Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 480 (2003) 67–74
www.elsevier.com/locate/ejphar

Anorexia nervosa: towards a neurobiologically based therapy

Per Södersten*, Cecilia Bergh, Ahmed Ammar

Section of Applied Neuroendocrinology, AB Mando, Center for Eating Disorders, Karolinska Institutet, Novum, S-141 57 Huddinge, Sweden

Accepted 25 August 2003

Abstract

Eating disorders, i.e. anorexia and bulimia nervosa, are disorders of eating behavior and body weight regulation. Most likely because there are few, if any, effective treatments, eating disorders are considered to be chronic disorders interrupted only by intermittent periods of short-lived remission. The neurobiology of eating, most of which explores hypothalamic mechanisms, has had no influence on the treatment of eating disorders, with the exception of psychopharmacology. However, while most patients are treated with psychoactive drugs, there is no evidence that these are effective. This may be because pharmacological attempts so far have targeted the wrong symptoms. We review the symptomatology of anorexia and bulimia and the outcome of presently used interventions. Everybody agrees that outcome must improve and to attack this clinical problem, we suggest a neurobiologically plausible framework for how the disorders develop and how they are maintained and outline a method of treatment and its results.

Keywords: Eating disorder; Anorexia; Bulimia; Hypothalamus; Peptide; Randomized controlled trial

1. Introduction

Research on the control of eating behavior and body weight has increased enormously because of the enormous increase in obesity. Thus, 65% of the population in the United States are now overweight, their body mass index is >25 kg/m^2, and 30% are obese, their body mass index is >30 kg/m^2 (Flegal et al., 2002). This remarkable situation has developed over a brief period of time and is a challenge to the commonly held view that eating behavior and body weight are homeostatically regulated, often expressed by a simple "energy expenditure = energy intake" equation. The hypothalamus plays a central role in this equation and we estimate that at least 90% of all of the research in this field is concerned with hypothalamic peptidergic neurons (see, e.g. Marx, 2003).

In contrast to obesity, the prevalence of anorexia (1%) and bulimia nervosa (1%) has not increased (Hoek et al., 2003). Many attempts to explain these states of altered food intake and body weight also aim at revealing hypothalamic dysfunction (e.g. Fetissov et al., 2002).

We will only briefly outline the hypothalamic hypothesis of food intake, because it has been reviewed many times before, yet we criticize it for its limited clinical significance and for neglecting that eating has redundant controls. We will then review the symptomatology of eating disorders and the outcome of treatments. Finally, we present a neurobiologically realistic treatment of eating disorders and its results.

2. The 50th anniversary of Stellar's hypothalamic hypothesis

The view that the hypothalamus has an important role in the control of eating was developed during the first part of the twentieth century and culminated in Stellar's (1954) hypothesis that: "The amount of motivated behavior is a direct function of the amount of activity in certain excitatory centers in the hypothalamus". Inhibitory centers, also located in the hypothalamus, were added to the hypothesis to allow for homeostatic balance. Stellar (1954), however, recognized the possibility of distributed neural networks in the control of behavior and carefully pointed out the limitations of the concept of centers: "strict localization of function within isolated anatomical entities is not intended," because: "no neural mechanism operates in isolation." Yet, while "+" and "−" hypothalamic centers are always found in overviews of the field, other brain areas, including the cortex, are sadly neglected (e.g. Marx, 2003).

* Corresponding author. Tel.: +46-8-5564-0602; fax: +46-8-5564-0610.
E-mail address: per.sodersten@neurotec.ki.se (P. Södersten).

0014-2999/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2003.08.093

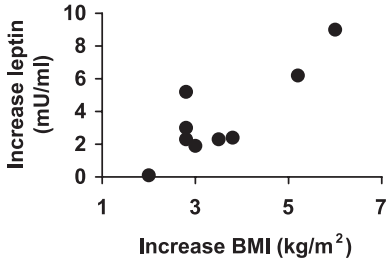

Fig. 1. Increase in body mass index (BMI) and leptin levels in anorexic patients from admission to remission, r = 0.88.

2.1. The gut–brain link

Peripheral adipose tissue is thought to provide signals to hypothalamic centers to make up for the homeostatic control of body weight. Leptin, which is produced by adipocytes, has a key role in this scenario (Friedman, 2003). Thus, with depletion of body fat stores, leptin levels decline and provide the signal to hypothalamic neurons, located in the arcuate nucleus, to up-regulate their synthesis of orexigenic peptides, e.g. neuropeptide Y, for transport to the relevant excitatory centers, located in the hypothalamic paraventricular nucleus, and activate the receptors which initiate eating (Marx, 2003).

This negative feedback model of gut-hypothalamic control is inconsistent with the clinical observation that anorexic patients, who have depleted peripheral fat stores and, as a consequence, low blood levels of leptin and elevated levels of neuropeptide Y in the brain (Kaye et al., 1989), do not eat. As a matter of fact, as anorexic patients eat more and gain weight during the course of treatment, leptin levels increase.

