Neurobiological Underpinnings of Anorexia Nervosa

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Abstract

Anorexia nervosa is an eating disorder characterized by persistent, restricted food intake, which leads to drastic weight loss and has the potential of leading to death. It disproportionately affects young females, with a peak onset age between 14 and 18 years old. Young women with anorexia nervosa have the highest mortality rate in their age group and of those suffering from other psychiatric disorders. Anorexia nervosa, however, presents an enigma for researchers. It has many clinical symptoms, an unknown etiology, and lacks a comprehensive animal model that can be used for therapeutic research. This mini-review presents two animal models that are used by researchers, the diet restriction model and the activity-based anorexia model. The diet restriction model recapitulates physiological and cognitive effects of reduced food intake observed in anorexia nervosa. Activity-based models reflect hyperactivity and self-induced starvation that are characteristic of anorexia nervosa. Currently, there are two competing hypotheses of the neurobiological underpinnings of anorexia nervosa: the reward-centred model and the habit-centred model. The reward-centred model is based on evidence from neuroimaging studies that show increased activity in the mesolimbic reward circuitry in anorexia nervosa patients associated with reduced food intake. The habit-centred model of anorexia nervosa posits that reduced food intake is a learned behaviour mediated by frontostriatal circuitry. Further research is required to gain a better understanding of the neurobiological underpinnings of anorexia nervosa and to better understand the dynamic involvement of mesolimbic and frontostriatal circuitry in the pathogenesis of anorexia nervosa.

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Introduction

Anorexia nervosa is an enigmatic eating disorder that is characterized by the maintenance of a malnourished, starved state and long-term restrictive eating that pose a threat to a healthy body weight. The importance of studying this disorder is highlighted in the fact that mortality among young women due to anorexia nervosa is the highest of any psychiatric disorder for their age group.[1] This disorder presents an enigma to researchers due to the heterogeneity of its clinical manifestations, diversity of symptoms and their neurobiological underpinnings, and the lack of a comprehensive animal model that can recapitulate the various aspects of this disorder. Neuroimaging studies on anorexia nervosa patients have provided us with important insights into neural circuits that show greater activity and have allowed identification of neural circuits that are active in response to reduced food intake. These studies led to the development of reward-centred and habit-centred models of anorexia nervosa.

This mini-review presents two animal models that are currently used by researchers, the diet restriction model and the activity-based anorexia model, and aims to examine the advantages and limitations of each. This review also presents evidence from various neuroimaging studies and analyzes it with respect to the reward-centred versus habit-centred models of anorexia nervosa to better understand the neurobiological underpinnings of this disorder. It draws on both human and animal studies to illustrate the complexity of this disorder, competing explanations for its neurobiology, and emphasizes the need for development of better animal models that can provide evidence for reward-centred and habit-centred models in animals. Development of animal models will allow for testing of potential therapeutic drugs that can help in treating patients with anorexia nervosa in the future.

Animal Models of Anorexia Nervosa

Diet Restriction Model

The diet restriction model of anorexia nervosa implements significant food restriction in animals, that is, less than half of the daily food intake. While it has previously been shown that reduced caloric intake can extend the lifespan of an animal, excessive caloric restriction can serve as a model for anorexia nervosa.[2] An important limitation of this model is that unlike the clinical manifestation of anorexia nervosa, the food restriction in the animal model is not voluntary. Nonetheless, the advantage of the diet restriction model lies in the opportunity it provides to elucidate the physiological, cognitive and neuro-endocrine effects of reduced food intake observed in

anorexia nervosa. A study by Avraham et al. investigated the effects of varying levels of food restriction on young female mice.[3] Results illustrated that while 60% diet restriction improved performance in the 8-arm maze, 40% diet restriction was associated with reduced performance in the 8-arm maze and greater mortality. Cognitive function measured by performance in the Morris water maze was also found to be lower in the 40% diet restriction mice than both control and 60% diet restriction mice. Interestingly, treatment with tyrosine mitigated these adverse effects: for instance, cognitive function improved in 40% diet-restricted mice to the level of 60% diet-restricted mice without any accompanying changes in body weight. These findings from a diet restriction model of anorexia nervosa are important because nutritional rehabilitation is a pre-requisite to any benefit that patients can gain from psychological treatment. This creates a barrier in commencing treatment because patients resist nutritional rehabilitation due to fear of weight gain.

