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How eating affects mood

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ABSTRACT

IOAKIMIDIS I, M. ZANDIAN, F. ULBL, C. BERGH, M LEON, AND P. SÖDERSTEN. How eating affects mood. PHYSIOL BEHAV 2011 (000) 000–000. We hypothesize that the changes in mood that are associated with eating disorders are caused by a change in eating behavior. When food is in short supply, the rhythm of the neural network for eating, including orbitofrontal cortex and brainstem, slows down and we suggest that this type of neural activity activates a partially overlapping neural network for mood, including dorsal raphe serotonin projections to the orbitofrontal and prefrontal cortex. As a consequence, people who restrict the amount of food that they consume, either by choice or by their limited access to food, become preoccupied with food and food-related behavior. Most eating disorders emerge from a history of dietary restriction and we suggest that disordered eating consequent upon food restriction produces the altered mental state of patients with eating disorders. Based on the present hypothesis, eating disorders are not the result of a primary mental disorder. Rather, this notion suggests that the patients should be treated by learning to eat an appropriate amount of food at an appropriate rate.

1. Introduction

Improving outcome in anorexia and bulimia nervosa and other eating disorders is desirable as many interventions have suboptimal effects [1,2]. A possible reason for the limited success is because the symptoms which are targeted may not be causally related to eating disorders. For example, therapies that alleviate anxiety or depression in patients without eating disorders are not effective in patients with eating disorders [3]. We offer an alternative hypothesis according to which disordered eating *causes* changes in mood by activating the 5-hydroxytryptamine (5-HT, serotonin) projections from the dorsal raphe nucleus to the orbitofrontal and prefrontal cortex, suggesting an alternative way to treat these patients.

In this review, we will first describe our perspective on the etiology and treatment of eating disorders. We then discuss the effects of dietary restriction on mood and eating behavior, followed by a discussion of the neurobiology of eating that will describe the overlap of that system with the neural system that is engaged in mood. A discussion of how eating and mood are causally related will follow, along with a suggestion of how such a relationship may be disrupted by pharmacological treatment. We then suggest how the hypothesis can be tested and put into clinical use. Finally, we mention some limitations of the hypothesis.

2. A framework for understanding eating disorders

> "A framework is not a detailed hypothesis or set of hypotheses; rather, it is a suggested point of view for an attack on a scientific problem, often suggesting testable hypotheses … A good framework is one that sounds reasonably plausible relative to available scientific data and that turns out to be largely correct." [4]

We have previously described a framework for the development and maintenance of anorexia nervosa [5]. Briefly, there are two known risk factors for anorexia nervosa, dieting and enhanced physical activity. Experiments on animals had demonstrated that both of these risk factors activate mesolimbic dopamine neurons and locus coeruleus noradrenaline neurons that are thought to play a role in reward and selective attention, respectively [5]. Hence, we suggested that anorexia develops because it is initially rewarding to eat less food and be physically active when the dopamine reward system is engaged and that anorexic behavior is subsequently maintained by conditioning to the situations that provided the reward when the noradrenaline attention system is activated [5]. In an update of this hypothesis, we provided information on how dietary restriction influences both behavior and neuroendocrine function, we described the brain mechanisms of reward and attention in further detail, and presented an experimental analysis of how hormones and behaviors are interrelated in anorexia nervosa [6,7]. A new study has confirmed our prediction that the dopamine innervations of the forebrain are engaged in anorexia nervosa [8]. Another study confirmed that the

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locus coeruleus noradrenaline neurons are activated when contextual cues induce a conditioned response [9] and yet another new study pointed out that such cues refer to the environment in which the learning event takes place [10]. Contextual cues play a significant role in both eating behavior [11,12] and eating disorders [13].

Although these studies have added plausibility to the framework that we have used to understand the onset and maintenance of anorexia, we have been reluctant to speculate on the means by which the brain produces the emotional problems associated with anorexia. Our aim is to fill this gap by explaining how eating behavior influences mood by connecting the brain and the mind, thus adding an essential part to the framework.

3. Restricted food intake and emotional responses

> "What I was not expecting was the effect it would have on the mind, the total feeling of depression and the total occupation with the idea of food…" A participant in a starvation experiment [14].

