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Epigenetics related to some behavioral disorders (Review Article)

Ishtar Imad

Abstract:

The cause behind behavioral disorders varies from environmental to lifestyle to interaction patterns. A new concept emerges with the implication of epigenetics and maltreatment on the behavioral biology of infants. For example, experiencing adversities during periods of maximal sensitivity to the environment, such as prenatal life, infancy, and early adolescence, may introduce lasting epigenetic marks in genes that affect maturational processes in the brain, thus favoring the emergence of dysfunctional behaviors, including exaggerating aggression in adulthood. All these facts lead me to conclude the unexpected effect of epigenetics on the development and formation of behavior depending on different inherited factors.

Keywords: Behavior, Epigenetics, infant, maltreatment, hereditary, offspring, DNA.

Review

Behavioral genetics and epigenetics shed new light on the fine interaction between genes and environment by providing a novel tool to understand the molecular events that underlie aggression. Overall, the findings from these studies carry essential implications not only for neuroscience but also for social sciences, including ethics, philosophy, and law.3

How does Descriptive Psychology (DP) address this question regarding one of psychology's most fundamental concepts, that of "behavior?" It begins by noting that all behavior is describable as an attempt on the part of an individual to bring about some state of affairs -- either to effect a change from one state of affairs to another, or to maintain a currently existing one. Jill combs her hair, drives to work, reads a book, plays her favorite song over again, and mentally calculates how many bottles of wine she will need for her upcoming party. In all of these behaviors, whether they involve overt physical movements or not, she is attempting to bring about some state of affairs -- to change her unkempt hair to a more presentable state, to continue her enjoyment of the song, to go from being unclear to being clear about how many bottles of wine she must purchase, and so forth. (NB: It may be noted that this characterization of behavior excludes phenomena such as patellar reflex movements and includes ones such as performing mental calculations.) Going beyond this general characterization, the DP position maintains that human behavior is an empirical phenomenon that is not amenable to either of psychology's traditional means of capturing the meaning of concepts, those of classical definition or of prototype analysis. It is instead amenable to a third procedure, that of parametric analysis. While little used within psychology, parametric analysis is a standard conceptual tool in other sciences (especially physics) and in mathematics. It may be illustrated briefly by recalling the familiar example of an empirical

phenomenon traditionally captured in this way, that of color. The concept “color” is neither formally definable nor well suited to prototype analysis. However, the empirical domain of color -- the set that has as its members all colors and possible colors -- can be captured completely for scientific (and other) purposes by employing a system that specifies values for three parameters: hue, saturation, and brightness.1

DNA is the unchanging template of heredity, is identical in all the cells and tissues of the body and is the sole agent of inheritance. Rather than being an unchanging template, DNA appears subject to a good deal of environmentally induced change. Instead of identical DNA in all the cells of the body, somatic mosaicism appears to be the normal human condition. And DNA can no longer be considered the sole agent of inheritance. We now know that the epigenome, which regulates gene expressivity, can be inherited via the germline. These developments are particularly significant for behavior genetics for at least three reasons: First, epigenetic regulation, DNA variability, and somatic mosaicism appear to be particularly prevalent in the human brain and probably are involved in much of human behavior; second, they have important implications for the validity of heritability and gene association studies, the methodologies that largely define the discipline of behavior genetics; and third, they appear to play a critical role in development during the perinatal period and, in particular, in enabling phenotypic plasticity in offspring. 2

recent studies indicate that experiencing aversive events modulates gene expression by introducing stable changes to DNA without modifying its sequence, a mechanism known as “epigenetics”. For example, experiencing adversities during periods of maximal sensitivity to the environment, such as prenatal life, infancy and early adolescence, may introduce lasting epigenetic marks in genes that affect maturational processes in brain, thus favoring the emergence of dysfunctional behaviors, including exaggerate aggression in adulthood. The present review discusses data from recent research, both in humans and animals, concerning the epigenetic regulation of four genes belonging to the neuroendocrine, serotonergic and oxytocinergic pathways—Nuclear receptor subfamily 3-group C-member 1 (*NR3C1*), oxytocin receptor (*OXTR*), solute carrier-family 6 member 4 (*SLC6A4*) and monoamine oxidase A (*MAOA*)—and their role in modulating vulnerability to proactive and reactive aggressive behavior. 3

Aggression, throughout evolution, serves an important role in the survival of a species. Being aggressive gives the best chances for survival and reproduction. This is true for all mammalian species, including human. However, when excessive, the consequences of aggressive acts can be maladaptive.

Experiencing repeated aversive life events or protracted stress during pregnancy, especially during the first trimester of gestation, results in increased risk of physically aggressive tendencies, delinquency and conduct disorder, both in early childhood and adolescence. During the first trimester, the neuroectoderm develops and becomes the source of neural progenitor cells, as well as the foundation of the neural tube. Similar outcomes are predictable by postnatal traumas. The risk of aggressive behavior in childhood is particularly high in infants neglected during their first 2 years of life, when the brain doubles its volume, and a massive synaptogenesis occurs. Neglecting to provide early-life basic physical needs and emotional support as a parent can later lead to higher scores of aggressions in childhood,

measured by the Child Behavior Checklist. Moreover, recurrent experiences of emotional abuse or witnessing violence throughout childhood predict physical aggressive behavior in adulthood.