In a later study, Avraham et al. go on to demonstrate that anorexia is associated with elevated hypothalamic serotonin levels and that tyrosine intake normalizes these levels.[4] In doing so, tyrosine improves cognitive performance, food intake, and activity performance. More recently, Hart et al. have demonstrated the validity of tyrosine supplementation as an adjunct treatment in anorexia nervosa.[5] This stems from the hypothesis that noradrenergic dysregulation is observed in anorexia nervosa, and tyrosine supplementation mitigates noradrenergic dysregulation, as tyrosine is a precursor for dopamine, serotonin, and noradrenaline synthesis. Hence, tyrosine supplementation as a strategy might have important implications to help with initiating treatment in patients with anorexia nervosa to improve their mood, lessen anxiety around re-starting food intake, and improve cognitive performance.

Activity-Based Anorexia Model

A defining characteristic of anorexia nervosa is self-motivated restricted food intake, a characteristic that is difficult to recapitulate in animals as food intake is usually controlled by experimenters. To overcome this limitation, Routtenberg and Kuznesof developed the self-starvation or activity-based anorexia (ABA) model where rats are placed in conditions where they have a choice between food intake and another rewarding condition such as exercise.[6] It is important to note that individuals with anorexia nervosa have high activity levels, even with restricted food intake and accompanying weight loss, and they compulsively engage in excessive exercise. Hence the ABA model recapitulates not only self-induced starvation but also hyperactivity that is characteristic of anorexia nervosa. Routtenberg and Kuznesof illustrate that self-starvation can be induced by exercise in rats using activity-wheels.[6] In this study, active rats consumed less food than control rats and eventually starved to death due to the inability to compensate for energy lost during exercise. In contrast, control rats on a feeding schedule of 1 hour/day maintained their body weight. This study established that the ABA model can reproduce some main characteristics of anorexia nervosa as hyperactivity, self-induced starvation, and weight loss. Furthermore, it has also been shown that female rats exercise significantly more than male rats, a finding that strengthens the ABA model and its clinical relevance, as it reflects the sex distribution of anorexia nervosa in humans.[2] This finding also raises important questions for future research to further investigate the underlying reasons of differences in sex.

A study by Pare compared the effects of high running activity and associated reduced food intake in younger versus older rats.[7] Interestingly, results showed that younger rats with high activity levels had a higher mortality rate than older rats with low activity levels. This finding is of significance, as anorexia nervosa disproportionately affects young females, and mortality among young women due to anorexia nervosa is the highest of any psychiatric disorder for their age group.[1]

Anorexia Nervosa and Reward Processing

Neural systems of reward processing entail the ventral striatum, nucleus accumbens, midbrain and ventral tegmental area, and the orbitofrontal cortex. The nucleus accumbens and ventral striatum are involved in the control of food intake energy balance and taste perception.[8] Previous animal studies have shown that restricted food intake heightens sensitivity of reward circuits.[1] Neuroimaging studies have analyzed neural substrates of reward processing in anorexia nervosa patients compared to healthy controls, using structural and functional MRI as well as positron emission tomography (PET). Fladung et al. conducted a fMRI study in which they recorded neural activity in healthy individuals and anorexia nervosa patients in response to images of under-weight, normal-weight, and overweight females.[9] The study illustrated that individuals with anorexia nervosa had decreased activity in the ventral striatum in response to normal-weight stimuli when compared to healthy controls, who show greater activation of ventral striatum when exposed to normal-weight stimuli. Titova et al. conducted structural MRI on anorexia nervosa patients and found that volumes of regions involved in reward processing, particularly the orbitofrontal cortex, are abnormal in anorexia nervosa.[10] While this study reported decreased volumes of reward-sensitive regions in anorexia nervosa patients, a later study by Frank et al. contradicted these findings and reported an increased volume in anorexia nervosa patients compared to healthy controls.[11] Frank et al. utilized a more accurate analysis software, and the patients taking part in the study were inpatients and had normal food and fluid intake for a week before brain imaging.[11]

