

Anorexia nervosa, self-starvation and the reward of stress

Reduced intake of food and enhanced physical activity, the main behavioral manifestations of self-starvation and anorexia nervosa, activate brain substrates associated with reward.

Anorexia nervosa, a common illness among teenage girls, has a very poor prognosis¹. Despite receiving considerable attention, the cause of the disorder remains unknown as does the reason for the marked difference in prevalence between the sexes.

The psychiatric diagnostic manual DSM-IV provides specified diagnostic criteria for each mental disorder. These criteria are supposed to "... reflect a consensus of current formulations for evolving knowledge..." In the case of anorexia nervosa, four criteria are offered: (1) weight loss, (2) fear of gaining weight, (3) disturbance in body perception and (4) loss of menstruation. However, loss of body weight and menstruation necessarily follow reduced food intake and criteria 2 and 3 are not consistently fulfilled by anorexic patients². We therefore think that the DSM-IV criteria are not very useful and that a new way of looking at the disorder would be useful.

There were two symptoms included in the original description of the disorder 120 years ago that have been included in many descriptions since then: self-starvation and enhanced physical activity³.

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Psychopathology and mental disorder?

We suggest that the reason self-starving patients do not fit the DSM-IV criteria of anorexia nervosa is because there is in fact no psychopathological basis of the disorder, as suggested 25 years ago⁴. To confuse matters, the definition of psychopathology is actually unclear in this context. The DSM-IV offers no definition, but it is reasonable to assume that a psychopathological basis of the anorexia nervosa would be reflected in a behavioral or cognitive marker. There is, however, no need to refer to self-starvation and enhanced physical activity as reflections of an underlying psychopathology.

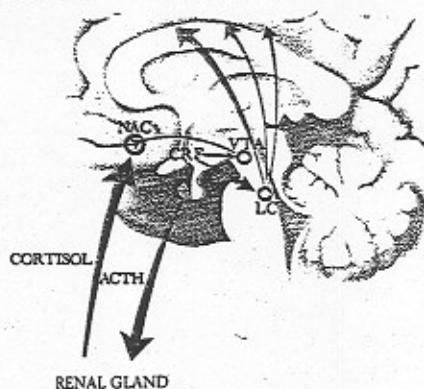
We suggest therefore that analyses of self-starvation should focus on the reduced food intake and enhanced activity, since these are the only behavioral measures that consistently distinguish anorexia from other conditions. We also suggest that whatever additional behavioral or cognitive phenomena ensue during the development of the illness,

they emerge from these two initial behavioral markers.

Just as the definition of psychopathology is unclear, so is the definition of a mental disorder. Again, DSM-IV offers no definition, but it seems likely that "mental disorder" denotes a disorder that has a neurochemical cause or consequence. In anorexia nervosa, the neurochemical marker is the increased concentration of corticotropin-releasing factor (CRF) in the cerebrospinal fluid⁵ and alterations in other neurotransmitters, probably secondary to the alteration in CRF⁶. However, we see no reason to refer to this neuroendocrine alteration (increased CRF) either as reflecting or caused by a "mental disorder" and suggest that in the absence of a psychopathology or clear idea of a specific mental disorder, it is more appropriate to refer to anorexia nervosa as self-starvation.

Stress and reward

On this framework, hypercortisolism is a manifestation of self-starvation⁷. Thus, restricted feeding or increased physical activity⁸ activates the hypothalamo-pituitary-adrenal (HPA) axis and causes a



loss of body weight. The concentration of CRF is increased to about 170% of normal in self-starvation. It has been established that CRF will cause a reduction in feeding when injected into the brain of animals⁷.

Thus, starving or overly active humans or animals have increased HPA activity and high blood levels of cortisol and/or corticosterone. Glucocorticoids can cause euphoria and dependence in humans and animals readily self-administer corticosterone⁸. Obviously, adrenocortical hormones have rewarding effects. Reward is mediated by mesolimbic dopamine (DA) neurons in the brain and adrenocortical secretions enhance the reward value by increasing the release of DA in the terminals of these neurons⁹. From these considerations it follows that the stress of physical activity and reduced food intake activates the reward mechanisms in the brain. We suggest that in an initial phase of stress the reward mechanism is sensitized and that in this state the organism is postulated to be particularly prone to conditioning. That is, an initially neutral stimulus is likely to get coupled to the primary reinforcer (the mesolimbic DA neurons).

Interestingly, 25 years ago Feighner *et al.*

Fig. 2 Female rats are able to control their body weight if allowed to run in running wheels. They will also maintain a normal body weight if allowed to eat for only one hour a day. If, however, the rats have continuous access to a running wheel (without being forced to run) and to food for one hour a day, they lose control over body weight and die within a brief period of time. This situation is remarkably similar to that of self-starvation.



