Chapter 11
Adaptive Regulations in Developing Rodents Following Neonatal Challenges

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Abstract Developmental phenotypic plasticity is a mechanism by which events early in life program brain for a pattern of neuroendocrine and behavioral responses in later life. The goal of this chapter is to give the reader a better understanding of what is developmental phenotypic plasticity and how it can lead to adaptive phenotypes in adulthood. Experimental evidences from rodents show that early experiences influence long-term development of behavioral, neuroendocrine, and cognitive functions. Different factors have been suggested to mediate the effects of neonatal conditions on offspring development, but their exact contribution as well as their interaction still needs to be clarified. Several studies demonstrated the important role of maternal behavior in mediating the effects of neonatal challenges on adaptive regulations in the developing rodents. It has been suggested that there is an inverse relationship between the amount of active maternal care received by the offspring and their later reactivity to stressful or challenging events. However, other studies found a dissociation between the level of maternal care and offspring phenotype. These results suggest that aside from the level of maternal care, non-maternal factor (gender, neonatal glucocorticoid levels) contributes to the adjustment of offspring phenotype to early environmental cues. Altogether, rodents-based evidence suggests that developmental plasticity is a very complex phenomenon mediated by multiple factors that interact one to each other. Ultimately, these researches will help to better understand how the conditions from the neonatal environment affect brain development and can lead to adaptive phenotypes in adulthood.

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11.1 Introduction

The discovery of the double helix structure of DNA by Watson and Crick in 1953 allowed scientists to explain all biological phenomena by the trio DNA–RNA–protein. However, the idea that an organism's phenotype is entirely explained by its genome has been revised. Indeed, "the concept of phenotypic plasticity has allowed researchers to go beyond the nature-nurture dichotomy to gain deeper insights into how organisms are shaped by the interaction of genetic and ecological factors" (Pigliucci 2001). For instance, the characteristics of the rearing environment affect the development of offspring leading to a wide variety of adult phenotypes within populations. This is referred to as "developmental phenotypic plasticity" or "programming." This mechanism has been shown to exist in many living organisms, including plants, insects, and mammals (Tollrian 1995; Agrawal 1999; Bateson et al. 2004). It allows organisms to develop a phenotype that will help them cope with the characteristics of their (future) environment. In this framework, the developing organism is not seen as a passive entity subjected to its environment, but rather it plays an active role based on specific characteristics of the environment. When environing conditions remain constant throughout the entire life span, this phenomenon may provide the organism with a better adaptive response to the future requirements and preserve health and survival. However, if the initial conditions are suddenly changed, the adaptive processes may be disrupted and predispose to certain diseases.

This programming phenomenon is particularly relevant in philopatric species such as rats and mice, in which the offspring inhabit the parental niche. Early environmental cues "inform" the developing offspring of the characteristics of their future environment, and the offspring regulate their phenotype accordingly. Laboratory rodents (e.g., rats and mice) became the preferred animal model for the study of developmental phenotypic plasticity. The pioneering work of Levine, Denenberg, and their colleagues, and later Meaney, Plotsky, and colleagues has shown that even quite subtle alterations of a rat's experience during the early postnatal period can have long-lasting consequences for defensive behavior, emotiveness, and stress responsiveness (for reviews, see Francis and Meaney 1999; Meaney 2001; Champagne et al. 2003; Cirulli et al. 2003). The dynamic interplay between the early environment, brain development, and stress reactivity later in life has since been extensively studied. Artificial manipulations of mother/offspring relationships during the early postnatal period of rats and mice suggest that subtle variations in the postnatal environment can have marked and persistent effects on rodent brain systems involved in coping with environmental challenges (e.g., Meaney et al. 1991; Liu et al. 1997). It was also suggested that there is an inverse relationship between the amount and quality of maternal care received during infancy and offspring stress reactivity in adulthood. This was called the maternal mediation hypothesis (Smotherman and Bell 1980; see also Würbel 2001). This hypothesis provides a mechanism by which variations in maternal care may adaptively mediate phenotypic plasticity of stress systems (e.g., hypothalamic–pituitary–adrenal [HPA] axis) of offspring. However, the maternal

