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Review

Behavioral neuroendocrinology and treatment of anorexia nervosa

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ABSTRACT

Outcome in anorexia nervosa remains poor and a new way of looking at this condition is therefore needed. To this aim, we review the effects of food restriction and starvation in humans. It is suggested that body weight remains stable and relatively low when the access to food requires a considerable amount of physical activity. In this condition, the human homeostatic phenotype, body fat content is also low and as a consequence, the synthesis and release of brain neurotransmitters are modified. As an example, the role of neuropeptide Y is analyzed in rat models of this state. It is suggested that the normal behavioral role of neuropeptide Y is to facilitate the search for food and switch attention from sexual stimuli to food. Descriptive neuroendocrine studies on patients with anorexia nervosa have not contributed to the management of the patients and the few studies in which hormones have been administered have, at best, reversed an endocrine consequence secondary to starvation. In a modified framework for understanding the etiology and treatment of anorexia nervosa it is suggested that the condition emerges because neural mechanisms of reward and attention are engaged. The neural neuropeptide Y receptor system may be involved in the maintenance of the behavior of eating disorder patients because the localization of these receptors overlaps with the neural systems engaged in cue-conditioned eating in limbic and cortical areas. The eating behavior of patients with anorexia nervosa, and other eating disorders as well, is viewed as a cause of the psychological changes of the patients. Patients are trained to re-learn normal eating habits using external support and as they do, their symptoms, including the psychological symptoms, dissolve.

1. Introduction

The aim of studies on patients with anorexia nervosa is to improve their condition, but there are as yet no neuroendocrine studies and few, if any other studies that have contributed the reaching this goal [21]. A new way to approach the problem is needed.

It was suggested long ago that the hormonal changes in anorexia nervosa are non-specific effects of starvation [62] and so far, endocrine interventions have had no effect on the behavioral condition of the patients. At the present state of knowledge, therefore, the cause–effect relationship between hormones and behavior in anorexia nervosa is unclear and needs to be reconsidered. We will expand on this topic in light of recent results suggesting that some so-called "orexigenic" peptides influence appetitive, rather than consummatory aspects of ingestive behavior [4,49,99]. This is a departure from the prevailing paradigm, according to which hormones from stored fat and pancreas, along with glucose, lipids and amino acids from ingested macronutrients feed back on brain networks to excite or inhibit eating such that body weight remains stable over time [15]. There are many excellent recent reviews on this topic, e.g. [39,101], on the neuroanatomical engagement during eating, e.g. [58,72] and of the endocrine changes, e.g. [114] and the medical aspects of anorexia nervosa, e.g. [110]. Reviewing these fields again would be redundant.

According to the conventional view, anorexia nervosa emerges as a symptom of an unknown underlying mental disorder and we have recently discussed the problems associated with this view in detail [149–152,176]. No effective treatment has been developed based on this point of view [160]. The little support that may exist for the conventional view is in stark contrast to the overwhelming evidence that starvation *causes* psychological change and even mental disorders. Because the conventional view still permeates thinking about the cause and treatment of anorexia, we will review the evidence that starvation causes mental problems in some detail.

We will discuss the effects of enforced starvation and subsequent re-feeding first and then suggest that the symptoms of anorexia nervosa are reversible, often physiological consequences of starvation. We will then review some aspects of the life of Australian Aboriginal hunter-gatherers, which is conspicuously similar to that of starved or semi-starved people and patients with anorexia

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nervosa. On the basis of these descriptions, we will re-evaluate the concept of body weight homeostasis and suggest that maintenance of a low body weight for a long period of time along with a high level of physical activity and retention of the capacity to eat large meals provide an example of a situation in which body weight is homeostatically regulated. We will then describe the way in which hormones and behavior interact in this situation; the human homeostatic phenotype. The description is admittedly selective and aims at proposing a new paradigm that does not conform to the conventional concept of homeostatic regulation. This step seems necessary, because the conventional view is incompatible with the neuroendocrinology of anorexia nervosa.

It is commonly thought that there are many risk factors and that anorexia nervosa has an unknown etiology, but this hypothesis has not resulted in effective interventions. We have considered some other problems associated with this view elsewhere [149–152] and will therefore not re-consider these in the present context. Instead, we have suggested that anorexia nervosa develops from the two known risk factors: reduced food intake and enhanced physical activity [20]. We have also suggested that a reduction in food intake would cause an increase in the release of dopamine in the ventral striatal terminals of the mesolimbic dopamine neurons via both adrenocortical hormone feedback on these terminals and activation of the dopaminergic cell bodies in the ventral tegmentum of the mesencephalon [20,95]. Release of corticotrophin-releasing hormone (CRH) in the hypothalamus is the primary mediator of both these mechanisms [20]. The mesolimbic dopamine system is associated with the short-latency experience of reward [105]. In addition, release of CRH in the brain activates the noradrenergic neurons of the locus coeruleus in the brainstem [87]. These neurons project to forebrain areas that are engaged whenever an individual needs to pay attention to ongoing events [130,135]. Hence, we suggested that anorexia nervosa develops because it is initially rewarding to eat less food and that anorexic behavior is subsequently maintained through conditioning to the situations that provide the reward [20]. Methods to treat patients based on this point of view were set up and the treatment was evaluated in a randomized controlled trial [17]. In this trial, 16 patients were allocated to treatment and 16 other patients were allocated to no-treatment using a randomized procedure. The number of patients needed in each group in order to demonstrate a significant effect was estimated based on preliminary results [18] and the possibility that patients may drop out was also taken into consideration. Very few exclusion criteria were used. Treatment was found to have a major effect on a series of strict outcome criteria; patients had to show normal eating patterns and perceive a normal level of satiety, have a normal body mass index (BMI), normal laboratory test values and normal levels of psychiatric symptoms, they had to be able to say that food and body weight were no longer a problem and they had to be back at school or professional activities [17]. All these criteria had to be fulfilled before a patient was considered in remission. Thus, a treatment based on a neurobiologically plausible framework was demonstrated to be effective. Furthermore, the treatment brought an estimated 75% of a group of 168 patients into remission and only 10% of a group of 83 patients relapsed within a year [17].

Finally, we will refine the framework for understanding anorexia nervosa delineated above and suggest how patients with anorexia nervosa and other eating disorders should be treated, based on this view.

2. The response to enforced starvation

During the last months of the Second World War, the supply of food to the Western Netherlands was severely restricted. The consequences of this enforced starvation have been extensively studied and the description below relies on the evidence presented in the first report of this phenomenon [29], unless otherwise noted.

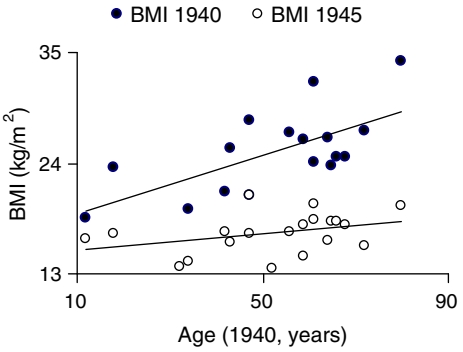

Fig. 1. Body mass index (BMI) in relation to age in 20 men in 1940 and after enforced starvation in 1945. Reproduced with permission from [29].

Before the enforced starvation, the people of the Netherlands had not suffered from lack of food as their energy intake had been about 2000 kcal/day during most of the war. However, starting in what was to be called the Hunger Winter of 1944–1945 [167], the supply of food was gradually restricted and reached a minimum of about 600 kcal/day. With the restriction of calories, public health deteriorated rapidly and eventually the level of starvation was extreme with perhaps as many as 18,000 people starving to death during that period.

2.1. Body mass index (BMI)

There was a massive loss of body weight in the Dutch population. For example, a group of 20 men, who were on average 52 (12–80) years old in 1940, had their BMI (kg/m^2) decline from 25.2 (18.5–34) to 17 (13.5–20.8) after the enforced starvation.[1] Fig. 1 shows that the well-known positive correlation between age and BMI in the "normal" condition in 1940 ($r = 0.67$, $p < 0.001$) had disappeared ($r = 0.26$, $p = 0.116$) as a result of the starvation in 1945.

Unfortunately, similar data for women were not presented although it was noted that men lost more weight than women and that more starving men than women died.

2.2. Psychological change

While observations on the psychological state were made on several hundred thousand starved people, systematic, quantitative data were not collected. However, the following psychological changes were often observed: depression and narrowing of outlook, including little interest in new ideas. Virtually everybody thought of food continuously: "... the whole day long we talked about food; and I went to bed hungry and dreaming about food". A hungry human is: "... little different from an animal and in the end consists only of a stomach plus some instincts and tools" [167]. Sexual interest was rapidly suppressed and women stopped menstruating. Furthermore, physical and mental fatigue was common, as was the failure to concentrate, along with a decline in memory. Visual and auditory impairment developed in rare cases, and psychosis, including delirium, paranoid traits and hallucinations, as well as refusal to eat food were also observed.

These observations show that normal people who starve develop abnormal psychological symptoms, which can be dramatic. And

[1] Throughout this paper, the mean value and the SD are used when the group is relatively homogenous with regard to the parameter described; the median and range are used when the range is large.

in people who have mental problems, these problems are enhanced by starvation. Thus, in a French mental hospital it was reported that the degree of starvation, as evidenced by the severity of oedema correlated with the prevalence of schizophrenia. Out of 47 patients with severe oedema, 25 had a diagnosis of schizophrenia, out of 36 who had less severe oedema, 9 had a diagnosis of schizophrenia and out of 37 who had no oedema, 3 had a diagnosis of schizophrenia ($Chi^2 = 20.55$, df = 2, $p < 0.001$) [8]. It is unclear from this observation whether schizophrenic subjects are more sensitive to the effects of restricted food intake or if starvation causes schizophrenia. However, there is evidence for the latter possibility in a study in which six out of 10 people, who had no record of mental illness, developed psychotic symptoms when reducing their BMI from 29.3 (19.5–34.6) to 23.8 (17.6–28) by eating less food over an 8 (4–24)-week period [131]. The psychotic symptoms were reversed when the BMI was restored to 26.4 (20.3–33.2), but since the participants were also treated with antipsychotics, the cause of the reversal is unclear. The four other participants in this study had a history of mental illness and all showed severe psychotic symptoms after a comparable weight loss. More recent evidence offers further support for the possibility that starvation can cause psychosis [157]. Similar observations on the psychological effects of starvation, including psychosis-like symptoms and self harm, were reported in a controlled experiment on men who were selected for being physically and mentally healthy and who volunteered to participate [92].

