Epigenetic Influence of Stress and the Social Environment

Kathryn Gudsnuk and Frances A. Champagne

Abstract

Animal models of early-life stress and variation in social experience across the lifespan have contributed significantly to our understanding of the environmental regulation of the developing brain. Plasticity in neurobiological pathways regulating stress responsivity, cognition, and reproductive behavior is apparent during the prenatal period and continues into adulthood, suggesting a lifelong sensitivity to environmental cues. Recent evidence suggests that dynamic epigenetic changes—molecular modifications that alter gene expression without altering the underlying DNA sequence—account for this plasticity. In this review, we highlight studies of laboratory rodents that illustrate the association between the experience of prenatal stress, maternal separation, maternal care, abusive caregiving in infancy, juvenile social housing, and adult social stress and variation in DNA methylation and histone modification. Moreover, we discuss emerging evidence for the transgenerational impact of these experiences. These experimental paradigms have yielded insights into the potential role of epigenetic mechanisms in mediating the effects of the environment on human development and also indicate that consideration of the sensitivity of laboratory animals to environmental cues may be an important factor in predicting long-term health and welfare.

Key Words: DNA methylation; epigenetic; histone modification; maternal; rodent; stress; transgenerational

Introduction

The context of early life can serve as a significant influence on development with implications for health and well-being. This context can be determined by the availability or quality of nutritional resources, exposure to toxins, nurturing social experiences, and the presence of threats or stressors in the environment. In humans, decades of longitudinal studies have suggested a link between variation in these early-life exposures and long-term risk of physical and psychiatric disease in adulthood (Tomalski and Johnson 2010). Although the effects of exposure to chemicals and/or hormones or deprivation of an essential vitamin or energy source would be predicted to have a biological effect determined by the nature of the particular exposure, it has been more challenging to discern the pathways through which nurturing, social interactions, and the experience of psychological distress are likewise capable of shaping neurobiological and behavioral outcomes associated with long-term risk. The development of animal models to study these questions has provided valuable insights into the cascade of molecular, cellular, and neurobiological changes that accompany variation in psychosocial experience.

The experimental study of the effects of social interactions and stressful life events has relied primarily on laboratory rodent models (typically involving rats and mice), although some primate work is available to provide further support of the profound effects of early-life experiences (Harlow et al. 1965; Suomi et al. 1976). The effects of prenatal stress, maternal deprivation and/or separation, variation in maternal care, juvenile social enrichment and/or isolation, and adult social stress have been explored in these models and suggest that the quality of social interactions or the experience of stress can induce neuroendocrine effects that influence social behavior, reproductive success, cognitive ability, and stress responses. Although it is clear that during prenatal and early postnatal development there is a period of enhanced sensitivity to these environmentally induced effects, there may also be plasticity beyond infancy that extends into adolescence and adulthood. An intriguing finding within these studies is the long-term effects of early- and later-life experiences on region-specific gene expression in the brain. For example, exposure to stressors during fetal development or in early infancy is associated with an upregulation of genes involved in the hypothalamic-pituitary-adrenal (HPA[1]) response to stress and a downregulation of genes that exert a dampening effect on these pathways (Ladd et al. 2004; Maccari et al. 2003). These findings have led to further exploration of the molecular mechanisms involved in gene regulation that may mediate this lasting effect.

Epigenetic mechanisms provide a dynamic strategy for changing the expression of genes and are increasingly the

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[1]Abbreviations that appear ≥3x throughout this article: Avp, vasopressin; BDNF, brain-derived neurotrohpic factor; CRF, corticotrophin-releasing factor; ERα, estrogen receptor alpha; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; LG, licking and grooming; mRNA, messenger RNA; Nr3c1, glucocorticoid receptor gene; PVN, paraventricular nucleus of the hypothalamus.

focus of studies examining the biological pathways through which early-life experiences exert long-term effects on gene expression (Curley et al. 2011). Across species, it is evident that epigenetic effects can be induced by a variety of experiences, including the quality of social interactions and exposure to stressors. Moreover, in some cases, these developmental effects can be transmitted across generations, leading to neurobiological and behavioral variation in offspring and grandoffspring (Champagne 2008; Franklin et al. 2010). In this review, we highlight research indicating a link between social and stressful experiences occurring over the lifespan and epigenetic variation and the transgenerational implications of these effects. Although motivated by interest in determining contributions to the pathophysiology of human disease, this research is drawn primarily from studies in laboratory rodents and thus can also provide insights into the conditions of life that induce persistent biological changes in laboratory animals. We discuss the implications of findings from the now rapidly advancing study of behavioral epigenetics for laboratory animal treatment and housing conditions. Manipulating the quality of these conditions may have significant long-term consequences for animal welfare and, in particular, the stress physiology and reproductive success of laboratory animals.

