Chapter 10
Epigenetic Influence of the Social Environment

Frances A. Champagne and James P. Curley

Abstract Social experiences occurring during infancy have been demonstrated to exert persistent effects on neurobiological and behavioral outcomes. This social modulation of the developing brain has been observed in humans and animal models of abuse, neglect, and variation in parental style. Although the mechanisms through which these effects are achieved likely involve diverse cellular and molecular pathways, there is emerging evidence supporting the hypothesis that epigenetic changes, such as DNA methylation and histone modifications, may mediate the effects of early life variations in the social interactions between mothers and infants. Moreover, there may be plasticity within these epigenetic pathways at later developmental time points, such that the social experiences of juveniles and adults may also induce epigenetic change. These findings have implications for behavioral variation observed both within and across generations and highlight the dynamic interactions occurring between genes and environments during the course of development.

Keywords Abuse · Epigenetic · Maternal · Neglect · Neurodevelopment · Parenting · Transgenerational

10.1 Introduction

The quality of the social environment can have a significant impact on physiology, neurobiology, and behavior. There is growing evidence from epidemiological studies in humans for the persistent effects of the early life experience of abuse, neglect, and variations in parenting style, which suggest that multiple neural

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systems may be subjected to modulation via the social context of development. Further, explorations of the mechanisms through which these effects are achieved have focused on experimental paradigms involving primate and rodent models of variation in the social environment, and in particular, disruption of postnatal mother–infant interactions. Although multiple molecular and cellular pathways are implicated in mediating the link between early life experiences and long-term changes in phenotype, recent evidence has highlighted the role of epigenetic mechanisms, such as DNA methylation and posttranslational modifications to histone proteins within the nucleosome. Although shifts in DNA methylation were once thought to be restricted to early embryonic development, studies of nutritional (Lillycrop et al. 2007, 2008), chemical (Onishchenko et al. 2008), and a broad range of environmental exposures (Mueller and Bale 2008; Roth et al. 2009; Weaver et al. 2004) occurring during pre- and postnatal development have implicated epigenetic regulation of gene expression as a critical target of experience-dependent change. In this chapter, we describe the experimental approaches that have been used to explore the long-term effects of early life social experiences; highlight evidence from humans, primates, and rodents for social modulation of the brain; and illustrate the role of epigenetic mechanisms in maintaining the effects of the social environment. Although plasticity in development is typically associated with the perinatal period, there is continued social modulation of gene expression and behavior among juveniles and adults and this plasticity may likewise involve epigenetic modifications. Moreover, the impact of the social environment may not be restricted to within-generation effects and may lead to the transgenerational inheritance of phenotypic variation that involves experience-dependent changes in DNA methylation (Champagne 2008). These findings suggest that an exploration of epigenetic mechanisms may advance our understanding of the complex and dynamic interplay between the genome and the environment.

10.1.1 From Epidemiology to the Laboratory: Strategies for Studying Early Life Social Influences

Epidemiological and longitudinal studies have provided significant support for the hypothesis that the quality of the early life social environment may shape developmental trajectories leading to either risk or resilience to later life psychiatric disorder. In humans, neglect and abuse have been demonstrated to reduce cognitive performance and impair social development (Trickett and McBride-Chang 1995) and is associated with a fourfold increase in personality disorders (Johnson et al. 1999). The severe neglect experienced by institutionalized infants, most recently explored among Romanian orphans, further demonstrates the persistent effects of these experiences. Delays in growth, social, and cognitive development observed in Romanian orphans are associated with later life impairments in attachment, heightened inattention, and increased autistic-like behaviors (Beckett et al. 2002;

MacLean 2003; O'Connor and Rutter 2000; O'Connor et al. 2000; Rutter and O'Connor 2004). Although it is difficult to identify the particular aspect of the neglectful or abusive childhood experience which contributes to this outcome, disruption to the mother–infant relationship, consisting of both physical and emotional contact, associated with these conditions is thought to be critical. Variations in the attachment relationship between mother and infant have been associated with either resilience to psychological distress or increased incidence of psychopathology (Sroufe et al. 1999; Sroufe 2005). Secure attachment, typically assessed by the Strange Situation Task (in which infants' response to separation followed by reintroduction of the mother is measured) is associated with increased social competence and cognitive performance, whereas disorganized attachment patterns predict increased rates of borderline personality disorder, dissociation, and self-harm in adulthood (Carlson 1998; Carlson et al. 2009). Studies using a retrospective assessment of the quality of the mother–infant relationship, such as the Parental Bonding Index (PBI), suggest that low levels of maternal care combined with controlling–overprotective parenting are a significant predictor of adult depression (Parker et al. 1979; Parker 1993). Overall, these studies indicate that disruption to the early social environment, particularly the interactions between mother and infant, can have sustained effects on numerous biobehavioral outcomes in adulthood.

