Neuroscience and Biobehavioral Reviews 33 (2009) 593–600

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Epigenetic mechanisms mediating the long-term effects of maternal care on development

Frances A. Champagne [a,*], James P. Curley [b]

[a] Department of Psychology, Columbia University, 406 Schermerhorn, 1190 Amsterdam Avenue, New York, NY 10025, United States
[b] Sub-Department of Animal Behaviour, University of Cambridge, UK

ARTICLE INFO

Keywords:
Mother–infant
Stress responsivity
Maternal behavior
Epigenetic
DNA methylation
Psychiatry

ABSTRACT

The long-term consequences of early environmental experiences for development have been explored extensively in animal models to better understand the mechanisms mediating risk of psychopathology in individuals exposed to childhood adversity. One common feature of these models is disruption of the mother–infant relationship which is associated with impairments in stress responsivity and maternal behavior in adult offspring. These behavioral and physiological characteristics are associated with stable changes in gene expression which emerge in infancy and are sustained into adulthood. Recent evidence suggests that these long-term effects may be mediated by epigenetic modification to the promoter regions of steroid receptor genes. In particular, DNA methylation may be critical to maternal effects on gene expression and thus generate phenotypic differentiation of offspring and, through effects on maternal behavior of offspring, mediate the transmission of these effects across generations. In this review we explore evidence for the influence of mother–infant interactions on the epigenome and consider evidence for and the implications of such epigenetic effects for human mental health.

Contents

In humans, environmental adversity occurring early in development is associated with an increased risk of both physical and psychiatric disorder in adulthood. Thus, the experience of childhood abuse and neglect has been demonstrated to increase rates of diabetes and cardiovascular disease (Baten et al., 2004; Goodwin and Stein, 2004) as well as increasing susceptibility to drug abuse (Dube et al., 2003; Anda et al., 2006), depression (Baten et al., 2004), schizophrenia (Read et al., 2005; Rutter et al., 2006) and anxiety-related disorders (Phillips et al., 2005). Though there has been progress in determining the neurobiological consequences of these experiences in humans (Teicher et al., 2006; Tarullo and Gunnar, 2006; Gunnar and Fisher, 2006), most of our understanding of these effects comes from animal models in which the relationship between variation in gene expression within the central nervous system and behavioral patterns can be explored in response to discrete environmental events. These studies provide evidence for the long-term impact of disruptions of the early environment, particularly of the mother–infant relationship or of peer–peer interactions during the juvenile period, on the neuroendocrine systems regulating stress responsivity and social behavior. Moreover, by altering social and reproductive behavior of offspring, these experiences have significant consequences for the development and behavior of subsequent generations (Champagne and Curley, 2005). One of the most intriguing questions to emerge from this research involves the mechanism mediating these effects: How are early environmental effects sustained into

* Corresponding author. Tel.: +1 212 854 2589; fax: +1 212 854 3609.
E-mail address: fac2105@columbia.edu (F.A. Champagne).

0149-7634/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2007.10.009

adulthood? Recent work suggests that the answer to this question involves understanding of epigenetic modifications of gene expression in response to environmental cues. In this review, we will explore evidence from animal models for the long-term consequences of mother–infant interactions both within and across generations, the emerging evidence for the role of epigenetics in mediating these effects, and discuss the potential relevance of these mechanisms to the pathophysiology of psychiatric disorders in humans.

1. Deprivation, separation and variation: studying maternal influence on offspring development

The profound effect of maternal deprivation on infant development that has been implied by longitudinal studies of orphans reared in institutional settings (Kaler and Freeman, 1994; Gunnar et al., 2001; Chugani et al., 2001; Roy et al., 2004) has been investigated experimentally in both primates and rodents. Harlow's artificial rearing paradigm in which infant rhesus macaques were socially isolated for periods of 3–12 months (Harlow and Suomi, 1971, 1974) illustrated that normal development requires more than simply access to adequate nutrition. Juveniles reared in this environment display marked deficits in play behavior, exhibit high levels of aggression with peers, perform poorly on learning and cognitive discrimination tasks and are behaviorally inhibited associated with a heightened fear-response to novelty (Suomi et al., 1971; Seay et al., 1964; Seay and Harlow, 1965). These behavioral patterns continue into adulthood and thus alter reproductive success, particularly of artificially reared females, who display high rates of infant abuse, neglect and infanticide (Arling and Harlow, 1967; Harlow and Suomi, 1971; Seay et al., 1964). Maternally deprived macaques that are permitted to interact with same-age same-sex peers also have an elevated hypothalamic–pituitary–adrenal (HPA) response to stress, impairments in learning and social behavior (Shannon et al., 1998; Fahlke et al., 2000) and altered serotonergic systems (Ichise et al., 2006; Shannon et al., 2005) suggesting that it is disruption of the mother–infant relationship rather than the general consequences of social isolation that contribute to these effects. Likewise, complete maternal deprivation of rodent pups during the postpartum period leads to increased HPA activity, reduces exploratory behavior in adulthood and is associated with locomotor hyperactivity, cognitive impairments and reductions in maternal care (Gonzalez and Fleming, 2002; Gonzalez et al., 2001; Lovic and Fleming, 2004) with females displaying deficits in hormonal priming of maternal behavior (Novakov and Fleming, 2005) and engaging in less maternal licking/grooming and contact toward their pups.

