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Review

Eating disorders, gene–environment interactions and epigenetics

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ABSTRACT

This review describes the various subtypes of eating disorders and examines factors associated with the risk of illness. It considers evidence that the development and maintenance of eating disorders is due to gene–environment interactions (GxE) that alter genetic expression via epigenetic processes. It describes how environmental factors such as those associated with nutrition and/or stress may cause epigenetic changes which have transcriptional and phenotypic effects, which, in turn, alter the long term risk of developing an eating disorder. It reviews theoretical and practical issues associated with epigenetic studies in psychiatry and how these are relevant to eating disorders. It examines the limited number of epigenetic studies which have been conducted in eating disorders and suggests directions for further research. Understanding the relationship between epigenetic processes and the risk of an eating disorder opens possibilities for preventive and/or therapeutic interventions. For example, epigenetic changes associated with diet and weight may be reversible and those associated with cognitive processes may be accessible to pharmacological interventions.

Contents

1. Eating disorders

Eating disorders (ED) encompass anorexia nervosa (AN), bulimia nervosa (BN), eating disorder not otherwise specified (EDNOS) and binge eating disorder (BED). Anorexia nervosa and bulimia nervosa typically affect young women and have a peripubertal onset: binge eating disorder occurs in both sexes and has a more varied onset (Hudson and Pope, Jr., 2007). Obesity is not classified as an eating disorder, but as eating disorders and obesity can occur simultaneously or sequentially in the same person and share some common risk factors, we have (when relevant) considered obesity-related issues.

Anorexia nervosa has existed for centuries and across cultures. In historical and non-Western cases, 'inappetence' and 'inability to eat' or ascetic/religious ideals have been used to justify food restriction, however in most cases of anorexia nervosa, concerns about weight and shape constitute the core psychopathology (Keel and Klump, 2003). Bulimia nervosa appears to be a 20th century Western phenomenon (Russell, 1979). Binge eating disorder was included in the Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV) (1994) appendix as "deserving further study"

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(Spitzer et al., 1992, 1993). The majority of eating disorders are "eating disorders not otherwise" specified (EDNOS) as they do not fit into these diagnostic groups (Ngai et al., 2000; Wonderlich et al., 2007). Diagnostic issues are compounded by pathoplasticity in eating disorders. Thus, the incidence and prevalence of anorexia nervosa and bulimia nervosa is stabilising in Western countries (Currin et al., 2005), whereas eating disorders not otherwise specified and binge eating disorder continue to increase, as does the combination of eating disorders and obesity (Darby et al., 2009; Hay et al., 2008; Pavlova et al., 2010). This pathoplasticity might arise from different gene environment (GxE) interactions which, as described below, may be associated with epigenetic processes.

Over 30 risk factors for anorexia nervosa and bulimia nervosa have been identified (Jacobi et al., 2004). For anorexia nervosa, these include obstetric complications, childhood feeding and sleeping problems, high levels of physical exercise, overanxious parenting, obsessive compulsive personality (OCP) traits, perfectionism and negative affect/self-evaluation (Pike et al., 2008). For bulimia nervosa, these include obstetric complications, dieting, childhood and parental obesity, alcoholism, pubertal timing, sexual abuse and negative self-evaluation (Fairburn et al., 1997). For binge eating disorder, these include childhood obesity, family overeating/binge-eating, high parental demands, negative affect, parental mood and substance misuse disorders, perfectionism, separation from parents, and maternal problems with parenting (Striegel-Moore et al., 2005). There are also overlapping and distinct environmental and developmental risk factors for different types of eating disorders and for obesity (Hebebrand et al., 2003; Keith et al., 2006; Stice, 2002). Shared risk factors for eating disorders and obesity include dieting, media exposure, body image dissatisfaction and weight-related teasing (Haines and Neumark-Sztainer, 2006), negative affect (Stice et al., 2005) and psychosocial stress (Bornstein et al., 2006; Connan et al., 2007a,b; Schmidt et al., 1997; Striegel-Moore and Bulik, 2007). Overall therefore, early environment contributes many of the risk factors and the others are related to personality traits and affect.