2.3. Physical hyperactivity

During the Hunger Winter, it was often observed that some people, despite their state of under-nutrition, would travel very far and at considerable physical expense, e.g., long bike rides, to forage food. Before the war, Holland had a population of eight million and half of these people owned a bike. It was estimated that in 62% of the families in Amsterdam at least one member went on a "hunger trip" to collect food [167]. The urge to procure food developed to such an extreme that some people "who in normal times were strictly honest ... came to steal food". Starvation-induced violence and the emergence of organized "thefts, assaults and plundering were the order of the day" [167].

2.4. The capacity to eat a large amount of food is retained in starvation

Interestingly, when the enforced starvation in the Netherlands was interrupted by a temporary supply of 800 g bread and 125 g margarine/person through foreign aid, some people consumed this food in a day or two [167]. Similarly, in the starvation experiment [92] it was noted that when the experimental supply of 1570 kcal/day was interrupted by a meal containing 2400 kcal, the men readily consumed the food and experienced relief from the mental symptoms of starvation immediately after the meal. In addition, in an experiment in which the body weight of 10 healthy men was reduced by 10% over a period of 4 months by restricting the caloric intake to 50–70% of the normal, the men could consume big meals (5264 kcal) and all men overate after the experiment [14]. Thus, the capacity to eat large amounts of food persists in starvation; no inhibitory control of eating emerges as a consequence of starvation.

2.5. The symptoms of anorexia nervosa are the same as those of starvation

Patients with anorexia nervosa show the same behavioral and psychological changes as the healthy people described above who were subjected to enforced starvation, or who volunteered in experimental starvation. Despite the similarity, it has been suggested that there are "psychopathological features" that distinguish anorexics from other starved people. Specifically, these features include the "fear of gaining weight" and the "undue influence of body weight or shape on self-evaluation" [81]. Although these features are used for diagnostic purposes [2], there is no experimental evidence that anorexics differ from controls with regard to the perception of body size [30,147] and when it was first suggested that they might, it was pointed out that this does not distinguish anorexics from other clinical groups [27]. More interesting, it was recently reported that these psychopathological features were induced in the healthy volunteers in the starvation experiment [46,92].

2.6. Summary

The effects of enforced or experimental starvation on healthy people are virtually identical to those of the starvation of anorexia nervosa. Similarly, the behavioral symptoms of starvation have little inter-individual variation. Most, if not all of the behavior of starvation and anorexia nervosa involve food-related activities, such as hoarding of food and enhanced physical activity. The psychological changes precipitated by starvation are more variable across individuals, although there are core symptoms, "semi-starvation neurosis", which are shared by most starving people [139]. One is reminded of an 11-year-old conclusion that: "...many of the symptoms that might have been thought to be specific to anorexia nervosa and bulimia nervosa are actually the results of starvation. These are not limited to food and weight, but extend to virtually all areas of psychological and social functioning. ... many of the symptoms that have been postulated to cause these disorders may actually result from under-nutrition ..." [66]. This conclusion is strengthened by two recent reports that question the evidence-basis for the conventional view that anxiety is a cause of anorexia [165,174]; it is the other way around.

3. The response to re-feeding

By the time the Germans had capitulated on May 7, 1945, 141,636,186 kg of food had been stored in southern Holland and the plan was to provide 2000 kcal/day to a population of 4.2 million. It was estimated that 400,000 people were in need of special treatment for starvation and that 30,000 needed acute treatment in a hospital. About 279,000 were actually treated and 3000 of these were treated in hospitals. Two hundred seventy-five (9%) of these died in hospital, most of them during the first week. Far more men than women had been admitted to hospital.

3.1. Starved people can eat normally

Because there was very limited information on the response to starvation and to the subsequent re-feeding in humans, two assumptions were made. Firstly, it was assumed that starved people are unable to ingest food via their mouth; it was even thought that starved people have difficulty drinking fluids. Secondly, it was assumed that the gastrointestinal tract of a starved individual is limited in its capacity to digest and absorb food. Both assumptions turned out to be wrong. Initial attempts to re-feed patients with pre-digested protein solutions failed because these solutions were rejected. Other attempts to use intravenous supply of nutrition were dangerous in that they led to thrombosis of the veins. Artificial re-feeding using a naso-gastric tube was only needed in patients who refused to eat as a consequence of starvation-induced psychosis. In the majority of cases, eating food as it is normally eaten was the most effective re-feeding strategy and intake of 1000 kcal/day was common in many cities within the second week

after food was made available. Re-feeding at levels of 2000–2500 kcal/day resulted in a prompt and all-around general improvement in health. While body weight was not fully or promptly restored, improvement in morale and well being was evident within a week to 10 days and was greatly improved after a month. At that time there were few if any signs of malnutrition in the Netherlands.

3.2. Summary

The results of re-feeding of several hundred thousand people in the Netherlands, who had been subjected to starvation, showed that eating normal amounts of food is the best way to reverse both the physical and psychological effects of starvation. There are no constraints for normal eating at any site throughout the oro-gastro-intestinal tract or along the neuraxis as a result of starvation. Normal eating restores both psychological functions as well as other functions. All in all, starvation is a reversible condition. This is not surprising because starvation has been a frequent condition during evolution and most of the responses to starvation are physiological responses to a common challenge, not signs of disease [151,152].

4. Maintenance of a BMI of 17 for 40,000 years

Australian Aborigines lived in small communities and maintained a relatively constant life style for perhaps more than 40,000 years [24]. It has been estimated that the size of this population of hunter-gatherers remained stable at about 300 000, with many mechanisms to maintain stability, e.g., prolonged breast feeding along with the associated lactational amenorrhea and infanticide of as many as 50% of the newborn children. Inter-tribal warfare and perhaps infections also contributed to keeping the size of the population constant, although it is thought that epidemics were uncommon among hunter-gatherers and appeared only with the emergence of agriculture [173].

4.1. Foraging for food

A decisive factor that contributed to population size was the availability of food and a substantial amount of time was devoted to the acquisition of food. Thus, both Aboriginal men and women spent 3.5 (0–7) hours each day to catch and prepare food [172]. Men could travel very far either alone or in small groups and return to their camp after one or several days hunting prey. Women spent as much time and effort as men foraging for food, although they used different strategies. "One woman some 55–60 yrs old returned to the camp with a 28.5 kg load of firewood herself 32 kg bw" [172].

4.2. A low BMI and the capacity to overeat

It is not surprising that these people had low BMIs. Thus, a group of 11 women and 7 men, who were 34 (15–68) years old, had a BMI of 16.7 (13.4–19.3) [123]. Equally interesting, their body fat mass was very low and their BMI did not increase with age. Despite their leanness, the Aborigines showed no biochemical signs of malnutrition [123]. Even more interesting, they retained a capacity to consume large amounts of food if offered the chance. Thus, they ate as much as 2–3 kg of a high-protein diet in 1 day [123].

This situation is conspicuously similar to that of starvation as described above. Thus, when a high level of physical activity is required for the acquisition of food, body weight is low, body fat is depleted and the correlation between BMI and age disappears, just as it did during the Hunger Winter (Fig. 1). Interestingly, the BMI of the Aborigines described above is virtually the same as the BMI of the food-restricted men described in Fig. 1. Correlatively, there was a high level of physical activity spent foraging for food in both situations and the capacity to eat a large amount of food was retained.

4.3. Anorexia nervosa: a low BMI, a high level of physical activity and the capacity to eat a normal meal

Anorexic patients maintain a low BMI for long periods of time. The BMIs in Fig. 1 (starved condition) and those of the Aborigines described above are in the range of those of anorexic patients. In fact, a BMI < 17.5 is used as a diagnostic criterion for anorexia nervosa [2]. Many patients with anorexia nervosa, however, have an even lower BMI. Anorexic patients, of course, have very little body fat and they display a high level of physical activity [81,94], although this can decrease with a very low BMI [25].

As noted above, some starved people refuse to eat when food is offered. Thus, starved people are similar to anorexic patients, who may eat only little food despite the fact the food is always present. However, as was also noted above, starved people with a low BMI can eat large meals. What about anorexic patients? Can they also eat a meal of a normal size?

Fig. 2 shows that food intake was virtually constant in a group of 24 anorexic patients, with an average age of 17 (2.7) years, who were in the early phase of treatment with a BMI of 15 (1) and who had been ill for 2.2 (2) years. Intake was recorded in 12 tests that were separated by 1–5 days and the patients ate normal food during these tests (Findus, Bjuv, Sweden, 580 kJ (140 kcal), 5.5 g protein, 6 g fat and 16 g carbohydrate/100 g). The figure also shows the food intake of another group of 24 anorexics. These patients, who were on average 16 (2.6) years old, had a BMI of 14.2 (1.8) and had been ill for 2.7 (2.3) years, also ate a constant amount of food. However, intake in this second group was interrupted by meals of a normal size in 4 (2–7) tests. While the highest intake during these tests was 432 g consumed by a 16.4-year-old girl whose BMI was 16.9, there was no correlation between the BMI and food intake either before ($r = -0.38$, ns), during ($r = -0.14$, ns) or after ($r = -0.14$, ns) the tests in which more food was consumed. However, there was a significant correlation between food intake before and during ($r = 0.75$, $p < 0.001$), during and after ($r = 0.64$, $p < 0.001$) and before and after ($r = 0.58$, $p < 0.01$) the episode of increased food intake. After the episode of increased intake, the patients went back to the constant low level of food intake. The number of tests before and after the episode of increased intake is arbitrarily set at four in the figure for comparison. There were more tests in which intake was constant and more than one instance of normal meals. The 24 patients who ate meals of a normal size were from a group of 78 anorexic patients admitted to our clinic for

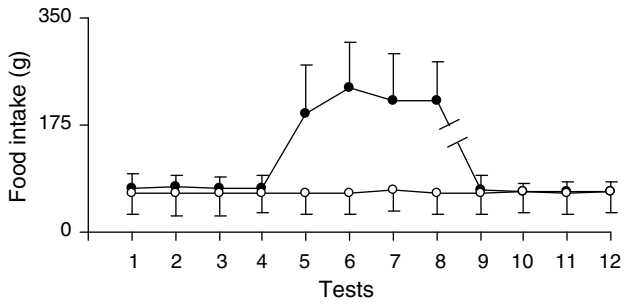

Fig. 2. Daily food intake in 24 anorexic patients whose low amount of intake was interrupted by normal meals during on average 4 (2–7) tests (black dots) and in 24 other anorexics who ate a low amount of food continuously (white dots). Values are means (SD).