Fig. 1 shows that the body mass index and the level of leptin, which were low in a group of anorexic patients admitted to our clinic, had increased significantly when the patients had been treated to remission. An increase in blood levels of leptin during the treatment, and an associated decrease in the level of neuropeptide Y in the brain (Gendall et al., 1999), is therefore correlated with an increase in food intake. This is the opposite to what should be expected from the hypothalamic hypothesis of homeostatic control.

2.2. A new role of neuropeptide Y in regulatory control

The paradoxical situation of a low level of leptin and a high level of neuropeptide Y and a reduced intake of food in anorexia may be more apparent than real because the common notion that neuropeptide Y is merely a potent orexigen is inconsistent with the published evidence of the behavioral effects of neuropeptide Y. Thus, in the original studies, neuropeptide Y was found to not only stimulate food intake but also stimulate drinking and physical activity and reduce sexual behavior (Clark et al., 1985; Levine and Morley, 1984; Stanley et al., 1984). In fact, the effect on drinking was as strong as the effect on food intake (Levine and Morley, 1984). Also, in the few studies in which dose–response experiments have been performed, the effect of neuropeptide Y on food intake is not impressive. An intake of about 8 g in a 2-h-long test is reported in rats infused with very high, if not enormous, doses of neuropeptide Y (7.2–24 nmol, i.e. about 30–120 μg) into the third ventricle, provided the rats are injected during the light phase of the daily light/darkness cycle, i.e. when they do not normally eat (O'Shea et al., 1997). If injected during the dark phase, when ingestion normally occurs, the effect is smaller (Clark et al., 1985).

Interestingly, neuropeptide Y has no effect on intake at all in rats infused intraorally with a nutritive solution (Seeley et al., 1995). In this test, rats do not have to approach to food; they merely chew and swallow the solution.

Fig. 2A shows that neuropeptide Y actually decreases intake of an intraorally infused solution of sucrose and that leptin increases intake. By contrast, the conventionally reported effects of both neuropeptide Y and leptin are easily replicated in a test that demands that the rat approaches the solution before ingesting it (Fig. 2B).

These results suggest that neuropeptide Y actually inhibits the intake of food and that leptin stimulates intake. Some neuropeptide Y-containing neurons that provide input to the hypothalamic nuclei, thought to be involved in feeding, co-localize norepinephrine (Cunningham and Sawchenko, 1988). Lesioning a population of these noradrenergic neu-

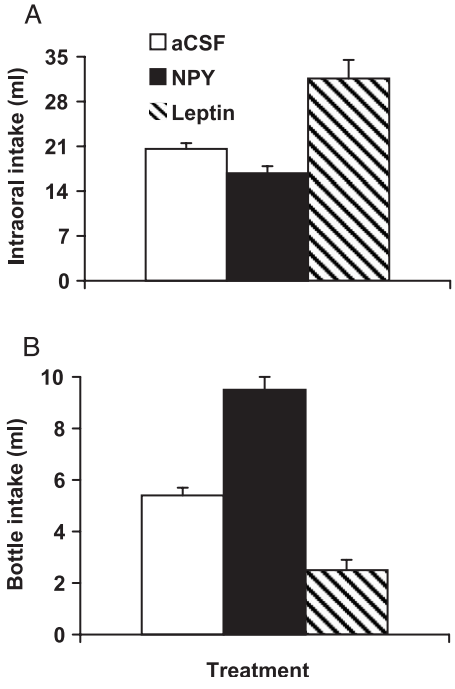

Fig. 2. Intracerebroventricular infusion of neuropepide Y (NPY, 10 μg) decreases and leptin (10 μg) increases ingestion of a 1 M solution of sucrose infused intraorally at a rate of 0.5 ml/min in female rats. The opposite effects are obtained on intake of the same solution from a bottle. From Ammar et al. (2000) with permission of the American Physiological Society.

rons unmasks the inhibitory effect on neuropeptide Y on intake. Thus, Fig. 3 shows that treatment with a neurotoxin, which reduced the levels of norepinephrine by 67% in the paraventricular hypothalamic nucleus, decreased the intake of an intraorally infused solution of sucrose; that pre-infusion of norepinephrine restored intake in lesioned rats; and that addition of neuropeptide Y in this model markedly suppressed intake (Ammar et al., 2001).

A new role for neuropeptide Y in regulatory control emerges. Thus, this particular peptide acts to stimulate behaviors associated with approaching and collecting food, while actually inhibiting the intake of food. Leptin is postulated to have the opposite effect (Ammar et al., 2000). This analysis is compatible with the observation that anorexic patients engage in a variety of food anticipatory behaviors, but do not eat (Tappe et al., 1998).

Perhaps because the peptidergic control of food intake has not yet been realistically related to the clinical features in anorexia nervosa, relatively little clinically useful information has been generated by the large amount of information on hypothalamic peptides that is presently available (Marx, 2003). One way to proceed would be to analyze the behavioral effects of peptides more carefully than merely labeling them stimulators/inhibitors of food intake. The simple distinction between behaviors related to the anticipation of food and those related to the ingestion of food is of considerable clinical significance but has not been implemented in any of the studies on peptides, with the exception of neuropeptide Y and leptin (see Ammar et al., 2000).

