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Editorial

Behavioral epigenetics: A new frontier in the study of hormones and behavior

The field of behavioral epigenetics has grown at a rapid pace. A key feature of this new approach is the identification of specific molecular modifications which can dynamically alter the expression of genes and lead to short- and long-term effects on neurobiology, physiology, and behavior. Though the molecular mechanisms that can exert these effects are many and diverse, much of the emphasis in the past 5 years has been on studies of DNA methylation, post-translational histone modifications, and more recently, the recruitment of proteins which bind to methylated DNA. There are several important foundations of this new field which have broad relevance to the study of hormones and behavior; including chromatin biology, the molecular basis of learning and memory, genomic effects of steroid receptors, and developmental psychology. These foundations have been instrumental in the study of neurogenesis and brain development, the processes underlying habituation, extinction, and other learning phenomenon, hormonal influences on steroid receptor activation or repression, and the influence of early-life mother–infant interactions on offspring behavior. Exploring the role of epigenetic mechanisms within these contexts has lead to a revolution in thinking that has inspired the integration of new approaches and new techniques with the field of behavioral neuroendocrinology. In this special issue, we highlight authors who have become leaders in this emerging field. The challenge that continues is in establishing the link between epigenetic effects, the experience of environmental variation, and the variety of phenotypic outcomes that emerge. In this special issue of *Hormones & Behavior* on the theme of *Behavioral Epigenetics*, the diverse and innovative approaches to addressing this challenge are highlighted.

Interplay between genes and the environment is critical within the process of development and there is emerging evidence that environmental factors may exert neurobiological and behavioral effects through epigenetic changes. “Environment” in this context can be used in the very broad sense and include hormonal, social, nutritional, and toxicological exposures occurring prenatally, postnatally, or in adulthood. During prenatal development, adverse experiences are associated with a heightened risk of physical and psychiatric dysfunction. The article by *Harris & Seckl* provides an overview of the literature illustrating “prenatal programming” of the hypothalamic-pituitary-adrenal (HPA) response to stress and the role of long-term changes in gene expression in linking prenatal experiences to later life variations in stress sensitivity. Epigenetic regulation of genes within HPA pathways, such as glucocorticoid receptors (GR) and the 11β-hydroxysteroid dehydrogenases, may be a potential mechanism through which these effects are established. Prenatal experiences of variation in maternal diet and/or stress may also induce transgenerational effects that persist in F2 and F3 generation offspring. *Dunn, Morgan, & Bale* review the evidence for the emergence of epigenetic variation in offspring as a function of prenatal exposure to adversity and highlight the sex-specificity and potential mechanisms through which this generational transmission may occur. When considering prenatal experiences, the placenta may be a central target of epigenetic dysregulation, with implications for subsequent alterations in growth and brain development. Prenatal exposure to endocrine disrupting chemicals such as bisphenol-A (BPA), which are ubiquitously present in the environment, can have a significant impact on neurodevelopmental and disease outcomes. In the review article by *Wolstenholme, Rissman, & Connelly*, the potential mechanisms of BPA action and the impact of BPA on DNA methylation are discussed. As outlined in this review, studies in laboratory rodents suggest that there are consequences of prenatal BPA exposure for anxiety-like responses, learning, and reproductive behaviors with particular effects on sexual dimorphism. The public health implications of this research is dramatic, particularly considering the high levels of exposure to BPA in humans and the persistence of the BPA-induced epigenetic changes across the lifespan and potentially to future generations. Evidence for a transgenerational impact of paternal exposure to drugs and toxins, particularly when exposure occurs prenatally, has been observed in both epidemiological and laboratory based studies. Increasing understanding of the plasticity of epigenetic mechanisms and potential heritability of epigenetic marks has lead to increasing exploration of the role of epigenetics in explaining these paternal effects. The article by *Curley, Mashoodh, & Champagne*, reviews evidence for paternal transgenerational effects on disease risk and behavior and examines the epigenetic pathways through which these effects may occur. An important issue raised by this article is the mediating or moderating role of maternal and offspring phenotype in studies of paternal effects.

Epigenetic plasticity can also be observed beyond the prenatal period. During the period of early postnatal development, the “programming” effect of experience continues and in the article by *Roth & Sweatt*, the effects of neonatal adversity on brain-derived neurotrophic factor (BDNF) are explored. BDNF plays an important role in brain development and plasticity and, as highlighted by this review, variations in DNA methylation within the BDNF promoter may account for the long-term effects of postnatal experiences. Drugs of abuse have been demonstrated to exert a profound influence on behavior, even when exposure occurs in adulthood. A critical question within the study of substance abuse involves the molecular and neurobiological changes through which addiction develops in individuals exposed to psychostimulants. In the article by *LaPlant & Nestler*, the cascade of histone modifications within the brain associated with cocaine administration is described. These findings may have implications for a broad range of experience-driven changes in motivated behavior in adult organisms.

Though environmental experiences can certainly induce long-term changes in the neuroendocrine system and behavioral phenotypes, there are typically individual differences in the degree of

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change or in the mechanisms through which these changes occur. Individual differences in epigenetic responses have also been documented in the growing behavioral epigenetics literature and the paper by *Hollis, Duclot, Gunjan & Kabbaj*, demonstrates how amongst individuals selected for level of activity/exploration (high vs. low responders) there are group differences in histone changes measured basally and associated with the experience of social defeat. These findings may have implications for our understanding of the molecular and neurobiological pathways underlying risk or resilience to environmental exposures.

