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A neurodevelopmental model for anorexia nervosa

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Abstract

This paper integrates genetic and biological data on aetiological risk for anorexia nervosa (AN) with cognitive and psychosocial explanatory models. We have reviewed clinical and basic science data from each of these domains and then used a developmental perspective to formulate a multifactorial threshold model. By positioning interpersonal stress as a central component of this model, psychological, social and biological conceptualisations of AN can be used to generate a data driven, neurodevelopmental hypothesis for the aetiology of this complex disorder.

Keywords: Anorexia nervosa; Aetiology; Developmental; Attachment; HPA axis; Chronic stress

1. Introduction

Anorexia nervosa (AN) is a disorder of complex aetiology, in which genetic, biological, psychological and sociocultural factors appear to contribute significantly to susceptibility. However, few of these risk factors are specific to AN and no single factor has been shown to be either necessary or sufficient to express the disorder. A multifactorial threshold model is therefore an appropriate explanatory model.

In the proposed model, genetic factors and early life experience interact to generate susceptibility to a chronic submissive type stress response and to hypothalamic–pituitary–adrenal (HPA) axis dysregulation. Psychosocial and biological changes associated with puberty exacerbate vulnerability, such that when stress is encountered, the coping response is maladaptive and an aberrant HPA axis response is elicited. Specifically, the HPA axis fails to adapt to the chronicity of a stressor, in that there is persistently elevated corticotrophin releasing hormone (CRH) activity rather than a switch to an alternative adrenocorticotrophic hormone (ACTH) secretagogue, such as arginine vasopressin (AVP). Prolonged elevation of CRH release leads to a persistent loss of nutritional homeostasis. Data from both basic sciences and clinical research will be presented to support this neurodevelopmental model for the aetiology of AN.

Before describing any model of aetiology, it is necessary to define the clinical condition. Although this may seem to be self-evident, in that the condition is easily recognised by the characteristic severe underweight, the criteria used to define the illness in modern diagnostic systems have been criticised for overemphasis upon pathoplastic features of the disorder such as fear of fat, which may be absent in a significant proportion of cases [1]. Furthermore, there is disagreement about whether there is disturbance of appetite. Reduced hunger and desire to eat, coupled with increased fullness and satiety after a test meal, have been reported in AN [2,3], although the capacity to respond to physiological hunger and satiety cues may not be entirely absent [4,5]. Some authors argue that these findings reflect tight cognitive control of normal appetite [6]. However, relative to healthy comparison women, those with AN show reduced salivation [7], a heightened autonomic response to food [8] and fear and disgust in response to images of food [9].

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Following recovery, there is a diminished response to the appetite suppressing effects of fenfluramine [10]. These objective data suggest that appetite regulation may indeed be impaired in AN [11].

The neurodevelopmental model of AN that is proposed does not address the fact that there are established restricting and binge-purge subtypes. Arguably, it is applicable to both subtypes because they both escape from normal weight and satiety-related mechanisms and differ more in terms of personality and behaviours [12].

2. Genetic factors

Family and twin studies indicate an increased risk of both AN and bulimia nervosa (BN) in relatives of AN and BN probands [13–15]. In addition, subthreshold forms of eating disorders (ED) appear to lie on a continuum of liability with full ED [16]. Genetic factors are estimated to contribute 58–88% of the risk for developing AN [17], but it is extremely unlikely that a single gene effect accounts for this heritability. Multiple genes probably contribute to the genetic liability via a range of phenotypic features, including components of nutritional homeostasis [18], and temperamental traits [14]. Multipoint linkage analysis using the broad diagnostic category of AN/BN did not yield evidence for suggestive linkage in the entire genome [19]. However, analysis of a much smaller subset of kindreds, characterised by those pedigrees with at least one pair of relatives with the narrow phenotype of restricting AN, yielded evidence for linkage to chromosome 1p34 [19]. Drive for thinness and obessionality tracked most closely with AN and there was also suggestive linkage to chromosomes 1, 2 and 13 [20]. BN and self-induced vomiting have been found to be linked to chromosome 10 [21]. In a study of the Amish, the heritability for disinhibition of eating and restraint was found to be 40% and 30%, respectively, but the areas of linkage for these eating behaviours did not relate to any of the regions found in pathological eating [22].