2.3. Redundant controls

No single endocrine factor that initiates eating has been identified and humans eat for reasons other than depleted energy stores (De Castro and Plunkett, 2002). In fact, many factors, biologic and social, affect eating behavior in humans, and, by itself, none of these accounts for more

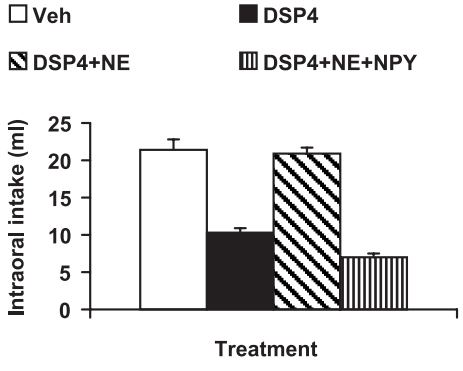

Fig. 3. Inhibition of ingestion of a 1 M solution of sucrose infused intraorally at a rate of 0.5 ml/min in male rats by DSP4 (2 × 50 mg/kg), reversal of the inhibition by intracerebroventricular infusion of norepinephrine (NE, 20 nmol), and suppression of intake by intracerebroventricular infusion of neuropeptide Y (NPY, 10 μg) in DSP4 + NE-treated rats. From Ammar et al. (2001) with permission of Lippincott, Williams & Wilkins.

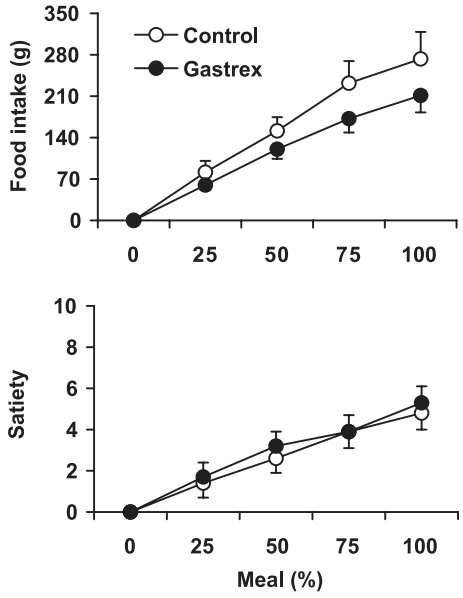

Fig. 4. Food intake and satiety in gastrectomized and intact humans. From Bergh et al. (2003) with permission of Elsevier.

than a small percentage of the variation (De Castro and Plunkett, 2002). This suggests redundant control mechanisms, i.e. if one mechanism fails to operate it is likely to be replaced by another. Given this potential, it is not surprising that many specific pharmacological attempts at weight control have failed.

An example of the extraordinary adaptability of the biological substrates of eating is provided by the observation that there is virtually no long-term effect of gastrectomy on eating and the perception of satiety in humans (Bergh et al., 2003a,b, Fig. 4). While there is no doubt that the stomach, a major endocrine organ, normally plays an important role in the regulation of food intake and satiety, its role is dispensable. Similarly, while the hypothalamic hypothesis of homeostatic control is compatible with the finding that some obese people have a mutated melanocortin 4 receptor, a receptor believed to be essential for satiety, normal-weight people may also have the same mutation (Jacobson et al., 2002).

It seems unlikely that research into the hypothalamic peptidergic mechanisms which are supposed to regulate homeostatic control will contribute to the development of effective strategies for treating eating disorders. Particularly so as the concept of negative feedback control of body weight at the level of the hypothalamus is questionable (Speakman et al., 2002) as is that of excitatory and inhibitory hypothalamic centers in the control of behavior.

3. Eating disorders

A review of available methods of treatment suggests that outcome in eating disorders has worsened if compared with

a report published 130 years ago (Gull, 1874). We will therefore reexamine this report.

3.1. Prevalence and diagnosis

Anorexia nervosa has a prevalence of about 1%, its age of onset is 14–19 years, and about 95% of the patients are girls (Hoek et al., 2003). The prevalence of bulimia nervosa is about the same, most patients are young women but the age of onset is somewhat later, about 20–22 years (Hoek et al., 2003). The prevalence of these eating disorders has not increased. However, it has been estimated that the risk that a woman will display episodes of bulimic behavior during her life without fulfilling all diagnostic criteria for an eating disorder is as high as 25% (Sullivan et al., 1998). For anorexia these criteria are: weight reduction to a body mass index of 17.5 kg/m^2, amenorrhea, a distorted body image, and a fear of gaining weight (American Psychiatric Association, 1995). The main diagnostic criteria for bulimia are: ingestion of large amounts of food in a short period of time followed by compensatory behavior, such as vomiting or purging, to counteract the caloric intake.

These criteria are based on consensus among clinicians, not on actual research findings.

3.2. Outcome and treatment

In a comprehensive review, Steinhausen (2002) summarized the outcome for patients with anorexia nervosa. Broadly, the outcome is good in less than 50% of the patients, fair in about 25% and poor in the remaining 25%. The rate of mortality can be as high as 25% (Keel et al., 2003). The chance of recovery is less than 50% in 10 years and about 25% of the patients remain chronic cases. Steinhausen (2002) concluded that outcome in anorexia has not changed during the last 50 years. Outcome in bulimia, although less well studied, is similar to that in anorexia (Steinhausen, 1999). For these reasons, many believe that anorexia and bulimia are chronic disorders.

