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Cause and treatment of anorexia nervosa

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Abstract

The hypothesis that eating disorders are caused by an antecedent mental disorder, presently believed to be an obsessive compulsive disorder, has been clinically implemented during many years but has not improved treatment outcome. Alternatively, eating disorders are eating disorders and the symptoms of anorexic patients and probably bulimic patients as well, are epiphenomena which emerge as a consequence of starvation. This hypothesis is supported by the observations of the effects of a 6 month long period of semi-starvation on healthy human volunteers, which demonstrated not only the emergence of psychiatric symptoms but also the reduction in eating rate which is typical of anorexia nervosa patients. On this framework training anorexic patients how to eat may be a useful intervention. We report that anorexic patients, either with a body mass index <14 or >15.5 display the same pattern of eating behavior, with a low level of intake, a slow eating rate and a high level of satiety. They also have the same, high level of psychiatric symptoms, including obsessive compulsive symptoms. Training patients to eat more food at a progressively higher rate reverses these symptoms and patients remain free of symptoms during an extended period of follow-up. It is suggested that the pattern of eating behavior mediates between the starved condition and the psychopathology of anorexia nervosa.

Keywords: Anorexia; Eating behavior; Psychiatric symptoms

1. Introduction

Eating disorders, including anorexia nervosa, bulimia nervosa and eating disorders not otherwise specified, are considered chronic psychiatric disorders which are difficult to treat and, most likely for these reasons, they are also believed to be multifactorial disorders or unknown etiology [1]. We first review the prognosis, outcome, treatment and current theories of the causes of eating disorders. Because outcome has not improved significantly over a considerable period of time, we offer an alternative framework of the cause of eating disorders and outline its clinical implementation. The major difference between patients with anorexia nervosa and bulimia nervosa is that anorexics are underweight but bulimics are normal weight. Most, if not all, other aspects are similar and it seems likely that anorexia and bulimia are two phases of the same disorder. Our discussion will concentrate on anorexia.

2. Prognosis, outcome and treatment

The published prevalence of anorexia nervosa varies between 0 and 1% and is about 0.3% on average and the age of onset of the disorder is 14–19 years [2]. Most patients (95%) are females. The chance of recovery is less than 50% in 10 years, about 25% remain ill and the mortality varies between 0 and 25% [3]. While weight restoration of malnourished anorexics is manageable, relapse is a problem [4]. These findings are the basis for the view that anorexia nervosa is a chronic disorder. This distressing scenario has not changed in 50 years [3].

Many anorexics display bulimic behavior and most bulimics have a history of anorexia. And so it is neither surprising that the prevalence for bulimia is about the same as that for anorexia nor that bulimic patients are older than anorexic patients [2]. Although the situation for patients with bulimia nervosa is considered less severe than that for anorexics, outcome in bulimia is also poor [5].

Guidelines for the treatment of patients with eating disorders have recently been launched in many countries (e.g., [6]) and these are based on the available scientific evidence. In the case of anorexia nervosa, the guidelines are based on very weak evidence. For example, “the only evidence that anything works in adult anorexics” is a study in which cognitive behavioral

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therapy reduced the rate of relapse from 53 to 22% [4]. A review of 5512 studies on the same topic found only six studies that fulfilled scientific criteria and out of these only two that indicated some effect of treatment [7]. Even this appears to be an overstatement. Thus, one of the studies [8] reported that 35% of the patients dropped out of treatment, that there was some response in the remaining five out of six patients in comparison with two patients in a control group and that 50% of the patients dropped out of the study upon follow-up 1 year later.

The scientific basis for the suggestion that family-based treatment is effective in children with anorexia nervosa is a randomized controlled trial [9] and a follow-up of the results 5 years later [10]. In these studies, 6 out of 10 patients had a good outcome compared to 1 out of 11 in the control group. Upon follow-up, all patients, regardless of treatment, had improved and the authors concluded that their results could be "attributed to the natural outcome of the illness", rather than to the treatment [10]. Subsequent studies on the same topic have yielded similar results.

