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REVIEW

ANIMAL MODELS OF EATING DISORDERS

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Abstract—Feeding is a fundamental process for basic survival and is influenced by genetics and environmental stressors. Recent advances in our understanding of behavioral genetics have provided a profound insight on several components regulating eating patterns. However, our understanding of eating disorders, such as anorexia nervosa, bulimia nervosa, and binge eating, is still poor. The animal model is an essential tool in the investigation of eating behaviors and their pathological forms, yet development of an appropriate animal model for eating disorders still remains challenging due to our limited knowledge and some of the more ambiguous clinical diagnostic measures. Therefore, this review will serve to focus on the basic clinical features of eating disorders and the current advances in animal models of eating disorders.

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Key words: animal models, eating disorders, anorexia, bulimia, binge eating, obesity.

Contents

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Abbreviations: AAPD, atypical antipsychotic drug; ABA, activity-based anorexia; AgRP, agouti-related hormone; AN, anorexia nervosa; ARC, arcuate nucleus; BDNF, brain-derived neurotropic factor; BED, binge eating disorder; BN, bulimia nervosa; CART, cocaine-amphetamine-regulated transcript; CSF, cerebrospinal fluid; DA, dopamine; HFD, high-fat diet; LH, lateral hypothalamus; MCH, melanin-concentrating hormone; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVN, paraventricular; SNP, single nucleotide polymorphism.

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Energy homeostasis is essentially a balancing act between food intake and energy expenditure via basic metabolism or physical activities (Feige and Auwerx, 2007; Gao and Horvath, 2007). Eating disorders, such as anorexia nervosa, bulimia nervosa, and binge eating, are described as disturbances in eating habits usually involving insufficient or excessive food intake. These abnormal eating patterns cause energy imbalance, resulting in the detriments to the individual's well-being (Sodersten et al., 2006; Thornton et al., 2011; Weiselberg et al., 2011). These disturbances are not limited to alteration of diet choices but also include abnormal psychological perceptions towards food, eating, body weight, and self-image. The etiology of eating disorders has yet to be characterized, but it is evident that the cause is multifactorial. The current identified causes of eating disorders are cultural pressures, biology, environment, and genetic predisposition (Sodersten et al., 2006; Weiselberg et al., 2011).

Animal models have been a powerful tool in researching neuropsychiatric conditions (Fernando and Robbins, 2011; Sarnyai et al., 2011). A well-characterized etiology is always a good basis for developing appropriate animal models for any disease state. For example, if genome-wide association studies have provided a potential risk gene for a disease in humans, the homologous genes can usually be easily mutated or deleted in animal models (Fernando and Robbins, 2011). While the causes of some diseases may not always be characterized, the understanding of disease progression and treatment may be useful in developing an effective animal model. Unfortunately, the lack of such information has hampered the efficient utilization of animal models to investigate eating disorders (Casper et al., 2008; Smith, 1989). Moreover, due to the complex nature of eating disorders, current animal models can only provide a few characteristic traits of the human psychiatric disease. Despite this setback, many scientists in the field are able to develop powerful paradigms to study specific aspects of eating disorders.

In this review, the clinical, behavioral, and physiological features of anorexia nervosa, bulimia nervosa, binge eating disorder, as well as obesity, although not specifically characterized as an eating disorder, will be discussed, followed by the understanding of how scientists can recapitulate these conditions in animal models. This will be followed by an overview of utility and limitations of the different available animal models for eating disorders and obesity relevant to the human condition.

One of the major hurdles animal models face is that they cannot show multiple traits of human psychiatric diseases. As

an alternative approach, nonhuman primate models have been utilized to investigate the complex behavioral, social, and genetic interactions (Nelson and Winslow, 2009). However, these nonhuman primate models have their own disadvantages; (1) nonhuman primates are much more expensive to maintain than nonprimates, (2) it is extremely time consuming to develop their model systems, and (3) behavior testing in primates is not standardized. Even with these limitations, nonhuman primate models have contributed greatly to certain experimental questions addressing social and complex cognitive interactions. Because of these drawbacks to the usage of nonhuman primates as models of eating disorders, it is necessary to develop other, more practical, vertebrate animal models.