Exposure to Prenatal Stress: Implications for Brain Development and Behavior

The prenatal period is a time of rapid growth and development of the fetus and thus a period of heightened plasticity. As such, adverse experiences during this period have been demonstrated to induce significant effects on neurobiology, metabolism, and physiology that can persist across the lifespan (Weinstock 2008; Weinstock et al. 1988). In rodents, prenatal stress effects can be induced through a variety of manipulations of the gestational female. Physical restraint, exposure to loud noises, bright lights, manipulation of the social environment, and predator odors have been used to induce heightened levels of circulating corticosterone in pregnant female rodents and to alter offspring development (Weinstock et al. 1988). The unpredictability and timing of these exposures is a significant predictor of the impact on maternal and offspring outcomes (Matthews 2002). Generally, the more variable the stressor and the earlier the stressors occur in the pregnancy, the more profound the effect on offspring development. The mechanism of prenatal stress effects is thought to be linked to fetal exposure to stress-induced maternal corticosterone, and studies in which the adrenal glands of prenatally stressed dams are removed provide support for this hypothesis (Barbazanges et al. 1996).

Prenatal stress has been linked to both perinatal and long-term outcomes in offspring. Increased mortality rates, smaller litter weights, and reduced litter sizes have been found after gestational stress (de Catanzaro 1988; Euker and Riegle 1973; Guo et al. 1993). The reduced pup weights associated with exposure to prenatal stress may account for metabolic dysfunction and weight gain in later life (Mueller and Bale 2006). In adulthood, a distinguishing characteristic of prenatally stressed offspring is increased activity within HPA pathways. The HPA response to stress involves neuronal activation within the hypothalamus, which triggers the release of corticotrophin-releasing factor (CRF[1]) and vasopressin (Avp[1]). CRF and Avp then stimulate the release of adrenocorticotropic hormone from the pituitary. The adrenocorticotropic hormone then stimulates the release of glucocorticoids (corticosterone in rodents) from the cortex of the adrenal gland (Stratakis and Chrousos 1995). In rodents, prenatal stress has been found to exert multiple effects on the HPA response to stress, including upregulation of hypothalamic CRF and increased adrenocorticotropic hormone and corticosterone levels after exposure to a stressor (Mueller and Bale 2008). Negative-feedback regulation of the HPA axis, generally achieved through the activation of glucocorticoid receptors (GRs[1]) in the hippocampus (Sapolsky et al. 1985), is also impaired in prenatally stressed offspring, and this impairment may account for the prolonged levels of stress-induced adrenocorticotropic hormone and corticosterone found in these animals (Welberg et al. 2001).

Behaviorally, these neuroendocrine effects are associated with depressive-like and anxiety-like phenotypes that include increased immobility in a forced swim test, decreased exploration of a novel or anxiogenic environment, and altered activity levels (Weinstock 2008). Cognition is also affected in prenatally stressed offspring, likely related to some degree to the impairments in "stress coping" apparent as a consequence of prenatal stress. Reduced reproductive success among male and female offspring who experienced prenatal stress has also been demonstrated, likely mediated through reduced sexual dimorphism and alterations in responsivity to gonadal hormones (Herrenkohl 1986; Kaiser and Sachser 1998). Importantly, the degree to which this early-life manipulation will impact the brain and behavior is dependent on methodological variables, such as the type, timing, and duration of the stressor, as well as the sex, strain, and species of animal being tested.

Maternal Influences on Development

In mammals, particularly among altricial species, the postnatal period is characterized by frequent mother–infant interactions that allow for the provisioning of nutrients, warmth, and somatosensory stimulation. Disruption to these interactions has been traditionally used as a model of childhood neglect in which the impact of early-life maternal deprivation is explored. In the laboratory, the maternal separation model has been frequently used in rats and, more recently, in mice and involves prolonged periods (ranging 1–24 hours) during the early postnatal period when pups are removed from the nest and housed without contact with the dam (Lehmann et al. 2002). The immediate effect of this separation involves separation-induced elevation in corticosterone in pups (Rosenfeld et al. 1992). Separation between mother and infants can also be induced through use of a variable