It is often claimed that cognitive behavioral therapy is effective in bulimia nervosa [1] and this type of treatment is therefore considered standard of care for bulimia in many countries. This also seems to be based on weak scientific evidence. Thus, a comprehensive review concluded that "there is a small body of evidence for the efficacy of cognitive behavior therapy in bulimia nervosa and similar syndromes, but the quality of trials is very variable and sample sizes are often small" [11]. A recent series of papers [12,13] has clarified the issue. Out of 194 patients who entered treatment, 54 (28%) dropped out or were withdrawn and only 58 (30%) of the 140, who completed treatment, went into remission. Upon examination 4 months after treatment, 21 (44%) out of 48 (ten could not be located) had relapsed. Thus, only 27 (14%) out of 194 patients who entered cognitive behavioral therapy bulimia were in remission 4 months after treatment.

The evidence that psychopharmacological treatment is effective in treating eating disorder patients is also weak [14].

We suggest that the reason why currently used treatments for eating disorders are ineffective is because they are based on erroneous assumptions and are often incompatible with well known facts in neurobiology. We outline these assumptions in the following paragraphs.

3. Current explanations of eating disorders

According to a main explanatory model for the development and maintenance of eating disorders, there is a mental disorder that predisposes an individual not only for anorexia but also for bulimia. The mental disorder is believed to have a genetic basis and an alteration in a brain transmitter system is thought to mediate the expression of the eating disorder [15,16]. While this hypothesis has been extensively tested, it has not yet yielded clinically useful results. In the following, we suggest a reason why.

4. Obsessive compulsive disorders and anorexia nervosa

While there have been many suggestions as to what kind of mental disorder causes anorexia (and bulimia), the hypothesis has recently been specified. Thus, it has been suggested that "childhood anxiety represents one important genetically mediated pathway towards the development of anorexia nervosa and bulimia nervosa" and that this is reflected in onset of obsessive compulsive disorder (OCD) before anorexia [15]. (We refer to this "genetically mediated pathway" as "genes" below.) A test of this hypothesis yielded the following results. Out of 94 patients with anorexia nervosa, 35% also had OCD. Upon examination of these, about 12% dropped out and of the remaining, 23% had OCD before they had anorexia nervosa. Thus, $94 \times 35\% \times 88\% \times 23\% = 7$ individuals out of 94 (7%) had OCD before they had anorexia nervosa [15]. As the majority of the patients had OCD simultaneously with anorexia nervosa, these data show that the expression of OCD before anorexia nervosa is rare.

The incidence of OCD increases exponentially when an individual approaches puberty with no difference between the sexes [17]. We must assume, therefore, that the major expression of the hypothesized genes for OCD and anorexia occurs simultaneously with the onset of anorexia or later and that the genes are expressed as anorexia only in girls (the prevalence of anorexia is very low in boys), but as OCD in both girls and boys. However, it was suggested that the genes may be expressed not only as OCD but as other anxiety disorders as well and that these disorders have a life time prevalence as high as 12–18% or even 30% [15]. Whether genes with such time-dependent, sexually dimorphic and phenotypically diverse expression patterns exist will be difficult to investigate.

Furthermore, while it is apparently possible to diagnose OCD retrospectively already at 5 years of age, it appears that childhood OCD is 8–12 times more prevalent in the USA (reported prevalence: 2–3%) [15] than in England (reported prevalence: 0.25%) [17]. If OCD causes anorexia, one would expect anorexia nervosa to be about 10 more prevalent in the USA than in England. There is no evidence that this is the case.

Another problem is that it is difficult to understand how the brain mechanisms which are involved in OCD might activate those that mediate the altered eating behavior of eating disorder patients. Thus, while the orbitofrontal and anterior cingulate cortex and the basal ganglia may play a role in OCD [18], their role in eating behavior is unclear. The neurobiology of eating engages mainly hypothalamic and brainstem regions [19]. The orbitofrontal cortex houses the secondary taste cortex and is concerned with the reward value of different taste, smell and visual stimuli and also has a role in learning [20], but we do not know if these functions are related to disordered eating behavior.

