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A Brief Review of the Biology of Anorexia Nervosa

Abstract

Background: The etiology of Anorexia Nervosa (AN) is unknown. A stress model for AN and other Eating Disorders, has been proposed by Connan and depicts risk factors and precipitating events, including biological, but several steps in this have yet to be evidenced. In order to elucidate the biology of AN, some studies have investigated the blood biochemistry in AN in the acute state, when BMI (Body Mass Index) is very low, and compared this to a recovered state. In this brief review, we present the results of a literature search on potential biomarkers of AN.

Method: A literature search using PUBMED and the following search terms: "Anorexia Nervosa" and "biomarker" revealed 180 articles (8th of May 2015). Additional searches included the search terms "gene", "genetic", "epigenetic", "appetite", "hormone", and a specific search on "biology" and "review". Furthermore, articles of interest were retrieved from the reference lists of the identified articles of the first PUBMED search.

Results: In general, there is a shortage of studies on biomarkers and the biology of AN, at least when you compare to similar fields of research in Affective disorders and Schizophrenia. The studies performed reveals that heritability is involved and that biological factors independent of BMI may play a role in the pathophysiology of AN. In the acute stage of AN, decreased levels of leptin and increases in ghreline and obestatin, hormones involved in the regulation of appetite, are often found.

Conclusion: In view of the rather few studies done, the small number of patients included in the studies, and the lack of additional information relating to behavioral and phenotypic characteristics, the results must be interpreted with caution. Preliminary findings indicate that factors independent of BMI may be involved in the pathophysiology of AN. During acute stages of AN, when BMI is lover than 17, 5, abnormal levels of appetite regulating hormones are often found.

Keywords: Anorexia Nervosa; Biomarker; Biology; Genetic; Hormone

Review Article

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Introduction

Anorexia nervosa (AN) is a serious and often long-lasting psychiatric condition. It is characterized by weight reduction induced by episodes of starvation. Often there is an accompanied abnormal self-body-image, preoccupation of fitness and avoidance of fat in food. The prevalence of AN is approximately 0.9% in women and 0.3% in men [1]. Treatment is usually given for longer periods of time and recovery is slow and incomplete. Potential life-threatening medical complications often occur that can affect almost every organ system [2]. Consequently, such impairments lead to the highest death rates (approximately 7%) of any psychiatric disorder [2,3]. In fact, the overall mortality rate in anorexia nervosa patients is about 10 times higher than the expected mortality for age-matched women in the US [2,3], and suicide rates are 56 times that expected for age and sex [4-6].

In the acute situation, current treatment guidelines propose hospitalization in order to stabilize the condition medically, when patients with AN reach a weight that is below 70% of their calculated ideal body weight (IBW), have severe bradycardia (≤50 beats/min), severe hypotension, or life threatening electrolyte abnormalities [2,7,8]. For treatment of the eating disorder in itself, there are few pharmacological options as stated by current guidelines, and of the less than 25 Randomized Controlled Trials that have been performed, most have failed to have an impact on the management of the disorder [9].

In spite of the that the condition of AN has been well-known for many years, the etiology is still unknown [10-12]. A number of risk factors have been proposed for the development of AN, from genetic to psychosocial risk factors, but these studies have also underscored how limited our knowledge is on the etiology of AN [12,13]. Previous models suggested the serotonergic system to be involved in the etiology of AN [14], but treatment attempts with serotonergic medicines have not been able to support this notion [9]. One of the more common factors listed is sociocultural, together with likely genetic predisposition [12,15,16], which together stresses that AN has a multifactorial etiology that involves complex interactions between genes and environment.

Method

A literature search was done in order to review the state of knowledge on the biology of AN. The search for articles included PUBMED and MEDLINE databases. The following search criteria were used: (("anorexia nervosa"[MeSH Terms] OR ("anorexia"[All Fields] AND "nervosa"[All Fields]) OR "anorexia nervosa"[All Fields]) AND ("biological markers"[MeSH Terms] OR ("biological"[All Fields] AND "markers"[All Fields]) OR "biological markers"[All Fields] OR "biomarker"[All Fields])).

This yielded 180 references (8th of May 2015). Additional searches included the search terms "Anorexia nervosa" AND "genetic", "gene", "epigenetic" "biology", "hormone" as well as specific searches on for examples "NPY", "MSH". An additional search was done on "Anorexia nervosa" AND "biology" AND "review".