3. Perinatal factors

3.1. Attachment

Prior to the birth of a child who goes on to develop AN, 25% of parents may have experienced severe obstetric difficulty and loss compared with only 7.5% of matched comparison parents [23]. In addition, the incidence of prematurity and birth trauma is elevated by two- to threefold in the birth histories of those with AN [24]. It is perhaps understandable in this context that mothers report heightened anxiety during pregnancy and the perinatal period and are possibly overcontrolling and overprotective throughout the child's development [23].

The neonatal period is a time of great plasticity in which psychosocial and biological development is influenced by genetic and environmental factors. Anxious, insecure attachment is a consistent finding in the ED literature [25] and is an understandable outcome in an environment of anxiety and unresolved loss. More specifically, dismissive attachment style is overrepresented in those with AN and possibly also their parents [26]. Dismissive attachment is associated with minimisation of emotional expression and deficits in emotional processing, which may set the child on a developmental trajectory in which emotional regulation and the capacity to resolve trauma and loss is impaired [27].

3.2. Early life experience and the HPA axis

Data from animal models demonstrate that early life experience, akin to the attachment experience of human infants, may have a critical role in shaping the development of biological systems of the brain. The HPA axis, a key component of the stress response system, is modified by maternal behaviour [28]. Rat pups experiencing optimal levels of maternal care develop highly efficient central negative feedback mechanisms, which tightly regulate the HPA axis. In contrast, those experiencing maternal deprivation have a relative impairment in these systems and hyperactivity of the HPA axis [29]. These alterations in HPA axis activity are mediated by altered frontal and hippocampal glucocorticoid receptor (GC-R) density, which persist throughout life [30], giving rise to impaired feedback inhibition and thus heightened CRH activity and hypercortisolaemia. 5HT system activity is also influenced by attachment experience and may mediate the developmental variation of GC-R density [31].

Both genetic and environmental factors appear to modify the developmental impact of early life events on stress response systems [32]. Developmental adaptation may commence as early as the first trimester [33], when exposure to maternal stress increases the susceptibility of the HPA axis to adverse events in the postnatal period [34]. A positive corollary of this is that good parenting in the neonatal period may reverse the impact of prenatal stress [35]. In animal studies, significant modulation can take place within the normal range of variability in parental care, indicating that early life experience need not be within the realms of abuse to give rise to HPA axis modulation [28].

Prolonged exposure to hypercortisolaemia is associated with hippocampal atrophy in animals and humans [36–38] and impairments of learning and memory [39–41]. Because the hippocampus exerts tonic inhibition on the HPA axis, hippocampal atrophy may exacerbate hypercortisolaemia, which in turn may further endanger the hippocampus and cognitive function [36]. In addition, the hippocampus is particularly vulnerable to hypoxia-induced damage [42] and birth trauma may also therefore contribute to individual differences in stress responses.

3.3. Early life experience and appetite regulation

By the time of adolescence, maternally deprived rats weigh significantly less than their nondeprived counterparts [43], suggesting that early functional alterations in the HPA axis and 5HT system may impact upon appetite regulation in later life. Adequacy of nutrition during the pre- and postnatal period can also affect appetite programming. For example, reduced nutrition during lactation results in reduced appetite throughout life [44]. In contrast, poor fetal nutrition is associated with a "thrifty phenotype" characterised by enhanced risk of the metabolic syndrome of obesity and type II diabetes in later life [45,46]. Thus, genetic and early environmental factors may contribute to down-regulation of appetite and the lean phenotype associated with AN [18].

3.4. Childhood development: affect, cognition and interpersonal style

Many of the childhood risk factors for AN may result from an interaction between genetic factors and early attachment experience shaping interpersonal relationships and the biopsychosocial response to stress. For example, minimal parental involvement and affection [47,48], lack of close friends [48,49] and poor recall for attachment-related memories [50] may reflect the turning away from emotional attachment needs, which characterises dismissive attachment. Such attachments may also contribute to impaired development of self-reflective function [26], with difficulty in developing a Theory of Mind [51] or metacognition [52]. Indeed, AN has been conceptualised as an empathy disorder with autistic features [53]. High alexithymia scores [54] and impaired emotional recognition [55] associated with AN likely reflect impaired emotional processing.

Given these deficits in emotional regulation, overdependence upon cognitive rules is a reasonable strategy for self-management [56] and perhaps contributes to the rigidity of cognitive and interpersonal style described in association with AN [57,58]. OCPD traits in childhood are associated with increased risk of AN [59] and both OCPD and cognitive rigidity persist after recovery [60].