5. 5-hydroxytryptamine and anorexia nervosa

It has been suggested that the neurotransmitter system mediating the expression of anorexia nervosa (and bulimia nervosa) is 5-hydroxytryptamine (5-HT). This hypothesis was first tested by measuring the concentration of 5-hydroxyidol-acetic acid (5-HIAA), a metabolite of 5-HT and an indirect measure of the turnover of brain 5-HT, in the cerebrospinal fluid (CSF) of anorexic patients. One must obviously be cautious in

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interpreting changes in 5-HIAA in the CSF as a measure of the turnover of 5-HT at central neural synapses related to behavior, but this is the method that was first used to test the hypothesis that "a disturbance of serotonin may contribute to the pathogenesis of anorexia nervosa and bulimia nervosa" [21]. Thus, low levels of 5-HIAA were found in the CSF of anorexics with a low body mass index (BMI) [22]. However, it was correctly pointed out that this result may be related to the reduced protein intake of anorexics rather than to a genetically mediated disturbance in neural 5-HT metabolism [22]. When the concentration of 5-HIAA was subsequently measured in the CSF of weight restored anorexics, it was restored to normal in one study [22] and slightly, yet statistically significantly, increased above the normal level in another study [16]. Thus, all studies agree that anorexic patients have a low levels of 5-HIAA in the CSF. Most likely this is an epiphenomenon to the reduced food intake in low weight anorexics. If this is the case, it is hardly surprising that when body weight is normalized, because patients eat more food, 5-HIAA increases in the CSF. The evidence that it increases above normal levels, however, is very weak and was not replicated in a further study [23]. Hence, when anorexic patients gradually increase their BMI, obviously because they eat more food, there is an increase in the turnover of 5-HT in the brain. 5-HT is one of the best known inhibitors of food intake [24] and it seems highly unlikely that an increased activity in a neurotransmitter system that inhibits food intake is causally related to an increase in food intake. Thus, the available evidence argues against a role of 5-HT in anorexia nervosa.

Attempts to relate alterations in brain 5-HT function to anorexia nervosa have also included measurements of 5-HT receptor function. Thus, increased binding to the 5-HT2A receptor has been suggested to occur in anorexia nervosa [25] and reduced binding to the same receptor has been reported in weight restored anorexics [26]. Such alterations in receptor binding should be expected given the changes in the endogenous ligand that occur from a starved condition (low ligand concentration — increased receptor binding) to normal weight (increased ligand concentration — reduced receptor binding). In subsequent studies, the 5-HT2A receptor gene was investigated in samples from anorexic patients and changes in promoter polymorphisms were reported in four studies. However, five studies failed to replicate the findings [25]. While these results, and the results on the concentration of 5-HIAA in the CSF discussed above, show that some aspects of serotonin neurotransmission are altered in anorexia nervosa, they suggest that these are consequences, rather than causes, of the eating disorder. Also, interpretation of the results of most studies is complicated by the fact that, while the patients who have been studied are in remission from their eating disorder, they are never free of symptoms. Thus, although patients may be in remission from anorexia as evidenced e.g., by an increase in body weight and presence of menstrual function, they still display psychiatric symptoms (e.g., [15]). Any change in some aspects of neurotransmission in such patients, perhaps best viewed as in partial remission, may simply be related to these psychiatric symptoms rather than their previous eating disorder.