Fig. 1 Proposed mechanism for the development of self-starvation. Physical activity combined with reduced food intake activates the hypothalamo-pituitary-adrenal axis, via CRF-ACTH-cortisol secretion. CRF activates dopaminergic neurons, whose cell bodies are localized in the ventral tegmental area (VTA) and whose terminals are localized in the nucleus accumbens (NAC) in the ventral striatum (a pathway concerned with reward). Cortisol enhances reward by stimulating release of dopamine in the NAC. CRF also activates noradrenergic neurons, whose cell bodies are localized in the locus coeruleus (LC). These neurons project extensively to the forebrain and are required for attention to sensory stimuli. It is suggested that the combination of physical activity and reduced food intake is rewarding and directs attention to stimuli that subsequently control the behavior of self-starvation.

*al.*⁴ pointed out that reducing food intake and losing weight is an "apparent enjoyment," "pleasurable," and "rewarding" to a self-starving woman. Equally interesting, 122 years ago Gull¹⁰, in discussing the paradoxical restlessness of an anorectic patient, pointed out that exercise was "agreeable" to the patient.

The cause of self-starvation

Stressful stimuli activate the CRF neurons in the hypothalamus, the DA reward neurons in the ventral medulla and the noradrenaline (NA) neurons in the locus coeruleus (concerned with selective attention). Activity in the DA reward neurons and the NA selective attention neurons is easily conditioned^{11,12}. In an initial phase of stress, therefore, an animal is not only sensitive to rewarding stimuli but also prepared to pay attention to these.

Thus, the demand to reduce food intake and to increase physical activity are the main reasons for self-starvation³. As a consequence, it comes as no surprise that the risk of self-starvation is markedly increased among female elite athletes⁵. The dramatic effect of these two risk factors was recently and remarkably provided by Novin and co-workers¹³. They showed that female rats, when given limited access to food, completely lose control over their own body weight if they are given the opportunity (not forced) to exercise in a running wheel. The rats increased their running despite losing weight and temperature and most of them died within a brief period of time. This symptomatology is conspicuously similar to that of self-starving women, who also increase their physical activity despite losing body weight.¹

Thus, a simple, parsimonious hypothesis is that self-starvation is initially rewarding and subsequently controlled by conditioning to previously neutral stimuli. An outline of this proposed mechanism is presented in the figure.

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- Eckert, E.D. *et al.* Ten-year follow-up of anorexia nervosa: Clinical course and outcome. *Psychol. Med.* 25, 143-156 (1995).
- Lee, S., Ho, T.P. & Hsu, L.K.G. Fat phobic and non-fat phobic anorexia nervosa: a comparative study of 70 Chinese patients in Hong Kong. *Psychol. Med.* 23, 999-1017 (1993).
- Davis, C. *et al.* The role of physical activity in the development and maintenance of eating disorders. *Psychol. Med.* 24, 957-967 (1994).
- Feighner, J.P. *et al.* Diagnostic criteria for use in psychiatric research. *Arch. Gen. Psychiatry* 26, 57-63 (1971).
- Hotta, M. *et al.* The response of plasma adrenocorticotropin and cortisol to corticotropin-releasing hormone (CRH) and cerebrospinal fluid immunoreactive CRH in anorexia nervosa patients. *J. Clin. Endocrinol. Metab.* 62, 319-324 (1986).
- Liu, J.-P. *et al.* Studies of the secretion of corticotropin-releasing factor and arginine vasopressin into the hypophyseal-portal circulation of the conscious sheep. II. The central noradrenergic and neuropeptide Y pathways cause immediate and prolonged hypothalamic-pituitary-adrenal activation. Potential involvement in pseudo-Cushing's syndrome of endogenous depression and anorexia nervosa. *J. Clin. Invest.* 93, 1439-1450 (1994).
- Dunn, A.J. & Berridge, C.W. Physiological and behavioral responses to corticotropin-releasing factor administration: Is CRF a mediator of anxiety or stress responses? *Brain Res. Rev.* 15, 71-100 (1990).
- Burden, V.R. *et al.* Activity of the hypothalamo-pituitary-adrenal axis is elevated in rats with activity-based anorexia. *J. Nutr.* 123, 1217-1225 (1993).
- Piazza, P.V. *et al.* Corticosterone in the range of stress-induced levels possesses reinforcing properties: Implications for sensation-seeking behaviors. *Proc. Natl. Acad. Sci. USA* 90, 11738-11742 (1993).
- Gull, W.W. Anorexia nervosa (apepsia hysteric, anorexia hysteric). *Trans. Clin. Soc. London* 7, 22-28 (1874).
- Cecatelli, S. *et al.* Expression of c-fos immunoreactivity in transmitter-characterized neurons after stress. *Proc. Natl. Acad. Sci. USA* 86, 9569-9573 (1989).
- Gratton, A. & Wise, R.A. Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats. *J. Neurosci.* 14, 4130-4146 (1994).
- Novin, D. *et al.* In the activity stress paradigm (ASP) there are close relations between vital signs which allows us to predict longevity in rats with unerring accuracy. *Obesity Res.* 3 (suppl. 3), 373S (Abstr.) (1995).

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