Each of these risk factors might contribute to susceptibility to AN via an impaired capacity to manage stressful events and difficulties. Indeed, the high prevalence of unresolved trauma and loss [25] attests to the difficulty individuals with AN experience processing emotional events. Furthermore, women suffering from AN report helplessness and lack of mastery prior to onset and avoidant (dismissive) coping response to the triggering event [61,62]. Paradoxically, poor self-regulation and coping increases attachment needs, whilst a dismissive attachment style and compulsive self-reliance [25] control expression of need and limit both quality and quantity of attachment relationships.

Those vulnerable to AN may therefore enter the important and challenging developmental phase of adolescence with significant impairments of self-management, interpersonal relationships and biological systems, such as those regulating stress responses and appetite.

4. Adolescence: transition and maturation

Adolescence is a time of profound biological, psychological and sociocultural change and demands a considerable degree of flexibility to successfully manage the transition into adulthood. Change may challenge the rigidity of those vulnerable to AN and open a window of vulnerability to dysregulation in relevant biopsychosocial systems. This may contribute to the timing of onset. In addition, the changes associated with adolescence differ in males and females and may therefore contribute to the sexual dimorphism of AN.

4.1. Biological changes at puberty

4.1.1. Metabolism

For women, adrenarche is associated with a rapid change in body composition so that fat stores increase to $\sim$17% of body mass [63]. This requires a period of plasticity in systems regulating appetite, weight and body composition. For example, leptin, synthesised and released from adipocytes, provides an important peripheral feedback signal to hypothalamic neurones involved in the regulation of appetite, weight and fertility [64]. Whilst nutritional intake is stable, leptin levels are proportional to fat mass in both AN and healthy women [65,66]. Peripubertal weight gain is therefore associated with a rise in circulating leptin levels, requiring the hypothalamus to maintain weight around a new set point. Thus, puberty may be associated with a window of vulnerability in the systems regulating appetite and weight. This concept may also be applicable to at risk groups, such as athletes: the combined effects of demanding physical exertion and of efforts to maintain extremely low body weight may serve to reenter the individual into this window of vulnerability. However, it is interesting to note that in a community sample risk factors for dieting did not enhance risk for developing AN [47].

In studies of the relationship between body mass index and eating behaviours in twins, the shaping of phenotype by genes and the environment appears to undergo a step change at puberty. Shared environment has an effect in the prepubertal twins, but this effect disappeared at puberty when additive genetic influences became the dominant contributor to the variance in ED scores. However, genetic influences on postpubertal eating behaviours appear to be largely independent of those affecting body mass index [67].

Taken together, these findings suggest that peripubertal expression of genetic influences on the biological systems governing weight and body composition may be more pertinent to the risk of developing AN than shared environmental factors, such as those promoting dieting.

4.1.2. Endocrine systems

The rise in oestrogen levels associated with puberty in females may also play a role in the sexual dimorphism of AN. Oestrogen modulates serotonergic function via a variety of mechanisms including altered 5HT receptor number and 5HT synthesis and metabolism [68]. CRH synthesis is also directly regulated by oestrogen via an oestrogen response element in the promoter region of the CRH gene [69]. Torpy et al. [70] have suggested that oestrogen-mediated stimulation of CRH contributes to gender differences in stress responses and that this may be important in AN. Oestrogen-induced down-regulation of hippocampal mineralocorticoid receptors (MR) [71], which make an important contribution to HPA axis feedback inhibition, may be a further mechanism by which oestrogen enhances stress responsivity. This concept is supported by the observation that in young men exogenous oestrogen enhances psychosocial stress-induced HPA axis activation [72]. The peripubertal rise in oestrogen may therefore have impact upon mood, stress responsivity and appetite regulation in women. Rising oestrogen levels may also contribute to the sexual dimorphism of adolescent brain maturation [73].