foraging-demand paradigm, in which the duration of time the dam must be away from the nest to obtain sufficient amounts of food is varied from day to day (Coplan et al. 2006; Coutellier et al. 2009). Complete maternal deprivation can also be used to disrupt postnatal development and can be achieved through rearing pups artificially, with nutrients, warmth, and somatosensory stimulation provided by the experimenter and no contact between the dam and pups after birth (Gonzalez et al. 2001; West 1993). Although there are wide variations in the methodological implementation of these maternal separation and/or deprivation paradigms, the consequences for offspring development typically involve alterations in neuroendocrine systems involved in the HPA response to stress. Similar to the effects of prenatal stress, postnatal maternal separation and/or deprivation is associated with an upregulation of hypothalamic CRF, downregulation of hippocampal GR, and increased stress-induced adrenocorticotropic hormone and corticosterone levels (Lehmann and Feldon 2000; Lippmann et al. 2007). Dopamine, oxytocin, and serotonergic systems are also modulated by this early-life experience, and the behavioral consequences include increases in anxiety-like and depressive-like behaviors as well as impaired learning and memory (Curley et al. 2011). Overall, these studies suggest that disruption to the quality of mother–infant interactions during the postnatal period can lead to widespread neuroendocrine and behavioral consequences.

Although rodent models of maternal separation and deprivation have dominated research on the effects of early-life experience, within the laboratory it is also possible to examine the effects of increased maternal interactions during the postnatal period. Natural variations in maternal care are evident across multiple species and can be observed in laboratory rodents (Champagne, Francis, et al. 2003; Fairbanks 1989; Hane and Fox 2006). Studies in Long-Evans rats indicate that lactating dams display individual differences in licking and grooming (LG[1]) of pups during the postnatal period and that the experience of high levels of LG compared with low levels of LG has significant long-term effects on offspring (Meaney 2001). In adulthood, male offspring reared by high LG dams have an attenuated response to stress, are more exploratory in a novel environment, and display improved performance on cognitive tasks (Caldji, Diorio, et al. 2000; Liu et al. 1997, 2000). These behavioral effects correspond to maternal LG-associated changes in gene expression and receptor and/or protein levels, including decreased CRF in the paraventrivular nucleus of the hypothalamus (PVN[1]) and increases in GR, brain-derived neurotrophic factor (BDNF[1]), and modification in γ-aminobutyric acid pathways in the hippocampus (Caldji et al. 1998; Caldji, Francis, et al. 2000; Liu et al. 1997, 2000). Among female offspring, the experience of high levels of postnatal LG induces an upregulation of estrogen receptor alpha (ERα[1]), oxytocin receptors, and estrogen sensitivity in the medial preoptic area of the hypothalamus (Champagne et al. 2001, 2006; Champagne, Weaver, et al. 2003). Consequent to these neurobiological changes, female offspring reared by a high LG dam display elevated levels of LG toward their own offspring. Interestingly, although high LG predicts increased maternal care in offspring, the converse is true of sexual behavior. Offspring reared by high LG dams are less sexually receptive and produce fewer litters after paced mating (Cameron, Del Corpo, et al., 2008; Cameron, Fish, et al. 2008). Thus, the experience of variation in postnatal maternal LG can lead to divergent reproductive strategies in offspring.

The quality of maternal care during the postnatal period can be modulated by a variety of environmental manipulations with implications for offspring development. In rats, maternal LG can be increased by housing postweaning females in conditions of increased social and physical enrichment (e.g., group housing with toys and a complex housing design) prior to mating (Champagne and Meaney, 2007). Conversely, LG can be decreased when female rats experience postweaning social isolation or stress during pregnancy (Champagne and Meaney 2006). In contrast with maternal separation paradigms used in rodents, which lead to disruptions in mother–infant interactions, brief separations between dams and pups (approximately 5–20 minutes in duration) during the postnatal period have been found to stimulate maternal behavior and attenuate offspring stress responses (Lehmann et al. 2002; Liu et al. 1997). In mice, adult females can be induced to increase pup-directed behavior when placed in a communal nesting paradigm (Curley et al. 2009).