mediation hypothesis has recently been exposed to scrutiny. The main concern is the emphasis placed on the role of active maternal care as opposed to other contributing factors (e.g., neonatal corticosteroid levels, offspring gender—Macrì et al. 2004, 2009; Tang et al. 2006, 2011; Coutellier et al. 2008b, 2009). It has been suggested that maternal care cannot be considered the sole and unique factor mediating developmental phenotypic adjustments in rodents. Other factors are now being studied to understand how they can favor phenotypic plasticity in response to neonatal environmental cues.

The main goal of this chapter is to better understand this "programming" or "developmental phenotypic plasticity" as a phenomenon by which neonatal cues change the organism's development. The aim is to give the reader a clear picture of how environmental challenges, acting in a critical period in life, affect the adult rodent phenotype and how it helps organisms to adapt to their environment in adulthood. First we will present how developmental challenges modulate individual adaptation to the future environment. We will then discuss the adaptive significance of developmental phenotypic plasticity and briefly explain how this process might become maladaptive. Finally, we will discuss the factors contributing to this programming phenomenon.

11.2 Individual Adaptation Following Developmental Challenges

Developmental phenotypic plasticity has been extensively studied in rodents. The early postnatal environment of the offspring has been challenged using a wide variety of manipulations ranging from mother–pup separation, exposure to stressors (e.g., predator odors), or variability in the foraging environment. The adult phenotype of the offspring has been analyzed to determine how these challenges affect the animals' capacity to cope with environmental challenges later in life. Early studies investigating the link between neonatal experiences and the regulation of adult stress and fear responses revealed that mild experimental challenges may help the organism to cope with acute stressors in adult life (Levine et al. 1957). Levine et al. (1957) showed that brief (3 min) daily mother–infant separations during the first 3 weeks of life have persistent effects on the rat pups' pituitary adrenal axis, as exhibited by reduced adrenal gland weight 24 h after a saline injection. This result has been replicated many times, and brief (3–15 min) daily mother–offspring separation (early handling, EH) during the first 1 or 2 weeks of life is consistently associated with reduced HPA axis and fear responses in the adult offspring (e.g., Meaney et al. 1991; Lui et al. 1997; Macrì et al. 2004), enhanced spatial working memory, and a greater competitive ability to obtain limited food rewards in the presence of a conspecific (Tang et al. 2006). This lent support to the hypothesis that early moderate environmental challenges (such as brief periods of maternal separation) affect the development of the offspring in a way that allow them to efficiently cope with acute stressors or challenges during their adult life.

Because of the artificial nature of these neonatal manipulations, new experimental designs using more natural settings have been recently developed and have confirmed further the importance of early environmental cues on the developing pups. For instance, dam–offspring rat dyads were exposed to different levels of foraging conditions (Macrì and Würbel 2007). Food availability was varied in space and time. Specifically, one group of dams had access to food ad libitum in the home cage (minimal challenges); one group had food ad libitum in an exploration cage located at some distance from the nest (mild challenges). Pups raised by dams with access to food away from the nest cage showed reduced fearfulness and HPA reactivity when adult (Macrì and Würbel 2007). Similarly, in mice, mild challenges in the maternal environment induced by a predator odor result in adult mice that are less fearful (Coutellier et al. 2008a) and that demonstrate better cognitive abilities (Coutellier and Würbel 2009). Altogether, a large amount of studies demonstrate that increasing levels of neonatal challenges result in adjustments in the offspring phenotype allowing them to effectively respond to acute stressors in adulthood. This efficient ability to maintain homeostasis despite the exposure to multiple stressors throughout life has been referred to as "resilience" (stability throughout development—McEwen 1998; Feder et al. 2009).