6. Clinical implementation of the 5-hydroxytryptamine hypothesis of anorexia nervosa

Because the evidence points to a correlation between an increase in BMI and an increase in brain 5-HT turnover in anorexic patients, it has been hypothesized that enhancement of 5-HT activity in the brain is a risk factor for this eating disorder [15]. This view was expressed clearly in a recent paper: "We hypothesize that people with anorexia nervosa have a trait-related *increase* (italics in paper) in 5-HT neuronal transmission that occurs in the premorbid state and persists after recovery" [27]. On this hypothesis inhibition of 5-HT turnover or blockade of 5-HT receptors should alleviate the symptoms of anorexic patients. Surprisingly, the opposite is part of the standard of care of patients with anorexia nervosa. Thus, use of selective serotonin reuptake inhibitors (SSRI), which enhance brain 5-HT activity [28], is wide spread. Less surprising, there is no evidence that SSRIs are useful in anorexia [14]. The idea that treatment with SSRIs might prevent relapse in weight restored anorexics is also inconsistent with available neurochemical evidence [16,22,23]. When partially weight restored anorexic patients were treated with an SSRI, 37% dropped out of the treatment within 8 months and when a comparable group of weight restored anorexics was treated with the placebo, 87% dropped out within 3.5 months [29]. All patients in this study showed elevated levels of psychiatric symptoms throughout the study and there were no differences between drop outs and non-drop outs. The main effect in this study, the dramatic drop out rate in both groups of patients, raises the issue of how the patients were treated to gain weight. These results were recently replicated [30].

Since there is no compelling evidence that alterations in any aspect of brain 5-HT function and anorexia nervosa are causally related, it is not surprising that clinical applications of the 5-HT hypothesis of anorexia have proven ineffective. A hypothesis that has yielded inconsistent results is best abandoned.

7. A framework for the treatment of eating disorders

As a recent review summarized: "The absence of authoritative evidence for treatment effectiveness makes it increasingly hard to protect resource intensive treatments in anorexia and bulimia nervosa, and existing theories of the causation of the disorders are too non-specific to generate effective programs of prevention. New models are urgently required" [31]. As a start, a new framework would be usefully. To cite another recent review (on a different topic): "A framework is not a detailed hypothesis or set of hypotheses; rather, it is a suggested point of view for an attack on a scientific problem, often suggesting testable hypotheses. Biological frameworks differ from frameworks in physics and chemistry because of the nature of evolution. Evolution produces mechanisms, and often sub-mechanisms, so that there are few 'rules' in biology which do not have occasional exceptions. A good framework is one that sounds reasonably plausible relative to available scientific data and that turns out to be largely correct. It is unlikely to be correct in all the details" [32].

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As a start, we pointed out that there are two known risk factors for anorexia nervosa: decreased food intake and enhanced physical activity [33]. It was pointed out long ago that anorexic patients, once they have started to eat less food, become physically overactive, that the physical hyperactivity is difficult to control and that it appears that the patients like to be active [34]. Both reduced intake of food and enhanced physical activity activate corticotropin-releasing factor (CRF) containing cells in the hypothalamus and these, in turn, activate mesolimbic dopamine (DA) neurons and locus coeruleus noradrenergic (NA) cells [33]. These are the neural basis for reward and attention. These facts allow the formulation of a framework according to which anorexia nervosa develops because it is initially rewarding to eat less food (CRF activation of DA-reward neurons) and is subsequently maintained because anorexic behavior is conditioned (CRF activation NA-attention neurons) to the stimuli which initially provided the reward [33]. The framework is outlined in Fig. 1.

On this framework, the symptoms of anorexic patients develop with the progression of starvation. Can it be extended to include the psychiatric symptoms in anorexia nervosa? Are they signs of starvation as well as? The answer to that question is available since 55 years. In a remarkable study, Keys et al. asked healthy male volunteer to eat less food during 6 months and these men developed most of the symptoms of anorexic patients, including the psychiatric symptoms [35]. As the participants in this study were healthy at the start of the study, the results suggest that anyone can develop the symptoms of eating disorder patients by eating too little food for too long. There is no need to postulate a predisposing mental, or non-mental, disorder.

We use this "explanatory model" as a framework in the sense outlined above. Alternatives that can assist in improving the condition of the patients are welcome and we will modify our views accordingly.