The hormonal environment of an organism, occurring during development and in adulthood, can lead to variations in behavior, sexual dimorphism, and disease risk. Epigenetic mechanisms may be influenced by hormone levels during the perinatal period and serve as a mechanism linking the organizational effects of hormones to the long-term sex differences in neuroanatomy and behavior that are observed. In the article by *Nugent, Schwarz, & McCarthy*, the developmental time course of sex differences in estrogen and progesterone receptor DNA methylation are discussed with a particular emphasis on the role of gonadal hormones in inducing this epigenetic shift. Likewise, in the article by *Imamura*, the molecular pathways through which estrogen receptor alpha (ERα) and androgen receptor (AR) are altered by gonadal hormones and the implications of these effects for masculinization of the brain are explored. Across different cell types and species, there is emerging evidence for epigenetic modifications responsive to changing hormonal exposures. In the review by *Wilson, Westberry, & Trout*, the theme of sexual dimorphism in DNA methylation patterns is explored further, with a particular focus on regulation of ERα by DNA methylation in the cortex of males and females. Cortical levels of estradiol can be neuroprotective and this effect is dependent on levels of ERα. Following stroke, there is a rapid decrease in DNA methylation of the ERα gene promotor of females but not males, and this sex difference may account for the reduced cell death observed in the cortex of females following ischemic injury. Thus, understanding the developmental origins of sex differences in the epigenome may identify novel approaches to preventing subsequent brain damage.

Though DNA methylation certainly plays a role in sexual differentiation, this epigenetic modification is one of many steps that ultimately lead to variations in gene expression. The article by *Auger, Jessen, & Edelmann* provides a review of the emerging evidence for the role of the methyl-binding protein MeCP2 and co-repressor complexes for driving sex differences in social play behavior. The hormonal and environmental sensitivity of each element of the molecular pathway linking DNA methylation to altered gene expression provides a route for complex behavioral outcomes. The phenotypic consequences of MeCP2 are further explored in the article by *Na & Monteggia*, with emphasis on the impact of this methyl-binding protein on synaptic functioning within the CNS. Mutations of the MeCP2 gene are largely responsible for the neurodevelopmental abnormalities associated with Rett syndrome and there is increasing evidence for the role of MeCP2 in neuronal morphology, connectivity, and plasticity.

One of the first examples of epigenetic regulation of gene expression is genomic imprinting. Imprinted genes are characterized by mono-allelic expression based on the parent-of-origin and illustrate the complexities of epigenetic regulation from both a genomic and non-genomic perspective. The review by *Swaney* discusses the behavioral and neuroendocrine consequence of imprinted genes, particularly in the context of reproduction, and the theories which have been proposed regarding the evolution of this mechanism of gene regulation. The discussion of genomic imprinting continues in the article by *Kopsida, Mikaelsson, & Davies*, who highlight the implications of disruption of imprinting for the risk of neuropsychiatric abnormality. The occurrence of X-chromosome linked imprinted genes is likely to be particularly relevant to our understanding of sex-differences in neuropsychiatric illness and further study of the function of these genes may yield important new insights. The theme of epigenetics and the X-chromosome is continued in the article by *Xu & Andreassi* which discusses the process and implications of histone methylation/demethylation. Interestingly, several histone demethylase genes are located on the X-chromosome and because they escape X inactivation they may account for sexual dimorphism in gene expression and development as well as the behavioral phenotypes observed in the four core genotypes.

Advances in our understanding of the role of epigenetic mechanisms in shaping behavioral variation have implications for theoretical frameworks within the study of developmental plasticity across the lifespan. In the article by *Crews*, several issues regarding the classification and study of epigenetics and behavior are discussed. In particular, the distinction between context-dependent and germline-dependent epigenetics is explored and the interactive nature of genetics, epigenetics, and environmental experiences occurring at various stages of development becomes evident.

Though studies of epigenetic mechanisms of gene regulation and their consequences have been primarily conducted in laboratory rodents, another perspective on the link between epigenetic variation and phenotype can be achieved in studies of honey bees. The review by *Miklos & Maleszka*, describes recent studies of DNA methylation within the honey bee genome and the developmental trajectories leading to caste differences that can be achieved through alteration of the levels of *de novo* DNA methyltransferases. Expanding the study of epigenetics to a greater diversity of species is certainly an approach that will allow the field of behavioral epigenetics to evolve.

With evolving fields comes evolving methodologies and technology. In the case of epigenetic and epigenomic analysis, there has been a rapid advancement in the techniques with which DNA methylation and histone modifications are measured. In the final article of this issue, *Stolzenberg, Grant* & *Bekiranov,* describe a variety of techniques available to map the location and frequency of methylated cytosines and provide an overview of the use of chromatin immunoprecipitation assays (ChIP) to identify specific histone modifications. DNA sequencing is a key element within these methodologies and this article explores the complexities of current sequencing approaches as well as the tools available to analyze and interpret the vast amounts of data that are generated. Understanding these techniques is a vital step in moving forward in the field of behavioral epigenetics and exploring the role of DNA methylation and post-translational histone modifications in novel behavioral and hormonal contexts.

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