Our understanding of the mechanisms linking these early life experiences to adult outcomes has come from the development of animal models, which incorporate aspects of neglect, abuse, or variation in the quality of the mother–infant interactions' that are evident in human longitudinal studies (see Fig. 10.1). The classic studies of Harry Harlow on the development of rhesus macaques exposed to maternal deprivation provide evidence that the absence of mother–infant interactions during the early phases of development can induce disruptions to social play, hyperactivity, and sensitivity to stressors (Harlow et al. 1965; Seay and Harlow 1965; Suomi et al. 1971). The importance of mother–infant contact is further

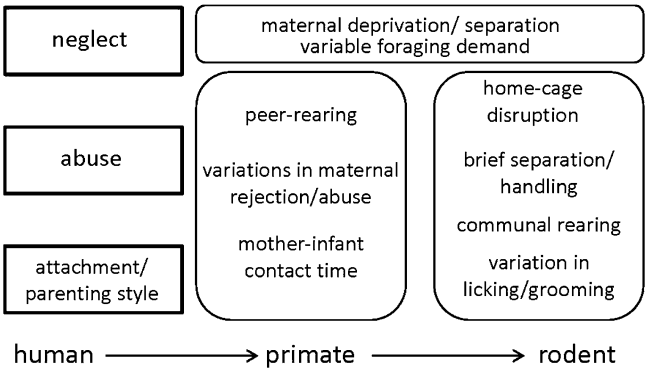

Fig. 10.1 Summary of paradigms used to study social modulation of brain and behavior during postnatal development in humans, primates, and rodents

demonstrated by the persistence of abnormalities in development that emerge in response to peer-rearing (Suomi 1991), where infants have social contact with the peers but not with the mother. In primates, variable foraging demand can also be used to disrupt the quality and quantity of mother–infant interactions (Coplan et al. 2006). When the duration of time that is needed to locate and retrieve sufficient amounts of food is inconsistent across weeks, the sensitivity of mothers to infant cues is disrupted, and consequently, offspring exhibit elevated levels of anxiety-like behavior and are less social in adulthood (Coplan et al. 1995, 2005; Gorman et al. 2002). These variations in mother–infant interaction are also observed to occur naturally among colonies of rhesus and pigtail macaques. Maternal abuse in the form of dragging and stepping-on infants occurs in isolation-reared and group-housed macaques at a frequency of 2–10% (Berman 1990; Carroll and Maestripieri 1998; Maestripieri 1998). Abused infants show a delayed onset in social play and are hyperaggressive in novel environments (McCormack et al. 2006). Abusive mothers also engage in high levels of maternal rejection, where infant attempts to make contact with the mother are rejected, and the experience of high levels of this parenting style may be associated with neurobiological outcomes associated with infant abuse (as discussed in the next section). High levels of mother–infant contact (characteristic of an over-protective parenting style) have also been observed in non-human primates and are associated with decreased exploration of a novel environment when infants are juveniles (Fairbanks and McGuire 1988). Thus, both experimental manipulation of the early social environment and observational studies of naturally occurring variations in mother–infant interactions can be used to explore the persistent effects of social experiences.

Although primate studies provide a useful model for exploring the effects of neglect, abuse, and variations in maternal behavior that may shape the developing brain and behavior, our understanding of the mechanisms through which this is achieved have relied primarily on studies of laboratory rodents. Maternal neglect and deprivation can be experimentally induced by separating pups from the dam for extended periods of time, a manipulation referred to as maternal separation (Rosenfeld et al. 1992), or through rearing pups in complete isolation from the dam, referred to as artificial rearing (Hall 1975). In general, prolonged separation or deprivation from maternal contact induces heightened anxiety-like behaviors, reduced performances on learning and memory tasks, and decreased social behaviors in adulthood (Lehmann et al. 1999; Lovic and Fleming 2004). The duration of separation is an important modulator of this effect, and there is evidence that brief maternal separations (often referred to as "handling") can stimulate maternal behavior and attenuate the stress response (Levine 1957; Meaney et al. 1991). The effects of abusive caregiving can also be studied in rodents. Removal or disruption of the bedding material normally included in the cages of laboratory rats and mice can induce dams to engage in rough handling, stepping-on, and avoidance of pups (Roth and Sullivan 2005). This paradigm has been used primarily for studying the factors influencing attachment to abusive caregivers and may also be a useful approach for studying the effects of early life trauma. Extended periods of maternal separation can also be induced in the laboratory by imposing foraging demands, and evidence

from studies in mice suggests that a variable foraging demand on dams is associated with increased anxiety-like responses in male offspring (Bredy et al. 2007; Coutellier et al. 2009). Interestingly, studies of biparental voles indicate that removal of the father can have lasting effects on neurodevelopment (Ahern and Young 2009), though the benefits of multiple caregivers for offspring development is not limited to biparental species. In laboratory mice, communal rearing can be used to study the effects of increased social interactions during the postnatal period (Branchi 2009). In a communal nest, multiple postparturient females are housed together with their own litters or foster pups and the litters are combined and cared for as a group by the lactating dams. When compared with standard reared pups, offspring reared in communal nests are found to exhibit changes in anxiety-like and social behavior that are dependent on the age distribution of pups in the nest and conditions of the testing environment (Branchi and Alleva 2006; Branchi et al. 2009; Curley et al. 2009). This rearing paradigm has been demonstrated to ameliorate many of the behavioral deficits characteristic of the highly anxious BALB/c mouse strain (Curley et al. 2009), suggesting the modulating effect of social experiences on strain differences in behavior.