Part of the risk of developing an eating disorder (and obesity) is inherited (Bulik et al., 2007a; Dai et al., 2008). Studies have implicated genes involved in weight regulation, eating behaviour, neuropsychological profiles, mood, neurodevelopment and stress responsivity (Monteleone and Maj, 2008; Volkow and Wise, 2005). However, effect sizes are typically small and there are few replicated findings. Furthermore, many studies are underpowered and negative or inconsistent findings may have occurred because of the limits of genetic technology, epistasis and heterogeneity in phenotypes. They may also have arisen because of the presence of GxE. In obesity, studies have implicated in excess of 100 genes, most of small effect (Hebebrand et al., 2010; Korner et al., 2008; Rankinen et al., 2006) for example, FTO (fat mass and obesity associated) (Fawcett and Barroso, 2010; Scuteri et al., 2007). At this point however, little is known about GxE (Caspi and Moffitt, 2006) in either eating disorders (de Castro, 2004; Mazzeo and Bulik, 2009) or in obesity (Yang et al., 2007) but, as described below, GxE (Andreasen and Andersen, 2009) and associated epigenetic processes (Rankinen et al., 2006) have been proposed to have an important role. The importance of GxE is also of note because, any genetic variant that is directly associated with the risk of a disorder that is associated with decreased fertility, for example, anorexia nervosa, would be under substantial evolutionary pressure through negative selection and would disappear from the genetic pool within relatively few generations (Uher, 2009). Therefore, accumulation of relatively rare genetic changes of recent origin and/or GxE with environmentally induced epigenetic changes, are more likely to underlie the heritability of disorders such as anorexia nervosa. Identification of such environmentally induced epigenetic changes will provide mechanisms that can be used to investigate the relative role of physiological/psychological factors in the development and the maintenance of these disorders. Epigenetic studies will also provide a way of examining biological processes underpinning psychological changes, for example, the behaviours that are learned during the development of illness and which are modified during maintenance and treatment.

2. Epigenetics

Epigenetic mechanisms regulate gene expression independently of DNA sequence. In most, but not all cases, they produce reversible changes in gene function by modifying DNA and associated histones and via the action of small non-coding RNA molecules (Dulac, 2010). Aberrant epigenetic processes have been linked to the aetiology of cancer (Baylin and Schuebel, 2007; Duman and Newton, 2007; Tsankova et al., 2007) but are also likely to contribute to the aetiology of numerous non-malignant complex disease phenotypes (Mariman, 2008; Mill and Petronis, 2008; Petronis, 2010; Stuffrein-Roberts et al., 2008).

The best understood and most stable epigenetic modification is DNA methylation on the cytosine pyrimidine ring (Lister et al., 2009a). Most commonly, this occurs where there are 5′-CpG-3′ dinucleotides ("islands") This disrupts binding of transcription factors and attracts methyl-binding proteins associated with gene silencing and chromatin compaction: aberrant methylation can induce silencing of tumour suppressor genes and contribute to tumour development (Feinberg, 2008). Short stretches of DNA relatively rich in CpG islands often occur close to transcription site. Methylation at these CpG islands reduces the availability of these sites for transcription initiation. Histone modification, the other major epigenetic mechanism regulating gene expression, affects chromatin structure via reversible methylation, phosphorylation and acetylation of lysine residues (Roth and Sweatt, 2009). Histone modifications are being examined as dynamic regulatory processes involved in tumour development, in biological responses to stressors and in many other instances where there is inducible gene expression. A third epigenetic system involves small interfering RNA (siRNA) that suppress the activity of specific genes via RNA interference (RNAi), a process likely to be integral to developmental gene expression (Hamilton et al., 2002).

Epigenetic changes in DNA or associated histones coordinate gene expression during development: the processes are not mutually exclusive and may be antagonistic (Zilberman, 2008). Epigenetic modifications are dynamic especially prenatally and early postpartum (Waterland and Michels, 2007). These epigenetically sensitive developmental periods are relevant to perinatal and early developmental factors associated with the risk of eating disorders (and obesity). Metastable epialleles are loci that can be epigenetically modified to produce a range of phenotypes from genetically identical cells. Importantly, many are environmentally-sensitive, for example to maternal stress, behaviour and diet, and thus may alter the risk of developing an eating disorder. In some cases, such changes might also occur throughout life as epigenetic differences between monozygotic (MZ) twins accumulate with age. This epigenetic drift may explain why monozygotic twins are often discordant for eating disorders. Peripubertal epigenetic changes might increase the risk of an eating disorder in women compared to men as sex hormones alter DNA methylation at specific loci (Saluz et al., 1986; Yokomori et al., 1995), and in this way, control specific gene expression. The maintenance of an eating disorder could be due to epigenetic changes that allow individuals to escape physiological processes underpinning appetite and weight regulation or alternatively, contribute to the urge to binge. In the context of eating disorders and obesity, it is of note that fat cells show altered DNA methylation/gene expression in response to calorie restriction (Bouchard et al., 2010).

