Neuroscience and Biobehavioral Reviews 60 (2016) 26–30

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Discussion

Dopamine and anorexia nervosa

P. Södersten*, C. Bergh, M. Leon, M. Zandian

Karolinska Institutet, Section of Applied Neuroendocrinology, Mandometer Clinic, Huddinge, S-14104 Huddinge, Sweden

ARTICLE INFO

Article history:
Received 29 June 2015
Received in revised form 30 October 2015
Accepted 1 November 2015
Available online 19 November 2015

Keywords:
Dopamine
Anorexia nervosa
Eating pathology
Mental consequences of food deprivation
Eating behavior
Anorexia treatment
Eating disorders

ABSTRACT

We have suggested that reduced food intake increases the risk for anorexia nervosa by engaging mesolimbic dopamine neurons, thereby initially rewarding dieting. Recent fMRI studies have confirmed that dopamine neurons are activated in anorexia nervosa, but it is not clear whether this response is due to the disorder or to its resulting nutritional deficit. When the body senses the shortage of nutrients, it rapidly shifts behavior toward foraging for food as a normal physiological response and the mesolimbic dopamine neurons may be involved in that process. On the other hand, the altered dopamine status of anorexics has been suggested to result from a brain abnormality that underlies their complex emotional disorder. We suggest that the outcomes of the treatments that emerge from that perspective remain poor because they target the mental symptoms that are actually the consequences of the food deprivation that accompanies anorexia. On the other hand, a method that normalizes the disordered eating behavior of anorexics results in much better physiological, behavioral, and emotional outcomes.

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1. Introduction

Bergh and Södersten (1996) suggested that the normal dopamine responses to hunger and exercise facilitate a progression into anorexia nervosa, but O'Hara et al. (2015) proposed that an abnormality in the dopamine-mediated reward system underlines the development, maintenance, and treatment resistance of anorexia. We will first discuss the studies on which these suggestions are based and then turn our attention to the implications of both points of view for the treatment of anorexia.

2. Dopamine may facilitate the development of anorexia

Mesolimbic dopamine neurons are thought to be involved with reward (Wise, 2004), and Bergh and Södersten (1996) suggested that dieting, along with high levels of exercise, can lead to a stress response (Hotta et al., 1986; Rojo et al., 2006) that increases cortisol and corticotrophin releasing factor (Estour et al., 2010; Gwirtsman et al., 1989; Schorr et al., 2015; Shibuya et al., 2011). Stress then increases dopamine levels through these mechanisms (Holly et al., 2015; Wanat et al., 2008) and the nucleus accumbens, i.e., a region of the dopamine terminals in the ventral striatum, is in fact activated in anorexics (Fladung et al., 2010, 2013; Foerde et al., 2015; Frank, 2014; Keating et al., 2012; O'Hara et al., 2015; Wierenga et al., 2014, 2015). The elevated dopamine response is then thought to assist the sequence from rewarding behaviors such as dieting and exercise to become habits not unlike drug dependency or self-starvation by conditioning of this kind of reward to initially neutral stimuli (Bergh and Södersten, 1996; Everitt and Robbins, 2005; Jansen, 1998; Méquinion et al., 2015; Södersten et al., 2008). The high corticotrophin releasing factor levels associated with the stress of diet restriction and exercise appear to increase the dopamine responses that facilitate foraging for food, while simultaneously suppressing food intake (Stengel and Taché, 2014). We should note that no premorbid dopamine comparisons have been made for those who become anorexic, and it is possible that anorexics have had chronically elevated dopamine levels before they develop their eating disorder.

3. Normal responses to food and dieting

A problem with understanding the implications of neural correlates of anorexia nervosa is that the patients are food deprived. Therefore, any observed neural changes may have no causative role in anorexia, but may simply be a *consequence* of the disorder. To meet the challenge of food deprivation, animals have developed efficient foraging strategies (McCue, 2012; Stephens and Krebs, 1986) and dopamine appears to play a critical role in facilitating foraging in a wide range of species (Bédécarrats et al., 2013; Berridge and Kringelbach, 2015; Faure et al., 2008; Masek et al., 2015; Moe et al., 2014; O'Connell and Hofmann, 2011; Richard and Berridge, 2011; Søvik et al., 2014). Moreover, appetitive conditioning using