Investigation of the consequence of prolonged periods of separation between mother and infant has also demonstrated the long-term impact of disruptions of the maternal environment on offspring development. In primates, this has been accomplished by increasing the variability of foraging demand placed on mothers such that the time required to acquire food fluctuates randomly across days (Rosenblum and Paully, 1984). Offspring reared under these conditions exhibit behavioral inhibition, reduced social behavior associated with increased HPA activity, reduced levels of growth factors, a compromised immune response, and altered neurotransmitter metabolite levels in the anterior cingulate and medial temporal lobes (Andrews and Rosenblum, 1991, 1994; Coplan et al., 2005, 2001, 1998, 2000; Rosenblum et al., 2001). In addition to creating prolonged maternal separation, variable foraging demand has been show to reduce the maternal responsivity of mothers when they are in contact with offspring (Rosenblum and Paully, 1984) suggesting that these effects may be mediated by changes in the quality rather than the simply the quantity of care received. Similar effects have been demonstrated in rodents, either by imposing variable foraging demand (Bredy et al., 2007) or by inducing forced periods of physical separation between mother and pups (Lehmann and Feldon, 2000). The maternal separation paradigm, involving hours of daily mother–infant separation has both short-and long-term effects on the responsivity of the HPA axis (Lehmann and Feldon, 2000; Plotsky and Meaney, 1993; Plotsky et al., 2005; Rosenfeld et al., 1992) and leads to a cascade of behavioral and neurobiological changes though the consistency and direction of these changes has been debated (Pryce and Feldon, 2003; Macri and Wurbel, 2006). These manipulations are typically associated with decreased exploration, behavioral inhibition, increased corticosterone releasing hormone (CRH) mRNA in the paraventricular nucleus (PVN), increased corticosterone response to stress and decreased levels of hippocampal glucocorticoid receptor (GR) mRNA (Plotsky and Meaney, 1993; Meaney et al., 1996; Lehmann et al., 1999). Cognitive ability is also modified by this experience as indicated by increased performance latencies on the Morris Water Maze, decreased hippocampal synaptophysin levels and increased apoptosis (Lehmann et al., 2002). Females separated from their mothers for 5 h per day during the pre-weaning period show reduced levels of maternal licking/grooming toward their offspring (Fleming et al., 2002) suggesting reproductive consequences of this disruption to the early environment.

A third approach to studying the influence mother–infant interactions on neurobiology and behavior comes from the study of individual differences in maternal care. Amongst humans, primates and rodents, females display considerable variation in the quantity and quality of care they provide for offspring (Fairbanks, 1989; Berman, 1990; Fleming et al., 1997; Champagne et al., 2003a) and this variability can be used in a longitudinal design to predict phenotype in adulthood. Maternal behavior of vervet monkeys living in undisturbed social groups has been found to vary along two-dimensions; (1) protectiveness, which consists of high levels of "contact-seeking" by the mother and (2) rejection, which is associated with frequent attempts to break contact or to leave the infant (Fairbanks and McGuire, 1988). Behavioral response to novelty in 1- and 2-year-old infants is associated with variation in maternal protectiveness, with increased latency to enter a novel environment associated with having a more protective mother (Fairbanks and McGuire, 1988). Individual differences in abusive behavior amongst postpartum rhesus and pigtail macaques are also associated with behavioral and neurobiological characteristics of offspring (Maestripieri et al., 1999, 2005, 1997). Infant abuse occurring during the first 3 months is associated with an increased frequency of screaming, yawning, and other indices of infant distress at 4–6 months (Maestripieri et al., 2005). The high levels of maternal rejection exhibited by these females is correlated with increased solitary play and decreased CSF levels of 5-HIAA of their offspring, implicating the role of serotonergic activity in mediating these effects (Maestripieri et al., 2005, 2006). Cross-fostering of infants from abusive to non-abusive mothers indicates that these effects are indeed mediated by the quality of care received rather than a genetic transmission (Maestripieri, 2005).

Postpartum maternal care exhibited by rodents has been found to vary significantly between individuals and display the same level of stability over time illustrated by human and primate females. During the first week postpartum, lactating female rats and mice display high levels of nursing/contact with pups accompanied by bouts of licking/grooming with the frequency of these behaviors varying both within and between strains (Shoji and Kato, 2006; Champagne et al., 2003a). Strain differences in adult blood pressure between offspring of spontaneously hypertensive (SHR) and Wistar Kyoto (WKY) rats have been correlated to