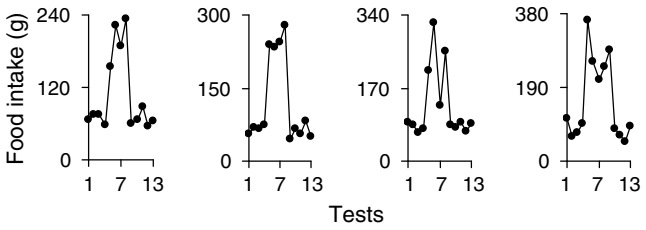

Fig. 3. Daily food intake in four anorexic patients whose low amount of intake was interrupted by normal meals.

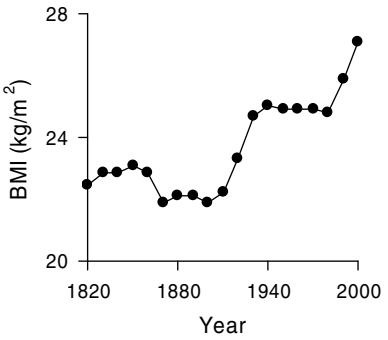

Fig. 4. Body mass index (BMI) in English men during 180 years. See Ref. [63] for a detailed discussion of the influence of differences in, e.g., age and nutritional factors on BMI over time. Reproduced with permission from [51,63,119].

treatment. The 54 other patients all ate a constant low amount of food and 24 of these were randomly selected for the comparison shown in Fig. 2. For a detailed description of how food intake is tested in anorexic patients and how the patients are treated see [17] and below.

Fig. 3 shows individual examples of food intake among the 24 anorexics whose intake increased. During these tests, the average intake increased by 307% to 230 (134–337) g. All but one of the 24 patients ate 240 g at least once and 13 (54%) ate 300 g at least once. Seventeen healthy women, who were 16.4 (1.7) years old years and had a BMI of 20.1 (1.6) ate 259 (186–389) g when tested under the same conditions [151]. The slight difference between the meals of the anorexic patients and those of the healthy women is not statistically significant.

Thus, about a third of anorexic patients with a very low BMI have the capacity to eat a meal of a normal size. Those who did eat normal meals did not differ with regard to diagnosis from those who did not eat such meals. About 20% of anorexic patients display bulimic behavior, and they therefore have a separate diagnostic category; binge–purge type anorexia nervosa [2]. However, the number of patients with this diagnosis was about the same in the group that showed increased intake (12.5%) as in the group that did not (16.7%). The capacity to eat a meal of a normal size in anorexic patients is similar to the capacity to overeat in starving people described above. It is also similar to the situation in normal weight people. Daily intake in people outside of the controlled setting of a laboratory fluctuates markedly [50]; people tend to overeat over prolonged periods of time such that body weight drifts upwards [127].

4.4. Summary

Humans in a setting that demands a high level of physical activity for hoarding and preparing food maintain a low BMI and have little body fat. Anorexic patients are similar in these regards. Furthermore, both these groups are similar in that they can eat a meal of a normal or above normal size.

5. The human homeostatic phenotype

Body weight is most often considered to be the outcome of the activity of neuroendocrine networks that "control" eating behavior in order to keep body weight constant. This paradigm originates with Claude Bernard's idea that the internal milieu of an organism must be kept stable, and if it is not, the organism will be entirely dependent upon fluctuations in the external environment [22].

5.1. The Bernard–Cannon concept of homeostasis

Bernard's hypothesis of the "constancy of the internal milieu", which was based on relatively few facts [38], suggested that there are mechanisms that counteract the influence of external variation [22]. Supporting evidence was subsequently collected by Cannon [33]. Cannon mostly studied situations of depletion, e.g., blood clotting and drinking after substantial loss of blood, and suggested: "... a special designation of these states, *homeostasis*. The word does not imply something set and immobile, a stagnation. It means a condition—a condition that may vary, but which is relatively constant." It was postulated that storage mechanisms develop when the external supply is variable, as is the case with food, but not when it is unlimited, as is the case with oxygen. A "tighter" homeostasis has therefore developed for oxygen need and usage than for food intake; you will not see someone who has taken in too much oxygen but you might very well see someone who has had too much to eat.

5.2. The homeostatic phenotype

The constant low body weight and the high level of physical activity among the Australian Aborigines described above provide an example of homeostatic regulation of body weight that is compatible with the original idea of Bernard–Cannon [22,33].

Interestingly, Cannon also suggested that there is homeostatic regulation at the other end of the starvation–obesity continuum as well: "Cooperating with hunger and thirst in a way not yet clearly defined is the sensation of having had enough. Protection of the organism of being overstocked with food and water is thus obtained. The feeling of satiation is little understood, but it is important and deserves further attention." However, neither Bernard nor Cannon studied the physiology of abundance.

When the history of the BMI in the Western world is examined it is obvious that body weight has not been stable. Fig. 4 shows that the average BMI of English men has fluctuated markedly during the last 180 years [51,63,119]. It is questionable if the variation of BMI shown in Fig. 4 is the expression of homeostatic regulation in the Bernard–Cannon sense.[2] The marked variation in the BMI during the last two centuries argues against homeostatic regulation of body weight under the conditions of life in Western Europe after the industrial revolution. During the same two centuries, the life of the Australian Aborigines changed dramatically as a result of the European settlement. The result was a massive breakdown of homeostasis, i.e., a marked reduction in the size of the population and an increase in obesity and related diseases [124]. Interestingly, body weight normalized and health returned, i.e., homeostatic regulation was resumed, when these people returned to the conditions of their normal life [124].

Absence of homeostatic control is most likely the result of a variation in the cost of food. According to this concept, meal size varies in proportion to the effort an animal needs to exert to obtain

[2] The instability of the human BMI in recent history was recently noted [133].

the food; animals, which have to work hard for food eat bigger and fewer meals [41,133]. If, however, there are no constraints and animals are provided with high caloric foods, they overeat and become obese [143]. Similarly, people eat in proportion to the time they need to spend obtaining food, the lower the cost, the more they eat [47].

5.3. Summary

A situation in which body weight is kept constant, i.e., homeostatically regulated according to the original Bernard–Cannon concept of homeostasis, is when the BMI is low and there is a high level of physical activity. We refer to this situation as the human homeostatic phenotype. This phenotype was maintained during 40,000 years among Australian Aborigines. We suggest that anorexia nervosa is a similar phenotype.[3]

Because the capacity for a high level of physical activity has been a major evolutionary asset, it has been suggested that the search for candidate genes of the human homeostatic phenotype should concentrate on the mechanisms of storage of glycogen and triglycerides in skeletal muscle, a prerequisite for efficient physical activity [35]. By contrast, the search for the candidate genes of anorexia nervosa has used some of the variable psychological effects of starvation described above as the phenotypic starting point [28] and probably for this reason yielded inconsistent or negative results [7]. Reliability in the measurement of phenotypic expression is a prerequisite for proper genotyping [120].

We suggest that the search for neuroendocrine correlates to anorexia nervosa should concentrate on the human homeostatic phenotype.

6. Descriptive versus predictive neuroendocrinology

Most studies on the relationship among the neuroendocrine system, eating behavior and body weight rely on the Bernard–Cannon concept of homeostasis as adapted to neural function [158]. As mentioned above, the model suggests that brain networks excite or inhibit eating behavior in response to feedback from endocrine and metabolic signals in order to keep body weight constant, e.g. [39,101]. Behavior is thought of as an outcome of neural control in this model; many publications are entitled: "Neural control of eating behavior". Animals in the sedentary condition of the laboratory with continuous, effortless access to food or animals that have been deprived of food for a few hours have been used as the homeostatic point of reference. This model clearly does not mimic the human homeostatic phenotype. A better model would be one in which an animal is maintained at a low body weight and with a constant demand to forage for food [40,133].

6.1. Descriptive studies

Neuroendocrine studies on patients with anorexia nervosa rely on the same concept of brain control of eating behavior and body weight homeostasis and most of these studies have described effects of starvation, e.g., reduced levels of 5-hydroxy-indol acetic acid in spinal fluid and elevated levels of cortisol in plasma, which are reversed upon weight restoration (reviewed in [152,176]). Unfortunately, these studies have not yielded anything that can be used to improve the condition of the patients. For example, patients treated with indirect serotonergic agonists experience no clinical improvement, most of them and their placebo-treated controls relapse into illness or drop out of the treatment program within a year, a brief period of time in this context [169]. This outcome indicates that changes in serotonin function among anorexic patients are not the cause of their symptoms.

A recent series of descriptive studies on leptin secretion has suggested that this particular hormone may be useful not only in diagnosing anorexia nervosa [81]. Thus, it is suggested that hypersecretion of leptin occurs within 11 weeks of treatment of anorexic patients thereby causing arrest of weight gain and predisposing the patients for relapse [84]. These findings have not been consistently replicated [81] and it seems unlikely that recovery of endocrine secretions, e.g., leptin, prevents a starved individual from further weight gain and even puts her/him at risk of relapsing into starvation. Recall that several hundred thousand severely starved people in the Netherlands gained weight within less than 11 weeks without problem. Many of these people must have developed leptin levels as high as the anorexics described in some of the studies of leptin secretion in anorexics [81,84]. As we have argued before, relapse in anorexic patients is more likely the consequence of an ineffective treatment than the consequence of the persistence of an underlying mental health or endocrine problem [151,152]. If properly treated [17], an increase in body weight in anorexics is not a problem; it is the obvious goal of treatment. Fig. 5 shows that 40 anorexic patients, who were 17.4 (11.8–35.6) years old reached remission in 17 (5.3–37.3) months without arrest of body weight gain [152]. As noted above, inhibition of normal eating does not develop as a consequence of starvation.

