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Social influences on neurobiology and behavior: Epigenetic effects during development

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Summary The quality of the social environment can have profound influences on the development and activity of neural systems with implications for numerous behavioral and physiological responses, including the expression of emotionality. Though social experiences occurring early in development may be particularly influential on the developing brain, there is continued plasticity within these neural circuits amongst juveniles and into early adulthood. In this review, we explore the evidence derived from studies in rodents which illustrates the social modulation during development of neural systems, with a particular emphasis on those systems in which a long-term effect is observed. One possible explanation for the persistence of dynamic changes in these systems in response to the environment is the involvement of epigenetic mechanisms, and here we discuss recent studies which support the role of these mechanisms in mediating the link between social experiences, gene expression, neurobiological changes, and behavioral variation. This literature raises critical questions about the interaction between neural systems, the concordance between neural and behavioral changes, sexual dimorphism in effects, the importance of considering individual differences in response to the social environment, and the potential of an epigenetic perspective in advancing our understanding of the pathways leading to variations in mental health.

1. Introduction

Though our understanding of the neurobiology of mood disorders has advanced through the use of modern imaging and pharmacological techniques, there are still significant gaps in our knowledge regarding the origins of increased susceptibility to psychopathology. Epidemiological studies of the impact of early-life abuse and neglect suggest that the quality of early social experiences is associated with an altered risk of depression and anxiety in adulthood (Batten et al., 2004; Bradley et al., 2008; Neigh et al., 2009; Stirling and Amaya-Jackson, 2008). These studies suggest that the quality of the early-life social environment may lead to a cascade of neurobiological changes with implications for numerous behavioral outcomes, including enhanced emotionality. Further support for the role of the social environment in shaping the brain comes from experimental studies in rodents, where targeted manipulation of postnatal mother—infant interactions has been demonstrated to induce long-term changes in behavior associated with effects on a wide range of neural systems. These results suggest that plasticity in brain development in response to the

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early social environment may account for the vulnerability that exists in individuals when they are exposed to disruptions in the quality of that environment. Interestingly, the social influence on risk and resilience may not be limited to these early developmental time-points. Here we will highlight literature from recent experimental studies in rodents illustrating how social experiences occurring during postnatal and juvenile periods, and in early adulthood, can shape neural systems that in some cases may lead to altered emotionality (*i.e.* behavioral and physiological responses to stress, novelty, *etc.*). Though questions still remain regarding the time-course, specificity, and behavioral consequences of these changes, there is emerging evidence that epigenetic regulation of gene expression may be a critical feature of this neural plasticity. We will explore the recent evidence supporting an epigenetic perspective on the origins of individual differences in behavior and identify critical issues raised by these studies that can guide future studies on the role of the social environment in shaping brain development.

2. Social influence on the developing brain

Studies of the impact of social experiences on development have examined a wide range of physiological, metabolic, immune, neurobiological, and behavioral outcomes. Within the framework of neurobiological consequences, there has been exploration of structural neuroanatomical changes, cell death/survival, synaptic plasticity, and region-specific variation in neurotransmitter and receptor levels/gene expression, all of which may lead to behavioral phenotypes associated with increased or decreased emotionality. Here we will highlight evidence from rodent studies (a discussion of studies in humans is reviewed elsewhere in this issue) for the influence of social experiences occurring during postnatal, juvenile, and in some cases, early adulthood on several neural systems, including monoamine (with a focus of serotonin and dopamine), GABAergic, glutamatergic, vasopressin, oxytocin, estrogen sensitivity and estrogen receptors, and receptors for corticotrophin releasing hormone (CRH) and glucocorticoids. Though the neurobiological substrates of emotionality spans beyond these systems as do the effects of the social environment, discussion of these select targets illustrates the wide range of social experiences that can shape the brain and explores neurotransmitter/receptor systems that may be regulated *via* epigenetic modifications (as will be discussed in subsequent sections).

2.1. Dopamine and serotonin

In rodents, social experiences during postnatal development are dominated by mother—infant interactions, with dams spending the majority of the first week post partum in contact with litters (Champagne et al., 2003). Long-term developmental consequences of variations in this early social environment have been most commonly addressed through utilization during the first few weeks of life of the maternal separation (pups are removed from the dam daily for at least 1 h per day) and 'handling' (pups are removed from the dam for 15 min per day — also known as brief maternal separations or maternal augmentation) paradigms (see Table 1 for a summary of paradigms). Prolonged periods of maternal separation during the post partum period are typically associated with increased anxiety-like and depression-like behavior, while brief separations stimulate interactions between mother and pups (Boccia and Pedersen, 2001; Liu et al., 1997) leading to an attenuation of the stress response and decreases in anxiety-like and depression-like behavior, especially in male offspring. Several studies have demonstrated that these behavioral changes are due in part to long-term modifications of the dopaminergic system. For instance, male and female rat pups who are isolated from both mother and sibling contact daily for 1 h from postnatal (PN) days 2 to 9 were found to have cocaine-induced elevations in dopamine (DA) within the ventral striatum at PN10, with both males and females showing 100—300% DA increases compared to controls (Kosten et al., 2003). Elevated levels of DA in the nucleus accumbens (NAc) also persist into adulthood (Hall et al., 1999; McCormick et al., 2002). Similarly, increased DA and decreased DOPAC (a dopamine metabolite) in adult mice have been documented in the striatum in offspring separated from their dams for 5 h/day from PN days 2 to 6 compared to handled mice (Ognibene et al., 2008). Moreover, compared to individuals who were handled (15 min/day) during the first 2 weeks of life, adults who are separated from their mother daily for 3 h per day are more hyperactive in a novel environment and exhibit a dose-dependent higher sensitivity to cocaine-induced locomotor activity (Brake et al., 2004). These behavioral changes are associated with increased dopamine D1 receptor binding levels in the NAc core and caudate putamen (CP), increased D3 receptor mRNA in the NAc shell, and a trend for increased D2 receptor levels in the NAc core. Additionally, dopamine transporter (DAT—which uptakes DA from the synapse) levels are significantly decreased in maternally separated animals in the NAc core and CP but not the ventral tegmental area (VTA) or prefrontal cortex (PFC) (Brake et al., 2004). Similar consequences to DA activity have been observed as a function of low levels of maternal care experienced in infancy, such that offspring of low licking/grooming (LG) dams have elevated stress-induced dopamine release within the medial prefrontal cortex (mPFC) (Zhang et al., 2005). Hence, these studies indicate that prolonged maternal separation and reduced maternal care is associated with long-term sensitization of dopaminergic activity *via* alterations of site-specific dopamine, dopamine receptor and dopamine transporter gene expression that may contribute to the observed increases in anxiety-like and depression-like behavior in these offspring.

Early-life maternal separation also significantly alters serotonin (5-HT) signaling and metabolism in adulthood. Maternally separated rat pups (3 h of separation twice daily from PN days 1 to 13) have decreased 5-HIAA and HVA (5-HT metabolites) levels in the amygdala and increased stress-induced 5-HT and 5-HIAA levels in the dorsal raphe nucleus (DRn), cingulate cortex, and NAc at 4 months of age (Arborelius and Eklund, 2007). Similar increases in 5-HT levels are found in the PFC, hippocampus, and striatum of mice that are maternally separated for 5 h daily during the first week post partum (Ognibene et al., 2008). Significantly, postnatal maternal separation not only affects 5-HT levels in the brain, but also modulates long-term changes in the functioning of 5-HT receptors and the serotonin transporter (5-HTT — which removes 5-HT from synapses). For instance, the maternal separation of rats (with separation carried out for 6 h sessions