Individual variation in maternal styles that are observed in humans and primates are also exhibited by laboratory rodents and can likewise be associated with divergent developmental outcomes. In rats and mice, there are individual variations in several aspects of maternal behavior during the first week postpartum (Champagne et al. 2003a, 2007). In particular, there are stable between-dam variations in the frequency of pup licking/grooming (LG). One strategy for studying the long-term influence of mother–infant interactions is to characterize the LG behavior of a cohort of lactating females and compare outcome measures between offspring reared by Low or High LG dams [with Low or High being defined as 1 SD below or above the cohort average LG (Champagne et al. 2003a)]. This approach has been used successfully to study the origins of individual differences in stress response, response to novelty, learning and memory, and numerous indices of social/reproductive behavior (Meaney 2001). Variations in LG during the postnatal period can also be induced by gestational stress (Champagne and Meaney 2006; Moore and Power 1986), postparturient exposure to predator odor (McLeod et al. 2007), and various manipulations of the postnatal and juvenile rearing environment of the dams (Champagne and Meaney 2007; Lovic et al. 2001), with consequences for offspring development. Thus, plasticity in maternal behavior in response to environmental conditions is one route through which the quality of the environment can shape offspring physiology, brain, and behavior.

10.1.2 Social Modulation of the Developing Brain

The rodent and primate models of neglect, abuse, and variations in mother–infant interaction described in the previous section have been used to explore the neurobiological impact of the social environment and have yielded target neural systems,

which have been subsequently explored in human cohorts. Disruption to the early life environment has been demonstrated to exert persistent effects on the hypothalamic–pituitary–adrenal (HPA) response to stress (for recent reviews see Korosi and Baram 2009; Lupien et al. 2009). Elevations in glucocorticoids associated with exposure to stress is achieved via release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus that acts on CRH receptors within the pituitary to trigger the release of adrenocorticotropin hormone (ACTH) and consequent release of glucocorticoids from the adrenal cortex. This HPA activity can be potentiated by neuropeptides such as vasopressin (AVP) and down-regulated through a negative feedback loop involving hippocampal glucocorticoid receptors (GR). In early development, social experiences that promote increased levels of mother–infant tactile stimulation generally lead to long-term reduction in HPA stress reactivity. Adult rats that were reared by High LG dams or exposed to postnatal handling have attenuated stress responsivity, reduced CRH mRNA expression in the PVN, and higher expression of GR in the hippocampus (Francis et al. 1999; Liu et al. 1997; Meaney and Aitken 1985; Meaney et al. 1985, 1989; Viau et al. 1993). In contrast, postnatal maternal separation induces increased stress reactivity associated with reduced GR expression in the hypothalamus and hippocampus, and regional changes in CRH receptor expression (Ladd et al. 2004; Plotsky and Meaney 1993). Thus, neural circuits involved in emotionality are susceptible to modulation in response to early life experiences, particularly those experiences affecting the frequency of mother–infant interactions.

The influence of the social environment is not limited to neuroendocrine pathways, which are primarily involved in regulating the stress response. However, it should be noted that most investigations of the neurobiological consequences of experimental manipulations of the early life environment use a target gene/neural system approach such that the specificity vs. breadth of the effects of particular manipulations are not well elucidated. Maternal separation is associated with increased dopamine (DA) in the striatum of mice (Ognibene et al. 2008). Moreover, compared with individuals who were handled during the first 2 weeks of life, adults who experienced postnatal maternal separation have increased dopamine D1 receptor binding levels in the nucleus accumbens (NAc) core and caudate putamen, increased D3 receptor mRNA in the NAc shell, and decreased levels of dopamine transporter (DAT – which uptakes DA from the synapse) (Brake et al. 2004). Maternally separated rat pups have decreased 5-HIAA and HVA (serotonin (5-HT) metabolites) levels in the amygdala and increased stress-induced 5-HT and 5-HIAA levels (Arborelius and Eklund 2007). Similar increases in 5-HT levels are found in the prefrontal cortex, hippocampus, and striatum of mice that are maternally separated during the first week postpartum (Ognibene et al. 2008). Handling-induced increases in gamma-aminobutyric acid (GABA) A central benzodiazepine (CBZ) receptors have been detected in the medial prefrontal cortex (mPFC), hippocampus, and amygdala (Bodnoff et al. 1987; Caldji et al. 2000; Weizman et al. 1999). Extended periods of maternal separation in rats have been reported to cause reductions in the expression of the hippocampal *N*-methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor subunits (Bellinger et al. 2006; Pickering et al. 2006;