Many also believe that eating disorders are difficult to treat. While weight gain is possible in anorexic patients, relapse is main concern. Thus, 30–50% of those who have regained a normal weight relapse within a year after treatment (Pike, 1998). Another concern is that the effect of most treatments is unknown (Ben-Tovim et al., 2001). The effect of medical interventions should be evaluated by random assignment of patients to the treatment to be evaluated or to a control procedure, most often the standard of care (Pocock, 1998). Relatively few such randomized controlled trials have been performed on patients with anorexia nervosa and those which have been undertaken have failed to demonstrate a clinically significant effect.

It is thought that cognitive behavioral therapy, which is the standard of care for patients with bulimia nervosa, is effective. However, while treatment in bulimia is better than no treatment, the evidence that cognitive behavioral therapy is better than other methods of treatment is not compelling (Hay and Bacaltchuk, 2000). Also, only 50% of the bulimic patients respond to treatment and very few follow-up studies have been performed. This is because the specific diagnosis of bulimia nervosa is a relatively recent one (Russell, 1979). However, a series of recent papers has clarified the situation. Thus, of the patients who entered treatment with cognitive behavioral therapy for bulimia, 25% withdrew from treatment or dropped out, only 41% of those who completed treatment went into remission and as many as 44% of those who were examined four months after treatment had relapsed. The patients who failed to respond to treatment with cognitive behavioral therapy also failed to respond to other treatments. These studies show that fewer than 20% of the patients who enter cognitive behavioral therapy for bulimia are in remission four months after treatment (Agras et al., 2000; Halmi et al., 2002; Mitchell et al., 2002). According to the authors of these papers, the results are similar to those reported by others.

3.3. Pharmacological treatment of eating disorders

Most eating disorder patients are treated with psychoactive drugs, many of which target serotonergic mechanisms. Indirect serotonergic agonists, selective serotonin reuptake inhibitors in particular, are often used. The rationale behind this clinical practice is the hypothesis that an underlying obsessive compulsive personality trait contributes to the development of anorexia and bulimia (Halmi, 2003). While it may be true that obsessive compulsive symptoms are alleviated in those suffering from such symptoms, there is no evidence that these drugs have a beneficial effect on patients with eating disorders (de Zwaan and Roerig, 2003). This is not surprising, because serotonin inhibits food intake, gonadotropin secretion and sexual behavior and, in addition, reduces body temperature (see Bergh et al., 2003a,b). All of these are highly undesirable effects in anorexic patients, many of whom are hypothermic peripubertal girls, suffering from primary amenorrhea. It should be added that the body weight of anorexics treated with selective serotonin re-uptake inhibitors may decrease (Bergh et al., 1996b). Pharmacological attempts to control body weight in eating disorder patients must be compatible with well-established facts in neuroendocrinology.

4. A treatment of eating disorders

It is clear that outcome in eating disorders must improve.

4.1. A framework for the treatment of eating disorders

A new framework might be useful. "A framework", to paraphrase a recent paper, "is not a detailed hypothesis, rather it is a suggested point of view for an attack on a clinical problem" (Crick and Koch, 2003).

We take as a starting point the incisive clinical observations by Gull (1874), who gave anorexia nervosa its name and was successful in treating his patients. It appears that the clinical situation for the patients has worsened since Gull (Bergh and Södersten, 1998), and it might be worthwhile, therefore, to reconsider Gull. He emphasized three symptoms in anorexia nervosa. First, he noted the emaciation and the markedly reduced food intake; second, he noted that the patients are hypothermic; and third, he pointed out that they are also physically hyperactive. Gull found the hyperactivity of anorexia paradoxical, since, obviously, the patient would be better off saving her energy. He pointed out two characteristics of the hyperactivity: that it is very difficult to control and that the patients seem to like to be active. It is difficult to precisely know how Gull managed his patients, but he provided them with nourishing diets and supplied external heat. While there is no mention of psychopathology in the description by Gull, there is no mention of physical hyperactivity or hypothermia in most of the papers on anorexia published after Gull's paper.

Anorexia, obviously, starts by a reduction in food intake. Most animal species display an increase in physical activity as they reduce their intake of food (Mistlberger, 1994). Reduced food intake and enhanced physical activity are, therefore, two known risk factors for anorexia nervosa. There may be more, but so far no others have been demonstrated.

Both dieting and physical activity activate the dopamine-containing mesolimbic neurons which mediate some aspects of the feeling of reward, and these two risk factors also activate the norepinephrine-containing neurons in the locus coeruleus, which are concerned with selective attention. It can be hypothesized, therefore, that anorexia develops because it is initially rewarding to eat less and move more and that the behavior of an anorexic is subsequently maintained because it is conditioned to the stimuli that provide the reward through activation of the brain's mechanism of attention (Bergh and Södersten, 1996). This framework is neurobiologically realistic and also consistent with the observation of Gull (1874) that physical hyperactivity is "agreeable" and that of Feighner et al. (1972) that losing weight is "rewarding, pleasurable and an apparent enjoyment" to an anorexic patient.

