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Psychoneuroendocrinology of anorexia nervosa

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Summary It is suggested that the symptoms of anorexia nervosa are physiological responses to starvation. There is no evidence of a neural or non-neural dysfunction that predisposes women for anorexia nervosa and the endocrine and psychological consequences of starvation are reversed once patients have re-learnt how to eat and regained a normal body weight. Because variability in the supply of food may be a common evolutionary condition, it is more likely that body weight is variable than constant in normal circumstances. The role of the neuroendocrine system in times of feast and famine is to allow the individual to adopt behavioral strategies as needed rather than maintaining body weight homeostasis. Treatment of anorexic patients should aim at reducing their high level of physical activity in order to facilitate eating.

1. Introduction

In many accounts, anorexia nervosa is considered a multifactorial illness of unknown etiology (reviewed by Södersten et al., 2006). This leaves the clinician without a clue as to the cause of the condition and with the difficult task of selecting the symptoms to be treated. Often symptoms thought to be related to an alteration in serotonergic neurotransmission are targeted by using selective serotonin reuptake inhibitors (SSRI). This is a reasonable starting point because serotonin has a role in both mood and eating behavior. However, as pointed out in the interesting paper by Mondelli (2006, this issue, p. 123), the evidence supporting the serotonin hypothesis of anorexia nervosa is weak and, probably for this reason, outcome of treatments based on this hypothesis remains poor. Recently, Walsh et al. (2006) reported that treatment with an SSRI does not prevent relapse in anorexic patients in remission. Most of the patients relapsed or dropped out of the study. Unfortunately, most other treatment methods are at best marginally effective (Bergh et al., 2006). Clearly, anorexia nervosa needs to be examined within a new framework.

2. Starvation and anorexia nervosa

Pioneering clinicians found no sign of organic damage in patients with anorexia nervosa (Gull, 1874) and more recent studies have provided

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no evidence that the disorder is associated with or caused by neural or non-neural damage. Similarly, it is long known that hormonal changes in anorexia nervosa "have little specificity for this disease and are mainly a consequence of nutritional factors and starvation" (Fichter et al., 1982). As an example, early studies on the functional changes in the hypothalamic–pituitary–adrenal axis of anorexic patients showed that these were reversed upon weight restoration (Gold et al., 1986). More interesting, it was recently pointed out that the endocrine changes in states of energy deficiency, perhaps including anorexia nervosa, are beneficial to the individual (Chan and Manzoros, 2005). This is not surprising, because, historically, starvation is a common condition. Human biology has evolved to adapt to recurrent periods of famine and individuals who have managed to meet this challenge have been at an advantage (Diamond, 2003). For example, cessation of ovulation and menstruation in starvation is not only a normal but a necessary physiological response to the shortage of food, not a sign of dysfunction or disease (Södersten et al., 2006).

When Richard Michael (1975) launched this journal, he predicted that psychoneuroendocrinology, in dealing "directly with the effects of hormones on affect, mood and behaviour", eventually will "give us a window on to the detailed physiology of man's emotional life". We will follow Michael's approach and suggest that most symptoms of anorexia nervosa are physiological adaptations to starvation and that treatment should aim at restoring a normal eating behavior. Once eating behavior has normalized, eating disorder symptoms dissolve.

3. The neuroendocrinology of starvation, the case of leptin

Many reviews of the neuroendocrinology of eating behavior and body weight regulation have been published recently (e.g., Kishi and Elmquist, 2005). Another one would be redundant. Let's instead briefly consider leptin. Originally thought to mediate negative feedback from adipose tissue and prevent overeating, leptin is now believed to have a rather different role in signaling energy shortage. Like other forms of starvation, anorexia is "a low leptin state" (Chan and Manzoros, 2005) and leptin is now examined in the context of anorexia nervosa. Thus, as anorexic patients start to eat more food and gain weight, the rate of leptin secretion increases (Haas et al., 2005). Obviously, leptin is not merely an inhibitor of food intake, as was originally proposed. An inhibitor of food intake cannot increase in the blood as an individual eats more food. Rather, the observation suggests that, if anything, leptin might actually stimulate food intake. However, it has been suggested that leptin does assume a role as an inhibitor of intake after the initial period of enhanced secretion and that the ensuing elevated levels of leptin not only cause an arrest of weight gain but also predispose anorexic patients for relapse (see Haas et al., 2005).

This work is descriptive, rather than experimental, and we do not know whether the changes in leptin affect behavior or if it is the other way around. The situation is similar for most of the endocrine changes which have been described in patients with anorexia nervosa. On occasion, hormonal therapy (estrogen, DHEA) has been used but no effects on the anorexic behavior were reported (Fisher, 2006).