Roceri et al. 2002). Postnatal maternal separation has also generally been associated with elevated AVP immunoreactivity and mRNA in the PVN (Vazquez et al. 2006; Veenema et al. 2006; Veenema and Neumann 2007), though some studies only find this increase in subjects undergoing a subsequent exposure to stress (Veenema et al. 2006). Maternal separation leads to increased vasopressin V1A receptor (V1Ar) binding in the lateral septum (LS) of juvenile males (Lukas et al. 2010). Maternally separated male rats have lower oxytocin receptor (OTR) binding in the LS and caudate putamen, and higher OTR binding in the medial preoptic area (MPOA) and ventromedial hypothalamus (VMH) (Lukas et al. 2010). Overall, these studies illustrate the broad effects of early life manipulations achieved through long and brief maternal separations.

Similarly, variations in maternal behavior have been demonstrated to exert long-term influences on dopaminergic, GABAergic, glutamatergic, oxytocin and vasopressin neuropeptide systems, and brain-derived neurotrophic factor (BDNF). Offspring of Low LG dams have elevated stress-induced dopamine release within the mPFC (Zhang et al. 2005). Variations in maternal behavior in the rat and between different strains of mice have been shown to regulate GABAA receptor subunit composition with implications for its receptor pharmacology (Caldji et al. 2000, 2003, 2004). Offspring of Low LG dams exhibit a deficit in NMDA hippocampal subunit mRNA expression as adults (Bredy et al. 2003, 2004; Liu et al. 2000). Similarly, in biparental species, reduced paternal contact results in increased NR2A and decreased NR2B NMDA subunit mRNA expression in the hippocampus (Bredy et al. 2007). Male offspring of High LG rat dams have elevated levels of V1Ar in the amygdala (Francis et al. 2002b), whereas communally reared female mice have reduced V1Ar binding in the LS (Curley et al. 2009). Communally rearing and the experience of High LG are associated with elevations in hypothalamic OTR of female offspring (Champagne et al. 2001; Curley et al. 2009; Francis et al. 2000). Finally, hippocampal levels of BDNF have been demonstrated to decrease in response to maternal separation and complete maternal deprivation (Burton et al. 2007; Roceri et al. 2002), and increase in response to communal rearing in mice (Branchi et al. 2006a, b) and high LG in rats (Liu et al. 2000). Social modulation of these target systems has implications for response to novelty, anxiety-like and social behavior, and cognition, such that these early life experiences can achieve diverse developmental effects that persist into adulthood.

The translation of these laboratory-based findings to primate and human studies has provided further support for the impact of social experiences on brain region-specific activation, neuropeptide/neurotransmitter levels, and variations in gene expression. As it is the case for early deprivation paradigms in rodents, reductions in mother–infant contact in primates have a profound impact on the HPA response to stress. Heightened stress-induced cortisol and decreased rhythmicity in basal cortisol release are common features of rhesus monkeys reared in the absence of maternal stimulation, typically using a peer-rearing strategy (Barr et al. 2004; Suomi 1991). Compared with mother-reared rhesus monkeys, peer-reared infants showed increases in the volume of stress-sensitive brain regions, such as the dorsomedial prefrontal cortex and dorsal anterior cingulate cortex (ACC), in later

life (Spinelli et al. 2009). Peer-reared infants also have decreased serotonin transporter binding in the hypothalamus, caudate and putamen, globus pallidum, anterior cingulate gyrus, amygdala, and hippocampus (Ichise et al. 2006); decreased CSF 5-HIAA concentrations (Shannon et al. 2005); and an altered density of 5-HT1A receptors (Spinelli et al. 2010). Exposure of infant marmosets to repeated separations from parents is associated with long-term changes in gene expression, with particular effects on 5-HT1A mRNA levels within the ACC and hippocampus (Law et al. 2009a, b). Comparisons between nursery- and mother-reared infants indicate decreased CSF oxytocin levels in maternally deprived rhesus monkeys, which may account for the decreased social behavior observed in nursery-reared infants (Winslow 2005). Disruptions of mother–infant interactions, through use of a variable foraging demand, have been demonstrated to increase CSF levels of CRH (when exposure occurs in infancy; Coplan et al. 2001), induce elevations in CSF 5-HIAA and HVA (Coplan et al. 1998), and alter metabolism within the ACC (Mathew et al. 2003). Likewise, natural variation in maternal rejection rates is associated with altered serotonergic activity in offspring (Maestripieri et al. 2005, 2006). Thus, studies in primates have confirmed the neurobiological pathways that had previously been implicated in rodent models of abuse, neglect, and variation in parental behavior.