Although standard laboratory rearing of rodents typically consists of a single lactating dam and her pups, under naturalistic conditions, a more common rearing strategy consists of multiple females caring for pups in a communal nest (Crowcroft and Rowe 1963). Lactating females who rear offspring communally are observed to display higher levels of nursing and pup LG during the postpartum period. Offspring reared in a communal nest are found to be more exploratory in a novel environment, display higher levels of social behavior, and have increases in hippocampal and hypothalamic nerve growth factor and BDNF (Branchi, D'Andrea, Fiore et al. 2006; Branchi, D'Andrea, Sietzema, et al. 2006; Curley et al. 2009). As adults, communally reared females display higher levels of maternal care toward their offspring and elevations in oxytocin receptor density in several hypothalamic brain regions (Curley et al. 2009). The development effects of communal rearing may be most pronounced when studying high-anxiety rodent strains and will certainly be dependent on the age of the pups within the communal nest (Branchi et al. 2009).

Animal models of abusive caretaking have been developed to explore the consequences of this form of early-life adversity and suggest that disruption to the postpartum maternal environment can increase the occurrence of aggressive mother–infant interactions. In laboratory rats, this disruption can be achieved by restricting the amount of nesting materials provided to dams during the postnatal period. This manipulation can induce reductions in maternal LG and increase the incidence of dams stepping on pups, aggressive grooming, and dragging of pups by a limb (Brunson et al. 2005; Ivy et al.

2008; Raineki et al. 2010). The long-term consequences of this experience include heightened stress responsivity and impairments in spatial memory (Avishai-Eliner et al. 2001; Brunson et al. 2005; Gilles et al. 1996; Raineki et al. 2010). Even when abusive caregiving is limited to brief contact with an abusive nonbiological mother, there are persistent effects of this adverse experience, and offspring are found to have reduced BDNF messenger RNA (mRNA[1]) in the prefrontal cortex (Roth et al. 2009). Thus, the quality of maternal care, not just the quantity, can have a significant impact on development, with implications for later-life functioning.

Neurobiological Impact of Social Isolation, Enrichment, and Stress

Although plasticity is certainly evident during prenatal and postnatal periods of development, the impact of later-life experiences occurring during juvenile development or in adulthood is increasingly apparent. Sensitivity to the quality of the social environment has been demonstrated in laboratory rodents exposed to postweaning social isolation and/or enrichment or adults that experience aggressive social encounters. Juvenile social isolation in rodents induces what has been referred to as an isolation syndrome, which is characterized by increases in anxiety-like and depressive-like behaviors (Heritch et al. 1990). These isolation-induced effects can be contrasted with those induced through the experience of social and physical enrichment. Increasing social and environmental complexity can, as has been previously noted, lead to increases in maternal LG (Champagne and Meaney 2007). However, this experience also has broad effects on neurobiological and behavioral outcomes, including increased synaptic plasticity, improved cognition, and reduced anxiety-like behavior (Nithianantharajah and Hannan 2006). As is the case for communal rearing, environment enrichment–induced effects may be most evident among rodents that have increased anxiety-like behavior or impairments in cognition.

Although social interactions are a critical feature of development, it is clear that the quality of those interactions (i.e., nurturing vs. abusive) is an important consideration in predicting long-term health outcomes. In adult rodents, exposure to aggressive social interactions has been used to induce increased depressive-like and anxiety-like phenotypes. The "social defeat" model is a classic example of this approach (Martinez et al. 2002; Tamashiro et al. 2005). Within this model, territorial aggression is induced by placing an "intruder" into the cage of a "resident," typically a larger, dominant, adult male rodent (Miczek, 1979). In this paradigm, the intruder is exposed to repeated aggressive encounters and is defeated in these interactions. The consequences of social defeat for the intruder male include reduced locomotion, social avoidance, and increased HPA activity (Blanchard et al. 1993; Keeney and Hogg 1999; Meerlo et al. 1996; Raab et al. 1986). This laboratory animal model has been used to induce in rodents a depressive-like phenotype that can be effectively treated with antidepressants (Rygula et al. 2008). Social defeat can be conceptualized as a chronic stressor and induces similar phenotypes to other stressors experienced in adulthood, such as exposure to predator odor, physical restraint, and chronic variable stress (combinations of different stress-inducing environmental manipulations) (Molina et al. 1990). Overall, it is clear that susceptibility to the long-term effects of stress is not limited to early development.

