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Review

Eating disorders, gene-environment interactions and the epigenome: Roles of stress exposures and nutritional status

Howard Steiger *, Lea Thaler

Eating Disorders Program, Douglas Institute, Psychiatry Department, McGill University, Canada

HIGHLIGHTS

- We review literature bearing upon the putative link between epigenetic factors and ED development.
- We propose that epigenetic processes mediate the action of ED-relevant environmental exposures.
- We comment on the clinical relevance of an epigenetically informed model of ED etiology.

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ABSTRACT

Epigenetic mechanisms are believed to link environmental exposures to gene expression, and in so doing, to provide a physical basis for the activation, by life experiences, of mental-health problems. This paper provides a background to the hypothesis that epigenetic mechanisms link life stresses (perinatal, childhood and adult) and effects of malnutrition to the eating disorders (EDs). The paper reviews literature bearing upon the putative link between epigenetic factors and ED development, and examines ways in which epigenetic alterations could account for risk of eating disturbances and commonly associated behavioral and emotional problems. Ultimately, we propose that epigenetic processes provide an intriguing (although hypothetical) biological "platform" upon which ED-relevant effects of perinatal insults, life stresses, and consequences of malnutrition may be registered, and argue that an epigenetically informed understanding may explain why EDs are triggered and maintained by excessive caloric restraint, why they coincide so frequently with mood- and impulse-regulation problems, and why they tend to become increasingly entrenched over time. Finally, we comment on the clinical relevance and implications of an epigenetically informed model of ED etiology.

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1. Introduction

Eating disorders (EDs) are characterized by intense preoccupations with eating, weight and body image and such maladaptive eating practices as excessive caloric restraint, binge eating, and compensatory

* Corresponding author at: Eating Disorders Program, Douglas institute, 6875 LaSalle Blvd, Verdun, Quebec H4H 1R3, Canada.
E-mail address: stehow@douglas.mcgill.ca (H. Steiger).

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gestures (such as self-induced vomiting or compulsive exercise). Main variants include Anorexia Nervosa (AN), Bulimia Nervosa (BN) and Binge Eating Disorder (BED). AN is characterized by intense restriction of energy intake (leading to a markedly low body weight), or persistent behavior to avoid weight gain (even though already at low weight). The syndrome includes two variants: AN-Restricting type (AN-R), in which there is restriction of food intake but no binge-eating or purging, and AN-Binge eating/Purging (AN-B/P) type, in which (as the label implies) regular binge or purge episodes occur. BN is similarly characterized by binge eating followed by compensatory efforts (e.g., self-induced vomiting, laxative misuse, intensive exercise, or fasting), but in individuals with relatively normal (or above-normal) weight. BED, like BN, is characterized by recurrent eating binges, but in the absence of compensatory behaviors (such as vomiting, exercise or fasting), so that the syndrome is commonly associated with (or leads to) obesity. The present review concerns a relatively new literature associating epigenetic processes with AN and BN. Data relevant to epigenetics in BED are insufficient to support an adequate review, and are not treated here.

Anyone who has had an ED (or who has been close to someone who has had an ED) knows–EDs are not solely "about" problematic eating. People affected by EDs show diverse concurrent psychiatric symptoms, including problems with mood (e.g., depression or mood lability) and anxiety (e.g., obsessive-compulsiveness, generalized anxiety, panic, social phobias). In addition, people suffering purely restrictive forms of ED (as exemplified by AN in its Restrictive form) display consistent propensities towards perfectionism, preference for order, emotional constraint and behavioral inhibition. In contrast, Bulimic ED variants (which include AN Binge-purge subtype, Bulimia Nervosa, and Binge Eating Disorder), tend to co-aggregate with traits of emotional instability, recklessness and impulse dyscontrol, and with propensities towards substance abuse and self-harm. Despite such "prototypes", many people with AN or BN show negligible psychopathology—which raises the important point that having marked psychopathology is not a necessary precondition for the development of an ED.

Current thinking has it that the complex of symptoms that characterizes the EDs often arises through the activation, by environmental exposures, of latent genetic potentials. Twin and family-epigenetic studies confirm that EDs are strongly heritable [21, 44, 54]—and molecular-genetic studies implicate genes linked to such factors as a) mood, anxiety and impulse-regulation, b) appetite, body weight, and related metabolic factors, and c) sex (e.g., genes influencing estrogen activity). This is not to mention the myriad of unknown genes that are potentially linked to EDs, that may be uncovered by genome-wide studies now underway [4, 5]. However, genetic liabilities, in all probability, need to be activated by environmental triggers which, in the case of EDs, are quite numerous. Evidence suggests that environmental risks for ED development include perinatal and obstetric insults [14, 46], early-life stressors, like childhood abuse [58], and later-life stresses—among which are likely to figure stresses linked to too much caloric restraint [13]. Fundamentally, you cannot develop AN or BN without undergoing a period of prolonged caloric restraint.