Advances in the development of noninvasive strategies for studying the impact of early life experiences on neural systems in humans have provided opportunities for translational studies on social modulation of the brain. Childhood neglect and abuse are associated with increased HPA activity and increased pituitary volume (Fries et al. 2008; Gerra et al. 2008; Neigh et al. 2009). CSF levels of 5-HIAA and HVA have been show to be negatively correlated with retrospective self-report scores of childhood emotional neglect (Roy 2002). Reduced levels of plasma BDNF associated with childhood neglect have also been reported in depressed patients and may account for cognitive impairments observed in these subjects (Grassi-Oliveira et al. 2008). Neuroimaging studies of Romanian adoptees that experienced severe neglect associated with institutionalization in infancy have indicated decreased overall white- and gray-matter volume and increased amygdala volume (Mehta et al. 2009). Positron emission tomography (PET) analysis indicates decreased metabolic activity within the orbital frontal gyrus, the infralimbic prefrontal cortex, amygdala, hippocampus, the lateral temporal cortex, and the brain stem of Romanian orphans (Chugani et al. 2001). Levels of vasopressin and oxytocin have also been found to be blunted in children who experienced early neglect (Fries et al. 2005). Variations in retrospective reports of parental care have also yielded significant negative associations with cerebrospinal levels of CRH (Lee et al. 2006). In nonclinical subjects, high levels of maternal care are associated with reduced trait anxiety and decreased salivary cortisol in response to stress, whereas low levels of maternal care are associated with increased DA release in the ventral striatum in response to stress (Pruessner et al. 2004). Other studies using the PBI have found a positive relationship between gray matter volume in the left dorsolateral prefrontal cortex (DLPFC) and paternal care score, whereas paternal and maternal overprotection were negatively correlated with the volume of this region (Narita et al. 2010). In a longitudinal study, observational ratings of parental

nurturance at age 4 predicted hippocampal volume in adolescence (Rao et al. 2010). These neurobiological studies of the effect of early life adversity suggest the persistent influence of these experiences on neural systems that regulate anxiety, social behavior, and cognition with implications for risk of later life psychiatric disorders.

10.1.3 Epigenetic Mechanisms and the Long-Term Effects of Social Experiences

The biological pathways, though which early life social experiences exert such a profound neurobiological and behavioral impact, are being explored within many of the rodent, primate, and human experimental designs described in the previous sections. Although there may certainly be neuroanatomical alterations through which these effects are achieved, one approach to advancing our understanding of the association between the social environment and phenotypic variation comes from experimental designs incorporating the study of epigenetic regulation of gene activity. This epigenetic regulation of transcription is a critical feature of the link between genotype and phenotype and refers to those factors which control accessibility of DNA to transcription and which can alter the levels of gene expression (either silencing genes or increasing transcriptional activity) without altering the sequence of DNA. The molecular mechanisms through which these epigenetic effects are achieved include, but are not exclusive to, histone protein modifications and DNA methylation (Feng et al. 2007; Razin 1998). Within the cell nucleus, DNA is wrapped around a core of histone proteins, which can undergo multiple post-translational modifications including methylation, acetylation, and ubiquination (Peterson and Laniel 2004; Zhang and Reinberg 2001). These modifications alter the dynamic interactions between the histones and DNA, which either reduce or enhance the accessibility of DNA to transcription factors and RNA polymerase. In particular, histone acetylation is associated with increased transcriptional activity, whereas histone deacetylation or methylation is typically associated with transcriptional repression. Acetylation of histones is mediated by the enzyme histone acetyltransferase (HAT), whereas histone deacetylase (HDAC) promotes removal of the acetyl group from the histone tails. Thus, through alterations in the conformation of histones, the accessibility of DNA can be rapidly and reversibly altered. In contrast, DNA methylation has the potential to be a more stable and enduring modification to the activity of genes. DNA methylation occurs when cytosine nucleotides, usually located in CpG islands, are converted to 5-methylcytosine. This process is mediated by methyltransferases, which promote either maintenance (i.e., DNMT1) or de novo DNA methylation (i.e., DNMT3) (Feng et al. 2007; Razin 1998; Turner 2001). The conversion to 5-methylcytosine does not alter the DNA sequence, but can alter the likelihood that the gene will be transcribed and reduce transcription factor-mediated responses, particularly when methylation occurs

within gene promoter regions. Methylated DNA attracts methyl-binding proteins, such as MeCP2, which further reduce the accessibility of the gene and are associated with transcriptional repression (Fan and Hutnick 2005). The stability of DNA methylation patterns within the genome permits the stable regulation of gene expression associated with cellular differentiation and the heritability of this modification can be observed during mitotic cell divisions (Fukuda and Taga 2005).