Epigenetic Perspectives on the Effects of Stress and the Social Environment

Evidence for the persistent effects of early- and later-life experiences has led to increasing exploration of the molecular and cellular pathways through which these effects are achieved. The study of epigenetic mechanisms within the context of effects of social experience and stressors has provided increasing support for the hypothesis that modifications to gene expression that are observed as a consequence of these experiences may involve epigenetic pathways (Champagne 2010). In particular, variation in DNA methylation and histone modifications has been observed in offspring exposed to prenatal stress, disruption to mother–infant interactions, variation in maternal care, and adult social stress and may account for the effects of postweaning social environments on the development of juveniles. DNA methylation is typically considered a potentially enduring epigenetic modification (particularly among postmitotic cells), achieved through addition of a methyl group to cytosines within the DNA sequence, and is dependent on the enzymatic function of DNA methyltransferases (e.g., DNMT1, DNMT3a, DNMT3b) (Razin 1998; Turek-Plewa and Jagodzinski 2005; Turner 2001). In contrast, posttranslational modifications to the *N*-terminus tails of histone proteins are highly varied and dynamic and include acetylation, methylation, phosphorylation, and ubiquitination (Peterson and Laniel 2004). These epigenetic processes are not independent (i.e., DNA methylation can influence histone modification and vice versa) and collectively influence the accessibility of DNA to transcription factors and RNA polymerase. The consequence of an epigenetic modification for gene expression will be dependent on the location and nature of the modification and the recruitment of cofactors, although DNA methylation is typically associated with reduced transcription and histone acetylation is typically associated with increased gene expression (Figure 1). Emerging evidence indicating the plasticity and stability of epigenetic processes has contributed significantly to our understanding of the dynamic yet stable changes in the brain that are apparent in response to environmental experiences. Here we highlight research in which an epigenetic perspective has been applied to rodent models of social modulation and response to stress.

Epigenetic Impact of Prenatal Stress

Chronic variable stress experienced by gestational females has been demonstrated to induce a long-term impact on HPA pathways, including altered gene expression within the hypothalamus. In mice, stress during the 1st week of pregnancy has been

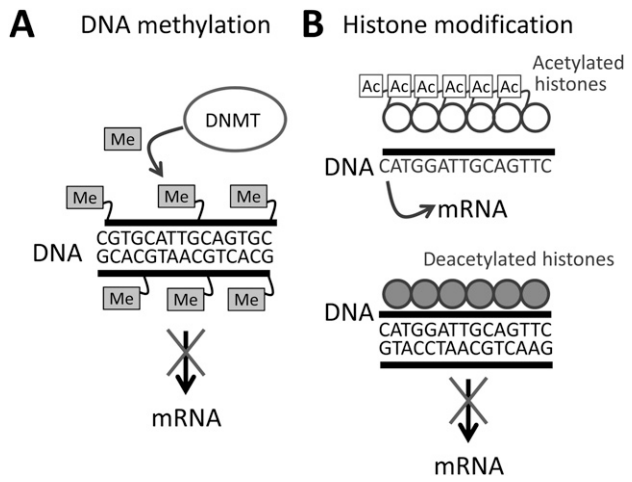

Figure 1 Illustration of the processes of DNA methylation and histone modification. (A) DNA methylation is a process in which methyl chemicals (Me) are added to cytosines in the DNA sequence by the enzyme DNA methyltransferases (DNMTs). Methylated DNA is highly compact, and DNA methylation typically leads to reduced gene expression or gene silencing. (B) The addition of an acetyl chemical (Ac) to histone proteins can loosen the interactions between histones and DNA and increase the level of gene transcription (top). In contrast, deacetylated histones cluster closely to the DNA and suppress gene expression (bottom). mRNA, messenger RNA.

found to induce significant impairments in male offspring (Mueller and Bale 2008). Among male pups born to a stressed dam, CRF gene expression is increased and GR gene expression is decreased in adulthood. Analysis of DNA methylation within the promoter region of the *Crf* gene in hypothalamic tissue of stressed offspring versus control offspring indicates stress-induced reduction in DNA methylation. In contrast, within the promoter region of the *Nr3c1* gene (encoding GR), prenatal stress is associated with increased DNA methylation. The direction of these epigenetic effects coincides well with the notion that increased DNA methylation leads to reduced gene expression. Although prenatal stress effects have been attributed to the direct exposure of the developing fetus to maternal glucocorticoids (Barbazanges et al. 1996), it is important to consider the placenta—the interface between maternal and fetal physiological systems—as a mediating mechanism of prenatal effects. The expression of DNMTs in the placenta of prenatally stressed mice has been examined, and elevations in DNMT1 were observed (Mueller and Bale 2008). Unlike the behavioral effects of this stress paradigm, stress-induced elevations in placental DNMT1 levels were observed in female offspring (with only a trend for an increase in males), which raises questions about the mechanisms of the sex specificity of prenatal stress.