Some epigenetic marks may not be erased during meiosis (Rakyan et al., 2002) and meiotic transmission of epigenetic alleles, ("soft inheritance"), may be common (Champagne, 2008; Lim and Ferguson-Smith, 2010; Richards, 2006). This provides another mechanism for transgenerational information transfer and suggests that insults might alter the phenotype and disease risk in subsequent generations. Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort have shown that early paternal smoking is associated with a higher body mass index (BMI) in their male offspring (Kaati et al., 2007). Furthermore, grandchildren of pregnant women exposed to the 1944/45 Dutch Famine, had reduced birth weights, independent of their mothers' birth weight (Painter et al., 2008a,b; Stein et al., 2006). It is possible that epigenetic processes underlie at least some of the effects of intergenerational lifestyle changes on psychiatric morbidity. In a similar way, nutritional effects in utero could contribute to vulnerability to an eating disorder in subsequent generations.

The potential contribution of early epigenetic changes to the lifetime risk of illness is supported by data often summarised in the developmental origins of disease (DOHaD) hypothesis. This posits that poor pre and postnatal environments alter metabolic processes in a way which is initially adaptive, but increase the risk of disease later in life (Barker, 2004; Phillip et al., 1994; Phillips, 2006). Susceptibility varies during pregnancy, with highest risk during "critical windows" (Armitage et al., 2004; McMillen and Robinson, 2005; Widdowson and McCance, 1963). 'Foetal programming' could contribute to the risk of an eating disorder (and/or obesity) if individuals exposed to a poor in utero environment are subsequently exposed to an 'obesogenic lifestyle' to which their metabolism is poorly adapted. Exposure to other environmental pathogens in utero such as maternal stress or noxious agents may also increase the risk of an eating disorder by causing long term epigenetic changes. Some (Culbert et al., 2008), but not all (Raevuori et al., 2008, 2009) twin data suggest that in utero exposure to different concentrations of male or female sex steroids alters the risk of an eating disorder.

These various studies emphasise how early physical environmental effects might alter physiological "set points" related to appetite, weight and energy homeostasis and thus contribute to the risk of an eating disorder or obesity. It is important however, to note that the psychiatric comorbidity, and the learning and the fear conditioning associated with eating disorders may also be factors which to some extent are regulated by epigenetic processing (Roth and Sweatt, 2009). In fact, epigenetic changes may be particularly important in relation to behaviour and to the risk of psychiatric illness as the brain has a relatively high number of genes that are "imprinted" i.e. only one allele is expressed and some of these are associated with psychiatric/neurological problems e.g. Prader-Willi syndrome (Wilkinson et al., 2007).

3. Do epigenetic modifications mediate the effects of stress in pregnancy and/or perinatal complications on the risk of eating disorder in the offspring?

Maternal stress during pregnancy has effects on neonatal outcomes, on childhood emotional and cognitive functioning, and on adult psychopathology (Talge et al., 2007). People with eating disorders have increased anxiety and anxiety disorders that predate the eating disorder (Raney et al., 2008; Swinbourne and Touyz, 2007) and persist to an extent after recovery (Wentz et al., 2009). When pregnant, women with current or past eating disorders are likely to be more anxious than other pregnant women, in part because of concerns about gestational weight gain (Micali et al., 2007a; Swann et al., 2009). Bulimic symptoms in pregnancy are associated with anxiety, depression, lower self-esteem and poorer quality of life (Knoph et al., 2008; Soares et al., 2008). Stress during pregnancy is likely to increase foetal glucocorticoid exposure (Glover et al., 2009) which may result in foetal growth retardation (Micali et al., 2007b) and adverse health consequences in adulthood, including obesity, anxiety, inflammation (Danese et al., 2007) and hypothalamic pituitary adrenal (HPA) axis malfunction. It is of note that altered stress responsivity and hypercortisolaemia, have been reported people with an eating disorder (Gluck, 2006; Lo et al., 2008; Schmidt et al., 1995, 1997) and chronic stress such as submission or threat to social rank has been implicated in the onset of both anorexia nervosa and bulimia nervosa (Connan et al., 2003, 2007a).

Prenatal/early postnatal stress leads to changes in foetal programming associated with susceptibility to a number of chronic diseases (Phillips, 2006, 2007). Such effects have at least in part been attributed to long term aberrant functioning of the offspring's HPA axis (Heim and Nemeroff, 2002; Jones et al., 2006; Seckl, 2008; Weinstock et al., 1992; Wust et al., 2005).