If endocrine changes are epiphenomena to starvation, it is not surprising that treatment with leptin can reactivate a physiological function such as ovulation in the "low leptin state" of hypothalamic amenorrhea, another state of energy deficiency (Chan and Manzoros, 2005). This observation merely suggests that leptin, possibly together with other hormones, normally mediates between body fat and the hypothalamic–pituitary–gonadal axis. In a similar manner, GnRH mediates between the hypothalamus and the pituitary in the same axis and, thus, can activate ovulation and normal menstrual cycles in patients with anorexia nervosa (Nillius et al., 1975). There is no evidence that women who develop anorexia nervosa have an adipose, hypothalamic, pituitary, gonadal or some other endocrine dysfunction that predisposes them for the disorder.

While there may be endocrine changes that are unfavorable to weight gain during treatment of anorexic patients, e.g., high levels of leptin (Haas et al., 2005), these may have been induced by improper treatment rather than by a factor that is related to the patient. Consider parenteral nutrition in starvation. Such treatment can be dangerous, even lethal (Weinsier and Krumdieck, 1981), not because there is something wrong with starving humans but because parenteral nutrition is wrong in this condition.

4. Orexigenic and anorexigenic peptides

Anorexic patients eat too little food and there are no reports that reversal of the endocrine conse-

quences of their starved condition affects their eating behavior. To the contrary, there is evidence that it does not. Thus, while treatment with GnRH activates ovulation and menstrual cyclicity it does not affect eating behavior and weight (Nillius et al., 1975). What about the changes in orexigenic and anorexigenic peptides that occur in starvation?

The fact that anorexic patients do not eat enough food violates the theory that body weight is homeostatically regulated. This theory postulates that peptidergic neural pathways keep body weight constant by stimulating and inhibiting eating behavior in response to signals from peripheral energy storing organs and the gastrointestinal tract (Kishi and Elmquist, 2005). However influential this theory has been, and still is, in guiding research on the neuroendocrinology of body weight regulation, it has not yet yielded anything that can be used to make anorexic patients eat more food. Nor has it generated anything that can be used to make the obese eat less food. We suggest that this is because the theory is overly simplistic and that there are no orexigenic or anorexigenic peptides. Neural pathways that are orexigenic under some circumstances can be anorexigenic under other circumstances. For example, leptin (Ammar et al., 2000) and neuropeptide Y (NPY) (Nergårdh et al., 2006) as well as CRH (Samarghandian et al., 2003) can both stimulate and inhibit food intake and the physiological contexts in which they do have not been defined.

Consider leptin once more. This time in the context of obesity, a ''high leptin state''. If leptin is an anorexigen, why do the obese eat too much food? The common answer is that their brain is insensitive to all the leptin and does not respond by down-regulating the production of orexigenic peptides, e.g., NPY. But this is not the case. High leptin levels have the expected effect on the brain of the obese in reducing the synthesis of NPY in the hypothalamus (Goldstone et al., 2002). We suggest that leptin stimulates food intake in obesity, a possibility which is supported by animal experimentation (Ruffin et al., 2004). We also suggest that body weight is not normally homeostatically regulated. As pointed out above, humans have evolved with unpredictable periods of famine and intervening periods of feast. Because of externally imposed constraints in the availability of food, body weight has most likely not been maintained constant in human evolution but has more likely fluctuated (Stubbs and Tolkamp, 2006). Homeostatic regulation of body weight may be a laboratory artifact and it is more likely that eating behavior is normally controlled by ''discontinuous distribution of resources rather than by cycles of physiological depletion and repletion'' (Collier and Johnson, 1997). On this perspective, it is not surprising that most of the presently used pharmacological methods of weight control have minor effects.

5. The psychology of starvation, the case of OCD

There is an abundance of reports that starvation causes reversible psychological change. To cite just one: ''Psychosis secondary to starvation was evident to a variable degree. In these cases it was important to administer large quantities of food, if necessary under compulsion. A quick change for the better was observed when this was done'' (Burger et al., 1945). This proves that eating too little food, in addition to endocrine change, also *causes* cognitive change. However, more often the opposite is hypothesized. Thus, anorexia nervosa is thought of as a mental disorder that is caused by another mental disorder. Most recently, it has been hypothesized that the cause of anorexia is a genetically determined anxiety disorder which is first expressed prepubertally as an OCD, then around puberty as anorexia nervosa and subsequently, later in life, as a variety of anxiety disorders. A trait-related permanent change in neural serotonergic function is thought to mediate between the ''anxiety'' genes and behavior (reviewed by Södersten et al., 2006).