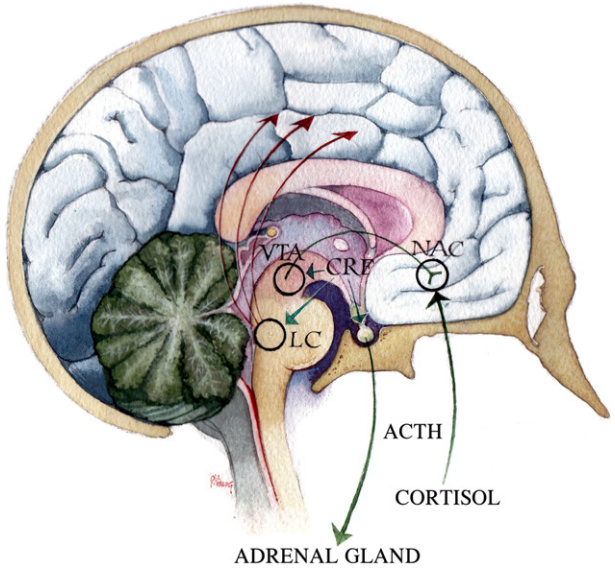

Fig. 1. Framework of the neural concomitants to starvation and the emergence of anorexia nervosa. Corticotropin-releasing factor (CRF) is released when food intake is reduced. This activates the pituitary–adrenal axis (ACTH-cortisol secretion) which enhances dopamine (DA) release from mesolimbic terminals in the ventral striatum (n accumbens, NAC). CRF also activates the DA-cell bodies in the mesencephalon (VTA, ventral tegmental area). This is why patients experience "reward" when first dieting. CRF also activates the noradrenergic neurons in the locus coeruleus (LC), the substrate for attention. Anorexia develops because it is rewarding to diet and it is maintained because the behavior becomes conditioned to the stimuli that provided the reward via the neural system for attention. Slightly modified from Ref. [33] with permission from Nature Publishing Group.

8. Clinical implementation of the framework

Teaching patients how to eat is of primary importance in the treatment of patients with anorexia nervosa assuming the framework outlined above is correct. Learning is dependent upon the physiological state of the individual and upon contextual cues during learning [36]. Recent evidence indicates that both NA [37] and DA [38] play roles in learning which are compatible with our framework. The clinical implication of these facts is that patients should learn to eat in an environment free of the contextual cues that were present when the anorexia developed. As patients re-learn to eat, they will enter a new state because their BMI will increase as they gain weight, and so learning will be facilitated. Further efforts to facilitate learning to eat include supply of external heat. This intervention was used 130 years ago [34] but, surprisingly, has been neglected since then. An experimental study indicated that warming rats in the activity-based anorexia model slows the animals down and enables them to eat [39]. In this model, rats have access to running wheels and as food is made available during progressively shorter periods of time, the rats run more and there is a threshold time period of food availability below which rats run excessively and lose control over body weight. This phenomenon, activity-based anorexia, is conspicuously similar to anorexia nervosa in the human and as rats can be rescued from its life threatening consequences by warming, supply of heat to hypothermic, physically hyperactive anorexic patients is advisable as well.

Fig. 2 shows preliminary results of the effects of training how to eat in a 16 year old anorexic patient [40]. The patient ate only a small amount of food at a very low rate and perceived a high level of satiety at clinical presentation when her BMI was very low and her psychiatric symptoms were high. Note that her pattern of eating normalized (Fig. 2A) before her BMI increased (Fig. 2B) and that, as a concomitant, the level of her psychiatric symptoms (Fig. 2C) and the concentration of serum alanine-aminotransferase (Fig. 2D), a marker of physiological recovery, decreased. She has remained in remission for 3 years. These preliminary results suggest that eating normalizes before the other symptoms of anorexia normalize. The details of training patients how to eat are outlined in the following paragraph.