4.2. A treatment of anorexia and bulimia nervosa

On this framework the following symptoms should be treated:

- distorted eating behavior and perception of satiety
- hypothermia
- physical hyperactivity
- the social consequences of the disorder

Obviously, patients who are severely emaciated need medical attention. However, medical symptoms are the consequence of the starved condition of an anorexic, not the cause of the starvation. While this appears reasonable to most clinicians, many have difficulty in accepting that the same might apply to the psychiatric symptoms, such as depression, anxiety and obsessive-compulsive behavior, which most anorexic patients show. Yet it is long known that such symptoms emerge if people are asked to starve themselves (Keys et al., 1950) and more recent work confirms this by showing that psychiatric symptoms yield as a normal body weight is approached (Matsunaga et al., 2000).

The reason bulimia nervosa is considered a separate disorder is probably that these patients appear quite different from anorexics in that they have a normal body weight. However, Russell (1979), in introducing bulimia nervosa a specific diagnosis, referred to it as a variant of anorexia. Also, bulimics show most of the symptoms that anorexics show, including hypothermia and physical hyperactivity, and they share the psychopathology of anorexics (see Bergh et al., 2002). In addition, about 20% of patients with anorexia nervosa binge-eat and vomit. They, therefore, constitute a diagnostic subgroup of anorexia, the so-called binge-purge type (American Psychiatric Association, 1995). The similarities between patients with anorexia and bulimia are therefore more conspicuous than the differences and there is no compelling reason to believe that the two disorders develop for different reasons. The patients can therefore be similarly treated.

4.2.1. Training of eating

During treatment, the patient eats from a plate placed on a scale, which is connected to a computer. The scale records the weight loss of the plate and the computer stores the data. During a meal, a rating scale appears on a monitor and the patient is asked to estimate how full she feels. The computer stores the ratings. In this manner, curves of eating rate and the development of satiety are obtained. Under these conditions, anorexics eat little food slowly and perceive a high level of satiety quickly. Bulimics behave the opposite way. Training curves are then used. The curve for eating rate has a higher slope and the curve for satiety has a less high slope than those generated by an anorexic patient and vice versa for a bulimic patient. The patient is then asked to follow the training curves during her meal, which is possible because she sees her own eating rate and fullness estimates appear on the monitor while she eats. The procedure, Mandometer®, was described by Bergh et al. (2002).

4.2.2. Supply of external heat

Gull (1874) warmed his anorexic patients because they were hypothermic. Such obvious clinical common sense has not been used in the 130 years after Gull. In fact, only one paper after Gull has paid attention to the hypothermia of anorexics (Wakeling and Russell, 1970). As part of our treatment, patients rest in warm rooms after each meal.

4.2.3. Reduction of physical activity

Gull (1874) correctly pointed out that it is difficult to reduce the physical hyperactivity in anorexia. There appears to be a relationship between this symptom and hypothermia. For example in activity-based anorexia, an animal model of anorexia nervosa, rats run excessively in wheels and lose weight continuously if the access to food is restricted. This whole phenomenon is blunted, even reversed, and rats resume eating if external heat is provided (Morrow et al., 1997).

4.2.4. Social restoration

Eating disorder patients gradually become socially isolated and so this needs to be reversed. Details of the procedures used to this aim are perhaps out of focus in the present context; a brief description is provided by Bergh et al. (2002).

We also withdraw all psychoactive drugs within the first months of treatment.

4.3. Randomized controlled trial of the method

It is necessary to perform a randomized controlled trial to evaluate any method of treatment before it can be implemented clinically. Based on preliminary results (Bergh et al., 1996a) and practical limitations in daily clinical work, we estimated that 16 patients should be randomized to treatment and 16 should be randomized to a control procedure, which was waiting for treatment. Exclusion criteria were kept at a minimum and strict outcome criteria were adopted. These included a normal eating behavior, normal laboratory test values, absence of psychiatric symptoms and resumption of social activities (see Bergh et al., 2002). Fig. 5 shows that treatment had a significant effect on outcome, 14/16 patients went into remission in on average 14 months, while only one of the control patients went into remission.

These results demonstrate that the treatment is effective. Results from all patients who had entered the treatment program showed that the estimated rate of remission with this treatment is about 75%. However, an additional 12% of the patients improve significantly, although they do not fulfill all of the remission criteria (Bergh et al., 2002). The remaining 12% do not respond to the treatment.

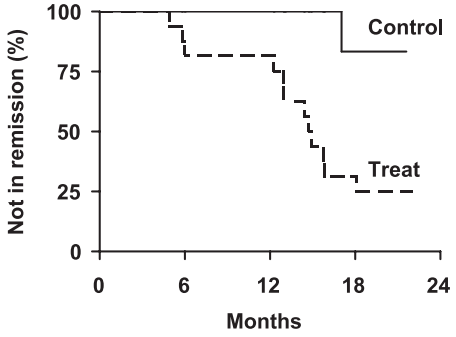

Fig. 5. Effect of treatment of 16 patients with anorexia or bulimia nervosa and no treatment of 16 other patients. From Bergh et al. (2002) with permission of the National Academy of Sciences, USA.