Biological findings in Anorexia Nervosa

Genetics: Heritability of Eating disorders in families has been demonstrated, and based upon twin and epidemiological studies it has been shown that additive genetic factors may explain between 40% to 60% of the liability to anorexia nervosa (AN; 48–88 %), bulimia nervosa (BN; 28–83 %), and binge eating disorder (BED) [4,17]. The remaining liability is most likely due to individual-specific (i.e. non-shared) environmental factors since a major impact of shared environmental factors could not be evidenced. A recent study showed that the majority of genetic influences on disordered eating behavior are independent on Body Mass Index (BMI) in both women and men [18].

Research on genetic factors have initially been hypothesis driven, concentrating on phenotype associated genes. Study designs have been case-control and family-based candidate gene association studies and linkage analysis of multiply affected nuclear families. These have used both clinical diagnoses and eating disorder-related intermediate phenotypes such as drive-for-thinness or body dissatisfaction. Examples of markers of candidate genes studied are neurotransmitters and neurodevelopmental system markers [e.g. serotonergic, opioid, cannabinoid and dopaminergic receptors, and brain-derived neurotrophic factor (BDNF)], appetite regulatory peptides and their receptors [leptin, ghrelin, agouti-related protein (AgRP), melanocortin receptors, neuropeptide Y], energy balance systems (e.g. uncoupling proteins), genes implicated in obesity (e.g. FTO) and sex hormone systems (e.g. oestrogen receptors), which were initially suggested based upon their function or identified as positional candidates from linkage analysis [18].

Phenotypic based research on genetic correlates have led to the notion that the serotonin pathway should be a relevant biological system in the development of eating disorders, since it is involved in a broad range of relevant biological, physiological and behavioral functions, for example body weight regulation and eating behavior [19-23]. Furthermore, serotonin could contribute to the psychopathological features of eating disorders such as perfectionism, obsessionality and impulsivity [23-25]. In addition, several studies have also implicated hyperserotonergic activity as a trait marker in eating disorders [21,26-28] which as well may predispose for the development of the disorder.

Linkage analysis have implicated 1p33-36 for AN, 1q31.3 for quantitative behavioral traits related to AN and 10p14 for BN, as well as other behavioral phenotypes across both disorders [29]. Candidate gene association identified e.g. BDNF, delta 1 opioid receptor (OPDR1) and AgRP [30,31].

With the advent of genome-wide association studies (GWAS), this have demonstrated linkage peaks for AN on chromosomes 1p33-36 and 4q13, for AN including behavioral covariates on chromosomes 1q31, 2p11 and 13q13, and for BN on chromosomes 10p13, and 14q22-23 [18]. More recently, GWAS analysis with microsatellite markers has implicated novel candidate loci for AN at 1q41 and 11q22, and further GWAS results are expected from the Anorexia Nervosa Genetics Initiative (ANGI) in the near future.

Since there seem to be mutual both genetic factors and phenotypic characteristics in AN and Bulimia Nervosa (BN) especially, but also Eating Disorder Not Otherwise Specified (EDNOS), and there is a considerable rate of cross-over between AN, BN and EDNOS, ranging between 4 and 36% [5,32-34], it has been proposed to describe them together. In addition, family studies have revealed that AN and BN do not aggregate independently within families, but rather that the risk of developing both disorders is elevated in family members of individuals with an eating disorder [35,36]. Furthermore, in a Swedish twin study, approximately half of the genetic factors contributed to liability of both AN and BN [37]. Future studies will need to clarify the relation further.

Epigenetics

Epigenetics studies external or environmental factors that switch genes on and off and affect how cells read genes, in relation to cellular and phenotypic traits. Thereby, epigenetic research seeks to describe dynamic alterations in the transcriptional potential of a cell. These alterations may or may not be heritable [38]. One of these epigenetic modifications is caused by methylation of DNA, which alters the function of DNA, typically acting to suppress gene transcription [38].

Hitherto, there are only a few published studies on epigenetic changes in ED. Using Genome-wide methylation profiles from women with AN and comparing that to normal eating women, discriminative methylation profiles were investigated in a study by Booij et al. [39] who found that AN patients showed higher and less-variable global methylation patterns than controls. Age of onset was significantly associated with differential methylation in gene pathways involved in development of the brain and spinal cord, while chronicity of illness was significantly linked to differential methylation in pathways involved with synaptogenesis, neurocognitive deficits, anxiety, altered social functioning, and bowel, kidney, liver and immune function [38]. In a study by Tremolizzo et al. [40] that included 32 patients with AN and 13 controls, it was found that whole-blood global DNA methylation in AN adolescents was modestly but significantly reduced compared to controls. The level of DNA methylation correlated with plasma leptin and steroid hormone levels. However, they did not find any correlation to clinical traits [40].