Typically, studies on anorexia nervosa report measures of endocrine and/or behavioral parameters, e.g., a relationship between plasma cortisol and physical activity [94], which may be followed over time but are seldom examined experimentally. A recent review listed most of these studies [114] and pointed out the cause–effect problem in descriptive neuroendocrinology. Such studies will at best generate hypotheses regarding the etiology of the disorder.

6.2. Predictive studies

In 1975, it was reported that treatment with a synthetic LH-releasing hormone (LRH) induced follicular maturation, ovulation, a functional luteal phase and menstruation in four women with anorexia nervosa [122]. Thus, the hypothalamic-pituitary-gonadal axis is functional but hibernating in anorexia nervosa. This finding is not surprising because cessation of ovulation and menstruation is probably the most universal response to shortage of food of female animals, and as soon as food becomes available and sufficient amount of body fat has accumulated, ovulation is resumed [140]. More interesting, there were no effects on mood, eating, body weight or sexual behavior among the anorexic women treated with LRH [122]. The results therefore show that the capacity for ovula-

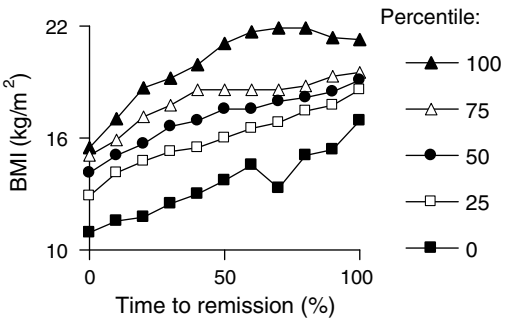

Fig. 5. Recovery of body mass index (BMI) in 40 anorexic patients treated to remission in 17.4 (11.8–35.6) months. Time to remission is expressed as percent. Reproduced with permission from [152].

[3] An evolutionary perspective on anorexia nervosa has been suggested before [77] although it differs substantially from the one presented here.

tion and menstrual cyclicity is unrelated to the cause of anorexia nervosa and suggest that anorexic patients should not be treated with LRH. The study demonstrated the power of the experimental approach; outcome of treatment of anorexic patients can be anticipated on the basis of predictive neuroendocrine studies but rarely, if ever, on descriptive studies.

A recent descriptive study indirectly confirmed these results [111]. Thus, it was reported that while one group of anorexic patients with a BMI of 17.1 (1.3) retained the capacity for ovulation, another group with approximately the same BMI (16.8 (1.7)) did not. Note that these anorexics had a BMI that is considerably higher than that of the anorexics in Figs. 2 and 5 and that of the anorexics in the study on induced ovulation [122]. Unsurprisingly, the body fat mass, and therefore the level of leptin, was higher in the group that ovulated than in the other group. As expected on the basis of the study on induced ovulation in anorexics [122], the psychological status was the same in both groups [111].

There are no studies on anorexic patients that have demonstrated that eating or body weight can be affected by hormonal treatment. In fact, the study on restoration of the menstrual cycle [122] is the only study which has shown that a physiological function can be normalized by endocrine treatment in anorexia. Another early study on the hypothalamic-pituitary-adrenal axis showed that the ACTH response to CRH was normal 6 months after weight restoration but reported no evidence that CRH can be useful in low weight anorexics [70].

A few other studies in which hormones have been administered to anorexic patients also reported no clinically useful effect. Thus, administration of estrogen had no effect on regional fat distribution in a study that suggested that an effect of estrogen on this particular compartment might have been to the benefit of the patients [74]. In another study, treatment with estrogen or recombinant human insulin-like growth factor-I increased the serum level of ghrelin but had no effect on food intake or BMI [75]. Combined treatment with estrogen and the growth factor caused a further increase in ghrelin levels but had no effect on food intake [75]. Ghrelin is produced by the stomach, is secreted in anticipation of a meal in animals with unrestricted access to food, and the secretion is enhanced after food deprivation [56]. As expected, ghrelin levels are elevated in anorexic patients, yet the patients do not eat and increasing the level of ghrelin further by treatment with estrogen and insulin-like growth factor-I had no effect on food intake [75].

Administration of testosterone was predicted to normalize regional blood flow in the brain of anorexic patients in another study [108]. In line with this prediction, testosterone had an effect on blood flow in the posterior cingulate cortex but the authors concluded that this effect needs to be replicated and its physiological and clinical significance determined. Yet another study predicted that spatial cognition would improve with testosterone treatment of anorexics [109] and a slight improvement was found. This effect would appear to be of limited significance because cognitive impairment is not prominent in anorexia nervosa [64].

The very few studies in which hormones have been given to patients with anorexia nervosa have not reported clinically beneficial effects. Such predictive neuroendocrine studies are necessary for an analysis of cause–effect relationships and for improving clinical outcome if endocrine interventions are to be useful.

6.3. Summary

There are no studies on neuroendocrine changes in anorexia nervosa that have predictive value for treating the patients. One is reminded of a 25-year-old conclusion that the hormonal changes in anorexia nervosa: "have little specificity for this disease and are mainly a consequence of nutritional factors and starvation" [62]. We suggest, however, that there is a causal relationship between neuroendocrine and behavioral changes in starvation and anorexia nervosa which emerges when the neuroendocrinology of the human homeostatic phenotype is experimentally analyzed.

7. The neuroendocrinology of the human homeostatic phenotype: the neuropeptide Y-paradox

As described above, the human homeostatic phenotype is one with a constant low BMI, a low body fat content, a high level of physical activity and retention of the capacity to eat more than required for maintenance of the low BMI. The neuroendocrinology of this phenotype is determined by the content of body fat. The lower the fat content the lower the level of leptin in the blood [81]. Leptin feeds back on the brain and causes a decrease in the synthesis and release of neuropeptide Y (NPY) and changes in the synthesis and release of other peptides and messengers as well [15]. Our discussion will selectively consider the role of NPY in this scenario. For a comprehensive summary of the neurobiology of NPY the reader is referred to a recent impressive review [59].

7.1. The neuropeptide Y-paradox

When body fat is depleted it is generally thought that NPY counteracts the deficit that emerges by stimulating eating in order to replenish body fat stores and restore homeostasis [15]. NPY is therefore considered an "orexigen" [12]. However, while anorexic patients have increased levels of NPY in the spinal fluid [67] and in the brain as well [71], they do not eat. This situation,"the NPY-paradox", is inconsistent with the idea that NPY is an orexigen and with the conventional model of feedback regulation of body weight.

We will review a series of experiments that resolves the NPY-paradox. However, first it is necessary to understand how "orexigenic" messengers were found in the brain and second it is necessary to describe the display of ingestive behavior and other types of goal-directed behavior in some detail.

7.2. The discovery of the "orexigenic" effect of NPY

The effect of two major brain "orexigens", noradrenalin and NPY, on food intake was discovered as epiphenomena to neuroanatomy. Thus, Grossman [76] discovered that noradrenalin stimulates eating if infused into the hypothalamus of rats after suspecting that it might be a transmitter in the brain as it had been previously found to be in the peripheral nervous system [113]. Similarly, the discovery that NPY stimulates food intake emerged from neuroanatomical news. Two of the first reports that NPY stimulates food intake by acting on the paraventricular hypothalamic nucleus [154,155] relied on the finding that NPY co-exists with noradrenalin in brainstem catecholamine-neurons [83] and on the possibility that these neurons project to the paraventricular nucleus of the hypothalamus [137]. However, the study on co-existence of noradrenalin and NPY in brainstem neurons did not mention the possibility that these neurons project to feeding relevant forebrain areas [83]. This possibility emerged from studies on the efferent connections of adrenergic neurons in the brainstem [164] and subsequent studies on the noradrenergic projections from the brainstem to the hypothalamus [136] including the paraventricular hypothalamic nucleus [137]. Eventually, it was demonstration that noradrenalin and NPY are co-localized in the pathway from the brainstem to the paraventricular hypothalamus [138]. Another early report that NPY stimulates food intake [36] emerged from the hypothesis that adrenergic hypothalamic neurons engaged in the control of pituitary LRH secretion may co-localize NPY just as brainstem adrenergic neurons do [83]. As part of this

hypothesis it was suggested that the same hypothalamic neurons are also engaged in food intake and that NPY is the long sought molecule that links reproductive and ingestive behavior [37,88]. This hypothesis is particularly relevant to the present discussion. Finally, the third experiment that pioneered to study of NPY as an "orexigen" [100] aimed at extending the results of one of the first studies [36]. These results were incorporated into the conventional framework for homeostatic regulation [158]. Grossman wrote: "I was greatly influenced by Eliot Stellar's postulation of dual hypothalamic 'centers' that controlled hunger and thirst by exerting interacting stimulatory and excitatory influences . . .. Stellar's enticingly simply hypothesis . . . was widely hailed as a model for appetitive motivation" [113]. However, Stellar's model did not address the human homeostatic phenotype described above.

7.3. The display of ingestive and sexual behavior by rats

In order to resolve the NPY-paradox it is necessary to examine the display of ingestive behavior in some detail. It is also necessary to examine how the motivation to eat relates to the motivation to reproduce, since these two motivations are closely related [1,88,90,140,141]. As described above, in times of famine humans are totally concerned with foraging food while their reproductive capacity is suppressed.

Ingestive behavior has two phases: appetitive behavior (the search for food) and consummatory behavior (chewing and swallowing) [43]. In general, appetitive behavior is goal directed and flexible; the same neuro-motor substrate can obviously be engaged in the search for different goals. Consummatory behavior, by contrast, is stereotypic and used for a specific purpose [43]. Appetitive and consummatory ingestive behavior can be dissociated experimentally. For example, by infusing a nutritive solution into the oral cavity of a rat, the need for appetitive ingestive behavior is circumvented; the rat needs only to consume the solution [73]. Display of other types of motivated behavior can be similarly separated into an appetitive and a consummatory phase.