4.1.3. Brain development

A major phase of synaptogenesis, pruning and myelination of predominantly frontal and limbic areas occurs around the time of puberty and adolescence and is thought to have a functional role in the integration of emotional processing with cognition [74]. Reaction time for emotional recognition increases during adolescence until pruning improves the efficiency of frontal circuitry [75] and speed of attentional set shifting increases as the anterior cingulate gyrus increases in size [76]. Thus, an arrest in brain development at this critical stage could contribute to the impairment of emotional recognition and cognitive set shifting reported in those vulnerable to AN [58]. In addition to reduced amygdala–hippocampal volume in women recovered from AN [77], grey matter volume is also reduced [78]. In functional imaging studies, women recovered from restricting AN show activation in brain areas responsive to food cues in healthy women (e.g., apical and lateral prefrontal cortex) but also in areas typical of the response in acute AN (orbitofrontal and anterior cingulate) [79]. Whether these abnormalities reflect neurodevelopmental processes underlying the illness or the effects of starvation upon the developing brain cannot be discerned from these studies.

Profound change in the hormonal environment and plasticity of neural networks around the time of puberty may exacerbate impairments of emotional processing and heighten HPA axis responsivity whilst elevating risk of dysregulation in systems governing appetite and weight. For those entering adolescence with susceptibility to AN, these biological changes may significantly enhance the risk of onset of disorder, particularly in women.

4.2. Psychosocial and cultural transitions

Transition from childhood dependence to adult autonomy is one of the major developmental tasks of adolescence. Poor self-reflective functioning, dismissive attachments, inflexible interpersonal and cognitive style and excessive compliance with anxious, overprotective and controlling parents are liable to hinder this process in those vulnerable to AN. Similarly, a lack of flexibility may contribute to the elevated risk of ED associated with cultural transitions [80], although it is likely that the majority of participants in these studies suffered BN rather than AN. Failure to successfully negotiate the transition into adulthood, both within the family and within the broader cultural context, is liable to expose an individual to significant intra- and interpersonal conflict and stress.

5. The HPA axis in AN

The HPA axis shows several abnormalities in underweight patients with AN. Plasma cortisol is raised in the context of normal plasma levels of ACTH [81–84] and raised levels of CRH in cerebrospinal fluid (CSF) [85]. Peripheral metabolism of cortisol is reduced, and the adrenal cortisol response to ACTH is increased, suggesting adrenal hyperplasia and hypertrophy [86]. Dexamethasone fails to suppress cortisol release in over 90% of patients with AN [86] despite intact feedback loops at the level of the pituitary [87]. These findings are consistent with HPA axis hyperactivity arising via dysregulation of the feedback inhibition loops at the level of the hypothalamus or above. Early studies suggested that HPA axis dysregulation may resolve with weight gain [82,85,88], but recent evidence indicates that lack of a cortisol response to a meal and hypercortisolaemia may persist even after full recovery from AN [10,89].

Hippocampal volume is reduced in women with acute AN (unpublished data) and reduced amygdala–hippocampal volume persists following recovery from the disorder [77], although neither study found evidence of an association with impaired HPA axis regulation. It remains unclear whether hypercortisolaemia and reduced amygdala–hippocampal volume in women recovered from AN reflect a vulnerability factor, perhaps arising from the developmental effects of early life adversity, or a scar of the illness.

The hypothesised relationship between HPA axis hyperactivity and early life experience is not specific to AN. Indeed, altered HPA axis function has been demonstrated in adults who have experienced parental loss [90] or abuse in early life [91,92], and plasticity of stress response networks has been hypothesised to play a role in vulnerability to depression, anxiety and posttraumatic stress disorder (PTSD) [28]. Nevertheless, the genetic context in which environmental factors operate and the interaction between

pre- and postnatal experiences may confer a degree of specificity to early modifications in the stress response systems.

6. The serotonergic system in AN

Altered serotonergic system function is well recognised in AN. During the acute disorder, indices of serotonin turnover are reduced [93], and some serotonergic challenge tests are suggestive of altered 5HT1aR and 5HT2R activity [94–96]. Again, these changes tend to normalise with weight gain (for example, Ref. [93]), although there is some evidence of persistent 5HT2R dysfunction and elevated serotonin turnover after long-term weight restoration [94,97,98]. More recently, positron emission tomography (PET) has demonstrated reduced 5HT2aR binding in the mesial temporal cortex (including amygdala and hippocampus) of women recovered from restricting AN, possibly reflecting a compensatory down-regulation of receptors in response to increased serotonin availability [99]. Serotonergic overactivity is associated with common features of AN, such as harm avoidance/behavioural inhibition, anxiety, obsessive compulsive symptomatology and enhanced satiety [100], adding credence to the hypothesis that serotonergic overactivity is a trait-related phenomena.