ANOREXIA NERVOSA

Anorexia nervosa (AN) is the most common eating disorder that primarily affects teenage girls at puberty. It is characterized by chronic food refusal, excessive weight loss, an intense fear of weight gain and a distorted self-image including body shape and weight (American Psychiatric Association, 2000; Attia, 2010; Weiselberg et al., 2011). It usually manifests with an innocent effort to reduce caloric intake, which gets out of control. Individuals with AN continue to feel hunger, yet deny themselves by restricting food intake (Attia, 2010; Garfinkel, 1974). The first major clinical symptoms are derived from psychological changes, which can be characterized as motivated refusal to eat and maintain a body weight above 85% of the standards, intense fear to gain weight. These symptoms can be exacerbated by physiological and endocrine changes caused by the shortage of food or energy intake. A significant weight loss below 85% of normal weight for age and height or a body mass index below 18 is generally the first noticeable signs of AN (American Psychiatric Association, 2000; Hebebrand et al., 2004). Obviously, the extreme weight loss associated with AN can lead to endocrine disturbances such as amenorrhea, the absence of menstrual periods for postpubertal females. Also, plasma leptin level, which normally is secreted from adipose tissue after feeding, is reduced in AN patients (Hebebrand et al., 2003; van Elburg et al., 2007). Most of the endocrine changes that influence the regulatory system in AN are a reflection of the body's adaptation to an extended exposure to malnutrition (Casper and Davis, 1977). Many people going through prolonged starvation due to either religious or clinical reasons experience fatigue and slowed activity levels (Casper, 1998). However, individuals with AN tend to exhibit high activity levels, as well as mental alertness, during their weight loss from food restriction. This in turn drives them to engage in excessive exercise, creating a detrimental positive feedback/reward cycle (Casper, 1998; Casper et al., 1991; Klein et al., 2007; Pirke et al., 1991).

AN patients commonly display comorbid psychiatric symptoms such as anxiety, obsessive-compulsive disorders, and depressive disorders (Attia, 2010; Casper and Davis, 1977; Casper et al., 1979; Mattar et al., 2011; Ploog and Pirke, 1987). Malnutrition is thought to augment these symptoms because the disturbance of neurotransmitter levels is restored after nutritional restoration. One of the classical studies by Keys et al. also showed that these psychiatric symptoms can be derived from malnutrition (Keys et al., 1950). In this study, healthy male volunteers were subjected to a semistarvation condition for 3 months. The group showed not only the typical physiological changes due to malnutrition but also psychiatric symptoms such as depression, obsessive-compulsive like, and psychosis-like behaviors, which are very common among patients with eating disorders (Keys et al., 1950). Since the publication of this study, it has been debated whether psychiatric symptoms observed in patients with AN, or any eating disorder, are the cause or consequence of malnutrition.

Recent studies have illustrated that most people with AN (or other eating disorders) show childhood anxiety and perfectionism or obsessive-compulsive, personality patterns prior to the onset of an eating disorder (Lilenfeld et al., 2006). These studies suggest that patients displaying these symptoms may be susceptible to developing eating disorders later in life. Malnutrition appears to enhance these premorbid behavioral traits rather than causing them. Moreover, studies have also shown that some traits such as perfectionism, negative emotionality, and harm avoidance (a multifaceted temperament trait that contains elements of anxiety, inhibition, and inflexibility) still persist long after a recovery from AN (Deep et al., 1995).

Patients with AN have significantly reduced cerebrospinal fluid (CSF) serotonin (5-HT) metabolites compared with control subjects (Kaye et al., 2005; Stanley et al., 1985). More recent imaging studies showed that 5-HT_{1A} receptor expression is increased, while 5-HT_{2A} receptor expression is unchanged in both ill and recovered AN patients' brains (Audenaert et al., 2003; Bailer et al., 2007; Galusca et al., 2008). These changes in receptor expression may be a compensatory mechanism to respond to a decrease in 5-HT levels. An increase in food intake, in particular carbohydrate intake, enhances extracellular 5-HT levels. This change may potentiate the effect of 5-HT_{1A}, which is positively associated with harm avoidance in patients suffering from AN. Therefore, it is possible to speculate that malnutrition in AN patients has reduced 5-HT levels and consequently decreased dysphoric mood. Despite numerous studies supporting the involvement of 5-HT in AN, serotonin reuptake inhibitors (SSRIs) showed very limited success in reducing moods or other core psychiatric symptoms in AN patients (Attia and Schroeder, 2005). Nevertheless, it is tempting to speculate that imbalances between 5-HT_{1A} and 5-HT_{2A} contributes at least in part to such traits of AN, but further studies are needed to make this conclusion.

People with AN engage in exercise compulsively, and this trait also tends to remain after recovery (Klump et al., 2004; Shroff et al., 2006). The dopamine (DA) pathway plays a critical role in compulsive and addictive behavior. Recently, it has been shown that DA metabolites in ill and recovered AN individuals are reduced in CSF (Kaye et al., 1999). Also, positron emission tomography (PET) studies show that those who recovered from AN had increased