The neurobiological mechanisms which are engaged in ingestive and sexual behavior are partially overlapping and if manipulated pharmacologically, changes occur in the display of both kinds of behavior [90]. We anticipated, therefore, that activation of one of these behaviors should affect the subsequent display of the other. We also anticipated that simultaneous activation of both behaviors would be impossible.

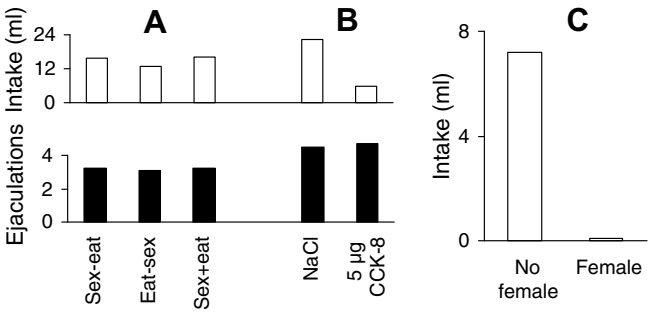

Fig. 6. Intake of a 1 M solution of sucrose infused intraorally at a rate of 1 ml/min and number of ejaculations in eight male rats (A,B). The rats were first tested with a sexually receptive female rat and then infused intraorally (Sex – eat), then tested in the reverse order (Eat – sex) and then infused intraorally and simultaneously tested with a female (Sex + eat) (A). The rats were then tested with a female and infused with sucrose intraorally and injected with CCK-8 or NaCl i.p. (B). Finally, the rats ingested the sucrose solution from a drinking spout in the absence (No female) or presence (Female) of a sexually receptive female rat (C). Values are means, measures of variability are omitted for clarity. Reproduced with permission from [90].

Fig. 6A shows that if male rats were first allowed to copulate with a sexually receptive female rat until they stopped ejaculating, there was no effect on the amount the rats ingested during the subsequent intraoral infusion of a 1 M solution of sucrose at a rate of 1 ml/min. Also, there was no effect on either intake or sexual behavior if the test order was reversed (Fig. 6A). Perhaps somewhat surprisingly, male rats showed consummatory ingestive and sexual behavior simultaneously if infused with sucrose intraorally and offered a sexually receptive female rat at the same time (Fig. 6A) [90]. Inhibition of sexual behavior occurs after ejaculation in male rats, but the rats ingested the sucrose solution continuously; no change was noted during the postejaculatory refractory period [90]. Intraperitoneal injection of 5 µg cholesystokinin octapeptide (CCK), a physiological intake suppressor [148] reduced intake of the sucrose solution but had no effect on the simultaneous display of sexual behavior (Fig. 6B). These results show therefore that the display of consummatory ingestive behavior is independent of the display of consummatory sexual behavior. Chewing and swallowing continues independent of excitation or inhibition of sexual behavior and conversely, sexual behavior continues whether or not consummatory ingestive responses are experimentally inhibited.

By contrast, if the rats had to search out a drinking spout to ingest the sucrose solution, i.e., if they had to show appetitive ingestive behavior before they could consume the solution, the presence of a sexual partner reduced intake from the spout to a minimum (Fig. 6C). Under this condition, the rats spent virtually all their time copulating. Similar results were obtained in female rats tested under the same conditions [90].

The results on the expression of ingestive and sexual behavior suggest that the brain mechanisms engaged in consummatory ingestive and sexual behavior operate independently; activation or inactivation of one of these behaviors does not influence the display of the other. However, the results also show that the search for one goal and the subsequent consumption of that goal prevents the search for competing goals.

7.4. Summary

Starving people think about food and search for food all the time. Sexual interest is absent and the neuroendocrine substrate for sexual function is hibernating but not inhibited. A large literature has demonstrated the evolutionary significance of an efficient strategy for foraging food [13,85,133,159]. Brain mechanisms that allow the effective search for food therefore have survival value in the sense originally proposed by Darwin [48]. Evolution of the human homeostatic phenotype has favored individuals with efficient foraging strategies, i.e., those who display effective appetitive ingestive behavior. Stereotypic consummatory responses, by contrast, are merely activated once a goal, either food or a sexual partner, is reached. Resolution of the NPY-paradox depends, as will be shown below, on the distinction between the appetitive and the consummatory phase of ingestive behavior.

8. Resolution of the NPY-paradox, part 1: NPY stimulates appetitive ingestive behavior

When an animal eats less food and loses weight, the synthesis and release of NPY increase in the brain [12]. The immediate behavioral response in this situation is hoarding, not eating [31,133,141]. The first indication that NPY might have a role in appetitive ingestive behavior was provided by an observation that intracerebral infusion of NPY does not stimulate consummatory ingestive behavior tested by intraoral infusion as described above [145].

8.1. NPY stimulates appetitive ingestive behavior and inhibits consummatory ingestive behavior

Fig. 7A shows that intracerebral infusion of 10 μg NPY does not affect ingestion of a 1 M solution of sucrose infused intraorally at a rate of 1 ml/min by male rats. In this experiment, the rats had also been trained to ingest the sucrose solution from a drinking spout and Fig. 7A shows that treatment with NPY increased the number of times the rats visited the spout. This observation indicated that NPY stimulates the search but not the consumption of food. However, intraoral infusion at a rate of 1 ml/min may be too high to allow the rat to ingest from the spout. Fig. 7B shows that as the rate of intraoral infusion was gradually decreased, the rats started ingesting from the bottle. While intraoral infusion at a rate of 0.5 ml/min activated consummatory ingestive behavior, it also allowed the rats to ingest from the bottle (Fig. 7B). Under this experimental condition, treatment with NPY reduced intraoral intake and increased the number of visits to the bottle and intake from the bottle (Fig. 7C). Interestingly, while treatment with NPY increased appetitive ingestive behavior it decreased to total amount ingested from 20.7 (2.7) to 17 (5.4) ml ($p < 0.01$) [4].

Ingestion from a bottle requires both appetitive and consummatory ingestive behavior and this simple test, therefore, confounds the appetitive-consummatory distinction. However, Fig. 8 shows that rats tested in this situation also visited an empty bottle and that treatment with NPY increased the number of visits to an empty bottle further, by about 50%, and, simultaneously, decreased the amount ingested from the intraoral infusion, by about 40% [4].

These results show that NPY acts specifically to stimulate appetitive ingestive behavior and at the same time reduces the display of consummatory ingestive behavior. The experiment models some aspects of the human homeostatic phenotype, including anorexia nervosa, as described above. Thus, an efficient strategy for the search for food, i.e., appetitive ingestive behavior, is a prerequisite for survival in times of famine and activation of the neural NPY-network may assist in such a strategy. Interestingly, the neural receptor system for NPY is one of the most ancient neurotransmitter systems in the nervous system and is likely, therefore, to have played an important role in evolution [97]. It is possible that the NPY Y1 receptor is particularly important in the present context, because it has been shown to mediate the effect of NPY on appetitive ingestive behavior [98,99]. This finding was recently confirmed [49,91]. Equally important for the present discussion, it has been suggested that the NPY receptor system mediates inhibitory effects on eating as well, perhaps via the NPY Y2 receptor [11].

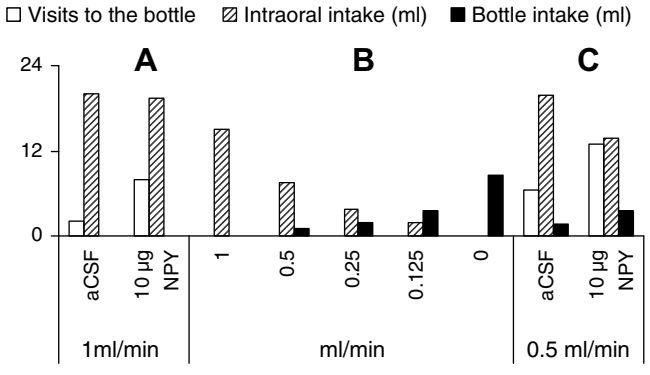

Fig. 7. Number of visits to a bottle filled with a 1 M solution of sucrose and intake of the solution during intraoral infusion or from the bottle in male rats. The rats were infused intracerebroventricularly with aCSF or NPY and infused intraorally at various infusion rates as indicated. There were 6–8 rats per group. Values are means, measures of variability are omitted for clarity. Reproduced with permission from [4].

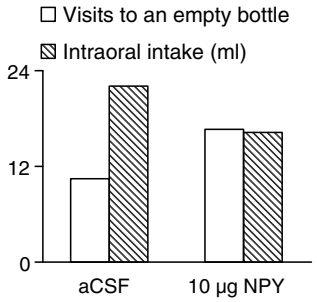

Fig. 8. Number of visits to an empty bottle and intake of a 1 M solution of sucrose infused intraorally at a rate of 0.5 ml/min infusion in seven male rats. The rats were infused intracerebroventricularly with aCSF or NPY. Values are means, measures of variability are omitted for clarity. Reproduced with permission from [4].

The finding that treatment with NPY increases appetitive ingestive behavior and, equally important, decreases consummatory ingestive behavior is part of the resolution of the NPY-paradox because the experimental situation in which these effects were obtained models the behavior of starving people, non-starving people with a low BMI, and anorexic patients as described above. At the same time, it is a surprising finding because there are many studies in which NPY has been found to stimulate food intake [12]. These studies, however, rarely make the necessary distinction between the two phases of ingestive behavior. Because inhibition of intake by NPY is unexpected within the conventional framework, we have replicated the finding that infusion of 10 μg NPY into the cerebral ventricles of rats reduces the amount consumed in response to intraoral infusion of a 1 M solution of sucrose at a rate of 0.5 ml/min five times [3–5,144]. It is important that the experimental conditions are properly controlled; if they are not, inconsistent results can be obtained, including the failure to obtain any effect of NPY [16,166]. For a recent, detailed analysis of the effects of NPY on appetitive and consummatory ingestive behavior see Ref. [9,10].

