Physiology & Behavior 171 (2017) 13–20

Contents lists available at ScienceDirect

Physiology & Behavior

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

Review

The importance of the hypothalamo-pituitary-adrenal axis as a therapeutic target in anorexia nervosa

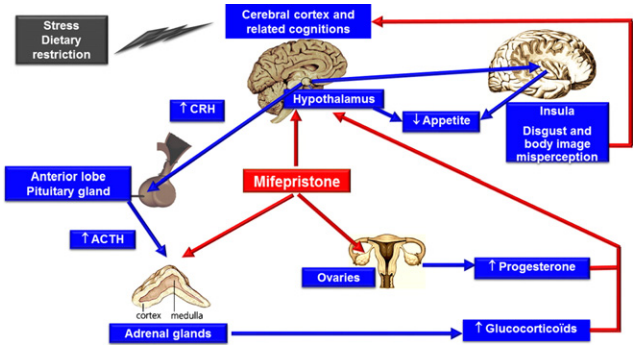
Rami Bou Khalil [a,*], Lama Souaiby [b], Nassim Farès [c]

[a] Hôtel Dieu de France, Department of psychiatry, Saint Joseph University, Beirut, Lebanon
[b] Saint Joseph University, Department of psychiatry, Beirut, Lebanon
[c] Saint Joseph University, Physiology and pathophysiology laboratory, PTS, Faculty of medicine, Beirut, Lebanon

HIGHLIGHTS

- A pharmacological approach to the treatment of anorexia nervosa (AN) is suggested.
- The hypothalamic-pituitary-adrenal (HPA) axis maintains AN pathophysiology.
- Insular and frontal functions generate negative emotions in patients with AN.
- Mifepristone (RU486) may counteract these mechanisms improving symptoms of AN.

GRAPHICAL ABSTRACT



The hypothalamo-pituitary-adrenal (HPA) axis plays a role in anorexia nervosa (AN) pathophysiology implicating that the progesterone and type II glucocorticoid receptor antagonist mifepristone (RU486) may have a potential therapeutic role in the treatment of this disorder. Dietary restriction, as well as other stressful life events, induces a hyperactivation of the HPA axis, leading, to the activation of the insular lobe on the one hand, and to the stimulation of the anterior pituitary gland by increasing plasmatic level of CRH on the other hand. Insular response leads to a decrease in appetite. This can also be modulated by the HPA axis leading to a further decline in food intake. In parallel, the enhanced secretion of adrenocorticotropic hormone (ACTH) leads to an increase in glucocorticoids concentration. Secreted neurosteroïds (glucocorticoids and progesterone) along with the hyperactivated insular lobe, are supposed to exert a negative feedback on the extent of activation of the HPA axis in non-anorectic individuals. However, this effect does not occur in patients with AN. Mifepristone (RU486) seems to act at the central and peripheral levels to modulate the deficiency in inhibiting HPA axis hyperactivation. CRH: Corticotropin releasing hormone; ACTH: Adrenocorticotropic hormone; (↑) increase; (↓) Decrease; Red arrow: Inhibition; Blue arrow: Stimulation.

ARTICLE INFO

Article history:
Received 9 October 2016
Received in revised form 26 December 2016
Accepted 27 December 2016
Available online 30 December 2016

Keywords:
Anorexia nervosa
Hypothalamo-pituitary-adrenal axis

ABSTRACT

Anorexia nervosa (AN) is an eating disorder, mainly affecting women, with a lifetime prevalence of about 1%, that can run a chronic course. While an effective pharmacotherapy is lacking, it is hypothesized that the progesterone and type II glucocorticoid receptor antagonist mifepristone (RU486) might be useful, as it is well known that the hypothalamo-pituitary-adrenal axis (HPA) is activated in AN. Even if secondary to the eating disorder, an active HPA axis may contribute to maintaining the neuroendocrine, emotional and behavioral effects observed in AN. More specifically, it is suggested that the HPA axis interacts with limbic structures, including the insular and prefrontal cortices, to uphold the changes in interoceptive and emotional awareness seen in AN. As such, it is proposed that mifepristone (RU486) reverses these effects by acting on these limbic regions. In conclusion, the

* Corresponding author at: Hôtel-Dieu de France, A. Naccache boulevard – Achrafieh, Beiruth, P.O. box: 166830, Lebanon.
E-mail address: ramiboukhalil@hotmail.com (R. Bou Khalil).

http://dx.doi.org/10.1016/j.physbeh.2016.12.035

Insula
Mifepristone
RU486

theoretical efficacy of mifepristone (RU486) in improving symptoms of AN should be tested in randomized clinical trials.