* Corresponding author. Tel.: +46 8 8 55640602; fax: +46 8 55640610.
E-mail address: per.sodersten@ki.se (P. Södersten)

http://dx.doi.org/10.1016/j.neubiorev.2015.11.003
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food as a reward increases dopamine levels in the mesolimbic dopamine neurons (Sunsay and Rebec, 2014). Hunger hormones also influence food-related responses by acting on these dopamine neurons (Cone et al., 2015). The responses of the mesolimbic dopamine neurons of anorexics therefore may be activating the search for food when anorexics deprive themselves of food.

4. Co-morbid symptoms vs. core symptoms of anorexia

In one study, subjective ratings of the sight and flavor of food were normal in patients who were reported to have "recovered" from anorexia nervosa, but the responses of their mesolimbic dopamine neurons to these stimuli remained enhanced (Cowdrey et al., 2011). The authors suggested that these responses of the dopamine neurons to food may be a biomarker for *anorexia nervosa*. But this proposal must be mistaken, because a symptom of a disorder cannot persist after recovery from that disorder. A more probable explanation is that hungry people are normally highly responsive to food stimuli. A problem, therefore, exists with brain studies of patients who are thought to be in remission from anorexia.

Indeed, both brain and behavior continue to be abnormal in many patients who are reported to have "recovered" from anorexia nervosa (e.g., Wierenga et al., 2015). The changes that are found in their brains may therefore be related to the disorder from which they are thought to have "recovered". A more reasonable standard for recovery should produce asymptomatic patients who have: (1) normal body weight for their height and age, (2) normal eating behavior, (3) normal psychiatric assessments, (4) normal physiological status, (5) no compensatory behaviors, such as purging, (6) no difficulty in dealing with food or body weight, and (7) a resumption of their normal social, educational and/or career activities (Bergh et al., 2002). In fact, patients who are treated effectively must meet this standard to be regarded as being in remission and they are regarded as being in recovery only if they maintain this status for five years (Bergh et al., 2002, 2013).

If anorexic patients can reach this fully recovered status, how can anorexics who have obviously not recovered, be considered to have recovered? To address this issue, researchers hypothesize that their ongoing symptoms are not core symptoms of anorexia, but are rather thought to be symptoms that are co-morbid with anorexia. Moreover, these co-morbidities, and their associated neurobiological abnormalities, are thought to reflect heritable traits for mental disorders that persist after weight normalization (Godart et al., 2003; Kaye et al., 2004; Wierenga et al., 2014). However, the concept of co-morbidity actually refers to a disorder or disease that is independent of the disorder with which it co-exists (Feinstein, 1970; Maj, 2005). This concept therefore has been used incorrectly in the study of eating disorders. Indeed, both the emotional and the neural symptoms of anorexia appear to be the *consequences* of starvation, rather than co-morbidities (Bergh et al., 2013). Therefore, a more plausible explanation is that the anorexics who are thought to have recovered, have not actually recovered. Such individuals would therefore constitute an inappropriate comparison group for anorexics that might well lead to inappropriate conclusions regarding the origins and treatment of the disorder.

5. Abnormal mentalistic processes vs. normal responses to starvation in anorexia

O'Hara et al. (2015) describe anorexia nervosa as a "severe, chronic, and refractory psychiatric disorder with debilitating impairments across physical, cognitive, and socio-emotional domains". They go on to describe the disorder as "... characterized by anxious, obsessional traits [and] ... pathological cognitions". As such, standard-care for anorexia concentrates on treating the emotional and cognitive symptoms that are associated the disorder. However, we regard these psychological issues in anorexics as problems that "merely distract us from the thing that really matters" (Wittgenstein, 1969). Moreover, the evidence that these same symptoms also emerge in healthy people during starvation is compelling, with semi-starvation rapidly leading to both anxiety and depression (Keys et al., 1950). Furthermore, the list of arguments against the hypothesis that an underlying mental disorder causes anorexia is long (Bergh et al., 2013). For example, the hypothesis that anxiety leads to anorexia (Kaye et al., 2004; Wierenga et al., 2014) has been rejected with compelling data for both humans (Sallet et al., 2010; Wu, 2008) and for a mouse model of anorexia (Wable et al., 2015). In addition, it was recently discovered that anorexia and anxiety have different genetic risk factors (Cederlöf et al., 2015). Moreover, all of the mental disorder symptoms seen in humans are readily reversed following the normalization of eating behavior (Bergh et al., 2002, 2013). Of course, it is possible that there are some anorexics who actually have co-morbid depression, anxiety, obsessions, compulsions, or delusions. However, none of the hundreds of anorexics whom we have treated to recovery have had such co-morbid disorders; their mental symptoms resolved as their eating behavior normalized (Bergh et al., 2002, 2013).