9. Training of eating normalizes the symptoms in anorexia nervosa

While it was claimed not long ago that it may be harmful for an anorexic patient to practice eating [43], at about the same

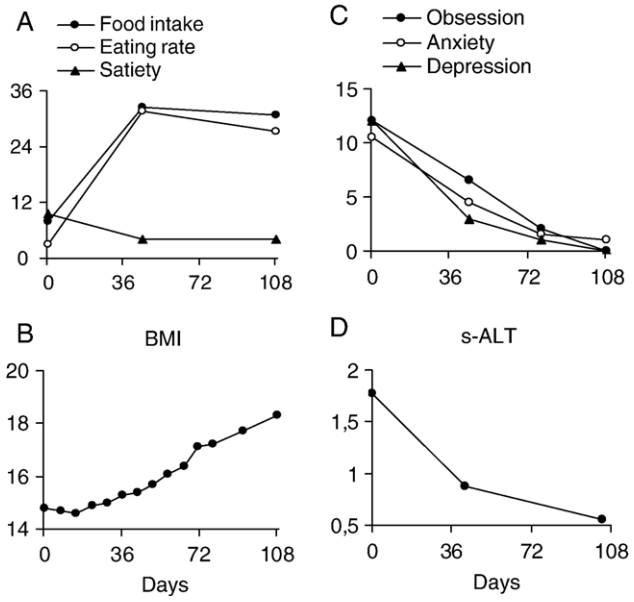

Fig. 2. A: Food intake (g/10), eating rate (g/min) and satiety (see Ref. [40] for a description of Mandometer®, used to diagnose and treat eating disorders), B: BMI (kg/m^2), C: psychopathology (comprehensive psychopathological rating scale self-rating scale for affective syndromes) [42] and D: serum concentration of alanine-aminotransferase (s-ALT, μkat/L) during 108 days of treatment. Reproduced from Ref. [40] with permission from Blackwell Publishers Ltd.

time an anorexic patient told us that she wanted to use Mandometer®, our devise for teaching patients how to eat, to re-learn how to eat.

On our framework, eating disorders are eating disorders (rather than "psychiatric disorders") and we hypothesize that the actual body weight of eating disorder patients is not important for their psychopathological symptoms. Rather it is their disordered eating behavior that is (perhaps causally) related to these symptoms. To examine this possibility we describe one group of anorexic patients with a very low BMI and another group of anorexics with a higher, yet low, BMI from admission to remission and through follow-up for about 5 years after remission.

9.1. Subjects

Fifty-eight female patients, who were diagnosed with anorexia nervosa and who were treated to remission and remained in remission for up to 5 years are described. The patients were divided into two groups. Group 1 (n=27) included patients with a BMI <14 (kg/m^2), their BMI was 12.9±0.2 (mean±SEM) at admission, and group 2 (n=18) included patients with a BMI >15.5, their BMI was 16.7±0.2 at admission. The other 13 patients had a BMI in between these two groups and were excluded from the comparison. There was no difference in the age of the patients at admission (16.3± 0.7 years for group 1 vs 17.6±0.6 years for group 2, ns, t-test). The patients had been treated 2.1±0.3 (group 1) and 1.6±0.3 (group 2) (ns) times before at other treatment sites without success and they had been ill for 2.4±0.4 (group 1) and 3.2±0.5 (group 2) (ns) years.

9.2. Methods

The method of treatment used at our clinic, including diagnostic procedures, medical supervision and follow-up procedures, is described in detail in Ref. [41]. The remission criteria are strict. Anorexic patients should not only have a normal BMI and normal laboratory test values, they should also be free of psychiatric symptoms, have a normal eating behavior and be able to eat in social situations and be back in school or professional activities. After remission, the patients are followed-up on 11 occasions during a period of 5 years.

9.2.1. Training how to eat

Patients practice eating using Mandometer®, which consists of a scale that is connected to a computer. The patient places her plate on the scale and puts food on the plate. While the patient eats, the computer records the weight loss of the plate and saves the readings. This yields a curve of eating rate. At regular intervals, a scale is displayed on the monitor and the patient records her level of fullness by pointing on a touch screen. This yields a curve of the development of satiety. Anorexic patients eat little food during a long period of time and estimate their level of satiety as very high.

