorticoid, has long been administered to mothers known to be carrying fetuses deficient in 21-hydroxylase and therefore at risk of congenital adrenal hyperplasia [35]. Because affected congenital adrenal hyperplasia individuals are impaired in their ability to produce cortisol, inadequate negative feedback leads to overproduction of adrenocorticotrophic hormone (ACTH) and hyperplasia of the adrenal glands. A secondary consequence is overproduction of adrenal androgens that can lead to varying degrees of genital androgenization [36]. Some studies have indicated potential effects on childhood and adult behavior, including sexual orientation, as well [37]. Dexamethasone is often administered to head off these consequences, since it readily crosses the placenta, is not metabolized by 11-β steroid-dehydrogenase, and interacts with GR receptors in the fetal hypothalamus to suppress excess production of ACTH and its corollary effects [39].

Although maternal stress may not be communicated to the fetus via maternal cortisol, there are other pathways possible, including alterations of placental blood flow [34] and changes in energy available for fetal growth. In addition, conditions that lead to fetal stress, such as restricted energy availability [34], may directly affect the level of activity of the fetal HHPA axis, as opposed to the maternal axis, with potential programming consequences. Achieving a better understanding the potential for prenatal conditions to have lasting effects on an individual's physiology, with possibly serious implications for psychiatric risk, must be considered one of the high priorities for psychological research stemming from the fetal programming hypothesis [40].

As sustained above, glucocorticoids play a role in the normal development of the brain and have been associated with neuronal maturation and survival. Thus, as mentioned above, fetal exposure to excess glucocorticoids during critical periods of brain development can lead to structural changes in neuronal dendritic morphology and the number of synapses [32]. Additionally, chronic exposure to glucocorticoid caused by maternal protein restriction alters the morphological structure of the hippocampus, and these changes in the structure of the hippocampus have been linked to learning and memory problems and long-term behavior. It is well established that children exposed to restriction of nutrients during fetal period have cognitive deficits as well as increasing the risk of psychiatric disorders development as depression and schizophrenia, changes in memory and learning, increased response to stress, and changes in drug sensitivity psychotropic. These disorders are usually studied in well-known brain regions such as the hippocampal formation where much of the internal and external connectivity and the chemical cellular architecture are well known.

Hippocampus and Memory

The different kinds of stresses affects neural regions including gestational hippocampus, amygdala, corpus callosum, neocortex, cerebellum, and hypothalamus and often results in a reduction in the volume of the tissues that make up these structures. It is known that the limbic system, particularly the hippocampus, plays a central role in the memory/cognition and control of emotions. The hippocampal
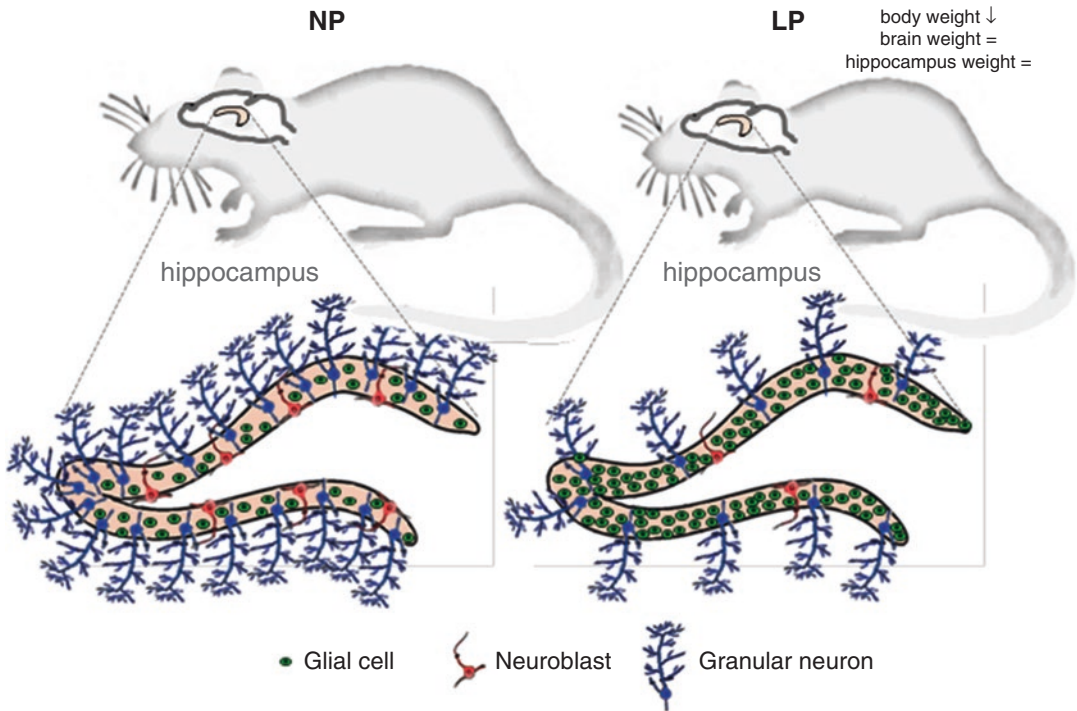
Fig. 12.3 The low-protein diet during gestation and lactation lead to marked cellular imbalances in dentate gyrus. We used male rats from mothers submitted to low protein (6% casein) comparatively to normal protein (17% casein) diet. The brain and hippocampus weight are not altered as well as cell number. However we found altered cell ratio (unpublished data)

gyrus has been the subject of several studies due to its importance in neural plasticity in neurogenesis and regulation of cognitive processes. Changes in efficiency and structural plasticity of hippocampal synaptic connections can compromise crucial neurobiological mechanisms involved in cognitive processes. As previously described, gestational protein restriction may produces, at long-term, deleterious consequences in offspring adulthood. Several animal studies have shown atrophy of hippocampal neurons and reduction in the number of neurons in this region, the result of disturbances in the maternal environment (Fig. 12.3) [41].