Investigations of the role of epigenetic mechanisms in maintaining changes in gene expression induced by the early social environment have been explored in rodent experimental designs that model maternal abuse, maternal separation, and variations in mother–infant interactions during postnatal development (see Fig. 10.2). Daily exposure to abusive social interactions leads to reduced expression of BDNF in the prefrontal cortex in adulthood associated with increased DNA methylation within the BDNF IV promoter region (Roth et al. 2009). The functional importance of DNA methylation in mediating the long-term effects of abuse is further supported by findings that central administration of zebularine, a compound that reduces DNA methylation, leads to increased BDNF expression in maltreated rats such that BDNF levels are equivalent among abused and nonabused offspring. Daily and prolonged maternal separation has effects on a broad range of neurotransmitter and neuropeptide systems, and in a recent study, significant increases in AVP mRNA in the parvocellular neurons of the PVN was explored in maternally separated mice (Murgatroyd et al. 2009). Within the AVP gene, there are four regions rich in CpG islands that may regulate gene expression through DNA methylation. Analysis of PVN tissue indicated that at one of the four regions (CGI3), maternally separated males have significantly reduced DNA methylation

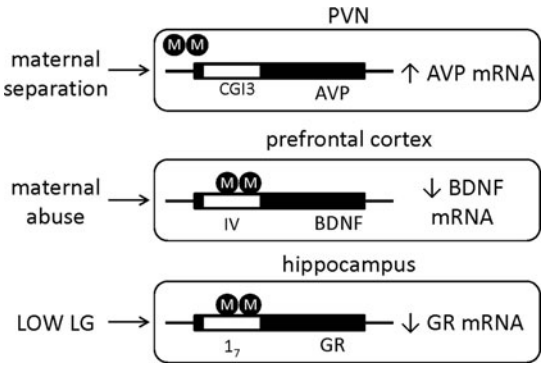

Fig. 10.2 Epigenetic effects of postnatal environmental experiences. In rodents, postnatal maternal separation is associated with decreased DNA methylation within the AVP promoter region leading to increased AVP mRNA in the PVN (Murgatroyd et al. 2009), whereas maternal abuse is associated with increased methylation within the BDNF promoter in the prefrontal cortex leading to decreased BDNF expression (Roth et al. 2009) and the experience of low levels of LG in infancy is associated with increased methylation in the GR promoter region leading to decreased hippocampal GR expression (Weaver et al. 2004)

compared with control males at 6 weeks, 3 months, and 1 year of age. Furthermore, this hypomethylation was significantly correlated with increased mRNA expression, and these effects were brain region-specific as no changes in AVP mRNA or DNA methylation were found between maternally separated and control males in the supraoptic nucleus (SON). Analysis of the time course of the molecular changes involved in this differential methylation suggests that short-term activation of MeCP2 may be critical within the pathways leading to AVP hypomethylation and increased AVP mRNA levels within the PVN (Murgatroyd et al. 2009). Conversely, in response to brief maternal separation (handling), reductions in CRH mRNA in the parvocellular neurons of the PVN can be observed as early as PN9 (Korosi et al. 2010). Within the regulatory region of the CRH gene, there is a binding element for the repressor neuron-restrictive silencer factor (NRSF) (Seth and Majzoub 2001). This factor recruits cofactors and other enzymes/proteins involved in epigenetic regulation leading to the repression of gene expression (Zheng et al. 2009). Among handled offspring, protein levels of NRSF are dramatically higher in PVN tissue at PN9 and throughout adulthood, suggesting a possible mechanism for the initiation and maintenance of reduced CRH gene expression in response to handling-induced stimulation of mother–infant interactions.

Natural variations in postnatal maternal LG in the rat are associated with changes in numerous receptor pathways, with effects on hippocampal GR being implicated in the high levels of HPA reactivity observed among offspring of Low LG dams (Liu et al. 1997). Analysis of the GR 1_7 promoter region suggests that low levels of LG are associated with increased GR 1_7 methylation, decreased GR expression and an increased HPA response to stress. Time course analysis has indicated that these maternally induced epigenetic profiles emerge during the postnatal period and are sustained into adulthood (Weaver et al. 2004). The pathways through which these effects are achieved are currently being elucidated and it appears likely that maternal LG mediated up-regulation of nerve growth factor-inducible protein A (NGFI-A) in infancy may be critical to activating GR transcription and maintaining low levels of DNA methylation within the GR 1_7 promoter among the offspring of High LG dams (Weaver et al. 2007). These experience-dependent shifts in epigenetic regulation of target genes within HPA stress pathways have also been observed to emerge prenatally in response to maternal exposure to chronic variable stress. Male offspring of mice exposed to gestational stress have decreased DNA methylation of the CRH gene promoter and increased methylation of the GR exon 1_7 promoter region in hypothalamic tissue (Mueller and Bale 2008). These epigenetic modifications are associated with exposure to stress during the early stages of prenatal development and may involve dysregulation of placental gene expression. These findings complement studies in humans illustrating that methylation status of the GR promoter, particularly at the NGFI-A-binding site, in cord blood mononuclear cells of infants is associated with exposure to third trimester maternal depressed mood. Maternal depression was found to be associated with increased GR 1F promoter methylation in fetal blood samples and these methylation patterns predicted HPA reactivity in infants at 3 months of age (Oberlander et al. 2008). The susceptibility of HPA responses to social modulation

suggests that genes within these stress-sensitive pathways may be the target of epigenetic dysregulation associated with many forms of early life adversity.