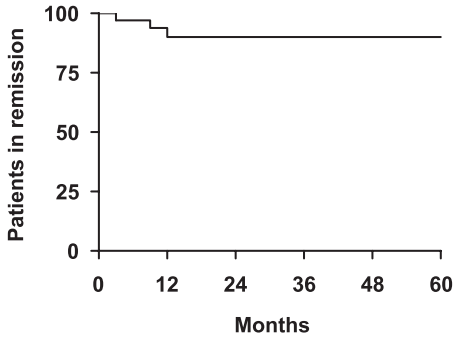

Fig. 6. Relapse in patients treated to remission from eating disorders. From Bergh et al. (2002) with permission of the National Academy of Sciences, USA.

As mentioned previously, relapse is a concern. We, therefore, follow all patients who have been treated to remission during 5 years after treatment. Fig. 6 shows that the rate of relapse is about 10% during this period of time.

It is reasonable to conclude from these results that most patients treated with this method recover. Fig. 7 shows that the reduction of psychiatric symptoms of depression, anxiety and obsessional-compulsive behavior after treatment is maintained during a 2-year follow-up. This is in contrast to most reports on patients in remission from an eating disorder. Such patients may not fulfill all of the diagnostic criteria of an eating disorder but they are virtually never free of symptoms (e.g. Kaye et al., 2001). They can, therefore, only be considered to be in remission if their psychiatric morbidity is thought of as independent of their eating disorder. More likely, they have not been optimally treated and relapse should not be a surprise.

Implementation of this method into a broader clinical context awaits a randomized controlled comparison with the standard of care.

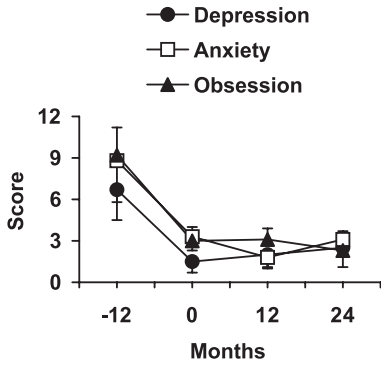

Fig. 7. Levels of psychiatric symptoms in patients with eating disorders at admission (− 12), remission (0) and at follow up (12, 24) during a period of 36 months. Measurements as in Bergh et al. (2002).

5. What kind of drug could improve treatment?

We criticized the homeostatic-hypothalamic-hypothesis above because of its simplistic ± analysis of behavior. There are as yet no reports that an agonist for a hypothalamic orexigenic peptide receptor makes an anorexic patient eat or that an antagonist makes a bulimic stop eating, as the clinical application of this hypothesis predicts. However, most drugs that are used clinically target psychiatric symptoms, i.e. depression, anxiety and obsessive-compulsive behavior. Interestingly, selective serotonin reuptake inhibitors, which are by far the most commonly used drugs, have no effect on these symptoms in low-weight anorexic patients (Bergh, 2003) and the evidence for their effectiveness in bulimia is not compelling (De Zwaan and Roerig, 2003). Perhaps, therefore, for a better future treatment of eating disorders, the other symptoms of anorexia and bulimia should be targeted. Just like physical inactivity is as big a problem for treating the obese, so is physical hyperactivity a major problem in anorexia. This was pointed out already by Gull (1874) but has been ignored in most subsequent clinical accounts. It should be recalled that in activity-based anorexia, a rat model of anorexia nervosa, supply of external heat reduces the activity, thereby allowing rats to eat (Morrow et al., 1997). Treatment with leptin has been reported to have a similar effect (Exner et al., 2000). Treatment with leptin might, therefore, offer a possibility. Leptin is unlikely to act as a mere anorexigen and more likely to affect body weight through its effect on thermoregulation (DiBona, 2003), physical activity (Exner et al., 2000) or on attentional mechanisms (Ammar et al., 2000).

Acknowledgements

This work was supported by the Swedish Research Council, the Karolinska Institutet and AB Mando.

References

Agras, W.S., Crow, S.J., Halmi, K.A., Mitchell, J., Wilson, T., Kraemer, H., 2000. Outcome predictors for the cognitive behavioral treatment of bulimia nervosa: data from a multisite study. Am. J. Psychiatry 157, 1302–1308.

American Psychiatric Association, 1995. Diagnositc and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC.

Ammar, A.A., Sederholm, F., Saito, T.R., Scheurink, A.J., Johnson, A.E., Södersten, P., 2000. NPY-leptin: opposing effects on appetitive and consummatory ingestive behavior and sexual behavior. Am. J. Physiol., Regul. Integr. Comp. Physiol. 278, R1627–R1633.

Ammar, A.A., Södersten, P., Johnson, A.E., 2001. Locus coeruleus noradrenergic lesions attenuate intraoral intake. NeuroReport 12, 3095–3099.

Ben-Tovim, D.I., Walker, K., Gilchrist, P., Freeman, R., Kalucy, R., Esterman, A., 2001. Outcome in patients with eating disorders: a 5-year study. Lancet 357, 1254–1357.

Bergh, C., 2003. Is psychopharmacological treatment of patients with eating disorders necessary? In: Maj, M., Halmi, K.A., López-Ibor, J.J., Sartorius, N. (Eds.), Eating Disorders. Wiley, Chichester, UK, pp. 307–309.