In another study in AN, investigating proopiomelanocortin (POMC)promoter-specific DNA methylation, it was found that this was not affected by diagnosis or nutritional status but was significantly, negatively associated with cigarette smoking [41], thus, albeit nutritional status influence one-carbon metabolism, there was no direct relation between gene-specific DNA methylation and folate levels. Yet another study, pilot sized, failed to identify any epigenetic changes in AN [42].

Appetite regulating hormones and Anorexia Nervosa

Although women with anorexia nervosa restrict their caloric intake, it is not clear as to whether they experience normal sensations of hunger. In addition, there is an increasing amount of support for signs of dysregulation of appetite regulating hormones in women with the disorder.

A common notion is that most of the secretory alterations of appetite/feeding regulatory substances are secondary to the nutritional changes occurring with the disorder. However, even if those changes should be state dependent, they may hypothetically still contribute to the continuation of both abnormal eating behaviors and/or other symptomatic features of Anorexia Nervosa [43]. A review of findings in regulatory substances reveals that

leptin, ghrelin, brain derived neurotrophic factor (BDNF) and endocannabinoids are consistently found to be affected, and they thereby may be particularly relevant in the modulation of both homeostatic and rewarding aspects of eating behavior.

Anorexigenic regulators

The anorexigenic regulators have been a target for investigations in AN. In addition to their homeostatic function, there are more and more support for that these appetite modulators also influence non-homeostatic for example cognitive, emotional and rewarding components of food intake as well as nonfood-related reward. Since both AN and BN have been pathophysiological linked to dysfunctions of reward mechanisms, these additional functions of the regulators may be especially important for the development of the disease as evidenced by the maintenance in self-starvation [43].

The anorexigenic hormone leptin, which is secreted by adipocytes after meals, and informs the brain on the amount of energy stored in the adipose tissues, and acts as a hunger suppressant signal, has been found to be lower in AN compared with controls, both in plasma and Cerebrospinal fluid [44-50]. In addition, the circadian changes in leptin has also been found to be abnormal with attenuation of the nightly surge in AN [51-53]. In contrast, the receptor through which leptin exerts its action, the OB receptor, is up regulated in AN [54], perhaps reflecting a compensatory mechanism. In weight restored AN patient, the levels of leptin in plasma normalize [45,48,50]. Interestingly, high leptin levels in weight restored AN patients may predict relapse [55]. Furthermore, low serum leptin has also been found to predict lifetime history of amenorrhea and subnormal levels of luteinizing hormone [56,57].

Leptin seems to be directly involved in reward mechanisms as leptin receptors have been found on dopaminergic neurons in the ventral tegmentum area (VTA), and seem to influence both the firing rate, dopamine release and concentrations in the nucleus accumbens (NAc) [58,59]. Furthermore, VTA dopaminergic neurons are activated by orexin pathways from the hypothalamus which has been found to regulate food- and drug-related reward [60,61], and leptin also decrease orexin tone in the NAc. A fMRI study in patients with congenital leptin deficiency, the exposure of visual food stimuli led to an activation of NAc and caudate, in spite of that the patients were in a positive energy balance. This effect was abolished after 1 week of treatment with leptin [62].

Another secretory regulator is the anorexigenic hormone Peptide YY which have been described as elevated in AN [63,64], and which do not normalize after treatment [65]. One study found normal Peptide YY levels at fasting state but a significantly higher increase after breakfast in AN compared to healthy controls. The number of individuals in this study was small and the graph (Figure 3 in the publication by Sedlackova et al. [66]) in the publication indicates a potential difference with already higher baseline levels in AN [66]. Yet another study found decreased Peptide YY levels in AN [67]. One potential confounder is that different assays for Peptide YY was used. The increase seen in AN in some studies of Peptide YY, which is secreted by intestinal L cells, is difficult to explain and appears contradictory, since it is released in response to food intake, which is reduced in anorexia nervosa. Peptide YY has thereby been proposed to be involved in the pathophysiology of AN.

Orexigenicregulators

Ghrelin is an orexigenic hormone, secreted by the oxyntic cells of the stomach [68]. Ghrelin levels increase immediately before meals, and reach its lowest concentration approximately 30 minutes after food intake in normal healthy individuals [68]. In AN, studies have reported increased fasting and overnight ghrelin levels [66,69-71], which are inversely associated with BMI, fat mass, and insulin. A potential difference exists between restrictive and binge-purge types of AN with ghrelin levels as compared to controls, having been found to be increased in the restrictive type [66,67,69] versus decreased in the binge/purging type of AN [67].