The hypothesis that a disordered eating pattern can alter emotional and cognitive processes has been strengthened by other kinds of data. For example, normal chewing rates are calming and abnormal chewing rates are stressful (Ioakimidis et al., 2011). In addition, anxiety is markedly increased among patients with temporomandibular joint disorders that alter the ability to eat normally (Eccles et al., 2015; Mallorquí-Bagué et al., 2014, 2015). Another example is that a reduction in the number of teeth, which makes eating difficult, is associated with cognitive decline (Cerutti-Kopplin et al., 2015; Listl, 2014; Reyes-Ortiz et al., 2013; Teixeira et al., 2014; Weijenberg et al., 2011). Chewing difficulties also are associated with depression (Al Jameel et al., 2015; Hwang et al., 2013). Conversely, normal chewing behavior reduces stress and anxiety (Kim et al., 2015; Kubo et al., 2015a,b; Ono et al., 2015), improves attention and cognition (Chen et al., 2015a; Johnson et al., 2013; Weijenberg and Lobbezoo, 2015), and alleviates the symptoms of depression (Allen and Smith, 2015; Erbay et al., 2013; Yu et al., 2013).

Misunderstanding the emotional responses to food deprivation has led to the proposal of hypothetical mentalistic processes underlying anorexia, including concepts such as "top-down cognitive control", "inability to experience reward", "aversive appraisal of food stimuli", and "cues of aberrant thinking" (O'Hara et al., 2015). However, there is no need to resort to such concepts, because the manner by which hunger signals act has been clarified through neurobehavioral analysis (Ammar et al., 2000; Scheurink et al., 2010; Södersten et al., 2008). For example, when food is in short supply, there is a rapid shift from other activities to food foraging activities (McCue, 2012). This pattern is also seen in anorexics; rather than eating, they become preoccupied with thinking about food, as well as shopping for food, and preparing food for others (Thurston, 1999). They also may collect cookbooks and recipes, much like healthy men who were subjected to experimental semi-starvation (Keys et al., 1950). This behavioral change can be modeled in experimental animals with intracerebral infusion of the neuroactive substances that are normally produced by the hypothalamic arcuate nucleus of food-deprived animals (Ammar et al., 2000; Södersten et al., 2008). For example, while neuropeptide tyrosine increases eating in non-deprived animals, it increases foraging for food at the expense of eating in food-deprived animals (Ammar et al., 2000). Conversely, leptin, which is considered to be an inhibitor of food intake, causes a marked increase in eating when

the need to forage for food is circumvented (Ammar et al., 2000). Clearly, "orexigenic" and "anorexigenic" neural messengers act mainly to excite or inhibit the search for food, rather than affecting food intake (Keen-Rhinehart et al., 2013; Teubner et al., 2012). Perhaps the most convincing demonstration of this phenomenon is that presentation of a high-calorie, fatty food immediately activates arcuate neurons that were previously thought to be internal sensors for monitoring long-term energy stores (Chen et al., 2015b). The rapidity with which these neurons respond, however, suggests that they actually inform the animals about changes in the immediate external food environment (Seeley and Berridge, 2015). Similarly, the increased "foraging" seen in anorexics may be a normal response to their low food intake.

The fact that the mentalistic concepts underlying eating disorders do not take the normal functions of the neuroendocrine system into consideration may be the reason why this approach has not led to an effective treatment. More importantly, the experimental analysis of how the foraging system responds to variations in the availability of food makes psychological explanations redundant. By contrast, an effective treatment for eating disorders that complies with the need for neural plausibility exists and it will be discussed in the final part of this commentary.