In rodents, a lack of postnatal maternal care leads to stress-related phenotypes in the offspring (Weaver et al., 2004; Schmidt et al., 2010) mediated by epigenetic modification of a NGF1-A transcription factor binding site in the promoter region of the glucocorticoid receptor (GC) gene (Weaver et al., 2004).

These data provide evidence that the risk of an offspring developing an eating disorder or obesity is altered by stressful events early in life and there is increasing evidence that the altered risk is associated with epigenetic changes. Together with the finding that stress in adulthood has marked and individually variant effects on appetite (Roberts et al., 2007), these data suggest potential interventions for pregnant women with a current or past eating disorder and/or high levels of stress or anxiety. Increased social support and/or education about the effects of poor maternal nutrition may buffer the maternal HPA axis from stress induced activation. Deleterious effects of stress on the offspring might be reduced by pharmacologically reducing glucocorticoid synthesis (Langley-Evans, 1997) or by dietary supplementation (Weaver et al., 2005).

4. Does nutrition in pregnancy alter the risk of an eating disorder in the offspring via epigenetic processes?

Women with current or past anorexia nervosa or bulimia nervosa have poorer obstetric outcomes (Blais et al., 2000; Ekeus et al., 2006; Micali et al., 2007b; Sollid et al., 2004). Fertility clinic attenders have high rates of eating disorders (Freizinger et al., 2008; Stewart et al., 1990) and treatment helps them conceive even at low weight. Pregnancy usually leads to symptom reduction or remission of pre-existing eating disorders (Micali et al., 2007b) but can be associated with new onsets (Bulik et al., 2007b). Pregnant women with eating disorders have altered eating behaviour, for example, undernutrition and/or bingeing, purging and restriction (Siega-Riz et al., 2008). Women with low pre-pregnancy body weights also have an increased risk of poor obstetric outcomes, and pre-pregnancy weight and gestational weight gain have a combined effect on foetal growth (Carmichael et al., 1997; Ehrenberg et al., 2003). As is the case with mothers with eating disorders, the risk of having a low birth weight baby is substantially accounted for by a low pre-pregnancy BMI (Micali et al., 2007a). Some of these effects may extend postpartum because of the way in which women with eating disorders feed their offspring (Stapleton et al., 2008; Ward, 2008).

The Dutch famine (1944–1945) has allowed in utero effects of maternal food deprivation to be studied in humans. Studies of adults born from pregnancies during the famine winter reveal wide-ranging effects on multiple traits relevant to nutrition and psychopathology and which are dependent on the timing of famine exposure during pregnancy and to some extent on gender.

In adulthood, those exposed to the famine in utero were, on average, 8 kg heavier than those not exposed. Early gestational exposure to famine was associated with greater adult obesity and more heart disease and exposure in mid/late gestation with higher rates of impaired glucose tolerance and Type II diabetes (Lussana et al., 2008; Ravelli et al., 2005; Roseboom et al., 2001). Those exposed in early gestation had higher rates of central nervous system (CNS) abnormalities, schizophrenia, schizoid personality disorder and addictions (Franzek et al., 2008; Hoek et al., 1998). Males exposed in early/mid gestation had an increased risk of antisocial personality disorder at age 18 (Neugebauer et al., 1999) and exposure in mid/late gestation increased the risk of affective illness (Brown et al., 2000). Thus, nutritional state in utero is associated with altered food preferences, increased risk of obesity and psychiatric morbidity in adulthood. To date however, no study has looked specifically at the risk for eating disorders. As described below, there are also data (largely from animal studies) that in utero nutrient restriction can affect HPA axis functioning and stress responsivity in later life (Bloomfield et al., 2003; Vieau et al., 2007).

Changes associated with a poor in utero environment may be adaptive, for example, the organism may be programmed for rapid reproduction in a potentially hostile world (Seckl and Holmes, 2007). Indeed, women exposed to the Dutch Famine in utero started reproducing at a younger age and were reproductively more successful (Painter et al., 2008a,b). However, this adaptation comes at a price. Early menarche carries an increased risk of a mismatch between biological and socio-emotional development (Gluckman and Hanson, 2004, 2006). This may expose girls to early social pressures regarding their body shape and they may experience a sense of "being out of sync" at a vulnerable stage and be prone to anxiety, depression and impulsivity (Ellis, 2004). Dieting may be an attempt to 'treat' these problems, thereby increasing the risk of eating disorder. It is of note therefore, that early menarche is an identified risk factor for bulimia nervosa and other types of risk taking and self-destructive behaviours (Day et al., 2010; Stice and Shaw, 2002). The in utero effects of the Dutch Famine on development raise the possibility that mothers who are ill with anorexia nervosa at certain gestational stages may produce children programmed to have an increased risk of developing obesity and behavioural problems. This would be abhorrent to mothers who often worry about their child's weight, although a Dutch Famine study did not find an association between maternal stress and HPA axis responsivity in offspring (de, Sr. et al. 2006).