Obestatin, a ghrelin gene product that inhibits appetite and gastric motility, has also been found to be increased in adults with AN [66,65,72-74], and positively associated with ghrelin [73,75]. The plasma ghrelin/obestatin ratio have been reported to be increased in anorexia nervosa [71], although there are reports of a decreased ghrelin/obestatin ratio [76].

Neuropeptide Y (NPY) is a neuropeptide that acts as a neurotransmitter in the brain and in the autonomic nervous system of humans.The stimulation of NPY-ergic activity via the administration of certain NPY agonists increases food intake in rats [77,78]. The production and release of NPY in the hypothalamus is stimulated by ghrelin, which signals hunger to the brain, subsequently leading to increased appetite and feeding behavior. Most studies of plasma or serum levels of NPY in AN patients have found normal [79-83] or decreased [84-86] levels as compared to controls, while two studies from the same group found increased levels [66,72]. Some have argued that the NPY system is not up-regulated under chronic under-nutrition suggesting that this may play a role in the inability of anorectic women to adapt food intake to their energy demand [81]. The results by Sedlackova et al. [66,72] stand in contrast to this and need further explanation. In contrast to NPY, low circadian α-Melanocyte-stimulating hormone (α-MSH) levels integrate the adaptive profile of appetite regulation of AN, and an evident α-MSH peak detected during lunchtime may explain why patients with constitutional thinness are rapidly food satisfied [81].

α-MSH is an endogenous peptide hormone and neuropeptide of the melanocortin family, and a non-selective full agonist of the melanocortin receptors. Its regulation of appetite, metabolism, and sexual behavior is mediated through both the MC3 and MC4 receptors. One study found that Plasma α-MSH levels were significantly lower in AN (vs controls) all over the day [81], while another study found no difference in AN to controls [87]. Interestingly, auto-antibodies towards α-MSH may play a role in the pathophysiology of AN [88].

Conclusion

Overall, there is a paucity of articles/studies on potential biomarkers of AN, at least as compared to the research fields of schizophrenia and affective disorders. This review managed to find only a few number of articles that included the term biomarker for AN. The emphasis in these articles was on the biology of the disease, and the terminology commonly used for biomarkers e.g. diagnostic biomarkers, trait and state biomarkers, were used only occasionally. A widening of the search criteria using terms

as genetic, epigenetic, and specific molecular markers, allowed for inclusion of articles that described biological changes in AN and the scope of this article consequently became to describe characteristic biological changes in AN.

There are few conclusive studies on genetics but more recent GWAS and larger studies find that genetic factors are risk factors for AN influencing the development of the disorder. Genetic risk factors are also independent of BMI.

Early studies which targeted genes that were hypothesized to be involved, based on the phenotype of AN, indicated the serotonergic system although no convincing evidence were found. Later studies, including GWAS, have mapped AN to chromosome 1p33-36 and potentially also 1q31. How these loci may mechanistically sub-serve the development of AN is currently unclear. Multiple loci may act conjointly and there may be more critical regions for AN development. Currently, there is a major initiative called the AN Genetics Initiative (ANGI) to investigate the whole genome in a large population of AN patients, and preliminary results indicate chromosome 1p33-36 as one og the loci involved. Future analyses in a larger population will clarify the gene contribution to AN.

Studies on epigenetic changes in AN have described hypomethylation or a normal degree of methylation of the genes in AN. There are only a few epigenetic studies as to date and interpretations must be made with caution..

With regard to the appetite regulating hormones, the most consistent finding is a decrease in leptine levels. Usually, leptine levels in plasma, being an anorexigenic regulator, increases after intake of a meal but in AN, the leptin levels are suppressed, at least during the acute stage when the BMI is very low. Leptin levels normalise with recovery from AN and thereby, leptine would qualify as a state biomarker in AN. Other findings in AN are increased levels of ghreline, an ortexigenic regulator, and increased obestatin. The changes in leptine, ghreline and obestatin may reflect the stress that the body is suffering during acute or prolonged starvation. The findings concerning biomarkers such as NPY and alpha-MSH are conflicting and the number of studies small so any conclusions cannot be drawn.

There are several potential confounders and limiting factors and the most evident is the small number of studies. Other confounders may be the use of different assays, non-standardized sample collection procedures, differences in age, and BMI range. There may also be yet unknown biological factors that should be corrected for or phenotypic aspects that influence biological factors. Overall, the few number of studies done limits the knowledge on biological changes in AN, and future studies will need to clarify the picture.

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