8.2. Leptin stimulates consummatory ingestive behavior

Because increased synthesis of NPY in the brain is a neuroendocrine response to decreased levels of leptin in the blood, we anticipated that treatment with leptin should have effects on ingestive behavior that are opposite to those of NPY.

Fig. 9A shows the conventional effects of intracerebral infusion of 10 μg NPY (an increase) or 10 μg leptin (a decrease) on intake of a 1 M solution of sucrose from a drinking spout. More interesting, Fig. 9B shows that while NPY decreased intake during intraoral infusion, leptin markedly increased intake in this test. Note that in a test that is specific for consummatory ingestive behavior, treatment with leptin increased intake by as much as 50% [4].

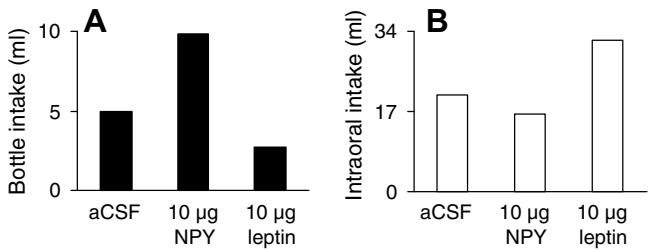

Fig. 9. Intake of a 1 M solution of sucrose from a bottle (A) or during intraoral infusion at a rate of 0.5 ml/min (B) in eight male rats. The rats were infused intracerebroventricularly with aCSF, NPY or leptin. Values are means, measures of variability are omitted for clarity. Reproduced with permission from [4].

The time cost analysis of ingestive behavior suggests that the lower the cost the more an individual consumes [40,47,133]. As no homeostatic control of overeating has emerged, it seems likely that as food is getting more easily available, intake will increase and, as a consequence, obesity will increase. We have suggested that leptin facilitates this development [19]. The stimulatory effect of leptin on consummatory ingestive behavior (Fig. 9B) is consistent with this suggestion.

8.3. NPY changes attention from sex to food

As discussed above, male rats engage in sexual activity if offered the choice between a bottle and a sexual partner (Fig. 6C). However, as we have also discussed, in the face of starvation, this priority is reversed. The reduction of sexual behavior and thought among starving people and the stimulatory effect of NPY on appetitive ingestive behavior in the experimental conditions discussed above suggest that the choice of sex over food may be influenced, perhaps reversed by treatment with NPY.

Fig. 10A shows that male rats which were treated with 10 μg NPY copulated as efficiently as rats treated with the vehicle. Thus, the rats ejaculated as often when treated with NPY as when treated with the vehicle and there were only minor differences in the parameters of sexual behavior under these two conditions [4]. However, the rats turned away from a sexually receptive female and to the bottle if offered the choice; the number of ejaculations was markedly reduced in the presence of the bottle (Fig. 10A) [4]. These results were implicated by the early observation that treatment with NPY does not affect the capacity for consummatory sexual responses but acts mainly to decrease appetitive sexual behavior [37], and corroborates similar findings in the snake [116]. Interestingly, infusion of leptin markedly enhanced consummatory sexual capacity, as reflected in the number of ejaculations, under these circumstances (Fig. 10A). While ingestion from the bottle was decreased by the presence of a sexually receptive female rat when the rats were treated with leptin or the vehicle, treatment with NPY markedly stimulated intake from the bottle, independent on the presence or absence of a female (Fig. 10B) [4].

The capacity for consummatory behavior seems little affected by treatment with NPY, the main effect of NPY is exerted on the display of appetitive behavior.

A word of caution in the interpretation of these results seems appropriate. Thus, the results rely on experiments in which very high doses of NPY were infused into the cerebral ventricles of rats. This is clearly an unphysiological method. Given this limitation, it is even more interesting that the behavioral effect, turning the attention of male rats away from a sexual stimulus and towards food, is very specific. The neuroanatomy of the details of ingestive, sexual and other types of motivated behavior in rats has been analyzed in considerable detail using proper experimental methods [34,60], but this analysis has not yet answered the question how the brain is engaged when animals chose between competing stimuli [90]. Renewed interest in this question has recently emerged in an interesting series of experiments of female hamsters [141]. Thus, deprivation of food causes an increase in food hoarding rather than food consumption and treatment with leptin reverses this effect confirming that leptin changes behavioral priorities favoring the choice of sexual rather than food stimuli [141].

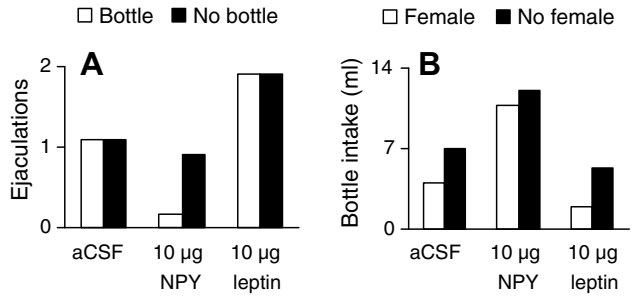

Fig. 10. Number of ejaculations (A) and intake of a 1 M solution of sucrose from a bottle (B) in 10 male rats. The rats were tested with a sexually receptive female rat in the absence or presence of the bottle and infused intracerebroventricularly with aCSF or NPY. Values are means, measures of variability are omitted for clarity. Reproduced with permission from [4].

8.4. Summary

In 2000, we summarized these findings by suggesting that: "... it is tempting to speculate that the leptin-NPY neuroendocrine system serves the purpose of directing attention to food acquisition when energy stores are depleted, i.e., when leptin levels are low and NPY levels are high, and to other activities when energy levels are high, i.e., when leptin levels are high and NPY levels are low" [4].[4] We suggest that leptin-NPY neuroendocrine system has the same role in the human homeostatic phenotype.

9. Resolution of the NPY-paradox, part 2: NPY facilitates activity-based-anorexia

A high level of physical activity is an important behavioral expression of the human homeostatic phenotype. The goal of the activity is the acquisition of food. In the present analysis, it follows that the activity equals appetitive ingestive behavior. It also follows that treatment with NPY should stimulate physical activity in a model of anorexia nervosa. Such a model is available for 46 years [153]. In that model, rats have access to running wheels and, if allowed continuous access to food, the rats run in the wheels and eat somewhat more food to compensate for the increase in energy expenditure. Just as in humans, physical activity in rats increases when the availability of food is gradually decreased and when the supply of food is reduced to 1–2 h/day the rats run excessively and may lose control over body weight [132]. This phenomenon is referred to as activity-based-anorexia.

9.1. Effect of food restriction on body weight and physical activity

Fig. 11A shows that sedentary female rats lost weight in proportion to the amount of food deprivation [121]. However, the decrease in body weight over time was different in each group of rats, i.e., rats with food available for 4, 2 or 1 h/day showed different time-dependent patterns of weight loss [121]. In similarly food deprived rats, which had access to a running wheel, weight loss was enhanced and also different between the groups. Loss of body weight after deprivation of food is not a simple function of the amount of available food suggesting that more than one or two neuroendocrine concomitants are engaged in this physiological phenomenon.

Rats with running wheels and food that was available at all times ate more food than the sedentary rats, but as the availability of food was gradually restricted, the rats ran in the wheels at higher rates and ate progressively less food. If food was available for only 1 h/day, some of the rats lost control over body weight and the experiment had to be terminated (Fig. 11B). Hence, as in most other species [112], deprivation of food causes an increase in physical activity in the rat, and just as in human starvation and anorexia nervosa, rats run excessively to the extent that they may lose control over body weight.

[4] A similar suggestion has been made before [65].

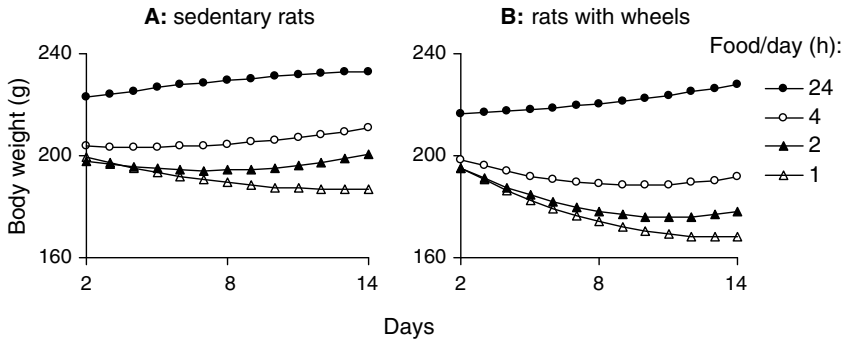

Fig. 11. Decrease in body weight in female rats with access to food during various periods of time. The rats lived under sedentary conditions (A) or had access to a running wheel (B). There were 5–6 rats per group. Values are predicted after model fitting, measures of variability are omitted for clarity. Reproduced with permission from [121].

9.2. Effect of NPY on physical activity

As anticipated, the synthesis of NPY was increased in the hypothalamic arcuate nucleus, a site of NPY synthesis, of rats in the activity-based-anorexia model [121]. With regard to the present hypothesis that enhanced physical activity is an expression of appetitive ingestive behavior and that NPY acts specifically to stimulate this aspect of ingestive behavior, we predicted that treatment with NPY should stimulate the development of activity-based-anorexia. In line with this prediction, intracerebroventricular infusion of 10 μg NPY increased wheel running (Fig. 12A), decreased food intake (Fig. 12B) and enhanced the loss of body weight (Fig. 12C) in female rats with access to food for 2 h/day [121]. The same treatment caused a slight, insignificant increase in wheel running, an increase in food intake and a small, statistically insignificant, increase in body weight in rats which had access to food at all times [121].