6. Effective treatment of anorexia nervosa

A learned increase in dopamine can be ameliorated by changing the contingencies of food reward (Sunsay and Rebec, 2014). Perhaps altering the contingencies for food reward by normalizing the eating behavior of anorexics, would thereby reduce their stress level, and eliminate both the rewarding dopamine stimulation that supports foraging behavior and the corticotrophin releasing factor that inhibits food intake (Bergh and Södersten, 1996; Bergh et al., 2002, 2013; Stengel and Taché, 2014).

Anorexics therefore had their eating behavior normalized using mealtime feedback, rather than treating their mental symptoms, and this behavioral approach markedly improved their outcomes relative to that of control subjects in a randomized controlled trial. The successfully treated experimental patients developed normal eating behavior, body weight, psychiatric profiles, physiological status, social interactions, and career/educational engagements, i.e., they met the criteria for remission listed above. In a group of 168 patients, the rate of remission was estimated to be about 75% after an average of one year of treatment. The relapse rate was estimated to be about 10% in 83 patients who were followed for five years after being treated to remission (Bergh et al., 2002). This treatment has now been used in six clinics in four countries on 1428 eating disorder patients with the same outcome: 75% in remission, 10% relapse, and 0% mortality (Bergh et al., 2013).

Standard-care for anorexia relies on attempting to normalize the abnormal mental states that may arise from abnormal dopamine responses, but the emotional symptoms that they target actually appear to be a consequence of starvation. Probably for this reason, standard-care outcomes for anorexia remain poor (Ben-Tovim et al., 2001; Keel and Brown, 2010; McElroy et al., 2015). Specifically, about 30% of the patients drop out of treatment, fewer than 50% respond to treatment, most patients remain symptomatic upon discharge, and the majority of those individuals relapse within a year. Moreover, the mortality rates of anorexics given standard-care are amongst the highest of any psychiatric disorder (Ackard et al., 2014; Arcelus et al., 2011; Steinhausen, 1999; Zipfel et al., 2014).

The marked difference in the outcomes of the normalization of eating behavior and the outcomes for standard-care cannot be explained by a difference in patient characteristic at admission. Indeed, the average BMI of the 571 anorexics in the eating normalization studies was 14.9 kg/m^2 (Bergh et al., 2013), which is much lower than the average BMI of most patients who enter standards of care (e.g.: 16.7 kg/m^2; Zipfel et al., 2014). In addition, 150 of the anorexic patients in eating normalization therapy required in-patient treatment with a BMI of <13.5 kg/m^2 (Bergh et al., 2013). Their BMIs were substantially lower than those of patients admitted to in-patient standard-care in Germany (BMI = 15.1; Herpertz-Dahlmann et al., 2014), or those recommended for in-patient treatment of anorexia in the USA (BMI = 16.5; Attia and Walsh, 2009). If anything, the patients entering eating-behavior normalization treatment are more seriously ill than those entering standard treatments.

It has been noted that randomized controlled trials cannot be used to improve behavioral interventions for eating disorders, because there are so many available interventions to compare (Kazdin, 2007). There are at least 34 standard therapies that are used to treat eating disorders (listed in Bergh et al., 2013). In order to make pair-wise comparisons between all of these treatments 1122 randomized controlled trials would be needed, a project that is clearly not feasible. Instead, it has been suggested that behavioral interventions should be based on basic science findings (Onken, 2015). The treatment that focuses on the normalization of eating behavior in anorexics is based on such evidence and is able to interrupt the starvation-dependent state, and return their brain and behavior to a healthy status. Needless to say, although this treatment has thus proven useful in restoring the mental and physical health of the patients, its neurobiological foundation needs to be further validated.

7. Conclusions

Recent studies on the relationship between dopamine and anorexia nervosa suggest that the changes in dopamine that were found in these patients are more likely to be normal responses to starvation than signs of pathology. Moreover, data regarding neural function in anorexics remain inconclusive because the patients who were studied remained symptomatic after therapy. Finally, treating the mental symptoms that emerge from starvation has not lead to an effective treatment for anorexia, but normalization of the disordered eating behavior in anorexics has largely accomplished that goal.

Acknowledgment

The work is supported by Mando Group AB.

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