10.1.4 Beyond Infancy: Epigenetic Effects of Juvenile and Adult Social Experiences

Although social modulation of brain and behavior has been primarily explored in response to early social experiences, and in particular, mother–infant interactions, there continues to be plasticity in response to social experiences occurring during juvenile development and into adulthood. Social isolation during the postweaning period has generally been found to increase anxiety-like responses, though this may not involve the same neuroendocrine pathways targeted by earlier social experiences (Francis et al. 2002a; Lukkes et al. 2009). In rodents, postweaning social isolation has been associated with decreased expression of several 5-HT receptor subtypes in the prefrontal cortex, hypothalamus, and midbrain (Bibancos et al. 2007); latent elevations in DA levels in the NAc (Shao et al. 2009); reduced GABAA/CBZ receptor binding (Insel 1989; Miachon et al. 1990); decreased neuronal plasticity associated with glutamatergic hypofunction (Lu et al. 2003; Silva-Gomez et al. 2003; Stranahan et al. 2006); and sex-specific effects on the numbers of OT-positive neurons in the PVN (Grippo et al. 2007a, b). This cascade of neuroendocrine changes is associated with a phenotype referred to as an "isolation syndrome," which can be attenuated by treatment with antidepressants (Heritch et al. 1990). In contrast, juvenile environmental enrichment (typically involving both physical and social environmental complexity) in rodents attenuates the HPA response to stress with a concomitant decrease in basal corticosterone levels (Belz et al. 2003), and there is evidence for enrichment-induced elevations in hippocampal NGFI-A and GR (Olsson et al. 1994). In addition, social enrichment during juvenile development is associated with increased levels of the DAT within the NAc (Zakharova et al. 2009), increased GAD enzyme activity and extracellular GABA concentrations within the hippocampus (Frick et al. 2003; Segovia et al. 2006), increased AMPA receptor expression in the hippocampus (Bredy et al. 2003, 2004), and elevated OTR binding in a number of forebrain and hypothalamic areas including the central nucleus of the amygdala (Champagne and Meaney 2007). The social enrichment paradigm has been used to reverse deficits associated with pre- and postnatal environmental exposures (Francis et al. 2002a; Laviola et al. 2004; Morley-Fletcher et al. 2003) and augment phenotypes associated with targeted genetic manipulations (Jankowsky et al. 2005; van Dellen et al. 2000). Interestingly, recovery of memory deficits induced through p25-mediated neuronal loss can be achieved through exposure to complex housing environments and this enrichment is associated with increased histone (H3 and H4) acetylation in the hippocampus and cortex (Fischer et al. 2007). Moreover, treatment with histone deacetylase inhibitors can mimic the effects of environmental enrichment on learning and synaptic plasticity. These findings suggest the role of epigenetic mechanisms in shifting gene expression and behavior at these later stages of development.

In adulthood, chronic social defeat has been used to illustrate the continued influence of social experiences on neurobiological outcomes. This form of social stress, in which an individual has prolonged exposure to agonistic behavioral encounters, is associated with disruptions in social and emotional responding (Keeney and Hogg 1999). In adulthood, even a single social defeat is associated with prolonged alterations to the HPA stress response and changes to the expression of CRH receptors (Buwalda et al. 1999; Cooper and Huhman 2007). Social defeat results in transient changes in GABA receptor levels in cortex, cerebellum, and hypothalamus (Miller et al. 1987); increases in NMDA and decreases in AMPA receptor binding in the hippocampus (Krugers et al. 1993); and increases in expression of AVP mRNA in the PVN (Erhardt et al. 2009). Exploration of the epigenetic pathways linking the experience of social defeat to the behavioral phenotype that emerges in response to this adult social stressor has focused primarily on BDNF, which serves as a trophic factor that is a common downstream mediator of the effects of the multiple neurotransmitter and neuropeptide systems. BNDF gene expression is significantly decreased in the hippocampus of socially defeated male mice and this effect appears to be mediated by specific decreases in the BDNF III and IV transcripts (Tsankova et al. 2006). These effects are observed a month following exposure to the social stress, indicating a persistent effect on gene expression. Chromatin immunoprecipitation (ChIP) analysis indicates increased histone H3-K27 dimethylation at the BDNF III and IV promoters among socially defeated males, which may account for the reduced BDNF expression. Histone deacetylase (HDAC5) mRNA levels are also found to be decreased in socially defeated males (Tsankova et al. 2006) and HDAC5 appears to be important in mediating the effects of antidepressant treatment in males exposed to chronic social stress (Renthal et al. 2007). The differential levels of histone H3-K27 dimethylation are also found across the genome within the NAc, both in response to chronic social defeat and prolonged adult social isolation (Wilkinson et al. 2009). Analysis of histone acetylation in the NAc indicates that H3-K14 acetylation is initially decreased and then increased following chronic social defeat associated with decreases in HDAC2 levels. These studies suggest that though there is plasticity beyond the postnatal period, and that epigenetic mechanisms are responsive to juvenile and adult social experiences, dynamic histone modifications may be more evident in response to these later life experiences.