11.3 Adaptive Significance of Developmental Phenotypic Plasticity

An important question is whether developmental phenotypic plasticity is an adaptive process. Living under conditions of high environmental demand represents an important cost for the organism because behavioral and endocrine stress systems need to be constantly activated. Thus, if an individual develops in a way to reduce its stress and fear responses in adulthood, it will minimize the cost of living in such a highly demanding environment. In this case, developmental plasticity can favor an individual if the conditions in which it develops are similar to the ones it is going to face in adulthood. It looks like developmental plasticity is an adaptive phenomenon since it induces attributes that help the organism to cope with the characteristics of the environment in which it lives (Gluckman et al. 2005).

However, in the case of dissociation between environmental cues during early development and the characteristics of the future habitat, phenotypic mismatch may occur: the adult phenotype does not match the needs of the habitat which may be costly in terms of both survival and reproductive success (Bateson et al. 2004). Studies in rodents demonstrate that exposure to adverse conditions during the neonatal period alters the programming of the neuroendocrine and neuroimmune systems. For instance, long periods (3–4 h) of daily maternal separations (MS) during the first 1–3 weeks of life induce enhanced HPA axis responses and increased fearfulness in adulthood (Plotsky and Meaney 1993; Huot et al. 2004), increased corticotropin-releasing factor (CRF) expression in the hypothalamus and reduced cortical glucocorticoid receptor (GR) expression (Huot et al. 2004), altered cognitive abilities

(Huot et al. 2002; Aisa et al. 2009), dysregulation of the serotonergic and cholinergic systems (Aisa et al. 2009), altered immune response to infection (Meagher et al. 2010), and increased vulnerability to influenza virus infection in lung (Avitsur et al. 2006) and to stroke (Craft et al. 2006). In this chapter we are not aiming at explaining in depth the adverse consequences of early postnatal stress. For this particular thematic we are directing the reader to Chap. 10. However, it is clear that a large number of experimental studies support the view that exposure to adversity during the neonatal period affects brain morphology, neurochemistry, and expression levels of genes in the central nervous system. This is associated with an increased vulnerability to psycho- and physiopathologies at adulthood. These aberrant phenotypes are clearly maladaptive under all environmental conditions (Gluckman et al. 2005).

Thus, the adaptive value of a phenotype depends on how accurately the factors or cues that mediate developmental plasticity predict the future environment (Windig et al. 2004). However, labeling a trait as an adaptation implies that it has evolved in response to a specific form of selection or that there is a cause-and-effect relationship between the trait and the environment in which it is found. For adaptive plasticity to evolve there must be a trade-off among traits that cause one phenotype to have higher fitness in one environment and an alternative phenotype to have higher fitness in another environment (Doughty and Reznick 2004). To assess the relative fitness of diverse phenotypes, offspring should be investigated in environments that differ in how demanding or challenging they are for the animals. For instance, components of reproductive success (i.e., Darwinian fitness), such as the age at which sexual maturity occurs, fecundity, or survival rate, might help to assess the adaptive value of different phenotypes depending on the environment to which they are exposed. More "naturalistic" experimental designs have been recently developed to better address this point (Macrì and Würbel 2007; Coutellier et al. 2008a, b, 2009; Coutellier and Würbel 2009).

11.4 Factors Mediating Environment-Dependent Regulations of Offspring Phenotypes

In the previous paragraphs we reviewed experimental evidence demonstrating that early experiences influence long-term development of behavioral, neuroendocrine, and cognitive functions in rodents. These phenotypic regulations are likely adaptive because they help organisms cope with the characteristics and challenges of the environment in which they live. However, the exact mechanism underlying this programming phenomenon remains unclear. Several maternal and non-maternal neonatal factors have been shown to influence offspring development, but the precise contribution and interaction of these factors still need to be clarified.