Variation in Early Postnatal Experiences: Effects on DNA Methylation and Histone Modifications

Animal models of neglect, abuse, and variation in maternal care are increasingly incorporating analyses of epigenetic mechanisms to account for the persistent effects of these experiences. In mice, maternal separation (3 hours/day on postnatal days 1–10) has been found to increase *Avp* gene expression in the PVN, and analysis of the promoter of this gene indicates decreased DNA methylation at several cytosine nucleotides within this region (Murgatroyd et al. 2009). These epigenetic effects are apparent at 6 weeks, 3 months, and 1 year after the experience of maternal separation. Hypomethylation of the *Avp* gene associated with maternal separation was also associated with reduced levels of binding of MeCP2 (a protein that binds to methylated DNA). By means of a similar maternal separation paradigm, male offspring exposed to postnatal separation were found to have elevated levels of DNA methylation within the *Mecp2* gene and decreased methylation within the *Crf* receptor (*Crfr2*) gene (Franklin et al. 2010). Abusive behavior toward pups has been found to induce significant changes in the epigenetic regulation of BDNF. Studies of Long-Evans rats indicate that daily exposure to 30 minutes of aggressive caregiving on postnatal days 1 through 7 is associated with increased DNA methylation of the *Bdnf* promoter at postnatal days 8, 30, and 90 (Roth et al. 2009). Although a limited range of targets has been explored, these initial studies suggest that epigenetic modifications, particularly DNA methylation, are associated with early-life manipulation of the quality and frequency of contact between dams and pups.

Natural variations in LG behavior in Long-Evans rats have been demonstrated to predict variation in DNA methylation and histone modifications. Male offspring reared by high LG dams have been found to have decreased DNA methylation within the promoter region of the *Nr3c1* gene in hippocampal tissue (Weaver et al. 2004). Cross-fostering of pups between high and low LG dams has indicated that these epigenetic effects are related to the quality of postnatal care rather than prenatal or genetic factors. Histone acetylation is also increased within the differentially methylated region of the *Nr3c1* promoter, such that among offspring reared by high LG dams there are elevated levels of histone acetylation. Within the hippocampus of high LG offspring, DNA methylation within the glutamic acid decarboxylase (*Gad1*) gene, the rate-limiting enzyme in γ-aminobutyric acid synthesis, is reduced compared with offspring reared by low LG dams (Zhang et al. 2010). Histone acetylation is likewise increased at the *Gad1* promoter associated with high levels of LG. These epigenetic effects within the hippocampus may be associated with the increased levels of DNMT1 among offspring reared by low LG dams. Among female offspring, the experience of high levels of LG during the postnatal period is associated with decreased methylation within the *Esr1* gene (encoding ERα) promoter, and transcription factor binding to this region is increased in high LG offspring compared with low LG offspring (Champagne et al. 2006). Within the communal nursing model, communal care is associated with increased histone acetylation at the *Bdnf* I, IV, VI, and VII promoter regions (Branchi et al. 2011). The changes in DNA methylation and histone modification that have been linked to variation in maternal care suggest that the long-term changes in

gene expression that characterize the offspring that have received high levels of maternal care versus low levels of maternal care may be maintained by these epigenetic processes.

Epigenetic Plasticity in Adolescence and Adulthood

Although plasticity in epigenetic pathways was initially thought to be limited to the early stages of embryogenesis, it is becoming increasingly evident that experiences occurring across the lifespan are capable of inducing epigenetic variation. Moreover, the capacity to modify DNA methylation and histone tails may be a critical aspect of learning and memory from infancy to adulthood (Miller and Sweatt 2007). In the context of studies on the influence of social interactions and stressors, epigenetic variation, likewise, has been associated with changes in gene expression and phenotype during the later stages of development. Among adult mice that have a genetically induced memory impairment, 4 weeks of exposure to complex housing environments was found to be associated with increased histone acetylation in the hippocampus and cortex and improvements in memory (Fischer et al. 2007). Interestingly, these enrichment-induced effects on both histones and learning and memory could also be achieved in non-memory-impaired mice with pharmacological treatments that promote histone acetylation. Histone modifications (particularly histone methylation) at the *Bdnf* III, IV, and VI promoter regions have also been observed in mice housed in enriched environments (Kuzumaki et al. 2011).