From these studies, it can be hypothesised that in those vulnerable to AN an interaction of genetic and early environmental factors gives rise to overactivity of the serotonergic system and HPA axis, such that the biological response to stress is enhanced throughout life. Serotonergic overactivity and early life experience may also have important implications for personality and psychological development throughout childhood.

7. Submissive responses and chronic stress

In social ranking theory, individuals low in the social hierarchy have little prospect of winning conflicts and must therefore resolve social conflict either by submission or by escape [101]. If escape is barred, an individual becomes trapped in a submissive stance. It has been hypothesised that it is this perception of involuntary submission to dominant others that gives rise to depression in humans [102].

A severe life event or difficulty, generally of an interpersonal nature, was identified prior to onset in 67% of a clinical sample of cases of AN [103]. Whilst low self-esteem [47], lack of mastery and helplessness [62] may confer low social rank upon these women, submissive behaviour may be further encouraged by the characteristic placation and perfectionism of AN and sociocultural prescriptions for powerlessness of women [104]. Indeed, women with AN rank themselves unfavourably in social comparison with others and report high levels of submissive behaviour [105] even after recovery (unpublished data). Thus, we hypothesise that when stress is encountered in the context of an impaired coping response and adolescent transitions it is perceived to be overwhelming, uncontrollable and inescapable. This can entrap the individual in an egodystonic submissive response from which chronic stress results. Data from animal models suggest that this type of stress may be particularly relevant to the aetiology of AN.

7.1. Animal models of AN

There are animal models that may be prototypes of AN in nature. An example of a severe, morbid type of AN is lean sow disease [106] in which a percentage of sows at the lower end of the social ranking develop anorexia, infertility, overactivity and severe lethal weight loss [107]. This "thin sow syndrome" can be successfully treated with the 5HT2R antagonist, amperozide [108]. It is interesting that the females exposed to the chronic social stress of low social rank are those at highest risk and that the condition has emerged in those breeds selected for leanness. It has been postulated that in AN a similar genetic vulnerability to leanness exists as a risk factor [18,106].

7.2. Animal models of chronic stress

Submission stress (in which individual animals are introduced to a novel environment where they compete for resources) is one of the few models of chronic stress that is ethically allowable in animal studies. The low ranking animals develop reduced aggressiveness, altered psychomotor activity and reduced sexual, reproductive and appetitive behaviours.

Both the HPA axis and the 5HT system undergo adaptation during chronic stress. In animals, for example, chronic submissive type stress is associated with increased 5HT turnover and 5HT2 receptor up- and down-regulation of 5HT1a receptors [109–111]. This is significant because the 5HT system exhibits complex reciprocal regulatory interactions with the HPA axis. For example, recent animal data demonstrate that CRH is capable of modulating 5HT activity in a specific mesolimbocortical 5HT system that plays a role in affective and cognitive elements of anxiety and conditioned fear [112]. Conversely, the 5HT system plays a role in stress-induced anorexia via a mechanism involving 5HT2aR modulation of CRH release [113,114].

The HPA axis response to stress varies according to the nature and duration of a stressor [115,116]. The response to social submission stress primarily involves AVP and oxytocin (OT) release [117], CRH having a permissive role [116]. AVP expression is also elevated in response to chronic stress [118,119] and this is accompanied by up-regulation of AVP receptors on pituitary corticotrophs [120], sensitising the axis to AVP-induced activation [121]. Additionally, AVP may inhibit hypothalamic CRH release [122]. This chronic stress-induced switch from CRH to AVP-induced activation of the HPA axis may be critical in

maintaining corticotroph responsivity in the presence of high cortisol levels [123].

8. The HPA axis response to chronic stress in AN

Despite high levels of depressive symptomatology in AN, the mechanism of HPA axis hyperactivity appears to differ from that of depressive disorder. The latter is associated with evidence of heightened AVP release and sensitivity [124,125], in keeping with findings in animal models of chronic stress. In contrast, the lack of an enhanced response to a combined DXM/CRH challenge test suggests that AVP activity is not increased in AN [126] despite elevated levels of AVP in the CSF [127]. Thus, there appears to be a failure of chronic stress-induced up-regulation of AVP in AN and a state-related impairment of pituitary sensitivity to AVP [89,128] appears to underlie this abnormality. In the absence of enhanced AVP activity, the HPA axis hyperactivity of AN must therefore be mediated by sustained elevations of CRH activity.