Furthermore, task-based fMRI studies have been employed to elucidate how responses to taste rewards differ in anorexia nervosa. A study by Fladung et al. showed that individuals with anorexia nervosa have heightened activity in the orbitofrontal cortex and nucleus accumbens in response to taste rewards.[12] Taken together, the structural MRI and fMRI studies provide evidence for the involvement of reward circuitry in the neural underpinnings of anorexia nervosa.

In addition to the starvation-induced sensitization of reward circuitry, another reason reward circuitry is central to understanding the neurobiology of anorexia nervosa lies in adolescent reward circuitry, where rewards have an increased salience.[1] Galvan et al. conducted a fMRI study where they

compared activity in the nucleus accumbens and orbitofrontal cortex in children, teens, and adults in response to a monetary reward.[13] The results showed that adolescents had the strongest activity levels in nucleus accumbens in response to a monetary reward. This finding supports the notion that adolescents experience increased salience of rewards.

Taken together, these studies suggest two main ideas, that food restriction sensitizes the mesolimbic reward circuitry and that adolescents show increased nucleus accumbens activity. Given that anorexia nervosa is characterized by decreased food intake and has a peak onset age between 14 and 18 years, these studies suggest that anorexia nervosa is associated with abnormalities in reward circuitry, also known as the reward-centred model of anorexia nervosa.

Anorexia Nervosa and Neural Circuits Underlying Habit Formation

Habit formation describes a process by which a behaviour is paired with a reward and when repeated several times, the behaviour becomes automatic and persists in the absence of the reward.[14] Studies show that as a behaviour undergoes the shift from intentional to habitual, the neural systems regulating the behaviour shift as well. Findings from animal and human studies show that when the behaviour becomes a habit, it comes under the control of the dorsal striatum. The dorsal striatum is composed of the putamen, basal ganglia, and caudate. The dorsal striatum is part of the frontostriatal circuitry, and this circuitry plays a role in maladaptive behaviours characteristic of various psychiatric disorders.[1] Delvenne et al. conducted PET studies of anorexia nervosa patients and showed elevated metabolic activity in the caudate.[15]

A central question in better understanding the underlying neural mechanisms mediating anorexia nervosa is why do people make maladaptive choices? In anorexia nervosa, persistent maladaptive food choices cause weight loss and can be accompanied by mortality. Individuals with anorexia nervosa repeatedly and persistently choose low fat foods over high fat foods.[16] This pattern of food choice continues when individuals change their goals (i.e. enter treatment) and hinders progress on weight gain. In this manner, anorexia nervosa can be viewed as an excellent model of persistent maladaptive behaviour. In a study by Steinglass et al.,[17] women with anorexia nervosa and a group of healthy female controls participated in a food choice task, where they were asked to choose food items from a list that contained both low fat and high fat food items.[1] Results showed that anorexia nervosa patients were less likely to choose high fat foods compared to healthy females. The study then examined if the results from the food choice task correlated with eating behaviour. It was found that the eating behaviour of anorexia nervosa patients was significantly correlated with the foods they chose in the food choice task.