In contrast with environmental enrichment, which has been demonstrated to increase levels of BDNF, chronic stress is associated with reductions in the expression of this gene, and there may be an epigenetic basis to these effects. In rats, immobilization stress combined with exposure to predator odor has been found to induce significant increases in hippocampal DNA methylation within the *Bdnf* gene (Roth et al. 2011). Within the social defeat model, reductions in BDNF are observed a month after exposure to the social stressor, and hippocampal histone dimethylation at the *Bdnf* promoter may account for this effect (Tsankova et al. 2006). Histone acetylation is transiently decreased and then exhibits prolonged increases among socially defeated mice, and this effect may be associated with long-term, stress-induced reductions in histone deacetylase levels (Covington et al. 2009). Similarly, in rats, increased histone acetylation has been observed for up to 24 hours after the experience of repeated social defeat (Hollis et al. 2010). Moreover, the behavioral consequences of social defeat, such as decreased social behavior, can be reversed pharmacologically with a drug that inhibits histone deacetylases (Covington et al. 2009). Interestingly, although social defeat has been found to induce long-term effects, a percentage of mice display resilience to this stressor. In a recent study, stress-susceptible mice were found to have increased levels of CRF mRNA in the PVN and decreased DNA methylation within the *Crf* gene (Elliott et al. 2010). In contrast, stress-resilient mice were found to have no changes in CRF mRNA or DNA methylation of this gene. Differential susceptibility to the effects of stress are an important consideration within these studies, and there is increasing support for strain- or genotype-specific epigenetic effects as a consequence of stress (Uchida et al. 2011).

Transgenerational Impact of the Social Environment and Stress

In the previous sections, the persistent epigenetic effects of environmental experiences were illustrated. These effects appear to play a critical role in shaping neurobiological and behavioral outcomes. However, it may also be the case that these environmentally induced effects can persist across generations. Transgenerational continuity in maternal behavior may be one mechanism through which this transmission occurs (Champagne 2008). In rodents, there is evidence that abusive caregiving and variation in maternal LG can shift the development of female offspring such that these maternal traits are also observed in both offspring and grand-offspring. Maternal LG has been demonstrated to alter the DNA methylation and expression of *Esr1* in the medial preoptic area of the hypothalamus of female offspring (Champagne et al. 2006). These effects emerge during the postnatal period and then persist into adulthood. In late gestation, levels of ERα play a critical role in determining the responsiveness of females to circulating estrogens, and this responsiveness predicts the quality and quantity of postnatal mother–infant interactions. 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 2008; Champagne and Meaney, 2007). A similar continuity of behavior has been observed across species in studies of infant abuse. In rats, the transgenerational continuity of abuse may be related to variation in DNA methylation and expression of *Bdnf* in the prefrontal cortex (Roth et al. 2009). Females that experience abuse in infancy have decreased *Bdnf* expression and increased *Bdnf* IV promoter DNA methylation in the prefrontal cortex, and the offspring of these females likewise have increased *Bdnf* IV promoter DNA methylation in the prefrontal cortex. Interestingly, cross-fostering studies suggest that the transmission of abuse and the epigenetic variation linked to this phenotype may be related to prenatal factors rather than postnatal experiences with the dam.

A second pathway through which perinatal epigenetic and behavioral effects may persist across generations is through direct inheritance of the epigenetic modification. Although it has long been assumed that there is complete erasure of epigenetic variation within the genome during the early stages of embryogenesis, the discovery of imprinted genes (genes that are expressed dependent on the parent from whom they are inherited) has led to increasing speculation that an epigenetic "memory" of the previous generation is

maintained within the genome and transmitted, like genes, through the germline (Weaver et al. 2009). Epigenetic inheritance of the effect of toxicological exposures has been explored and indicates the persistence of these effects across multiple generations in the patriline (Anway et al. 2005). More recently, the transgenerational effect of maternal separation has been explored in offspring exposed to separation (F1), the offspring of separated males (F2), and the grand-offspring of separated males (F3) (Franklin et al. 2010). In this paradigm, mice were exposed to unpredictable separation from the dam during the postnatal period. Depressive-like behaviors that were induced in the F1 generation offspring were found to be present in F2 and F3 generation mice. Separation-induced DNA methylation patterns were found to be present in the sperm and brains of F1 male mice and the brains of F2 males. These epigenetic effects included hypermethylation of the *Mecp2* gene and hypomethylation of the *Crfr2* gene. Thus, it would appear that epigenetic variation that is induced through the quality of the early-life environment can become encoded into the germ cells, leading to a transgenerational inheritance of the effects of stress and social experiences.