Bergh, C., Södersten, P., 1996. Anorexia nervosa, self-starvation and the reward of stress. Nat. Med. 2, 21–22.

Bergh, C., Södersten, P., 1998. Anorexia nervosa: rediscovery of a disorder. Lancet 351, 1427–1429.

Bergh, C., Eklund, S., Eriksson, M., Lindberg, G., Södersten, P., 1996a. A new treatment of anorexia nervosa. Lancet 348, 611–612.

Bergh, C., Eriksson, M., Lindberg, G., Södersten, P., 1996b. Selective serotonin reuptake inhibitors in anorexia. Lancet 348, 1459–1460.

Bergh, C., Brodin, U., Lindberg, G., Södersten, P., 2002. Randomized controlled trial of a new treatment for anorexia and bulimia nervosa. Proc. Natl. Acad. Sci. U. S. A. 94, 9486–9491.

Bergh, C., Ejderhamn, J., Södersten, P., 2003a. What is the evidence basis for treatment of eating disorders? Curr. Opin. Pediatr. 15, 344–345.

Bergh, C., Sjöstedt, S., Hellers, G., Zandian, M., Södersten, P., 2003b. Meal size, satiety and cholecystokinin i gastrectomized humans. Physiol. Behav. 78, 143–147.

Clark, J.T., Kalra, P.S., Kalra, S.P., 1985. Neuropeptide Y stimulates feeding but inhibits sexual behavior in rats. Endocrinology 117, 2435–2442.

Crick, F., Koch, C., 2003. A framework for consciousness. Nat. Neurosci. 6, 119–126.

Cunningham Jr., E.T., Sawchenko, P.E., 1988. Anatomical specificity of noradrenergic inputs to the paraventricular and supraoptic nuclei of the rat hypothalamus. J. Comp. Neurol. 274, 60–76.

De Castro, J., Plunkett, S., 2002. A general model of intake regulation. Neurosci. Biobehav. Rev. 26, 581–595.

De Zwaan, M., Roerig, J., 2003. Pharmacological treatment of eating disorders: a review. In: Maj, M., Halmi, K.A., López-Ibor, J.J., Sartorius, N. (Eds.), Eating Disorders. Wiley, Chichester, UK, pp. 223–285.

DiBona, G.F., 2003. Thermoregulation. Am. J. Physiol., Regul. Integr. Comp. Physiol. 284, R277–R279.

Exner, C., Hebebrand, J., Remschmidt, H., Wewetzer, C., Ziegler, A., Herpertz, S., Schweiger, U., Blum, W.F., Preibisch, G., Heldmaier, G., Klingenspor, M., 2000. Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. Mol. Psychiatry 5, 476–481.

Feighner, J.P., Robins, E., Guze, S.B., Woodruff Jr., R.A., Winokur, G., Munoz, R., 1972. Diagnostic criteria for use in psychiatric research. Arch. Gen. Psychiatry 26, 57–63.

Fetissov, S.O., Hallman, J., Oreland, L., Af Klinteberg, B., Grenback, E., Hulting, A.L., Hökfelt, T., 2002. Autoantibodies against alpha-MSH, ACTH, and LHRH in anorexia and bulimia nervosa patients. Proc. Natl. Acad. Sci. U. S. A. 99, 17155–17160.

Flegal, K.M., Carroll, M.D., Ogden, C.L., Johnson, C.L., 2002. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 288, 1723–1727.

Friedman, J.M., 2003. A war on obesity, not the obese. Science 299, 856–858.

Gendall, K.A., Kaye, W.H., Altemus, M., McConaha, C.W., La Via, M.C., 1999. Leptin, neuropeptide Y, and peptide YY in long-term recovered eating disorder patients. Biol. Psychiatry 46, 292–299.

Gull, W.W., 1874. Anorexia nervosa (apepsia hysterica, anorexia hysterica). Trans. Clin. Soc. Lond. 7, 22–28.

Halmi, K.A., 2003. Classification, diagnosis and comorbidities of eating disorders: a review. In: Maj, M., Halmi, K.A., López-Ibor, J.J., Sartorius, N. (Eds.), Eating Disorders. Wiley, Chichester, UK, pp. 1–33.

Halmi, K.A., Agras, W.S., Mitchell, J., Wilson, T.G., Crow, S., Bryson, S.W., Kraemer, H., 2002. Relapse predictors of patients y with bulimia nervosa who achieved abstinence through cognitive behavioral therapy. Arch. Gen. Psychiatry 59, 1105–1109.

Hay, P.J., Bacaltchuk, J., 2000. The Cochrane Library. Update Software, Oxford, UK.

Hoek, H.J., van Hoeken, D., Katzman, M.A., 2003. Epidemiology and cultural aspects of eating disorders: a review. In: Maj, M., Halmi,

K.A., López-Ibor, J.J., Sartorius, N. (Eds.), Eating Disorders. Wiley, Chichester, UK, pp. 75–104.