This paper addresses the potentials of epigenetic science to inform the understanding of ED pathophysiology. We believe that an epigenetically informed etiological model may allow for a principled understanding of why people develop eating disorders, and why they have the particular phenomenological characteristics and combinations of risks that they do. With respect to the latter concerns, we make three empirically supportable assumptions: 1) As already noted, you do not have to display marked psychopathology to develop an ED—even though studies of individuals who develop EDs indicate that comorbid anxiety, affective and impulse-control problems are, realistically, more the rule than the exception. A first challenge for an adequate etiological theory is thus to account for why psychopathological expressions, although not a necessary precondition or feature, are so common in the EDs. 2) You do not have to arise from a dysfunctional family, or have had a traumatic development. Available evidence discounts the outdated notion that there is an ED-prone family type, or that EDs necessarily reflect the effects of adverse development [24]. At the same time, it is true that roughly a third of adults with an ED (and particularly those with binge-purge symptoms) report unwanted childhood sexual experiences, and over half, past physical maltreatment. This being the case, any adequate etiological model would seem to have to accommodate a role (again, a common but not necessary one) for developmental adversity. 3) It is rarely (perhaps never) the case that AN or BN occurs without a previous period of prolonged and intensive caloric restraint—i.e., excessive efforts to restrict food intake and reduce weight [13, 39]. The latter point indicates an intriguing invariant—as it suggests that nutritional deprivation (too much "dieting") is a necessary trigger to ED development. The question we pose, then, is: Can epigenetic science accommodate the reality of disproportionately high, but variable loadings of psychiatric problems and exposures to life stresses among people who develop EDs—and also the fact that virtually all sufferers evince a history of severe caloric restraint.

2. Epigenetic mechanisms

When speaking of epigenetic mechanisms, we refer to processes by which environmental exposures leave physical "marks" on the genome that can influence later gene expression. It is in this manner that epigenetic mechanisms are thought to provide the physical substrates for effects underlying the environmental activation (or silencing) of genetic potentials. Epigenetic mechanisms appear to mediate the contributions of various environmental pressures, acting throughout the lifespan, to the shaping of various mental illness phenotypes [22, 53] including EDs [6, 50]. Various mechanisms are involved, including DNA methylation/demethylation and hydroxymethylation, histone acetylation/deacetylation, histone phosphorylation/dephosphorylation, noncoding RNA and microRNAs, and transcriptome actions. The most widely studied of these processes is DNA methylation, which involves the addition of methyl to genomic regions in which cytosine is followed by guanine—commonly called CpGs. Although variations occur, when gene promoters become methylated, gene expression tends to become reduced, with loss of function occurring directly (due to inhibition of the binding of transcription factors to recognition elements in the gene), or indirectly (via the recruitment of proteins that precipitate inactive chromatin). Evidence suggests that DNA methylation is influenced by diverse environmental exposures, including obstetric and perinatal insults, early-life experiences of adversity and nurturance and (importantly for this discussion on EDs) dietary factors [10, 11, 30]. The present review is organized around documented epigenetic effects attributable to 1) the perinatal environment, 2) infancy and childhood exposures and 3) an individual's current nutritional status.

3. Which environments?

3.1. Gestational distress

Epigenetic mechanisms act at various stages during the life cycle, with the womb providing the first locus at which epigenetic programming effects are known to occur. Intrauterine stress exposures, due to mothers being nutritionally deprived [27, 45] or emotionally distressed [35, 46] during pregnancy, can adversely impact epigenetic status in exposed children and, along with this, later physical status, emotional adjustment, stress reactivity, and physical health. Maternal depression during gestation has, for example, been linked to specific increases in methylation of offspring's glucocorticoid receptor (NR3C1) gene. In keeping with NR3C1's role in moderating sensitivity of the hypothalamic-pituitary-adrenal axis, affected offspring show altered cortisol responses and increased stress reactivity [36, 57]. One of our group's recent studies indicates an ED-linked effect of environmental stress exposures in utero. It showed that children of mothers who were exposed to intense, third-trimester gestational distress during