9. Appetite regulation and the catabolic spiral caused by dysfunctional HPA axis response

Persistent, dysregulated release of CRH can significantly affect nutritional homeostasis [129]. CRH is a key effector in the catabolic network of the hypothalamus and produces anorexia when injected into the ventricles of rats [130]. This is at least in part because CRH is a powerful inhibitor of the synthesis of neuropeptide Y (NPY) [131], which is one of the key hypothalamic anabolic effectors, increasing food intake and fat storage [132]. Accordingly, stress-induced CRH release results in loss of appetite in addition to its role in stimulating release of cortisol, the end product of the HPA axis. Cortisol at concentrations attained in response to stress mobilises energy from liver and adipose tissue stores [133]. These catabolic effects of HPA axis activation are adaptive in response to acute stress when energy must be reserved for fight or flight. However, as stress becomes chronic, the ability to respond must be maintained; however, at the same time, unless the individual adapts to heightened HPA axis activation, weight loss will ensue.

As starvation develops, lowered insulin stimulates NPY release, thus activating anabolic pathways of the hypothalamus [134]. In turn, NPY stimulates HPA axis activity [135], further elevating cortisol, which increases NPY activity in central anabolic pathways. This feed-forward system for restoration of appetite and weight is dependent upon effective cortisol feedback inhibition, which suppresses CRH release; and the consequent catabolic response [129]. If cortisol feedback is ineffective, CRH release remains persistently elevated and both stimulates catabolic pathways and inhibits NPY activity in anabolic networks.

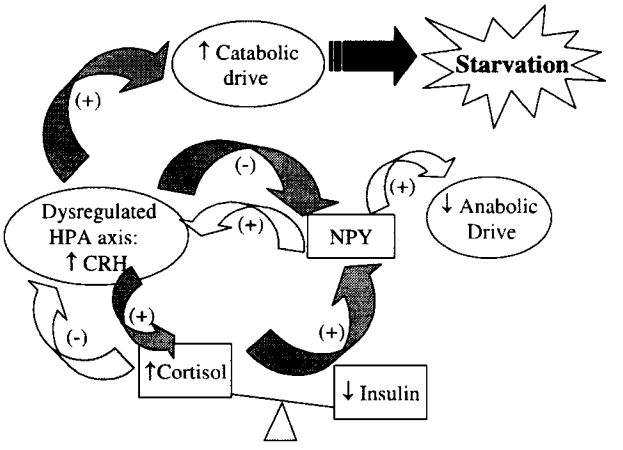

Fig. 1. When the HPA axis is activated in response to stress, CRH activity stimulates cortisol release. The ratio of cortisol to insulin rises, stimulating hypothalamic NPY release. However, because CRH inhibits NPY activity, activation of anabolic pathways is prevented. As starvation ensues, low insulin levels further stimulate NPY release, which in turn stimulates further cortisol release from the HPA axis. A feed-forward system promoting activity in anabolic pathways is therefore generated. However, this system is dependent upon effective cortisol feedback inhibition to inhibit CRH release and thus reduce inhibition of NPY. In the context of impaired feedback regulation of CRH, a catabolic spiral is initiated, in which rising cortisol can neither stimulate NPY nor inhibit CRH release.

Thus, a catabolic spiral may ensue in which loss of appetite and weight persist [129] (see Fig. 1).

The switch from CRH-induced to AVP-induced activation of the HPA axis as stress becomes chronic may be critical in facilitating a sustained HPA axis response whilst reducing CRH-mediated inhibition of appetite. Our hypothesis is that there is a failure of this adjustment to chronic submissive type stress in AN that leads to a pathological dysregulation of the HPA axis and appetite system. Those vulnerable to AN fail to up-regulate AVP activity and CRH is therefore persistently elevated and dysregulated, such that there is a failure of nutritional homeostasis and life-threatening starvation. Serotonergic modulation of the HPA axis both during development and in response to chronic stress may be important in the aetiology of this aberrant HPA axis response. Once initiated, dysregulated CRH release may result in weight loss both via inhibition of anabolic pathways of the hypothalamus and via modulation of serotonergic function.