Implications for Laboratory Animal Welfare

The development of laboratory animal models in which variation in social experience and exposure to stress is used to examine epigenetic effects has led to increasing exploration of the role of these molecular pathways in humans. There is increasing evidence that prenatal stress (Oberlander et al. 2008; Radtke et al. 2011) and childhood abuse (McGowan et al. 2009) can induce epigenetic variation in humans, and thus these animal models have provided essential insights into the target genes and types of epigenetic modifications that may account for these effects. However, emerging evidence from animal models can also be applied to the better understanding of the contextual variables that may alter the traits of laboratory animals, with implications for experimental design and animal welfare.

Maternal behavior of laboratory rodents exhibits a high degree of plasticity in response to environmental cues. The life history of a female, inclusive of experiences occurring from prenatal development into adulthood, can shape the neurobiological substrates of maternal behavior, and, as we have described in previous sections, there are epigenetic mechanisms that may account for these neurobiological effects. Moreover, modulation of maternal behavior can lead to epigenetic variation in offspring that can, in some cases, persist across multiple generations. These findings highlight the importance of considering the environmental factors within a laboratory context that could contribute to variation in the quality or quantity of mother–infant interactions. Transportation of pregnant females between animal facilities, temperature and humidity conditions during the postnatal period, unpredictable noise and/or disruptions, and exposure to anxiogenic olfactory cues (e.g., predator odors) can potentially have a lasting impact on maternal behavior and offspring HPA function. When the severity of these experiences is high, a suppression of reproductive success may occur. For example, in wild populations of snowshoe hares, the persistence of predator-induced reproductive suppression can be observed across generations (Krebs et al. 1995; Sheriff et al. 2010). In the lab, the effects of adversity on breeding and mortality rates will have implications for the overall health of the colony and may severely impact ongoing study of these populations. The difficulty in replicating behavioral results across animal facilities (Crabbe et al. 1999; Wahlsten et al. 2003) may be attributed to variation in the contextual cues that either promote or inhibit the frequency of mother–infant interactions.

Although social interactions are typically thought to simulate improved health and welfare, an important consideration raised by the animal models discussed in this review is the nature of that interaction. Abusive caregiving and social defeat models illustrate the long-term epigenetic impact of agonistic social experiences, whereas communal care and juvenile social enrichment demonstrate the benefits of social contact. As is the case for maternal behavior, modulation of the impact of social experiences will likely depend on contextual factors, particularly factors that increase or decrease HPA responses. Assessment of the dominance status of individual animals placed in social housing conditions may also predict the nature of the effect of subsequent social interactions. Differential responses to social context as a function of dominance status have been illustrated in primates (Morgan et al. 2002), and the social defeat model in laboratory rodents involves an application of this effect to the study of social stress. Thus, housing conditions within the laboratory and manipulations of those conditions during experimental protocols may induce molecular changes followed by a long-term impact on social and anxiety-like behaviors.

Summary

Rodent models demonstrating the effects of prenatal stress, maternal separation and/or deprivation, maternal care, infant abuse, juvenile social environment, and adult social stress have significantly advanced our understanding of the mechanistic pathways through which environmental experiences induce long-term biobehavioral consequences. In particular, these studies provide evidence for the role of epigenetic mechanisms, such as DNA methylation and histone modifications, in mediating the effects of early- and later-life experiences. The plasticity in these mechanisms, which was once thought to be limited but has been revealed to be highly responsive to physiological and neurobiological experiences (LaPlant et al. 2010; Renthal et al. 2007), may account for the dynamic changes in neuroendocrine function that accompany variation in the quality of the social environment. In addition to being sensitive to these cues, it appears that epigenetic mechanisms can also confer the stability of

environmentally mediated effects on various outcome measures—a finding that raises challenging questions about the specific molecular pathways that mediate plasticity versus stability. Although the HPA response to stress has been the focus of these studies, stress and social experiences may have a profound impact on a diverse range of phenotypic outcomes, including cognitive ability and reproductive behavior. Moreover, there is increasing evidence for the transgenerational impact of early-life experiences and the involvement of epigenetic pathways in these effects. The development of laboratory rodent models to study epigenetic effects has been instrumental to the study of epigenetic pathways in humans and will continue to serve as a critical tool for developing hypotheses about the timing, targeting, and persistence of environmentally induced effects. These studies also highlight the importance of contextual variables to the health and welfare of laboratory animals and illustrate the molecular mechanisms through which the quality of social experiences can shape development and impact variation in behavior.

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