In relation to eating disorders, most studies of the risk of an offspring developing an eating disorder have involved investigations of maternal undernutrition. However, it is important to recognise that there is an extensive clinical and animal literature on the effects of maternal obesity on the health of the offspring and how epigenetic processing may be involved (Heerwagen et al., 2010; Jungheim et al., 2010; Regnault et al., 2010; Vasudevan et al., 2010). These studies tend to be focussed on physical outcomes such as BMI and on changes that increase the risk of metabolic problems later in life. However, given that parental obesity and overeating are risk factors for bulimia nervosa and binge eating disorder, it seems very reasonable to include cases of maternal and paternal obesity in epigenetic studies related to the development of eating disorders.

In animals, poor nutrition in utero has long term effects on the offspring mediated by epigenetic processes (Ke et al., 2006; MacLennan et al., 2004). In the context of eating disorders (and obesity), an example is the agouti viable yellow allele in mice in which a promoter-region transposon is epigenetically altered by dietary manipulation of pregnant females. This affects agouti gene expression and produces a distribution in offspring coat colour phenotype (Cooney et al., 2002) and prevents transgenerational amplification of obesity. Another example of an epigenetically linked change in phenotype is seen with a transposon-associated metastable epiallele in Axin Fused mice that produces a kinky tail phenotype correlated with the degree of DNA methylation across the region (Waterland and Jirtle, 2004). Supplementing maternal diet with methyl donors increases transposon DNA methylation in offspring, dramatically reducing the tail-kink phenotype (Fraga et al., 2005).

A major influence on DNA methylation is the availability of methyl-donors and co-factors, required for S-adenosyl methionine (SAM) formation. SAM is a methyl-donor for cytosine methylation on DNA (Chmurzynska, 2010). Dietary factors required for SAM formation include vitamins B2, B6, and B12, folate, methionine and choline. Extreme folate deficiency causes SAM depletion, genome-wide hypomethylation, oncogene activation and cancer (Duthie, 2001; Duthie et al., 2002). B12 and folate deficiency are linked to impaired CNS development and some psychiatric conditions which share aetiological factors with eating disorders (Reynolds et al., 2007; Sugden, 2006): in animals, methyl donor supplements prevent transgenerational amplification of obesity (Waterland, 2003). In the present context, it is noted that six decades after the Dutch Famine, individuals exposed prenatally had less DNA methylation of the imprinted insulin-like growth factor 2 (IGF2) gene compared to their unexposed siblings, thus providing evidence that early environment can cause lifelong epigenetic changes (Heijmans et al., 2008).

These data indicate that the risk to the offspring of developing an eating disorder (or obesity) is changed by maternal nutrition and that some of these effects could be due to epigenetic changes. This route into illness is likely to account for a minority of cases but in the case of mothers with a history of an eating disorder, it defines a trajectory relevant to a high-risk group and their offspring. Cohort studies of pregnant women and their offspring will allow assessment of the risk of an eating disorder in the adolescent/young adult off-spring of mothers with a current or past eating disorder during pregnancy, and hopefully, an exploration of associated epigenetic changes. Dietary issues especially surrounding the availability of methyl donors/vitamin B12 should be reviewed and as well as the possibility of using dietary interventions to treat illness (Mariman, 2008).

5. Candidate genes for epigenetic studies in eating disorders

As stated above, biological factors associated with weight regulation and energy homeostasis may contribute to vulnerability to an eating disorder, to obesity and to some of their shared risk factors. There is an extensive literature on how gastrointestinal and energy sensing systems in the periphery interact with central loci especially in the hypothalamus (Luquet and Magnan, 2009; Pirnik et al., 2010; Smith and Ferguson, 2008; Wren, 2008) but also with higher brain areas (Batterham et al., 2007). How these systems develop in utero or in childhood and how, for example, an individual regulates weight around a "set point" could, at least in part, be due to early epigenetic encoding. Such regulatory systems might then remain relatively stable throughout life. On the other hand, there is the possibility that in some cases, they can be substantially altered in adulthood as a response to environmental influences. In this context, five genes (FTO [fat mass and obesity associated], leptin (and its receptor), pro-opiomelanocortin [POMC] and BDNF) are used as examples that might be epigenetically modified in ways that alter risk.