Jacobson, P., Ukkola, O., Rankinen, T., Snyder, E.E., Leon, A.S., Rao, D.C., Skinner, J.S., Wilmore, J.H., Lönn, L., Cowan Jr., G.S., Sjöström, L., Bouchard, C., 2002. Melanocortin 4 receptor sequence variations are seldom a cause of human obesity: the Swedish Obese Subjects, the HERITAGE Family Study, and a Memphis cohort. Melanocortin 4 receptor sequence variations are seldom a cause of human obesity: the Swedish Obese Subjects, the HERITAGE Family Study, and a Memphis cohort. J. Clin. Endocrinol. Metab. 87, 4442–4446.

Kaye, W.H., Berrettini, W.H., Gwirtsman, H.E., Gold, P.W., George, D.T., Jimerson, D.C., Ebert, M.H., 1989. Contribution of CNS neuropeptide (NPY, CRH, and beta-endorphin) alterations to psychophysiological abnormalities in anorexia nervosa. Psychopharmacol. Bull. 25, 433–438.

Kaye, W.H., Frank, G.K., Meltzer, C.C., Price, J.C., McConaha, C.W., Crossan, P.J., Klump, K.L., Rhodes, L., 2001. Altered serotonin 2A receptor activity in women who have recovered from bulimia nervosa. Am. J. Psychiatry 158, 1152–1155.

Keel, P.K., Dorer, D.J., Eddy, K.T., Franko, D., Charatan, D.L., Herzog, D.B., 2003. Predictors of mortality in eating disorders. Arch. Gen. Psychiatry 60, 179–183.

Keys, A., Brozek, J., Henschel, A., Mickelsen, O., Taylor, H.L., 1950. The Biology of Human Starvation. The University of Minnesota Press, Minneapolis, MN.

Levine, A.S., Morley, J.E., 1984. Neuropeptide Y: a potent inducer of consummatory behavior in rats. Peptides 5, 1025–1029.

Marx, J., 2003. Cellular warriors at the battle of the bulge. Science 299, 846–849.

Matsunaga, H., Kaye, W.H., McConaha, C., Plotnicov, K., Pollice, C., Rao, R., 2000. Personality disorders among subjects recovered from eating disorders. Int. J. Eat. Disord. 27, 353–357.

Mistlberger, R.E., 1994. Circadian food-anticipatory activity: formal models and physiological mechanisms. Neurosci. Biobehav. Rev. 18, 171–195.

Mitchell, J.E., Halmi, K.A., Wilson, G.T., Agras, W.S., Kraemer, H., Crow, S.A., 2002. A randomized secondary treatment study of women with bulimia nervosa who failed to respond to CBT. Int. J. Eat. Disord. 32, 271–281.

Morrow, N.S., Schall, M., Grijalva, C.V., Geiselman, P.J., Garrick, T., Nuccion, S., Novin, D., 1997. Body temperature and wheel running predict survival times in rats exposed to activity-stress. Physiol. Behav. 62, 815–825.

O'Shea, D., Morgan, D.G., Meeran, K., Edwards, C.M., Turton, M.D., Choi, S.J., Heath, M.M., Gunn, I., Taylor, G.M., Howard, J.K., Bloom, C.I., Small, C.J., Haddo, O., Ma, J.J., Callinan, W., Smith, D.M., Ghatei, M.A., Bloom, S.R., 1997. Neuropeptide Y induced feeding in the rat is mediated by a novel receptor. Endocrinology 138, 196–202.

Pike, K.M., 1998. Long-term course of anorexia nervosa: response, relapse, remission, and recovery. Clin. Psychol. Rev. 18, 447–475.

Pocock, S.J., 1998. Clinical Trials. Wiley, New York.

Russell, G., 1979. Bulimia nervosa: an ominous variant of anorexia nervosa. Psychol. Med. 9, 429–448.

Seeley, R.J., Payne, C.J., Woods, S.C., 1995. Neuropeptide Y fails to increase intraoral intake in rats. Am. J. Physiol. 268, R423–R427.

Speakman, J.R., Stubbs, R.J., Mercer, J.G., 2002. Does body mass play a role in the regulation of food intake? Proc. Nutr. Soc. 61, 473–487.

Stanley, B.G., Chin, A.S., Leibowitz, S.F., 1984. Feeding and drinking elicited by central injection of neuropeptide Y: evidence for a hypothalamic site(s) of action. Brain Res. Bull. 14, 521–524.

Steinhausen, H.-C., 1999. Eating disorders. In: Steinhausen, H.-C., Verhulst, F. (Eds.), Risks and Outcomes in Developmental Psychopathology. Oxford Univ. Press, Oxford, UK, pp. 210–230.

Steinhausen, H.-C., 2002. The outcome of anorexia nervosa in the 20th century. Am. J. Psychiatry 159, 1284–1293.

Stellar, E., 1954. The Physiology of motivation. Psychol. Rev. 61, 5–22.

Sullivan, P.F., Bulik, C.M., Kendler, K.S., 1998. The epidemiology of bulimia nervosa. Psychol. Med. 28, 599–610.

Tappe, K.A., Gerberg, S.E., Shide, D.J., Andersen, A.E., Rolls, B.J., 1998. Videotape assessment of changes in aberrant meal-time behaviors in anorexia nervosa after treatment. Appetite 30, 171–184.

Wakeling, A., Russell, G.F., 1970. Disturbances in the regulation of body temperature in anorexia nervosa. Psychol. Med. 1, 30–39.