1. Maternal behavior as a mediator of the effects of neonatal challenges on offspring development

(a) Qualitative aspects of maternal care

Due to the altricial nature of rodents, pups stay in the confines of a safe and stable nest while brain plasticity is at its highest. Their mother is, however, directly exposed to their future environment during her foraging trips. Since she is the only connection the pups have to their future environment, it could be an adaptive response if their brain systems involved in coping with environmental challenges were modulated by the mother's behavior. In fact, many studies have shown that environment-dependent variations in maternal behavior are associated with variations in the development of the offspring's phenotype. Furthermore, postnatal environmental manipulations that were shown to affect adult behavior and brain morphology were also shown to alter maternal behavior. For instance, conditions such as EH (e.g., Meaney et al. 1991), environmental enrichment (e.g., Chapillon et al. 1999; Coutellier et al. 2008b), cross-fostering (e.g., Anisman et al. 1998), exposure to predator odor (e.g., McLeod et al. 2007; Coutellier et al. 2008a), or variability in food availability (e.g., Léonhardt et al. 2007; Macrì and Würbel 2007; Coutellier et al. 2008b, 2009) have all been shown to increase the level of active maternal care and to down regulate the fear and stress reactivity of the adult offspring. Increased active maternal care may be a protective response by the dams toward their pups under environmental conditions that may be perceived as threatening. In comparison, low challenging conditions such as non-handling (NH, i.e., leaving rat pups completely undisturbed during the first 2 postnatal weeks) or easy access to food (Macrì and Würbel 2007; Coutellier et al. 2008b, 2009) are associated with lower levels of active maternal care and higher HPA axis reactivity and fearfulness in the offspring. Interestingly, it was also found that naturally high levels of active maternal care in NH rats are associated with reduced stress and fear responses in the adult offspring (Lui et al. 1997; Caldji et al. 1998). These results provide support to the maternal mediation hypothesis exposed by Smotherman and Bell (1980). It is proposed that the effects of the early environment characteristics on offspring phenotype could in fact be mediated indirectly via its effect on maternal care (Richards 1966; Denenberg et al. 1969; Lui et al. 1997; Caldji et al. 1998; Macrì et al. 2004 also see reviews by Meaney 2001; Macrì and Würbel 2006) and, more generally, that developmental plasticity of fear and stress responses in rodents is maternally mediated (Bell et al. 1974; Smotherman et al. 1977).

The mechanism by which active maternal care affects the expression of the HPA axis in offspring has been proposed to be based on epigenetic processes. Weaver et al. (2004) found that the level of active maternal care affects the offspring's epigenome at the glucocorticoid receptor (GR) gene promoter in the hippocampus: offspring receiving high levels of active maternal care showed reduced DNA methylation of the exon 17 region of the promoter, which was associated with an increased expression of GR in the hippocampus and, therefore, enhanced negative feedback sensitivity to glucocorticoids. These findings provide a mechanism by which variations in maternal care may adaptively mediate phenotypic plasticity of the HPA system.

(b) Other maternal factors: nest attendance

Aside from the quality of maternal care received by the pups (active vs. passive nursing), other aspects of maternal behavior have been recognized to influence the development of offspring. Various studies have highlighted the importance of maternal presence. Specifically, Moriceau and Sullivan (2006) demonstrated in rats that maternal presence controls pups' learning abilities in an odor-shock conditioning paradigm through modulation of pup corticosterone. Macrì et al. (2004) showed that despite receiving similar levels of active nursing, offspring reared in the condition of EH or MS showed different HPA responses to restraint and behavioral fear response. The authors demonstrated that the temporal distribution of maternal care by EH and MS dams was significantly different and might contribute to the difference observed in offspring. Similar findings in mice have demonstrated that offspring reared by mothers with access to environmental enrichment have reduced behavioral fearfulness in comparison to offspring reared by unenriched dams, despite receiving a similar amount of maternal care (Coutellier et al. 2008b). It was observed that enriched dams spend less time in their nest; this lower level of nest attendance might mediate the effects observed on the offspring. This idea has been further supported by a multiple regression analysis showing an inverse relationship between the time the mother spent away from the nest and adult offspring fearfulness. These experimental evidences suggest that not only the quality of maternal care influences the development of the offspring in rodents but also the presence of the mother in the nest.