People with two copies of a common polymorphism in the FTO gene have a 70% increased risk of obesity and variants of FTO are associated with obesity and increased BMI (Frayling et al., 2007; Hunt et al., 2008; Scuteri et al., 2007; Wardle et al., 2008; Yang et al., 2007). Furthermore, the FTO-associated risk of obesity is reportedly enhanced by a lack of physical activity (Andreasen et al., 2008). FTO is highly expressed in the hypotha-

lamus (Gerken et al., 2007b) and FTO null mice are small, have decreased fat mass, decreased lean mass and are hyperphagic, which is explained by them having increased energy expenditure (Fischer et al., 2009). The gene encodes a 2-oxoglutarate oxygenase dependent nucleic acid demethylase, preferentially demethylates 3-methylthymidine, and decreased food intake in mice is associated with decreased FTO mRNA (Gerken et al., 2007b; Jia et al., 2008). Thus, increased FTO activity would be predicted to increase DNA demethylation and stimulate expression of genes regulated by FTO activity, and FTO null mice would be predicted to have increased methylation at specific (unknown) loci.

In people, early epigenetic changes mediated by FTO associated DNA demethylation might set levels of resting energy expenditure which could impart a lifetime propensity to high or low weight. Alternatively, FTO activity may be environmentally sensitive throughout life. If there are societal pressures to be slim, people with FTO variants associated with increased BMI, may adopt compensatory behaviours which increase the risk of an eating disorder. Thus, (especially in relation to bulimia nervosa and binge eating disorder) a case can be made for examining GxE involving FTO and also for establishing which genes might be demethylated by its actions. Linking FTO with anorexia nervosa is more difficult but arguably, the risk of illness may be partially due to an enhanced ability to escape from the physiological drive to eat and this could arise from epigenetic changes associated with this gene.

Leptin and its associated receptor provide two candidate genes. Leptin is a peptide produced by adipocytes and it is involved in processes related to energy storage and utilisation (Considine, 2005; Maffei et al., 1995; Morton, 2007; Zhang et al., 1994). It is actively transported across the blood brain barrier (BBB) and leptin receptors are widely distributed in the adult brain (Zhang et al., 2005). Leptin has been implicated in a variety of physiological processes several of which are germane to eating disorders. For example, it is involved in reproduction (Caprio et al., 2001) in bone metabolism (Cornish et al., 2002; Reid, 2010) and low levels are apparently related to the hyperactivity seen in many patients with anorexia nervosa (Hebebrand et al., 2003). It has also been implicated in the modulation of brain reward circuitry related to eating (Farooqi et al., 2007; Fulton et al., 2000;) and lastly, common polymorphisms in both the leptin gene and its receptor are associated with birth weight but also with the development of metabolic diseases in adulthood (Souren et al., 2008). In terms of epigenetic changes that might alter the risk of developing an eating disorder, it can be proposed that leptin, its transport system across the BBB, its receptor(s) and the associated receptor effector system are all potential loci for epigenetic modification. This is especially so during development when leptin and its receptor are involved in neuronal migration, survival and outgrowth (Pan et al., 2008). Within this context, it is of note that in the leptin gene promoter sequence, there are highly variable densities of cytosine methylation and these are apparently subject to dynamic epigenetic regulation (Stoger, 2006, 2008). However, it is important to recognise that any epigenetic changes that might involve the leptin axis may only occur during development, for example, at a time when the "set point" associated with energy homeostasis is defined. In this scenario, the functioning of such systems in adulthood may involve no epigenetic modifications and there will be no longitudinal epigenetic changes associated with the development, maintenance or recovery from an eating disorder.

POMC is a polypeptide hormone precursor which gives rise to adrenocorticotrophic hormone (ACTH) and melanocortin stimulating hormone (MSH): the former is an integral part of the HPA axis and the latter an anorexigenic peptide in the hypothalamus (D'Agostino and Diano, 2010). It has been reported that changes in methylation of the POMC gene promoter region are associated with being underweight (Ehrlich et al., 2010) and in addition, there is a study which indicates that there is increased DNA methylation in the POMC gene promoter associated with craving in alcohol dependence (Muschler et al., 2010). This latter observation is of interest as there are models of bulimia nervosa and binge eating disorder which propose that they are associated with altered reward processing which gives rise to addiction-like behaviours such as craving (Davis and Claridge, 1998; Van den et al., 2010; Volkow and Wise, 2005).