The patients eat three to five diagnostic meals using Mandometer® and, based on the results, training curves, a linear curve for eating rate and an s-shaped curve for the development of satiety, are then presented on the monitor during subsequent meals. The patient is asked to follow the training curves during treatment. She can do this because she sees her own eating rate and satiety estimations develop on the monitor while she eats and hence can adapt to the training curves. In this way, patients are trained to eat progressively more food at a higher rate and, simultaneously, adapt their feeling of fullness. The treatment aims at having patients eat about 300 g food in 10–15 min and perceive a satiety level of about 6 on a scale from 0–10. These reference data were generated by healthy volunteers [41]. Patients reach this goal by adapting to training curves that initially increase the amount of food to be consumed by on average 20% and then shorten the duration of the meal by on average 5 min. These parameters, i.e., amount of food and meal duration, were changed on average 5.5 (3–9) times (median and range) for group 1 and 5 (3–7) times (ns) for group 2 during treatment.

It is important to note that training to eat is one of several interventions that we use to treat eating disorder patients [41].

9.3. Results

It took about twice as long for the patients with the low BMI to go into remission compared to the patients with the higher BMI (22±3.3 months vs 10.9±1.4 months, p<0.01) and they were at more treatment occasions than the patients with the higher BMI (125±17 vs 51±8, p<0.01). Thus, the time to remission was different between the patients in group 1 and group 2 but it has been normalized in Fig. 3 to facilitate comparisons between the groups. The parameters of eating behavior, i.e., food intake, the duration of the meal, the eating

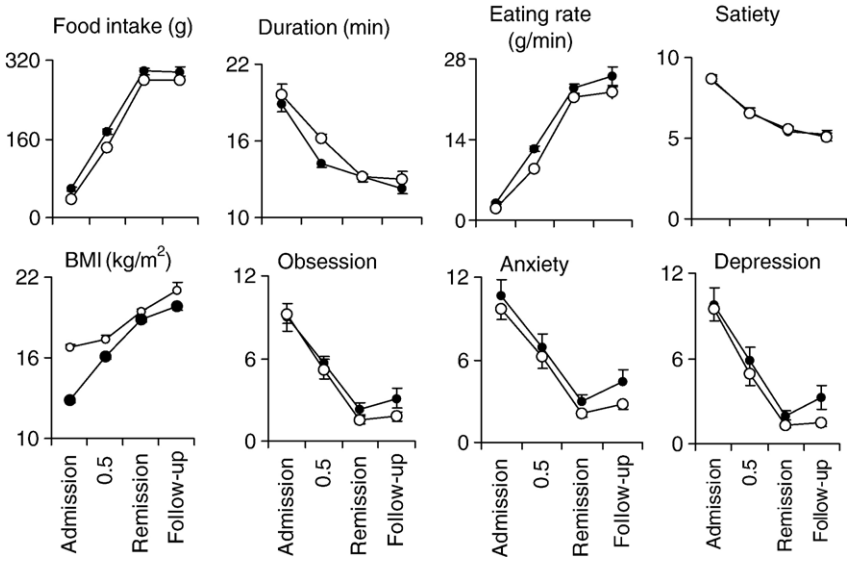

Fig. 3. Food intake, meal duration, eating rate, satiety, BMI and psychopathology (comprehensive psychopathological rating scale self-rating scale for affective syndromes) [42] in a group of anorexic patients with a BMI <14 (n=27) and another group of patients with a BMI >15.5 (n=18) treated from admission to remission and followed-up. The data are mean±SEM and the values are normalized setting the time to remission and the time of the last follow-up at the same x-axis points.

rate and the perception of satiety, as well as the levels of psychiatric symptoms were similar in both groups of patients from admission to remission and during follow-up (Fig. 3).