10. The broader role of CRH

CRH-containing neurones and CRH receptors are widely distributed in the brain and are particularly dense in the hypothalamus, pituitary, limbic system, prefrontal and cingulate cortices and autonomic structures. CRH projections are therefore well placed to mediate emotional, behavioural and physiological responses to stress (see Ref. [136] for review). In addition to activation of the HPA axis, CRH

release stimulates autonomic system activity and endorphin release, modulates noradrenergic, dopaminergic and serotonergic neurotransmitter systems and acts as a central neurotransmitter in its own right (see Ref. [137] for review). Via these mechanisms, stress-induced CRH release gives rise to suppression of reproductive hormones, reduced sexual behaviour, cardiovascular changes that include hypotension and bradycardia, delayed gastric emptying, altered locomotor activity, decreased pain sensitivity, increased anxiety behaviour, reduced social interactions, decreased exploratory behaviour in novel environments, altered conditioned avoidance, increased vigilance, altered immune system function and the effects on appetite and feeding described above [137]. These features appear strikingly consistent with the presentation of AN.

11. A neurodevelopmental model of AN

Persistently elevated and dysregulated CRH release is hypothesised to be the central common pathway generating sustained suppression of appetite and thus severe weight loss in AN. Clearly, stress-dependent changes in HPA axis function are not in themselves the cause of the disorder: were it the case, subjects with PTSD would develop AN. In a similar way, it is unclear why some individuals who experience chronic severe childhood adversity are prone to depression rather than AN. However, differences in the mechanism of HPA axis hyperactivity between the disorders may be pertinent: for example, AVP appears to contribute to the HPA axis hyperactivity of depressive disorder, but not AN. Furthermore, a complex interaction between multiple genetic factors, early life experience and the biopsychosocial environment around the time of puberty may confer specific risk for AN through effects upon regulation of emotion and appetite. Further research is clearly needed to test this hypothesis, as the limited data currently available provide only weak support for a biological dysregulation of appetite in AN.

It is proposed that genetic factors interact with early attachment experience to modify HPA axis regulation, resulting in protracted and poorly regulated stress responses throughout life. In addition, these same factors may set a developmental trajectory for maladaptive emotional, cogni-