The last example of a candidate gene is brain derived neurotrophic factor (BDNF). BDNF affects neural development and polymorphisms in the BDNF gene have been associated with eating disorders (Mercader et al., 2007; Nakazato et al., 2009) BDNF apparently regulates neuronal histone deacetylase2 (Nott et al., 2008) and thus it may influence epigenetic regulation of other inducible genes that is, it may alter the risk of an eating disorder via histone modification. Furthermore, chronic social defeat stress in adult animals alters the regulation of BDNF expression in the hippocampus through tissue-specific epigenetic histone modifications (Berton et al., 2006; Tsankova et al., 2006, 2007).

Using the functions of these genes as exemplars shows how epigenetic models of eating disorders can be created that have neural development, nutrition, stress, craving and/or cognition as core components.

6. Epigenetic changes associated with psychological processes: implications for eating disorders

Psychiatric comorbidity is common in eating disorders and they may share some susceptibility genes with mood, impulse control and substance misuse disorders (Hudson and Pope, Jr., 2007; Spindler and Milos, 2007). All of these problems are related to temperamental traits. People with eating disorders typically have a fear of food, eating and fatness which does not habituate even during prolonged treatment with regular meals. In individuals who are temperamentally anxious and whose emotion circuitry is highly sensitive to environmentally induced plasticity, the development and maintenance of eating disorders may involve pathological fear conditioning (Strober, 2004; Strober et al., 2007). In this scenario, eating disorders can be seen as developing from learned behaviours with weight-related symptoms arising from a combination of physiological and psychological risk factors. This model of eating disorders is attractive as the learned behaviours associated with illness may, in part, arise from epigenetic modifications: this is supported by evidence that long-term memory formation and fear conditioning are epigenetically controlled (Levenson and Sweatt, 2005; Tsankova et al., 2007) and that cognitive function can be affected by epigenetic changes (Reichenberg et al., 2009). However, as discussed below, there are practical problems related to the study of epigenetic processes associated with psychological events/states. On the other hand, it seems likely that in the relatively near future, there will be psychological interventions which will have epigenetic change embedded in their conceptual frameworks. For example, in studies related to fear extinction, it has become clear that the reconsolidation phase can be used as a window to rewrite emotional memories (Schiller et al., 2010): increasingly, such studies involve the use of drugs such as propanolol (Kindt et al., 2009), D-cycloserine (Hofmann, 2007; Norberg et al., 2008) and glucocorticoids (Aerni et al., 2004; Bentz et al., 2010) and at least in the case of glucocorticoids, memory associated changes have been shown to involve chromation modification (Roozendaal et al., 2010).

7. Epigenetic research and eating disorders

Epigenetic studies of psychiatric/behavioural diseases, are relatively recent and methods are still being developed (Mill and

Petronis, 2007). There have however, been some epigenetic studies in eating disorders. Significant global DNA hypomethylation has been found in lymphocytes from patients with anorexia nervosa, but not bulimia nervosa (Frieling et al., 2007). This included decreased expression of the alpha synuclein gene (SNCA) associated with hypermethylation of the SNCA promoter in patients with anorexia nervosa. They also investigated epigenetic regulation of vasopressin and atrial natriuretic peptide (ANP) (Frieling et al., 2008). No differences were seen for vasopressin, but there were lower levels of ANP mRNA in patients with eating disorders: this was accompanied by hypermethylation of the ANP gene promoter in the bulimia nervosa subgroup suggesting that epigenetic changes contribute to the change. The same group have also reported that there are epigenetic changes in dopaminergic genes (Frieling et al., 2009) and in the POMC gene (Ehrlich et al., 2010) in people with eating disorders.