Prenatal stress (PS) has complex neurological, behavioral and physiological consequences for the developing offspring. The phenotype linked to PS usually lasts into adulthood and may even propagate to subsequent generations. The often-uncontrollable exposure to maternal stress and the lasting consequences emphasize the urgent need for treatment strategies that effectively reverse stress programming. Exposure to complex beneficial experiences, such as environmental enrichment (EE), is one of the most powerful therapies to promote neuroplasticity and behavioral performance at any time in life. A small number of studies have previously used EE to postnatally treat consequences of PS in the attempt to reverse deficits that were primarily induced in utero. This review discusses the available data on postnatal EE exposure in prenatally stressed individuals. The goal is to determine if EE is a suitable treatment option that reverses adverse consequences of stress programming and enhances stress resiliency. Moreover, this review discusses data with respect to relevant hypotheses including the cumulative stress and the mismatch hypotheses. The articles included in this review emphasize that EE reverses most behavioral, physiological, and neural deficits associated with PS. Differing responses may depend on the timing and variability of stress and EE, exercise, and potentially vulnerable and resilient phenotypes of PS. This study suggest that enrichment may provide effective therapy for clinical populations suffering from the effects of PS or early life trauma.4

Possible mechanisms of the effects exerted by stress (in the broad sense of the term) on the human genome and manifested in modifications of behavior are described in this review. Behavioral epigenetics opens new prospects for interpretation of the evolution of behavior induced by changes in living conditions. Epigenetic labels (imprints, methylation of DNA and/or covalent modifications of histones) appear under the influence of actual stress environmental influences, including social interactions. The appearance of such labels is not random; it is determined contextually and leads to behavioral disorders that can be transmitted through future generations. Stress phenomena of modern life, which are psychosocial in their nature, realize their effects via quite definite biological mechanisms. Epigenetic modifications are the most probable candidates for the role of relatively fast genetic mechanisms determining changes in behavior and mental health of great contingents of individuals living under contemporary conditions of ever-increasing stress loading.5

The relationship between genes and behavior is reconsidered in terms of epigenetic mechanisms acting after birth and prenatally, as traditionally held. Behavioral epigenetics shows that our behavior could have long-term effects on the regulation of the genome function. In addition, epigenetic mechanisms would be related to psychopathology, as in the case of schizophrenia. In the latter case, it would be especially relevant to consider epigenetic factors such as life adversities (trauma, disorganized attachment, etc.) as related to its clinical manifestations, rather than genetic factors. Moreover, epigenetics implies overcoming classical dualist dichotomies such as nature-nurture, genotype-phenotype, or pathogenesis-pathoplasty6. Paradigm-shifting research in the past decade has provided evidence that epigenetics serve as candidate pathways by which experiences can leave their mark on genes to drive sustained changes in behavior. Though we still lack a complete understanding of the

cause-and-effect role of epigenetic mechanisms in health outcomes and disease, evidence shows that epigenetic alterations are biological consequences of early-life and later-life environmental input. Furthermore, the evidence at hand suggests these alterations likely play a role in the development of and enduring nature of psychopathology7.

Maternal care also promotes epigenetic changes of additional genes and epicenters of stress regulation, cognitive control, addiction, and maternal behavior. For example, some of our work has shown that infant rats repeatedly exposed to an adverse caregiving environment exhibit significant methylation of Brain-derived neurotrophic factor (Bdnf) DNA in their prefrontal cortex that either persists throughout (DNA associated with exon IX) or evolves (exon IV) during development8. Aberrant caregiving behaviors were elicited by the combination of environmental novelty and resource deprivation (lack of nesting material), factors in our hands, and those of others capable of producing abnormal caregiving behaviors that include a high proportion of rough handling, pup stepping on and dragging, active avoidance (neglect), and decreased LG of pups 8&9.

Abuse during early life, especially from the caregiver, increases vulnerability to develop later-life psychopathologies such as depression. Although signs of depression are typically not expressed until later life, signs of dysfunctional social behavior have been found earlier. How infant abuse alters the trajectory of brain development to produce pathways to pathology is not entirely understood. Here we address this question using two different but complementary rat models of early-life abuse from postnatal day 8 (P8) to P12: a naturalistic paradigm, where the mother is provided with insufficient bedding for nest building; and a more controlled paradigm, where infants undergo classical olfactory conditioning. Amygdala neural assessment (c-Fos), as well as social behaviour and forced swim tests, were performed at preweaning (P20) and adolescence (P45). Our results show that both models of early-life abuse induce deficits in social behavior, even during the preweaning period; however, depressive-like behaviors were observed only during adolescence. Adolescent depressive-like behavior corresponds with an increase in amygdala neural activity in response to the forced swim test. A causal relationship between the amygdala and depressive-like behavior was suggested through temporary amygdala deactivation (muscimol infusions), which rescued the depressive-like behavior in the forced swim test. Our results indicate that social behavior deficits in infancy could serve as an early marker for later psychopathology. Moreover, the implication of the amygdala in the ontogeny of depressive-like behaviors in infant abused animals is an essential step toward understanding the underlying mechanisms of later-life mental disease associated with early-life abuse10.

Odor-maternal maltreatment pairings within a seminatural setting and odor-shock pairings both resulted in paradoxical odor preferences. Learning-induced gene expression was altered in the olfactory bulb and anterior piriform cortex (part of olfactory cortex) but not the amygdala. Infants appear to use a unique brain circuit that optimizes learned odor preferences necessary for attachment. A fuller understanding of infant brain function may provide insight into why early maltreatment affects psychiatric well-being. 11

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