In a following study, Foerde et al. (2015) used a similar food choice task and conducted imaging of anorexia nervosa patients and healthy controls as they chose low versus high fat foods.[16] Similar trends as observed in the study by Steinglass et al. (2015) were seen in the food choice task: anorexia nervosa patients were significantly more likely to choose low fat foods.[17] More importantly, significantly greater neural activity in the dorsal striatum of individuals with anorexia nervosa during the food-choice task was observed than in healthy controls where there was no difference in activity in the ventral striatum. These results suggest that specifically the dorsal striatum, and not the ventral striatum, is a neural substrate of persistent maladaptive choices observed in anorexia nervosa. In addition, Foerde et al. also conducted a functional connectivity analysis to elucidate the role that frontostriatal circuits play in food choice decisions made by anorexia nervosa patients.[16] Results showed that food choice is associated with functional connectivity between the striatum and the dorsolateral prefrontal cortex (dlPFC). Analysis of differential connectivity between these areas showed that anorexia nervosa patients show greater connectivity for low fat foods, whereas the opposite is seen in healthy controls. These results suggest that a neural circuit between the dorsal striatum and the dlPFC may be important in the underlying neural mechanism mediating persistent maladaptive food-intake choices characteristic of anorexia nervosa. The results from this study have important implications towards improving our understanding of the neurobiological substrates and circuitry underlying anorexia nervosa. Some recent studies have proposed a role for neural circuitry involved with habit formation in anorexia nervosa. This habit-centred model of understanding anorexia nervosa views restrictive dietary intake in anorexia nervosa as a habit, one that is learned, not innate and elicited by specific stimuli. The involvement of frontostriatal neural circuitry in food choice decisions by anorexia nervosa patients, as shown in this study, strengthens the habit-centred model of anorexia nervosa, as dorsal striatum is associated with habit formation.

Conclusion

Anorexia nervosa is defined by persistent, self-motivated starvation that leads to reduced food intake and is accompanied by excessive exercise.[16] Anorexia nervosa, however, is difficult to study due to its complex etiology and the lack of a comprehensive animal model that can be used for therapeutic research. This mini-review evaluates the diet restriction and the activity-based anorexia animal models. There is a need for further research to develop an animal model for anorexia nervosa that can not only recapitulate the clinical symptoms but also allow researchers to study decision-making in food choices and study the underlying reward circuitry and habit-formation circuitry as the animals engage in these tasks. Recent technological advancements in neuroscience such as the ability to do live calcium imaging in vivo are promising ways through which such investigations can be done. For instance, in vivo circuit and cellular level functional imaging as described by Gulati et al. can help to better understand the role of mesolimbic and frontostriatal circuitry in animal models of anorexia nervosa.[18]

Despite the evidence from fMRI studies of neural circuits linked with habit formation in anorexia nervosa, behavioural studies need to be done to establish that restricted food intake is in fact a habit. In addition, studies in animal models are also needed to examine whether animals can develop the habit of restricted food intake. This will help to confirm if

similar neural circuitry is involved in anorexia nervosa in animal models. In addition, it is unknown if the circuits engaged by individuals who diet but do not develop anorexia nervosa are the same as, or differ from, the neural circuits associated with anorexia nervosa. Structural and functional imaging studies will help to address this question. It is also unknown how neural circuits change over time as an individual has anorexia nervosa for longer durations or as a patient recovers from anorexia nervosa. In the future, this knowledge will be essential to find treatments for anorexia nervosa. Furthermore, while studies show that cues can impact food restriction in anorexia nervosa, more work needs to be done on how cues and emotional factors influence neural circuits linked with food choice.

In future studies, animal models of anorexia nervosa should be used to study changes in the mesolimbic reward circuitry and the frontostriatal circuitry associated with habit formation. This will facilitate better understanding of the currently-competing hypotheses of the neurobiological underpinnings of anorexia nervosa: reward-centred versus habit-centred models. The reward-centred hypothesis argues for the involvement of the ventral striatum, whereas the habit-centred hypothesis argues for increased activity of the dorsal striatum in anorexia nervosa patients. Animal research will also make it possible to test therapeutic drugs that may help with treating anorexia nervosa in humans.

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