The OCD hypothesis is problematic. First, the supporting evidence is weak (Södersten et al., 2006). This is not surprising considering that genetic networks interact in producing variable phenotypic expression patterns (pleiotropy), particularly those involved in behavioral, neural and biochemical function (van Swinderen and Greenspan, 2005). Second, on the OCD hypothesis, pharmacological treatment of OCD should be effective in treating anorexia as well, but it is not (Södersten et al., 2006). Pharmacological treatment (most often SSRI) is in fact marginally effective also in OCD, probably because the neural systems engaged in OCD are only partially understood (Chamberlain et al., 2005). Third, knowledge of the neurobiology of OCD does not help us understand anorexia nervosa. Why would someone who has an OCD eat less food?

By contrast, it is easy to understand why someone who is starving would develop an OCD. Shortage of food gradually increases the time spent thinking about food, and eventually most of the time is spent thinking about food and searching for

food (Keys et al., 1950). This appears to be not only a natural, but a necessary adaptation to the shortage of food. Thus, on Michael's (1975) physiological framework for psychoneuroendocrinology, the question arises whether the "OCD of anorexia nervosa" is an OCD. We suggest that it is not. Just as the cessation of ovulation is a physiological response, so is thinking of food in anorexia nervosa an adaptation to starvation. Interestingly, an "obsessive" trait was recently suggested to be asset in other circumstances as well: in scientific work (Lawrence, 2006)!

6. Treatment

There are no reports of patients who are free of symptoms upon discharge from a clinical program. A common interpretation of this is that patients have a trait-related disorder (e.g., high neural serotonin turnover or OCD), which makes them prone to develop anorexia. As we have argued here, however, starvation is a common state, and it is unlikely that there is something inherently wrong with a starved individual. A second, more likely interpretation is, therefore, that there is something wrong with the treatments that are offered to patients with anorexia nervosa. And when patients are discharged from such treatments they are at best in partial remission and at risk of relapse.

Rather than questioning the existence of OCD as a mental disorder, we would like to underline that the analysis of such disorders in the context of anorexia nervosa has not yielded treatments that have improved outcome, the obvious aim of research in this field. In fact, outcome has remained poor during at least 50 years (Steinhausen, 2002). However, neither have neuroendocrine studies improved the outcome of treatment of anorexia.

To improve this situation, we have developed a treatment in which re-learning how to eat is important along with other interventions. The treatment has been evaluated in a randomized controlled trial and found to bring about 75% of the patients into remission in on average 14 months. For a detailed description of this treatment see Bergh et al. (2002).

Figure 1 shows the recovery of a normal body mass index (BMI, kg/m^2) in 40, 18$\pm$7.7 years old (mean$\pm$SD) anorexic patients, who were treated to remission in 17.6$\pm$9.7 months with this method. There are very few exclusion criteria for participating in this treatment and so the patients reach their target BMI in somewhat variable times. For example, they reached an average BMI of 17.4$\pm$0.4 in 6 (2–30) months (median and range). Attainment

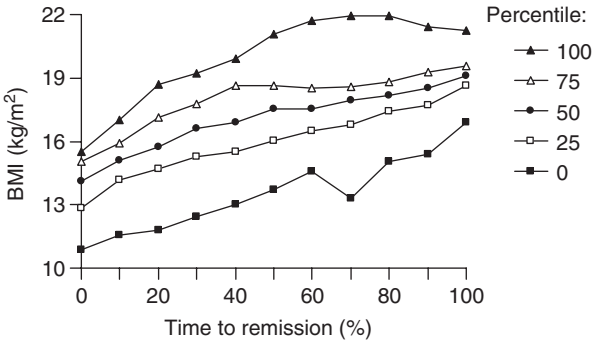

Figure 1 Recovery of body mass index (BMI) in 40 patients with anorexia nervosa. Time from admission to remission is expressed as percent. The low BMI values are from patients who were only 12 years old.

of this particular BMI in about 2–3 months has been associated with high levels of leptin, arrest of body weight gain and risk for relapse (Haas et al., 2005). Several of the patients in Fig. 1 reached a BMI of 17.4 in this time but all patients eventually regained a normal BMI and fewer than 10% relapse during a five year follow-up program (Bergh et al., 2002). These observations suggest that there are no psychoneuroendocrine constraints for anorexic patients to regain a normal weight. However, we have been unable to find any information on how women normally recover from starvation under other circumstances and so the physiological significance of the results reported in Fig. 1 remains to be determined.

7. Final remark

It is long known that patients with anorexia nervosa are hypothermic and physically hyperactive and that their activity is difficult to control (Gull, 1874). Supply of warmth is useful in reducing the activity and facilitating food intake (Gull, 1874; Bergh et al., 2002). We suggest that any other intervention aimed at reducing the physical hyperactivity of anorexia nervosa should be researched. Interestingly, leptin may do just that (Chan and Manzoros, 2005) and, if it does, patients may experience relief from some of the psychological effects of starvation as an extra benefit (Lu et al., 2006).

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