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Cost-based anorexia: A novel framework to model anorexia nervosa

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A B S T R A C T

Anorexia nervosa (AN) is an eating disorder that is thought to emerge through biological predisposition(s) within sociocultural context(s). Practical and ethical concerns limit study of the etiology of this disorder in humans, and in particular the biological aspects. Laboratory animal models have a pivotal role in advancing our understanding of the neurobiological, physiological and behavioral aspects of this disorder, and developing new treatment strategies. One shortcoming of animal models, including activity based anorexia (ABA) in rodents, is that they cannot fully capture the contextual aspects of AN. In this article we discuss the merits of an alternate approach, cost-based anorexia (CBA). CBA is conceptually founded in behavioral economics and its magnitude is influenced by several relevant contextual aspects of feeding.

1. Introduction

Anorexia nervosa (AN) is an eating disorder characterized by low body mass index, severe self-imposed restriction of food intake, fear of weight gain, and a distorted perception of body size (American Psychiatric Association, 2013). AN has the highest mortality among all mental health disorders (Birmingham, Su, Hlynsky, Goldner, & Gao, 2005; Sullivan, 1995). In the past it has had up to a 10-fold higher prevalence in females than males, but this difference is now narrowing. AN patients are particularly resistant to treatment and, even after recovery, relapse is frequent (Carter et al., 2012). Two subtypes of AN are recognized, the restricting type and the binge-eating/purging type, each affecting about half of the cases. Excessive exercise occurs in about two-thirds of clinical AN populations, although the incidence depends on the population sampled and the definition of excessive activity (Davis, Katzman, & Kirsh, 1999; Hebebrand et al., 2003). Compulsive exercise may more accurately describe this activity which includes fixed routines and resistance to reduction even in the face of injury or harm, especially in restricting AN (Dalle Grave, Calugi & Mareschini, 2008; Davis & Kaptein, 2006; Noetel, Dawson, Hay, & Touyz, 2017; Young et al., 2018). Such a dimension of compulsion is consistent with other psychiatric abnormalities in AN patients, including OCD and anxiety (Davis et al., 1999; Guarda, Schreyer, Boersma, Tamashiro, & Moran, 2015; Young, Rhodes, Touyz, & Hay, 2013). The conclusion from these studies is that exercise itself is not a cause of the AN syndrome, but the progression of AN is exacerbated by neurobiological or personality traits that predispose to compulsive exercise and associated increase in energy expenditure.

AN is associated with characteristic patterns of eating. Sunday and Halmi (1996) examined hunger and satiety ratings and behavior of young adult female AN-restricting, AN-bulimic and healthy control subjects eating a 3-item breakfast after an overnight fast. Healthy controls ate a mean of 527 kcal (range ~100–1000) with approximately equal or balanced amounts from each food choice. Further, their hunger ratings were high before the meal, declined during the meal, and were low afterwards. Fullness ratings showed an orderly, inverse pattern. About one third of the AN-restricting subjects ate more (> 1000 kcal) than any control, especially the sweetest item. AN patients reported feeling less hungry and more full than controls before the meal, even though their intake was comparable, and the progression of hunger and fullness ratings during the eating episode was often non-monotonic. That is, AN patients seem to have abnormal perception or interpretation of feelings related to hunger and fullness. These authors also noted that AN patients tended to have small bouts of eating punctuated by pauses.

This has been corroborated in a more recent video analysis of lunch in AN subjects (Gianini et al., 2015). Although AN and control subjects consumed comparable amounts, AN subjects showed much higher frequency of cutting or dissecting food into small pieces before ingestion, inappropriate utensil use (that may be a consequence of the food dissection), and nibbling or picking at the food. This abnormal behavior was associated with high reported distress during the meal. This is consistent with a report by Steinglass et al. (2010) that intake of a high energy density lunch (macaroni and cheese) was highly negatively correlated with premeal state anxiety, but the correlation was weaker with a low energy density snack (yogurt). Thus, in such test meals, a

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variety of abnormalities including anxiety and inappropriate feelings of fullness contribute to generally slowed eating, but not invariably to reduced energy intake. It should be noted that this fragmentation of intake and eventually lower intake, especially in relation to BMI, is entirely elective or determined by the subject within that eating context.

Given the limitations to etiologic studies of this disorder in humans, it is useful to develop animal models that allow further analysis of its neurobiological, physiological and behavioral aspects. Due to the complex social and cultural aspects of psychological disorders such as AN, it is unrealistic to fully model these disorders in protocols using laboratory animals. Instead, animal models are particularly useful to further a reductionist understanding of the specific mechanisms underlying these disorders and to develop potential new intervention strategies. Reasonable translational validity of these animal models is an important consideration given the seriousness of the disorder and the need for improved or more effective treatments.

2. Anorexia in biological perspective

The term anorexia is used to describe a state of lack or loss of appetite for food compared to a normative or prior level. It is usually associated with anhedonia, a reduced reward value of food. Thus, before we can identify anorexia, it is necessary to define normative behavior. Purely homeostatic models of control of food intake have largely been replaced with “dual” models which have a homeostatic or need-based component as well as an hedonic or reward-based component (e.g., Berthoud, 2012; Ferrario et al., 2016; Volkow, Wise, & Baler, 2017). If we accept the principle of this or any other multi-system model, we have in effect altered the key investigative question to ask about the relative contribution of the component parts under specific conditions. Such a point was made in a structural modeling approach to human eating that derived both compensated (homeostatic) and non-compensated (hedonic) factors (De Castro, 2010). Relevant to this analysis, humans (and other animals) have been referred to as **opportunistic eaters** (Bryant, King, & Blundell, 2007; Rowland & Splane, 2014) meaning that, at least in the absence of food security and storage, food should be consumed whenever the opportunity arises, more or less independent of physiological state such as indexed by BMI. But, in an environment of predictable or secure food, if the (cognitive) objective is to maintain a constant BMI then some degree of food-directed restraint is adaptive or necessary. In both of these patterns, opportunism and restraint, the environment is a principal determinant.