The most common approach until recently has been to examine polymorphisms in candidate genes (especially in promoter regions) to establish whether they could be loci for epigenetic modification, e.g., CpG islands: this may increase explanatory options for observed risk and help to elucidate the potential effects of polymorphisms in genes that regulate epigenetic processes. To date, no genome-wide survey of epigenetic changes associated with eating disorders has been performed, although this may change as an 'epigenome' scan has recently been completed (Lister et al., 2009a). Elsewhere, particularly in oncology, studies of histone modifications are ongoing. However, although methods for screening the epigenome are available, epigenetic studies related to psychiatric illness face methodological challenges. One is the likelihood of some tissue specificity in environmentally induced epigenetic changes. This means that examination of the primary sites of disease manifestation are preferable. However, postmortem brain may be difficult to obtain especially from people who had eating disorders and secondly, its use is confounded by factors such as cause of death and, in some cases, restrospective diagnosis. In addition, numerous neuroimaging studies have shown the diversity of neural processes associated with the symptomatology of eating disorders, its subtypes and the responses to treatment (Uher et al., 2003; Friederich et al., 2010). Thus, being able to associate discrete symptoms of eating disorders with changes in specific brain areas and to incorporate them into epigenetic studies is at a relatively early stage. However, the use of more broadly based neural models of eating disorders, for example those that hypothesise that a cortical-subcortical imbalance is a core element of the illness (Kaye et al., 2009), may be of more value to epigenetic studies. If the part of the risk and/or of the maintenance of an eating disorder (or obesity) is associated with epigenetic changes in the stress axis or alternatively with altered cognitive processes (Nakazato et al., 2009; Tchanturia et al., 2005, 2007), such changes might not occur/have occurred in peripheral tissues. On the other hand, many epimutations are not limited to the affected tissue or cell type. Examples are the epimutations at IGF2 in lymphocytes and MLH1 in sperm cells seen in colon cancer patients, and epimutations at KCNQ1OT1 in the lymphocytes and skin fibroblasts in Beckwith-Wiedemann syndrome (Pembrey et al., 2006; Weksberg et al., 2002). Thus, given that there is some evidence for early-developmental effects on the subsequent risk of eating disorders, studies on peripheral tissues may reveal epigenetic changes resulting from embryogenesis when cell replication is high and epigenetic marks controlling development are being established (Weaver et al., 2004). Lastly, given the possible involvement of metabolic processes in the aetiology of eating disorders, some epigenetic changes in peripheral cells, for example adipocytes, may be directly involved in the pathogenesis of these disorders.

Another approach to the problem of studying brain tissue is to use rodent models of anorexia nervosa (Carrera et al., 2006; Gelegen et al., 2007, 2010) or bulimia nervosa (Avena et al., 2006; Boggiano and Chandler, 2006). These have potential for investigating interactions between energy balance, reward and stress. They will also allow investigation of how environmental factors cause eating disorder related epigenetic changes and establish the extent to which epigenetic changes in specific brain regions are detectable peripherally. Rodent studies will also enable candidate genes for specific neuronal systems to be investigated. For example, it will be of interest to establish the extent to which learning is underpinned by epigenetic change as it is arguable that, especially in eating disorders, learned behaviour is a component of the development, maintenance and recovery from illness.

8. Conclusions

Disorder salient changes that increase the risk of an eating disorder may be present in systems that regulate and/or contribute to weight and energy homeostasis. If these systems function normally, individuals with the same psychological profile may be primarily at risk of other psychiatric problems such as anxiety or obsessive compulsive disorder (OCD). Adaptability in systems regulating energy homeostasis may be diverse in the population and individual differences could contribute to the lifetime risk of an eating disorder (or obesity) in people who have a general predisposition to psychiatric disorders. Adaptability is likely to be a combination of genetic and epigenetic factors ie how these combine to confer flexibility on the epigenome. The risk of developing an eating disorder (or obesity) could therefore be increased because of early exposure to poor nutrition, an obesogenic environment or to stressors which promote adaptive epigenetic changes which are maladaptive later in life because of a changed environment. Alternatively, in adulthood, an individual may be unable to make appropriate adaptive epigenetic changes to changing environments. These possibilities are not mutually exclusive. Finally, as it can be argued that cognitive flexibility and ability to learn new behaviours are key elements of healthy mental functioning, it is important to establish if (or to what extent) epigenetics is involved in learning and memory and to develop clinical and dietary strategies for altering the processes involved.

In terms of the future, studies will address issues related to tissue specificity and epigenetic change and some will examine GxE in relation to epigenetic changes in candidate genes. Genome wide epigenetic studies will be more widely used to compare the epigenome in health and disease and in response to treatment interventions. Studies which seek to integrate histone and DNA changes are likely to prove more challenging. Finally, with specific reference to eating disorders, it is likely that there will be therapeutic studies which will seek to alter the epigenome by dietary and/or pharmacological interventions.

Conflict of interest

The authors have no conflicting interests.

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