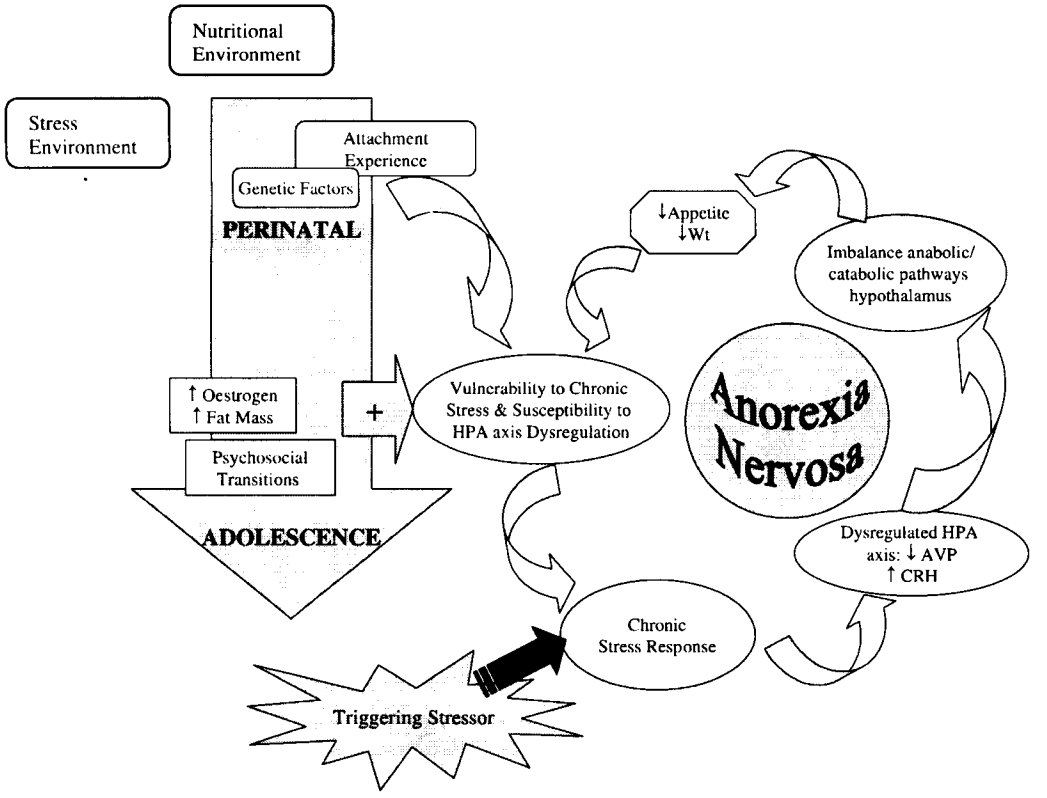

Fig. 2. Early attachment experiences interact with genetic factors to modulate personality features, childhood psychosocial development and HPA axis development. In individuals at risk of AN, these factors result in impaired coping and a tendency to submissive responses. By the time of adolescence, there is increased vulnerability to chronic stress and susceptibility of the HPA axis to dysregulation. These vulnerabilities are exacerbated by the biological and psychosocial changes associated with puberty, especially in females. Exposure to a significant stressor at this critical time triggers a dysregulated HPA axis response, which is characterised by a failure to up-regulate AVP activity and persistently elevated CRH activity. This results in disruption of the balance between anabolic and catabolic pathways of the hypothalamus, causing loss of appetite and weight. Once initiated, underlying susceptibility factors and the impact of starvation upon psychological and biological systems maintain the vicious cycle of AN.

tive and social functioning and thus a limited capacity to cope with and to resolve stress. Low self-esteem, disempowerment and the temperamental traits of placation and perfectionism may foster a tendency toward chronic stress analogous to chronic submissive stress in animals. Thus, the individual vulnerable to AN enters adolescence with a susceptibility to both HPA axis dysregulation and poor coping style. The biopsychosocial changes associated with puberty, many of which show significant sexual dimorphism, further exacerbate these susceptibility factors.

Difficulty negotiating adult autonomy may in itself represent a significant stressor, but it is more usual for there to be additional difficulties. We propose that chronic stress in individuals predisposed to AN leads to an aberrant HPA axis response, characterised by failure of AVP up-regulation and persistently elevated CRH release. Serotonergic dysfunction may be both the cause and the effect of this dysregulated stress response.

Excessive CRH activity is associated with many of the symptoms of AN, including loss of appetite and weight. Appetite impairment likely arises from the direct impact of CRH on the delicate balance between anabolic and catabolic pathways of the hypothalamus, particularly in those with a predisposition to leanness (see Fig. 2).

Once established, predisposing and precipitating factors for AN are likely to be of continued importance in maintaining HPA axis dysregulation and thus weight loss. The adverse effect of ensuing starvation on the maturing brain and psychosocial development may further contribute to maintenance of disorder. Putative cognitive behavioural reinforcers of the illness, such as a pseudo sense of control, safety and specialness, are also likely to contribute to chronicity [138,139].

12. Implications

In taking a developmental, biopsychosocial perspective on the aetiology of AN, this neurodevelopmental model may be easily and meaningfully applied to the individual experience of patients. Whilst many of the risk factors for AN may not be reversible, the tendency to maintain or trigger the disorder may be attenuated through psychotherapy. For example, the hypothesised vulnerability associated with anxious, insecure attachment relationships and impaired stress management may be ameliorated with a judicious mix of cognitive behavioural and attachment-based interventions. An association between AN and a tendency to submissive behaviour draws attention to the importance of avoiding power differentials in the therapeutic relationship and to a focus on enhancement of self-esteem and self-efficacy.

Whilst psychotherapy is an appropriate mainstay of treatment, psychopharmacological interventions to facilitate restoration of appetite and weight could be a useful adjunct. CRH antagonists attenuate the behavioural, neuroendocrine and autonomic responses to stress in rodents and primates and are currently being examined as potential antidepressants [140,141]. These compounds might also have efficacy in stimulating appetite whilst reducing the anxiety and arousal associated with refeeding in AN. It is certainly of interest that exercise-induced anorexia, a severe and lethal animal model of AN [142], can be prevented with CRH antagonists [143].

The proposed neurodevelopmental model for the aetiology of AN is supported by data from a wide range of disciplines. Further studies are clearly needed to test specific components of this expansive model. A multidisciplinary perspective embracing biological, psychological and social factors will be vital to an improved understanding of the aetiology and treatment of this complex and serious disorder.

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