Optimal foraging refers to the amount and pattern of food procured given a spectrum of ecological costs associated with obtaining food. When food opportunities are frequent and/or cost is low, food intake exceeds expenditures, and positive energy balance or weight gain will occur (McNamara, Houston, & Higginson, 2015; Rasmussen, Robertson, & Rodriguez, 2016). In contrast, when food opportunities are infrequent and/or cost is high, food intake will not meet expenditures, and negative energy balance or weight loss will occur (Rowland, Minaya, Cervantez, Minervini, & Robertson, 2015). Importantly, this approach predicts that animals in high cost situations will exhibit anorexia relative to their own normative behavior in low cost situations. The concept of cost in animals has been considered as a multidimensional or even cognitive construct (Hursh, Raslear, Shurtleff, Bauman, & Simmons, 1988; Sherwin & Nicol, 1995; Van den Bos, van der Harst, Jonkman, Schilders, & Spruijt, 2006). Collier (2005) referred to such foraging-related factors as *global economic strategy* but, beyond a general relation to decision making (Berke, 2018; Salamone, Correa, Yang, Rotolo, & Presby, 2018), very little is known about the neural instantiation of this strategy.

Several natural circumstances are known in which animals voluntarily sustain a negative energy balance. These examples mostly relate to survival or breeding behaviors including hibernation, territorial defense, stress of predation, incubation of eggs, foraging, and migration (Mrosovsky & Sherry, 1980; Wang, Hung, & Randall, 2006). Laboratory conditions that precipitate acute anorexia include tail pinching, cold swim, and maternal separation (Liu et al., 2007; Méquinion et al., 2013; Shimizu, Oomura, & Kai, 1989; Wong, Licinio, Gold, & Glowa, 1993). Activity-induced anorexia (ABA) in rodents is the most widely-used laboratory protocol for the study of anorexia because of its relative procedural simplicity and amenability to mechanistic analyses such as genetic vulnerability or pharmacological approaches. In this article, we briefly explore the benefits and limitations of ABA as a model of restricting-type AN, and present a novel alternative conceptualization that we call cost-based anorexia (CBA; Rowland, Minaya, & Robertson, 2017).

3. Activity-based anorexia (ABA)

Hall and Hanford (1954) reported that rats with access to running wheels and given only 1-h food access per day showed increased running activity and decreased body weight. This self-starvation protocol was extended by Routtenberg and Kuznesof (1967) and the term ABA was introduced by Epling, Pierce, and Stefan (1983). Compared to their counterparts without running wheels, rodents with free access to wheels and time-restricted daily access to food show more rapid weight loss either to a criterion level or death (see reviews by Adan et al., 2010; Gutierrez, 2013; Klenotich & Dulawa, 2012; Méquinion et al., 2013). This model incorporates restricted energy intake and exacerbation of weight loss by activity. Also, emulating some characteristics of AN, variables including species, strain, age, initial weight, gender, and behavioral phenotype play a role in determining the proportion of animals that will adopt food-anticipatory running and severe anorexia in the ABA protocol (Boakes & Dwyer, 1997; Boakes, 2007; Cerrato, Carrera, Vazquez, Echevarría, & Gutierrez, 2012; Gelegen et al., 2007; Paré, Vincent, Isom, & Reeves, 1978; Sherwin, 1998; Woods & Routtenberg, 1971).

The role or mechanism of wheel running in the context of ABA is far from clear. Locomotion is often considered to be a natural foraging response to depletion of corporeal energy stores, and the wheel may serve as a channel for this activity. However, there is evidence that wheel running is a category of activity distinctly different from natural or spontaneous ambulatory behavior, and is a reinforcer (Collier & Hirsch, 1971; Novak, Burghardt, & Levine, 2012; Sherwin, 1998). Thus, it is possible that wheel running substitutes or compensates for diminished food reward in ABA (Foldi, Milton, & Oldfield, 2017). However, that begs the question about why animals without wheels but on restricted time food schedules do not engage in increased spontaneous locomotion, at least to the extent of posing an energetic threat to survival. Clearly, there is something that is not satisfactorily understood about the unique status of wheel activity in relation to ABA.

Animals on predictable restricted schedules of food access learn to anticipate food delivery, for example by spending more time in the vicinity of the feeding location or, in the case of rodents with access to wheels, by anticipatory running. Indeed, food anticipatory activity (FAA) has been used as a measure of circadian timekeeping (Honma, Von Goetz, & Aschoff, 1983). Dwyer and Boakes (1997) showed that, across days of study, rats with access to food for 1.5-h at the end of the daytime shifted almost all of their running from the night to the daytime. Another experiment in the same paper gave access to wheels for only 4-h immediately preceding food access (i.e., allowing FAA). It was found that the intensity of FAA (wheel revolutions/h) during this 4-h increased about 5-fold over a 10 day period, while food intake increased progressively over that time. Thus, food intake increased in parallel with FAA, a relationship that is at apparent odds with a view that running reward is substituting for food. More usually, FAA accounts for only a relatively small fraction of total daily wheel running and Wu et al. (2014) presented an analysis of ABA that demonstrates convincingly that FAA is not the key component causing vulnerability to the syndrome. Specifically, dividing rats into three groups on the