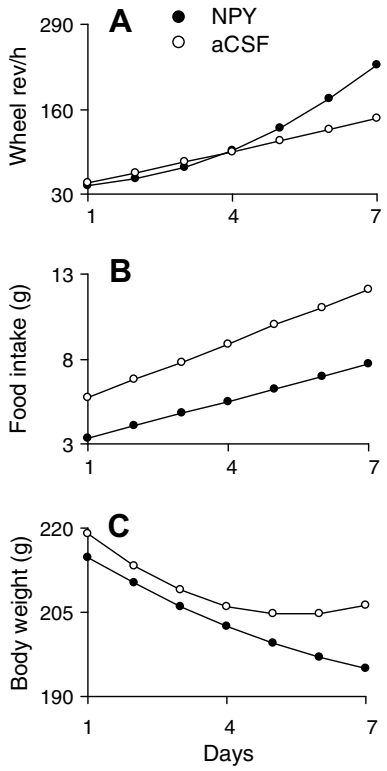

Fig. 12. Wheel running (A), food intake (B) and bodyweight (C) in female rats with food available for 2 h/day. The rats were infused intracerebroventricularly with aCSF or NPY. There were 5–6 rats per group. Values are predicted after model fitting, measures of variability are omitted for clarity. Reproduced with permission from [121].

These results show that the effect of NPY depends on physiological state. NPY-treated rats eat more food when food is present at all times but less food when the availability of food in restricted. In times of famine, the effect of NPY on appetitive ingestive behavior is unmasked. The NPY Y1 receptor mediates the appetitive phase of ingestive behavior [91,98,99]; mice lacking this receptor and maintained with continuous access to food become obese and show a reduction in locomotor activity [126]. Apart from the metabolic consequences of the absence of functional NPY Y1 receptors [126], these mice therefore have a reduced ability to search for food and it would be of interest to examine if they eat less and lose weight if challenged in a test with a high cost for the access to food [40]. These results are in line with the present analysis that as the demand for appetitive ingestive behavior is decreased or prevented, as might be in the case in mice lacking the NPY Y1 receptor, there is an increase in body weight. Conversely, in times of food shortage, the demand for foraging food is increased and NPY serves the purpose of facilitating this behavioral response.

9.3. Summary

The conventional view of NPY as an "orexigen" has emerged firstly from neuroanatomy dissociated from physiological context and secondly from laboratory tests on sedentary rats dissociated from the hardships of normal life. We suggest that the normal role of brain NPY is to facilitate the high level of physical activity needed for foraging food, a main behavioral expression of the human homeostatic phenotype.

10. The capacity to eat a large amount of food

Research on meal initiation and termination has typically studied situation "when food is freely available" [161] or after brief periods of deprivation and as pointed out above these models may not be applicable to the human homeostatic phenotype. An important aspect of that phenotype is the capacity to eat large amounts of food when the BMI is low. At the present state of knowledge, there is therefore limited information on the factors that allow an individual to eat much more food than required for maintenance of a low body weight. As mentioned above, an important determinant of meal size is the cost of the meal in both rat and man [41,47,133]. However, it was pointed out that rats eat large meals only after adapting to the higher cost of the meal for several days [161]. This is in contrast to starved people, Australian Aborigines and anorexic patients, who can eat more food immediately if offered the chance. And, as will be seen below, rats, that have developed activity-based-anorexia share the same capacity with these groups of people.

10.1. Recovery from activity-based-anorexia

Rats recover immediately from activity-based-anorexia if food is made continuously available after a period of deprivation [121]. Fig. 13 shows that when food was reduced to 1 h/day in rats with running wheels, running increased and body weight decreased. When food was subsequently made abruptly available, the rats immediately ate more food and reduced their running activity. Interestingly, the average intake after the period of food restriction (28.3 (2.4) g) was 24.7% higher than the average intake before the period of food restriction (21.3 (2.1) g) and the wheel running after food replacement did not reach as high levels as before the period of food restriction (Fig. 13). These results confirm previous findings [54] and suggest that inhibition of food intake does not develop in rats as a consequence of a period of decreased food intake, increased physical activity and decreased body weight. Rats can immediately eat more food. Thus, there was an increase of 593% in the daily food intake in the rats that were allowed to eat freely (28.3 (2.4) g) after the condition of food restriction (4.8 (1.7) g) (Fig. 13). Just as after enforced or experimental starvation in man, inhibition of food intake does not develop after a period of food restriction in rats [121].

10.2. Disruption of the mechanism of satiation

It is generally thought that eating is terminated as a consequence of the action of satiety signals secreted in response to ingested food [161]. One of the most thoroughly studied satiety signal is CCK [148]. Interestingly, the inhibitory effect of exogenous CCK on food intake in baboons was eliminated when the period of food deprivation was prolonged [156]. Also, as the period of food deprivation was prolonged in rats, there was an expected reduction in plasma levels of CCK and a decline in CCK mRNA in the duodenum, the origin of the CCK thought to produce satiety in rats [89]. The decline in the synthesis of CCK in the duodenum was specific; no reduction in duodenal synthesis of either somatostatin or β-endorfin was noted [89]. Thus, it is possible that the satiating effect of CCK and perhaps other satiating hormones as well, is decreased in humans and animals with a low body weight thus allowing intake of large amounts of food as is characteristic of the human homeostatic phenotype. However, we found no blunting of the feeding inhibitory effect of CCK after treating rats with NPY [3]. The limited amount of information presently available on this topic makes further speculation redundant.

10.3. Summary

The meal is thought of as the behavioral unit for the analysis of food intake [161] and most often meals of a constant size are analyzed. However, humans and rats with a low body weight as a consequence of limited availability of food and a high level of physical activity can eat normal meals and bigger than normal meals. While this particular aspect of the human homeostatic phenotype has not been extensively explored, it seems possible that the satiating effect of gastrointestinal hormones is blunted in this situation.

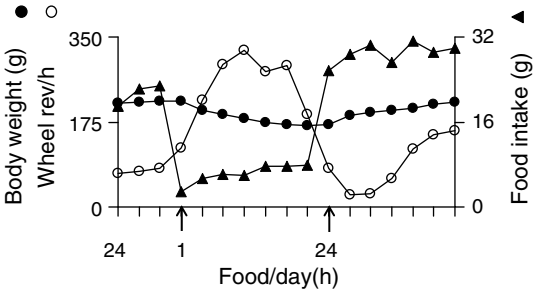

Fig. 13. Food intake, body weight and wheel running in six female rats. The access to food was reduced from 24 to 1 h/day (1 arrow) and then increased from 1 to 24 h/day (24 arrow). Values are means, measures of variability are omitted for clarity. Reproduced with permission from [121].

11. A modified framework for anorexia nervosa

Twelve years ago, in a preliminary framework for understanding the etiology and treatment of anorexia nervosa, we suggested that anorexic behavior is maintained by conditioning to the situations that provided the reward that was initially experienced during the reduction of food intake. The overlapping neural engagement in food intake and reward has since then been studied in detail [171]. We also suggested that the noradrenergic projections from the locus coeruleus to the cortex are engaged in this process [20]. The present hypothesis that NPY is a hormone of choice that directs attention to food and facilitates collection of food can be incorporated into this framework as described below.

11.1. Cue-conditioned eating

It is long known that eating is not only influenced by the neuroendocrine factors of homeostatic regulation but also by the sensory cues associated with eating [128,170]. The neural networks engaged during cue-controlled eating have recently been studied and found to be separable from those engaged in intrinsic, homeostatic regulation in both rats [129] and humans [6,93,96]. Beyond hypothalamic areas, cue-conditioned, extrinsically motivated eating involves the amygdala [107] and the prefrontal cortex [82], in particular, its medial part [125,129].[5]

The dopamine and noradrenalin innervation of the cortex converge in the prefrontal cortex [53,146]. Interestingly, NPY Y1 receptors are abundantly present in the human medial prefrontal cortex [32] and the NPY innervation of this part of the human cortex increases at an age of increased cognitive functioning [52], supposedly a prerequisite for making choices. Early research suggested that denervation of catecholamine projections to the forebrain did not change the level of NPY immuno-like reactivity in the hypothalamus [80], amygdala [79] or cortex [61]. However, it was subsequently found that the mesolimbic and mesocortical dopamine innervation of the medial prefrontal cortex controls the synthesis of NPY in this cortical area [168]. Also, it has been reported that release of NPY in anticipation of food is blocked by destruction of the noradrenergic afferents to the hypothalamus [175]. Similarly, we found that lesioning the noradrenergic cells of the locus coeruleus markedly reduced consummatory ingestive behavior and blocked the inhibitory effect of NPY on this aspect of ingestion [5]. While it is presently unknown if release of NPY in anticipation of food also occurs in the cortex, it is known that infusion of NPY into the prefrontal cortex stimulates food intake [106].

Thus, the medial prefrontal cortex in the rat, in particular its ventral part, and its human equivalence, the medial orbitofrontal cortex, may be related to the motivation to eat which has been formed as a consequence of Pavlovian conditioning [129]. While these findings are consistent with our framework for understanding the development and maintenance of anorexia nervosa [20], our tentative dissociation between the neuroanatomical engagement in reward and attention was overly simplistic. Recent work has suggested overlap between reward and attention, conceptually as well as anatomically [104,142]. Also, the anatomical connection

[5] A model of cue-control of binge eating has been suggested, although no reference to neural function was included [86].

between the medial prefrontal cortex and the nucleus accumbens [129], as well as the influence of epithalamic afferents on the ventral tegmental dopamine neurons [103], suggest versatility rather than strict compartmentalization among the substrates of reward and attention.

11.2. A possible role of NPY in cue-conditioned eating

The evidence discussed above allows us to add the neural network engaged in cue-conditioning to the process whereby anorexic behavior is maintained as originally proposed [20]. Thus, we speculate that NPY Y1 receptors, which mediate appetitive ingestive behavior [91,98,99], in the medial prefrontal cortex are important in maintaining anorexic behavior once it has been conditioned to food-related situations. Interestingly, it has been shown that repeated intracerebral infusion of NPY prepares rats to anticipate food and food-related situations [57]. The connections between the medial prefrontal cortex and the primary reward mechanisms in the dopamine terminals in the nucleus accumbens [129] are likely engaged is this process as well.

The discussion above is admittedly speculative and is offered as a neurobiologically realistic point of view. Most conventional hypotheses on the cause of anorexia nervosa lack neural plausibility [151] and, possibly for this reason, have failed to contribute to the development of effective treatments. Crick [44] has discussed the problems with neurobiologically unrealistic models of behavior and cognition. The hypothetical view that anorexia is maintained by cue conditioning is the basis for some of the aspects of the treatment described below.