Contents

1. Introduction

Anorexia nervosa (AN) is a chronic psychiatric illness with a lifetime prevalence of approximately 1% in women and less than 0.5% in men [1]. The disease is characterized by an intense fear of weight gain and unremitting efforts to lose weight. It has significant psychological and medical complications [2] and almost all major organs are adversely affected as a direct result of weight loss and malnutrition. AN is one of the psychiatric diseases that have the highest mortality rates. Standardized mortality ratios show that the rate of death in AN is at least 5 times greater than that in the general population [3].

Although substantial advances in AN treatment occurred in recent years, the outcome of the disease is often poor, with a recovery rate of less than 50% [4]. However, an estimated rate of remission of 75% was obtained by normalizing eating behavior, physical activity and social habits in a large study [5]. There is some evidence supporting the efficacy of family-based interventions for adolescents with AN [6], but superior efficacy of this therapy over other therapy models has not been demonstrated [7,8]. In adults, no specific psychological approach has shown superiority [9] and interventions such as cognitive behavioral therapy (CBT-E), focal psychodynamic psychotherapy (FPP), specialist supportive clinical management (SSCM) and recently, Maudsley model of anorexia nervosa therapy for adults (MANTRA) are only moderately effective with respect to weight gain, recovery at 12-month follow-up and improvements in overall psychopathology of the disease [1].

To date, patients with AN do not benefit from effective drug treatment. Pooled meta-analyses failed to find a significant effect of antidepressants and antipsychotics for weight gain and relapse prevention [1]. Other drugs (ghrelin agonists, tumor necrosis factor and dronabinol) [10] and other interventions such as neuromodulation treatments [11,12] are under investigation but there is no evidence for their use at this stage.

Improved understanding of the role of some neuroanatomical structures in the pathogenesis of AN such as the hypothalamic-pituitary-adrenal (HPA) axis, limbic structures concerned with stimulus saliency, including the insular and frontal cortices, has given rise to the exploration of new drugs in this disease. The salience network (involving several limbic and paralimbic structures especially the anterior cingular cortex and the anterior insula) has the role of identifying, integrating and processing, among a myriad of internal and external stimuli, what is really relevant for interoceptive and autonomic regulation [13]. Here, we review the evidence suggesting a causal relationship among the HPA axis and the limbic system in the symptoms of AN. Subsequently, the findings will be linked to the potential efficacy of the progesterone and type II glucocorticoid receptor antagonist mifepristone (RU486) in modulating the hyperactivation of the HPA axis and improving AN symptoms. Throughout the text, the term "stress" designates a feeling of strain and pressure when individuals face threatening experiences and the term "distress" designates an aversive state accompanied with maladaptive behaviors in which an individual is unable to successfully cope with stress.

2. The role of the HPA axis activation in AN

Several studies have shown that AN involves a hyperactivation of the HPA axis [14,15]. In fact, patients with AN have significantly elevated 24 h concentrations of plasma cortisol, increased central corticotropin-releasing hormone (CRH) and significantly less cortisol suppression following dexamethasone than controls [16,17]. However, there is a difficulty in establishing whether the HPA axis abnormalities are related to starvation and weight loss or to AN itself. In fact, it has been demonstrated that weight loss, reduced caloric intake, and catabolic state have a powerful influence on the HPA axis. In their article, Gold et al. [18] found that abnormal changes in the activity of the HPA axis observed in patients with AN, including hypercotisolism, were reversed by body weight restoration. A more recent study confirmed the hypothesis in which the eating behavior, including food restriction, is viewed as a cause for the physiological and psychological changes of patients with AN [19]. Moreover, hormonal changes do not seem to be specific for AN and are found in other diseases or in healthy subjects as a consequence of malnutrition and starvation [20]. Patients who have malnutrition caused by diseases other than AN or induced by starvation in healthy subjects have elevated levels of plasma cortisol and reduced rate of cortisol metabolism, and these abnormalities seem to be reversed by weight restauration [21]. Of note, overall obesity also appears to be related to a HPA axis activation in many studies where acute reactivity to stress has been examined [22]. In addition, sex differences in response to stressful events appear to underlie the fact that females present a heightened HPA axis activation and a lack of sensitization in front of different stressful events [23,24]. However, cessation of ovulation could be an adaptive response to the shortage of food rather than a sign of pathology. In an earlier study, follicular maturation and ovulation were induced by synthetic LH-releasing hormone (LRH) in 4 patients with AN [25].

Stress and distress tolerance have been suggested as important factors in determining the onset and course of AN [26]. Severe life events often precede eating disorders and have been implicated in the pathophysiology of AN. Physical and psychological stress increases activity of the HPA-axis and adrenocorticotropic hormone (ACTH) gene expression with secondary anorectic effect [27]. In healthy individuals, glucocorticoid secretion induces anxiety, which is important and useful to cope with stressful events. However, this phenomenon becomes deleterious when stress becomes chronic and regulation mechanism of the