Prior studies have shown that changes in memory and learning from fetal exposure to glucocorticoids is the result of many cellular and molecular events which include downregulation receptors [42], reduced dendritic branching [41, 43], changes in the synapses [44], inhibiting LTP which is the best-documented neuronal substrate for memory formation [45], and impairment of energy metabolism [46]. Moreover, there may still be a reduction in BDNF, a factor involved in tropism and survival of neurons and synapses (unpublished data). There is also evidence of the interaction between fetal exposure to glucocorticoids and the serotonergic and cathecolaminergic systems by the modulation of the $5HT_1A$ and $5HT_2A$ receptors [47]. Furthermore, there is evidence that gestational protein restriction impairs the inhibitory control of the HHPA axis, leading to excessive secretion of CRF/ACTH and increased plasma levels of glucocorticoid, contributing to further damage in hippocampal and consequently higher cognitive deficits neurons, impairing the different types of declarative memory (verbal memory, social memory, and spatial memory). Chronic exposure to glucocorticoids by GRs activation induces neuronal death and mitigation of neurogenesis.

We and others have demonstrated that maternal nutritional restriction during pregnancy or in early postnatal life results in hippocampus cognitive impairment and structural abnormalities in the 16-week-old offspring. In an attempt to analyze whether gestational protein restriction might induce learning and memory impairment associated with structural changes in the hippocampus, we carried out Morris water maze (MWM) test and a detailed morphometric analysis of dendritic cytoarchitecture of the hippocampus from male adult rats [41]. In addition, we analyzed the dorsal and ventral hippocampal expression and localization of mineralocorticoid (MR) and glucocorticoid (GR), type 1 angiotensin II receptor (AT_1) and serotonin-specific receptors ($5HT_1A$ and $5HT_2A$). By MWM we did not found significant differences between LP and NP groups, in any of the parameters analyzed, suggesting that such functions of the hippocampus were not altered by gestational protein restriction. However, by applying three-dimensional analysis of dendrites from the dorsal hippocampus, this study demonstrates that gestational protein restriction leads to decreases in total basal dendritic length and in apical intersections of CA3 pyramidal neurons. The dendritic architecture of CA1 and dentate gyros was unchanged. This study revealed a clear dissociation between behavioral test response and hippocampal neuron changes as a consequence of fetal programming. We found different patterns of dorsal and ventral expression of analyzed receptors, and we suggests that reduced GR and $5HT_1A$ and enhanced $5HT_2A$ expression are involved in anxious behavior and that AT1 downregulation may have a protective effect. These neurochemical alterations may have important consequences for anxiety- and depressive-like behavior. A recent study in our lab (unpublished data) assessed the effects of maternal protein restriction, during pregnancy and breastfeeding, on the structure of the hippocampus, their duties on the memory and emotions (anxiety/fear) as well as on the cellular composition of this brain structure and influence over these morphological and behavioral parameters, and the exposure of the offspring of male rats to the enriched environment. The findings of this study represent the perinatal impact of malnutrition protein in the hippocampus, which is involved in emotional behavior as well as in memory and learning. The study revealed decoupling the behavioral test response and changes in the number of hippocampus neurons, as a consequence of fetal programming. The absence of basal changes in performance of these tests occurred in spite of reduction in the number of neurons in the dentate gyrus of the hippocampus. Several authors have suggested that the observed atrophy in the hippocampus may be a compensatory response to protect the hippocampus of additional damage. We have demonstrated, for the first time, that maternal exposure to protein restriction during neural development of offspring that cause important morphological changes in the hippocampus may make these animals vulnerable to neural disorders in adulthood. This study, at least under morphological aspect, confirmed the "selfish brain" theory, a recent paradigm that posits that in order to keep its own energy supply stable, the brain modulates the energy metabolism in the periphery by regulating both the allocation as the intake of nutrients. In this work, the unmodified brain mass do not match with the intensity of cytological composition changes, particularly of the hippocampal nucleus, in different experimental groups. Although it seems that the nutritional changes promote irreversible changes in body mass, but not in the brain and some of its fundamental structures, composition, and neuronal structure and its recovery from primordial cells, are deeply modified by the maternal dietary restriction and, surprisingly, by exposure to oxygen-enriched environment. Thus, we can affirm that the selfish brain theory explains the maintenance of brain matter; however, the proportion of the different cell types has profoundly changed what can expand our understanding of the adaptation to stress and neuron regeneration in neuron behavioral states regarded as abnormal. Moreover, we must emphasize that, while we have observed a significant reduction in the number of neurons after the period of breastfeeding, we also demonstrate, for the first time, that this parameter is reversed by stimulus in enriched environment. Ours studies are not able to answer the question whether these alterations are related to in utero underdevelopment or results from a postnatal adaptation to programmed physiology in adult life. Further time course studies should be done to answer this question.

Conclusions

Fetal gestational programming protein restriction leads to intrauterine growth restriction, which is associated with the decrease in the supply of substrates crucial to the fetus affecting growth and development. This situation has repercussions in birth weight and several changes in organs and tissues in adult life. These changes from adaptations to the maternal environment have long-term effect producing numerous structural and neurochemical deficits in key brain regions for the development of the offspring. In addition, these changes can achieve brain systems that play a key role in behavioral processes and memory and learning. Moreover, considerable attention has been focused, therefore, on the degree to which HHPA axis reactivity may be established in utero, the potential for maternal nutritional status to affect these aspects of metabolic physiology, and the cellular mechanisms by which these effects are mediated.

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