2. Non-maternal factors contribute to the effects of neonatal challenges on developing rodents

(a) Evidence for the implication of non-maternal factors

We previously described a series of studies demonstrating the importance of maternal behavior in mediating the effects of neonatal challenges on the adaptive regulations in developing rodents. Another line of evidence in rats and mice indicates that early environmental effects on stress reactivity and fearfulness cannot be fully explained by variations in maternal behavior (Macrì et al. 2004; Macrì and Würbel 2006; Tang et al. 2006; Coutellier et al. 2008a, b). For example, Macrì et al. (2004) demonstrated that both long (MS) and brief (EH) periods of maternal separation early in life result in high levels of active maternal care, but while EH offspring were less fearful and had a downregulated HPA axis, MS offspring were found more fearful and highly stress reactive. Thus, indistinguishable maternal styles resulted in differential adult offspring, supporting the idea that maternal care is not the unique factor mediating the effects of the early environment on offspring development. Another set of evidence supports this idea. Highly challenging foraging conditions (variable foraging demand—VFD) and moderately challenging foraging conditions (high foraging demand—HFD) in mice have both been associated with increased active maternal care. However, VFD male offspring were found more fearful than HFD offspring (Coutellier et al. 2009). Thus, while offspring received a similar

level of active maternal care, their adult phenotype differed significantly. This finding indicates that a high level of active maternal care is not the only parameter that leads to a downregulation of the fear and stress systems of the offspring and may not be sufficient in explaining developmental phenotypic plasticity. Tang et al. (2006, 2011) further developed this idea by using a split-litter methodology: half of the litter was exposed for 3 min daily to a novel environment and the other half remained in the home cage. The dam was removed prior to the separation and was returned to the home cage upon litter reunion to insure that all pups received the same amount of maternal care. They showed that pups that were separated from their mother and placed in a novel environment for brief periods have a more effective HPA axis when confronted to unexpected stressors and better spatial memory during adulthood compared to pups that were left in the home cage. These changes occurred in spite of both groups of pups receiving the same amount of active maternal care throughout their lactation period. The dissociation between the level of maternal care and offspring phenotype suggests that other factors than maternal factors contribute to the adjustment of offspring phenotype to early environmental cues.

(b) Corticosteroids as a possible contributing factor to individual adaptations to developmental challenges

A possible contributing factor to the adaptive development of rodents is the level of neonatal corticosteroids. Challenging and stressful environmental conditions are known to induce an increase in the circulating plasma level of stress hormones (e.g., corticosterone in rodents—Sapolsky 2004). This hormone could be passed from the mother to the offspring via milk during suckling episodes. Studies in rats and mice demonstrated that when lactating dams are supplemented with corticosterone in the drinking water, pups show high concentrations of plasmatic corticosterone (Catalani et al. 1993; Macrì et al. 2009). Therefore, because maternal corticosterone varied according to environmental conditions and because offspring's HPA axis is sensitive to the level of maternal corticosterone, it is likely that maternal corticosteroids contribute to offspring development.

Experimental evidence supports the idea that corticosterone levels during the neonatal period modulate individual development. Specifically, low levels of neonatal corticosterone have been associated with increased glucocorticoid receptors in the hippocampus, with reduced stress reactivity and improved cognitive abilities in rats (Catalani et al. 1993, 2000) and mice (Macrì et al. 2009). Interestingly, while low doses of neonatal corticosterone result in individual adaptation, high doses seem to lead to negative outcomes. Offspring exposed to elevated corticosterone levels during their development are found to have increased HPA-axis activity and behavioral anxiety (Brummelte et al. 2006; Macrì et al. 2007), reduced hippocampal levels of brain-derived neurotrophic factor (BDNF), and cell proliferation in the dentate gyrus (Brummelte et al. 2006; Macrì et al. 2009). These evidences suggest that exposure to different levels of corticosteroid during the neonatal period might interact with the level of active maternal care affecting offspring development.