There was an increase in food intake and a decrease in meal duration and, as a consequence, an increase in eating rate in both groups during treatment. The patients in both groups also reduced their rating of the feeling of fullness during treatment. In parallel, their BMI increased. The psychiatric symptoms decreased during treatment and all symptoms of anorexia nervosa were normal at the time of remission (Fig. 3).

The patients were followed-up regularly during 5 years after remission (4.5±0.3 and 4.8±0.4 years for group 1 and 2, respectively) and their eating behavior, BMI and psychiatric symptoms remained normal (Fig. 3).

9.4. Discussion

In reviewing the effects of famine on human behavior, Keys et al. [35] wrote: "food becomes the central topic of conversation and … intrudes constantly into the consciousness … (such that) … coherent and creative thinking is impaired. The amount and time spent in seeking food increases until the major part of the waking hours are so engaged, directly or indirectly" (p 784). Sexual activities are reduced or cease and family and social behavior are disrupted (pp 884–5) and there is an "increase in thievery, violent crime etc" (p 785). Psychiatric symptoms such as depression are the rule and even suicide has been described (p 785). Food hoarding occurs frequently and may contribute to the shortage of food for others (p 786). Anxiety develops due to the expected consequences of famine (p 787) and there is an increase in the incidence of mental illness (p 790), including psychosis, which, interestingly, was reversed by re-feeding (p 794). Hence, it is long known that psychiatric symptoms are induced by shortage of food and that these symptoms are reversible.

Many of these observations were replicated during an experimental 6 month long period of semi-starvation in healthy male volunteers and Keys et al. pointed out the similarities between the effects of starvation and anorexia nervosa [35]. Considering that starvation is one of the most common challenges during human evolution [44], we suggest that many of the consequences described by Keys et al. [35] have evolved as physiological adaptations to the shortage of food. Some of these adaptations are beneficial. For example, cessation of reproduction, particularly in the female, is obviously not a symptom of disease but a necessity when there is too little to eat to raise offspring [45]. Concentrating on obtaining food is, therefore, more likely a helpful strategy than a pathological obsession. Food preoccupies the thoughts of anorexic patients, whose fear of becoming fat seems rather more realistic than "inexplicable" [27] as they would indeed become fat if they ate all the food they think about. Becoming fat is conceived as an aversive event by virtually everyone and the anxiety that ensues is "a normal adaptive response" [46] to an expected aversive event.

We conclude from these observations that there is an increase in psychiatric symptoms when food intake is reduced for an extended period. Interestingly, in the study of semi-starvation [35] was noted that "towards the end of starvation some of the men would dawdle for almost two hours over a meal which previously they would have consumed in a matter of minutes" (p 833). That is to say, shortage of food causes a decrease in eating rate. These results were confirmed by the present observations. Also, we found that disordered eating behavior, rather than body weight, is related to the psychiatric symptoms. Thus, anorexic patients with a BMI <14 and those with a BMI >15.5 displayed similar parameters of eating and psychiatric symptoms.

As eating behavior normalized, there was an expected increase in body weight and a decrease in psychiatric symptoms.

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These effects were maintained during an extended period of follow-up. Patients with a low BMI at the start of treatment took longer to go into remission but the time-course of symptomatic improvement was the same in both groups.

Based on these findings, we launch the hypothesis that disordered eating behavior mediates between starvation and the psychiatric symptoms in anorexia nervosa. While the support offered in this paper is correlational, experiments aiming at elucidating cause–effect relationships are underway.

10. Concluding remarks

Outcome in anorexia nervosa, and other eating disorders, has been poor during many years and the evidence basis for most of the presently used treatments is weak. This situation has probably developed because of failure to realize that many of the symptoms of anorexic patients are consequences of starvation rather that signs of an endogenous mental disorder. We offer a new framework in which anorexia develops as a consequence of the activation of the neural substrates of reward and attention. Teaching patients how to eat is an essential intervention and once eating behavior is normal, the other symptoms, including the psychiatric symptoms, dissolve.

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