The effects of voluntary or enforced food restriction on mood and behavior were documented long ago [14,15]. Thus, if the availability of food is reduced, people start thinking only about food, they will become entirely concerned with finding food and eventually they will experience depression, anxiety among other emotional symptoms [15]. Also, they eat slowly; "Toward the end of starvation some of the men would dawdle for almost two hours over a meal which previously they would have consumed in a matter of minutes." [14]. These emotional and behavioral effects of voluntary or involuntary food restriction have been described in hundreds of thousands of people and the similarities with anorexia are compelling [6,14,15].

How does the brain turn food restriction into serious mood and behavioral states? The role of the brain in the functional changes that occur when someone is deprived of food should be characterized as permissive, rather than controlling. This distinction is important, as we have found that while the hypothalamic messenger neuropeptide Y increases food intake if infused into the brain of rats when food is easily available, it has the opposite effect when the availability of food is restricted [6]. The physiological ambiguity of neuropeptide Y suggests that the brain has a subtle role in the sequence of events that evolve when the supply of food is reduced.

4. The neural engagement in eating and mood

A pattern generator for chewing and swallowing is located between the caudal facial nucleus and the trigeminal motor nucleus in the brainstem [16,17]. If experimentally isolated from input, its inherent rhythm is expressed in the presence of excitatory amino acids [16], but the rhythm is normally modulated by sensory input which can be communicated via adjacent brain regions such as the serotonin cells of the raphe nuclei [16,18,19]. Thus, while serotonin neurons in the dorsal raphe are activated during chewing and licking [20], serotonin neurons in the caudal raphe are activated during swallowing [21]. These brainstem areas, and additional hypothalamic areas, along with the orbitofrontal and prefrontal cortex, make up a neural network with bidirectional connections that are engaged during eating [shown by the blue lines in Fig. 1].

Eating behavior emerges in rhythmic bursts when neonates are suckling, and this behavior is transformed into the rhythmic muscular activities of chewing and swallowing [22]. Normal eating behavior in adults is characterized by an initial rapid rate of eating, eventually followed by a decelerated rate of eating over the course of a meal as the individual approaches satiety [23].

The neural pattern generator for chewing and swallowing and the neighboring serotonin neurons innervate the orbitofrontal and prefrontal cortex and other limbic forebrain areas [18,24,25]. Cortical activity during chewing activates the ascending serotonin neurons in the dorsal raphe nucleus [26,27] that project to the orbitofrontal and prefrontal cortex and thereby *causes* mood changes [27–29; shown by the red arrows in Fig. 1]. These may include mood and hedonic changes associated with vomiting [30,31], importantly involved in eating disorders. Food is a major entrainer of circadian rhythms [32], food restriction is a potent arousing stimulus, which may phase shift circadian rhythms via the same dorsal raphe serotonin projections [33]. Interestingly, the availability of food during the course of a day can change the temporal expression of eating [34,35], producing mood changes [36,37]. Equally interesting, many of the endocrine and metabolic derangements in an experimental model of this situation are reversed by re-entrainment of the rhythm by food [38].

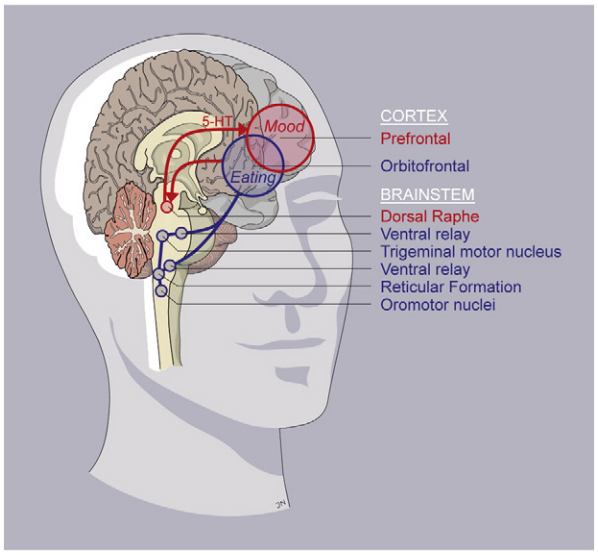

Fig. 1. The neural engagement in eating including orbitofrontal and prefrontal cortex and brainstem areas, shown in blue, which are hypothesized to mediate changes in mood via the serotonin (5-HT) projections of the dorsal raphe to the prefrontal cortex, shown in red. Lines without arrows indicate bidirectional connections.