(c) Gender as an important factor influencing the trajectory of effects of early life challenges on the development of rodents

Most research aiming to unravel the link between early environmental and maternal cues and the adult offspring phenotype has focused on males. Males have been favored because the estrous cycle is known to affect both the behavioral and physiological responses of females (e.g., Romeo et al. 2003). As a consequence, the conclusions made are based mainly on data coming from only male offspring, preventing scientists to determine whether neonatal variations affect offspring in a sex-specific manner. This point is very important especially if experimental neonatal manipulations in rodents are used to model early life events and to examine developmental hypotheses on the etiology of human psychopathologies such as anxiety, schizophrenia, and depression. These diseases, and other mental and neurological disorders, are highly sex-specific in human. Experimental studies using rodents as a model should take into account possible sex-specific effects.

Studies analyzing the effects of neonatal cues on both male and female offspring consistently demonstrate sex-specific results. For instance, Barha et al. (2007) showed that, in rats, the level of maternal licking/grooming affects working memory and stress reactivity more in female than in male offspring. Similarly, Noschang et al. (2010) found that females subjected to an EH paradigm showed impairments in spatial learning when compared to a non-handled group, while this effect was not observed in males. This cognitive impairment in females was associated with a decrease in nitric oxide production, an important cellular messenger molecule. Desbonnet et al. (2008) showed increased CRF immunoreactivity and increased colocalization of c-Fos and CRF following stress in the hypothalamus of maternally separated females but not males. Gender differences were also observed in mice. Coutellier et al. (2008a) and Coutellier and Würbel (2009) demonstrated that variations in the postnatal foraging maternal environment of mice affect female's corticosterone response to an isolation/novelty stressor and behavioral fearfulness, whereas there were no effects on male offspring. Gross et al. (2012) found that the level of expression of the glycoprotein Reelin, a master molecule for development and differentiation of the hippocampus, was increased in EH males when compared to NH males, while this difference was not observed in females.

Taken together, these findings suggest a significant role of the offspring's sex on the development of neurobehavioral and neurocognitive functions. They indicate that gender is an important factor influencing the trajectory of neonatal challenges effects on the development of rodents. These evidences point to the necessity of including both sexes in the analysis of early life influences on phenotypic plasticity. More work is needed for a better understanding of the mechanisms underlying sex-specific effects on adaptive regulations in developing rodents.

11.5 Conclusion

This chapter focused on the phenomenon by which early life events, even seemingly minor ones, program rodent's brain for a pattern of neuroendocrine and behavioral responses in later life. Early experiences are capable of enhancing or suppressing the expression of certain genetic traits and, by doing so, may change the outcome for behavioral and cognitive performance in adulthood (de Kloet et al. 2005). Many experimental evidences support this idea and show that developmental phenotypic plasticity is a powerful phenomenon that helps the organisms to live according to the characteristics of their environment.

The exact mechanism by which this plasticity occurs remains unclear. Many factors seem to interact and contribute to the development of the offspring's phenotype. There is increasing support for a broader view of the factors mediating adaptive regulations in developing rodents, than the one-factor maternal mediation hypothesis once proposed. However, the exact contribution of each of these factors as well as their interactions remains to be determined. Recently, new paradigms have been developed (Macrì and Wurbel 2007; Coutellier et al. 2008a, b, 2009; Coutellier and Würbel 2009) helping to answer these questions. The ultimate goal is to understand how the conditions from the neonatal environment affect brain development and can lead to adaptive or abnormal phenotypes in adulthood.

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