10.1.5 Transgenerational Epigenetic Effects

Although use of the term "epigenetic" has its origin in the study of development and the notion that divergent gene activity plays a critical role in phenotypic variation, more recent conceptualizations of "epigenetic" are derived from the root "genetic" meaning the study of the units of heritable material (Jablonka and Lamb 2002). The notion that meiotic inheritance can be considered outside the realm of the DNA sequence is an area of growing philosophical and scientific interest, and there are

two distinct pathways via which epigenetic modifications are currently believed to be involved in the transmission of traits across generations. The first pathway, often referred to as epigenetic inheritance, involves incorporation of an epigenetic mark into the DNA which is then transmitted and perpetuated in subsequent generations through the germline (Morgan et al. 1999). The second pathway builds on the role of experience-dependent epigenetic modifications in developmental plasticity illustrated in the previous sections. Through these pathways, DNA methylation has been demonstrated to play a critical role in the transgenerational impact of early life experiences. The role of social experiences in shaping transgenerational effects is associated with experience-depended changes in the activity of genes that will, in adulthood, alter the reproductive behavior of females, leading to variations in the quantity and quality of mother–infant interactions (Champagne 2008). Natural variations in postnatal maternal care have been associated with altered gene expression and receptor levels within the MPOA, a brain region that is critical for maternal behavior (Fleming 1986). Females reared by Low LG dams have a reduced sensitivity to estrogen-mediated increases in neuronal activation within the MPOA (Champagne et al. 2001, 2003b) and analysis of levels of ERα in the offspring of High and Low LG dams suggest that differences in estrogen sensitivity are mediated by variations in ERα levels such that expression of ERα in the MPOA of both lactating and nonlactating female offspring of Low LG dams is significantly reduced (Champagne et al. 2003b). Analysis of levels of DNA methylation within the 1B promoter region of the ERα gene in MPOA tissue indicates that the experience of High LG is associated with decreased promoter methylation, whereas Low LG is associated with increased promoter methylation, leading to reduced gene expression and an attenuated response to hormonally primed behaviors (Champagne et al. 2006). ChIP assays demonstrate that this differential DNA methylation has consequences for the binding of transcription factors such as STAT5a to the 1B promoter. Maternal LG is associated with increased levels of STAT5a during the postnatal period and the increased levels of this factor may lead to sustained activation of transcription and reduced DNA methylation (Champagne et al. 2006). As a consequence of these epigenetic modifications, individual differences in maternal LG are transmitted from mother to offspring (F1 generation) and to grand-offspring (F2 generation) (Champagne and Meaney 2007; Champagne 2008). A similar experience-dependent transmission of behavior is observed in response to exposure to abuse. Female rat pups exposed to abusive caregiving in infancy engage in abusive caregiving toward their own offspring and F2 offspring of these F1 females have elevated levels of methylation within the BDNF promoter in the PFC and hippocampus (Roth et al. 2009). Interestingly, postnatal cross-fostering of F2 females to nonabusive dams did not reverse these epigenetic effects, suggesting that there may be prenatal factors that contribute to the generational transmission of altered DNA methylation patterns. The transgenerational inheritance of stable individual differences in behavior, mediated through epigenetic mechanisms, provides an alternative route of inheritance of phenotype that may allow for the environmental conditions and social experiences of previous generations to influence development.

10.1.6 Concluding Remarks

Development occurs within a social context and there is increasing evidence that epigenetic mechanisms may play a critical role in linking experiences to long-term neurobiological changes. Although much of the evidence supporting the hypotheses that DNA methylation and histone modifications are altered by the social environment has come from studies in rodents, translational studies are emerging, which suggest that, for example, the experience of abuse in infancy can lead to epigenetic variation in the human brain (McGowan et al. 2008, 2009). Thus, the animal models of abuse, neglect, and variation in parental care that have been used to study social modulation of the developing brain can continue to inform and inspire hypothesis-driven epigenetic research in humans. Given the brain region specificity of many of the gene expression changes that have been observed in these models, one critical question that must be addressed relates to the ability to predict epigenetic changes in the brain using peripheral markers of transcriptional activity measured in blood lymphocytes. Establishing this relationship will enable the application of an epigenetic approach to longitudinal studies in humans where in vivo changes in DNA methylation and histone modifications can be associated with variations in social experience. In addition, the plasticity of the epigenome in response to both behavioral and pharmacological intervention in later life that has been observed in rodent studies (Roth et al. 2009; Weaver et al. 2004, 2005) may provide a novel therapeutic approach to the treatment of disorders related to early life adversity. The dynamic yet stable nature of epigenetic variation may be a critical feature of both within- and across-generation individual differences in phenotype that expand our concept of the origins of variation in brain and behavior.

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