Normal activation of this neural network is associated with positive emotions. For example, breastfeeding has a calming effect on both the mother and her baby; by sucking on the nipple, the newborn rat activates the neural network of emotion in the mother and, very likely, also in itself; thereby promoting a strong emotional bond between the two [39]. In the adult, chewing activates parts of the same brain network [25,26] and has a relaxing effect [40]. However, experimental damage of this network can cause both chewing disorders and anxiety [18]; mood disorders are common among patients with bruxism and other disturbances of the muscles used for chewing [41] and patients with eating disorders can suffer from bruxism [42]. Indeed, disruption of normal mastication was recently suggested to account for cognitive decline in aging and dementia [43,44]. Thus, when chewing goes wrong, mood and cognitive disorders seem to emerge. Conversely, food-restricted volunteers often used large amounts of chewing gum, possibly to alleviate the depression and anxiety they experienced in the food deprived condition by restoring normal levels of mastication [14]. A recent study supports this possibility by showing that chewing gum reduced anxiety in response to an external stressor [45].

The proposed eating network and the mood network share areas of the brain that support a variety of functions, such as the cortical masticatory areas [46,47], the brainstem pattern generator for eating [17,48–50], the motoneurons related to eating [51], the orbitofrontal cortex [52], and the serotonin neurons that are involved with cognition,

emotion and aggression [28,29,53–55]. Given the shared neuroanatomy, we hypothesize that both positive and negative emotions can be caused by changes in eating behavior.

5. Mastication and the mind

We make up our mind before we do something; thought precedes action. The cause of eating disorders is often analyzed in a similar way; altered states of mind, such as anxiety and mood disorders are thought to predate and therefore cause eating disorders [3]. However, both events may have a common cause, and although mental states often correlate with behavior, the correlation is not necessarily causal. While research has suggested that state of mind and action can be dissociated experimentally [56], an individual is often convinced that a change of mind caused the change in behavior. The intention to act is taken for granted also when the behavior of others is considered; a mental cause is offered as an explanation even after the action has occurred [56,57]. The argument of mental causation is compelling, but on occasion the mind draws conclusions about cause-effect relationships that do not exist [56,57].

We suggest that mood changes in eating disorders are effects of disordered eating and the associated mental changes are state-dependent emergent properties. In fact, the evidence for the hypothesis that eating disorders are caused by pre-existing mental disorders [3] has been questioned in two comprehensive reviews [58,59]. We also suggest that the cognitive changes in eating disorders and during shortage of food are realistic; one should be concerned if little food is available and more concerned, perhaps even "obsessed" with food as the shortage persists. Mind and action need to be coupled; there are many clinical examples that patients feel out of control if they are not [56].

6. Why pharmacological treatment fails

The cell bodies of the serotonin neurons in the brainstem, which are part of the neural network for eating and emotion, express 5-HT_{1A} receptors [24], which mediate many of the effects of serotonin on emotion and cognition [24,29]. These receptors are the target of selective serotonin reuptake inhibitors (SSRIs), which are successfully used to treat depression and anxiety [24,29]. However, SSRIs are ineffective in treating either the disordered eating behavior, the depression, or the obsessive behavior typically associated with eating disorders [3]. SSRIs can unfortunately cause chewing disorders [60] probably by affecting the serotonin-innervations of the brainstem cholinergic motoneurons involved in chewing [51,61,62], perhaps further exacerbating the difficulties that anorexics have while eating and these drugs may therefore enhance, rather than alleviate anxiety and mood disorders in those patients.