11.3. Summary

A useful definition of "framework", which is intended in the present context, is as follows: "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 .... 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." [45]. While our framework for anorexia nervosa is reasonably plausible from a neuroendocrine point of view, the more important question is whether it is useful for the attack on the clinical problem of anorexia nervosa, the ultimate goal of any framework for eating disorders. A randomized controlled trial indicated that it is largely correct [17], although we agree that it is unlikely to be correct in all the details. We will end our discussion by suggesting how to treat anorexia nervosa.

12. Treatment of anorexia nervosa

"How can we change the eating habits of today's children? I think that these questions require more thought than worrying about people trying to clone themselves." Sydney Brenner [26].

Our answer to Brenner's question is: through external support. In this review, we have argued that a situation in which humans maintain a constant body weight is when there is a demand for a high level of physical activity to obtain food. Anorexic patients are captured in this situation and there is no compelling evidence that they can escape through neuroendocrine or neuropharmacological treatment. They need external support.

12.1. Learning to eat

On the hypothesis that anorexic eating behavior is maintained by conditioning to the situations where a reduced intake of food was originally rewarded [20], learning normal eating patterns in a new environment is an essential intervention [17].

The method to teach anorexic patients how to eat involves a scale that is connected to a computer. The patient puts a plate on the scale and then she/he puts food on the plate. As the patient eats from the plate, the scale records the weight loss of the plate and the computer stores the measures and generates a curve of eating rate. At regular intervals, a rating scale appears on the computer screen and the patient indicates her/his level of fullness by touching at the proper level on the scale on the screen. The computer stores the ratings and generates a curve of the development of satiety. Anorexic patients eat a small amount of food at a low rate and estimate their fullness as high. They are then asked to adapt their eating rate and their feeling of fullness to curves that are displayed on the computer screen during the subsequent training sessions (Fig. 14). A curve for eating more food at a higher rate is displayed on the computer screen and the patient adapts to the curve, which is possible because she/he can see her/his eating rate appear on the screen during the meal (Fig. 14). Patients eat progressively more food (regular food is used as described above) at progressively higher rates during training. Eventually they eat about 300 g in about 15 min.

Because learning depends on place [55], the cues that maintain anorexic eating are eliminated when anorexics eat in a new place. As patients do, body weight increases. Because learning also depends on state [55], anorexics will enter a new state as they gain weight and eventually, when they reach their normal weight, the patients are no longer bothered by their previous condition. Their serious psychological problems resolve completely [17].

12.2. Behavior as a cause of psychological change

The essence of the psychological changes in starvation initially was described as "semi-starvation neurosis" [139] and it was subsequently shown that the same symptoms also appeared when 10 obese people, who were 27 (20–40) years old reduced their BMI from 51.7 (34–59.8) to 34.8 (27.4–44) by eating less food (600 kcal/day) over a period of 16–20 weeks [68,69]. These same symptoms were also shown by obese patients with binge-eating disorder, who had no weight reduction [118]. Patients with this

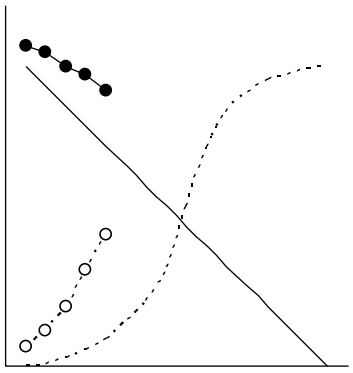

Fig. 14. Patients with eating disorders re-learn how to eat by adapting their intake of food to a curve displayed on a computer screen during their meal. This is possible because a patient sees her rate of eating (black dots) appearing on the screen as she eats and can adapt her intake to a training curve that is simultaneously displayed on the screen (solid line). A rating scale for satiety appears on the screen at regular intervals and the patient rates her level of fullness by pressing on the screen. Patients re-learn how to feel full by adapting their ratings (white dots) to the sigmoid curve that mimics the development of satiety in normal weight people (dotted line). There are no numerical values on the axes and the display looks the same throughout treatment. The figure displays an anorexic patient who fails to keep up with the eating rate and overestimated her level of satiety. Reproduced with permission from [151].

eating disorder are at the opposite end of the starvation–obesity continuum compared to patients with anorexia nervosa both with regard to their body weight and their neuroendocrine state [115], yet they show the same psychological symptoms. In addition, patients with bulimia nervosa, who most often have a normal body weight, also show the same psychological symptoms [151]. Apart from the difference in body weight, there is little, if any difference among patients with anorexia nervosa, bulimia nervosa and patients with binge-eating disorder. In the first descriptions of bulimia nervosa [134] as well as the first description of binge-eating disorder [162], it was pointed out that most of these patients have a history of anorexia. Hence, the psychological changes and mental symptoms of anorexia nervosa are not specific to starvation; disordered eating involving bingeing produced similar psychological symptoms. The main problem of these patients is their disordered eating behavior. Note, however, that their behavior has evolved from various forms of starvation or semi-starvation. The thesis here is that their behavior is subsequently maintained by cue-conditioning. We have suggested, therefore, that the behavior of eating disorder patients mediate between their physiological and psychological condition [176]. On this hypothesis, training eating disorder patients how to eat should alleviate their psychological symptoms, independently of their BMI. Eating behavior is thought of as a cause rather than as a mere outcome of brain activity, as is more often the case (see 6 above).

Fig. 15 shows that food intake, meal duration, eating rate and the perception of satiety as well as the level of psychiatric symptoms were similar in a group of 27 anorexic patient with a low BMI (12.5 (1)) and in another group of 18 anorexics with a higher, yet low, BMI (16.2 (0.8)) at the time of admission for treatment. The figure also shows that as eating behavior normalized during treatment to remission, the BMI and the psychiatric symptoms normalized in both groups and remained normal during a 5-year period of follow-up [176].

We use the same method to treat anorexia and bulimia nervosa and binge-eating disorder and also eating disorders not otherwise specified [17,19]. While teaching patients how to eat is an important intervention, there are other interventions as well. A description of these interventions is beyond the scope of the present discussion, the reader is referred to the report of the treatment [17].

12.3. Summary

Teaching anorexic patients normal eating patterns is an important intervention; once eating is normal, the other symptoms dissolve. A main obstacle in eating normally is the high level of physical activity in anorexia. As was pointed out in one of the first descriptions of the condition, the physical hyperactivity is very difficult to control [78]. Supply of warmth is used to facilitate eating in anorexic patients [17,78] because this intervention decreases the hyperactivity of activity-based-anorexia and facilitates eating [117]. An attempt to increase body weight in anorexic patients by use of warmth during three weeks failed but this should not discourage from the use of warmth because the patients in that study had been ill for almost 14 years [23]; the hope for an improvement in three weeks in such patients is overly optimistic. More interesting, an increase in hunger and food intake and in measures of well-being was reported in depressed patients treated with warmth [102]. Other methods of reducing the physical activity of anorexia nervosa would be very helpful. To further improve the treatment of anorexia and other eating disorders, independent replication of these results [17,19] is important; we recently pointed to the importance of a randomized controlled trial comparing the present treatment with other methods [42].

13. Conclusions

This review has attempted to switch attention from the conventional model of homeostatic regulation of body weight, which is based on tests of animals with continuous effortless access to food, to one in which the acquisition of food demands an effort. The conventional model does not mimic the normal human condition. Instead, we have argued that the human homeostatic phenotype is one in which body weight is controlled mainly by external factors; the most important is the availability of food. We have also argued that food is normally available only at the expense of a considerable amount of physical activity. Body weight is maintained at a low level under these circumstances, body fat content is low and, as a consequence, peptides such as NPY are up-regulated in the brain. The main role of NPY is to facilitate physical activity in order to search for food and prepare food. In this state, humans are able to eat large amounts of food.

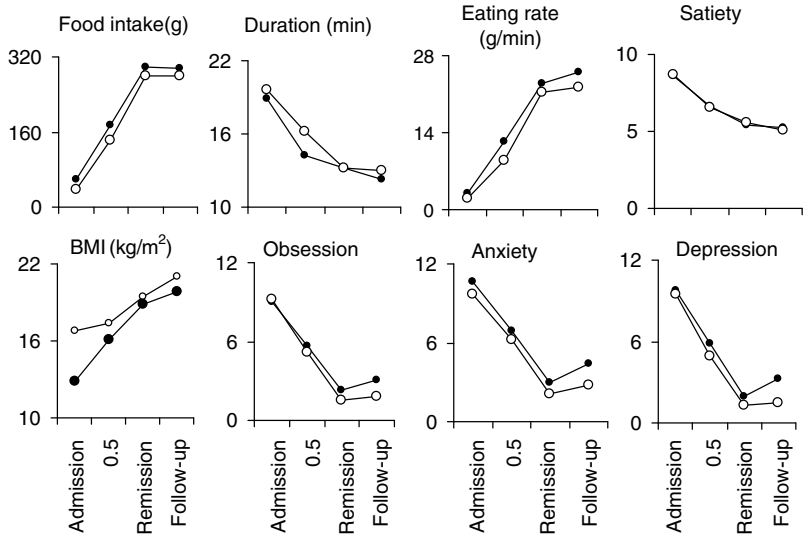

Fig. 15. Food intake, meal duration, eating rate, satiety, body mass index (BMI) and psychopathology (comprehensive psychopathological rating scale self-rating scale for affective syndromes [163] in a group of 27 anorexic patients with a BMI of 12.5 (1) and in another group of 18 anorexics with a BMI of 16.2 (0.8) at admission. The patients were treated to remission and followed-up for 5 years. Values are means, measures of variability are omitted for clarity. Reproduced with permission from [176].

We have argued that NPY plays a role in both the search for food and in conditioning to external cues that subsequently maintain eating habits. We have suggested that such conditioning maintains the disordered eating of patients with anorexia nervosa and other eating disorders as well. Re-learning normal eating habits is essential for the management of these patients and we predict that the development of a pharmacology targeting the NPY Y1 receptor at an as yet unspecified neural site will facilitate this process. Once patients have learned to eat, their other problems dissolve. Many aspects of the present point of view await scientific testing and are offered as starting points necessary for advancing a clinical field that has not yet generated effective treatments for a serious condition in young women.

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