Interestingly, the 5-HT_{1A} receptor has a role in the ontogeny of neural networks that support behavioral rhythms; stimulation of the receptor by SSRIs can disrupt normal development, thereby causing both rhythm disorders [63] and emotional disorders [64] in adulthood. These disorders are characterized by a slowing of the behavioral rhythm [63,64], exactly what is seen with the slowing of the eating rhythm in long term food restriction [14].

7. Testing the hypothesis

Because eating behavior has a proposed causal role in producing anxiety and mood disorders, varying the speed of eating and examining both dorsal raphe serotonin neuron activity and anxiety in experimental animals would test the hypothesis. Conversely, the hypothesis predicts that activity in the brainstem-to-cortex serotonin projections should have a minor effect or no effect on eating behavior. It is noteworthy, that the dorsal raphe serotonin pathways to the cortex, which have a central role in the present hypothesis, are sexually dimorphic [65]. Whether this sex difference is related to the marked sex difference in anorexia remains to be determined. Further testing of the hypothesis should involve studies on the interconnections among the raphe serotonin neurons in the brainstem and their projections to other brain areas engaged in eating, as well as the interrelation among the cortical areas involved with both mastication and mood.

Thus, the aim of the present hypothesis is to place eating behavior and mood into neurobiological context. Cognitive and emotional models of eating behavior, by contrast, often do not take the brain into consideration [66,67] postulating "cognitive processes" which control how people eat that are independent of physiology [23,68].

> "That such models may have little resemblance to the way the brain actually behaves is not seen as a serious criticism. If it describes, in a succinct way, some of the psychological data, what can be wrong with it? Notice, however, that by using such arguments, one could easily make a good case for alchemy or for the existence of phlogiston." [69]

The quote above [69] reminds us that models of behavior emancipated from neurobiology are at risk of creating both a dualistic problem and a validity problem. Cognitive explanations of eating disorders have not been fruitful and may continue unrewarded unless they relate realistically to the normal functions of the brain.

8. Implementing the hypothesis clinically

In line with the present point of view, re-learning how to eat normally is part of our treatment for eating disorders [70]. We have reported that practising eating at the default decelerated rate normalizes cognitive function [68] and validated our method clinically [71]. Importantly, practicing eating at a normal rate is a critical aspect of an effective method for treating anorexics, a method that not only normalizes the disordered eating behavior, but also eliminates the anxiety and depression associated with the disorder [70]. A reduced food intake is a cause not only of anorexia, but also bulimic behavior, because bulimics restrict their food intake until they cannot resist bingeing on available food [72]. Their disorder is similarly effectively treated by normalizing their disordered eating behavior [70]. The treatment has been found to be effective in a randomized controlled trial, bringing 75% of a group of 168 patients into remission in on average 14 months, and preventing relapse within one year in 93% of a group of 83 patients [70]. Regaining the proper pattern of eating appears to be the critical factor in the treatment. A randomized controlled trial comparing the outcome in a group of patients who practice eating at the normal decelerated rate [23] with the outcome in another group of patients who do not practise eating is an important step in translating the present hypothesis into clinical practise.

9. Limitations

This model, of course, does not inform us about the reason why the eating pattern becomes disordered in some individuals and not in others, nor does it explain how eating behavior fails to self-correct when it becomes disordered. Also, it does not account for the marked sex difference in the prevalence of eating disorders. At the same time, however, the model points to the successful intervention that is capable of normalizing both the disordered eating patterns and the disordered emotions that follow food restriction.

The neurobiological support for hypothesis presented here is derived from a mixture of animal and human studies and although the link between the two is not always possible to make, the comparative approach has proven particularly useful in the case of eating and the associated hedonic responses and moods [31]. In addition, there is a considerable amount of direct support from human studies that the serotonin innervation of the prefrontal cortex is involved in mood as outlined in the hypothesis, although activation of this neural substrate

was achieved in a different manner than chewing in these studies [73]. Obviously, as with any hypothesis, the present hypothesis is in need of testing.

Conflict of interest statement

C Bergh and P Södersten each have 28.35% and M Leon has 3% of the stock in Mando Group AB. The Section of Applied Neuroendocrinology, Karolinska Institutet, provides the research basis for the clinical work at Mando Group AB.

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