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Emerging role of autoantibodies against appetite-regulating neuropeptides in eating disorders

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Abstract

Objective: Recent findings of autoantibodies directed against melanocortin peptides suggest that these autoantibodies may represent a source of variability in peptidergic signaling that can be responsible for altered appetite and emotion in eating disorders. However, it is still unknown if autoantibodies directed against some other appetite-regulating neuropeptides and peptide hormones exist in healthy human subjects and if these autoantibodies can regulate appetite and emotion.

Methods: We determined the presence of autoantibodies against some key appetite-regulating neuropeptides and peptide hormones in sera of human subjects and in rats, and used animal models to study the role of α-melanocyte-stimulating hormone autoantibodies in food intake and anxiety.

Results: Immunoglobulin G and A autoantibodies against α-melanocyte-stimulating hormone, neuropeptide Y, agouti-related protein, ghrelin, leptin, and some other neuropeptides or peptide hormones involved in appetite control were present in healthy humans and rats. Animal models including active and passive transfer showed that α-melanocyte-stimulating hormone autoantibodies are involved in the regulation of feeding and anxiety. Sequence homology was found between neuropeptides and proteins from some members of intestinal microflora, whereas germ-free rats showed altered levels of autoantibodies directed against several neuropeptides.

Conclusion: Autoantibodies directed against appetite-regulating neuropeptides and peptide hormones are emerging as important participants in the peptidergic mechanisms controlling motivated behavior. Furthermore, these autoantibodies could provide a link in the gut–brain axis and may represent new biological targets for the diagnosis and treatment of eating disorders.

Keywords: Anorexia nervosa; Bulimia; Hypothalamus; Gut–brain axis; Neuropeptides; Autoimmunity; Microbiota

Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are two main forms of eating disorders characterized by a lack of physiologic control of appetite and disturbed emotions including high anxiety. The etiology of eating disorders is believed to be multifactorial, which signifies that the exact biological mechanisms responsible for development of these disorders are still poorly understood [1]. Nevertheless, neuropeptides may appear as key molecules involved in the pathogenesis of eating disorders based on numerous data showing that alterations of central and/or peripheral neuropeptidergic signaling are accompanied by disturbed regulation of body weight, appetite, or emotion as has been presented during 9th neuropeptide Y (NPY) meeting and reviewed in this issue [2–9].

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There is growing evidence implicating the immune system in normal brain functions and in neurologic disorders [10], where T-cells [11], proinflammatory cytokines [12,13], or autoantibodies (autoAbs) directed against neurotransmitter receptors [14,15] play important roles. This review summarizes recent data showing that the immune system might also be responsible for the appearance of eating disorders via altered production of autoAbs directed against neuropeptides involved in the regulation of appetite and emotion.

Initial finding of neuropeptide autoAbs in eating disorders

By applying sera from patients with eating disorders on rat brain sections and immunohistochemically detecting immunoglobulin (Ig) G binding, a distinct staining pattern characteristic for peptidergic neurons was found in the arcuate nucleus of the hypothalamus (Fig. 1). Using absorption of the patients' sera with several neuropeptides, α-melanocyte-stimulating hormone (α-MSH) was identified as the molecule responsible for immunostaining of these arcuate neurons. The same study also identified autoAbs directed against adrenocorticotropic hormone (ACTH) and gonadotropin-releasing hormone in the sera of several patients with eating disorders [16]. The logical suggestion that α-MSH autoAbs could only be associated with bulimia by a neutralizing satiety effect of α-MSH was not confirmed, because α-MSH autoAbs were detected in restrictive AN and in BN. However, an increased incidence of α-MSH and ACTH autoAbs binding to the rat brain and pituitary by sera from patients with eating disorders versus controls suggested that these autoAbs could be relevant to the mechanism of both eating disorders [16]. The importance of finding of α-MSH autoAbs in subjects with eating disorders is emphasized by the fact that α-MSH in the brain integrates several behavioral modalities including appetite and emotion [17], whereas activation of melanocortin receptors appears as the final common pathway for satiety signaling [18]. In addition, a follow-up study in patients with eating disorders and healthy controls identified the presence of autoAbs directed against oxytocin (OT) and vasopressin (VP) in their sera [19].

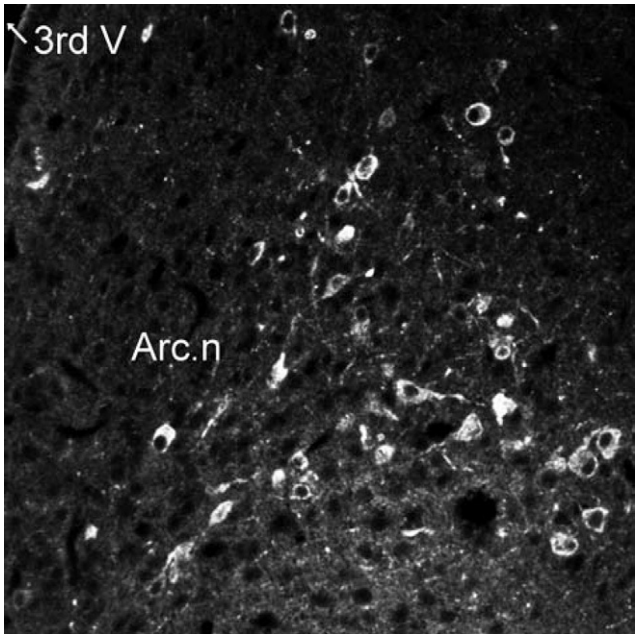

Fig. 1. Immunohistochemical detection of binding of immunoglobulin G autoantibodies from a patient with bulimia nervosa to a rat brain section at the level of the arcuate nucleus. Rats were pretreated with an intracerebroventricular injection of colchicine that elevated intracellular peptide levels, allowing visualization of neuronal cell bodies containing α-melanocyte-stimulating hormone. Arc.n, arcuate nucleus; 3rd V, brain ventricle III.

Link between α-MSH autoAbs and psychopathologic traits in eating disorders

To determine if neuropeptide autoAbs are associated with clinical symptoms of eating disorders, serum levels of autoAbs directed against α-MSH, ACTH, OT, or VP were measured by enzyme-linked immunosorbent assay in patients with restrictive AN or BN who had been evaluated by the Eating Disorders Inventory-2 scale (EDI-2) [20]. Significant correlations between the total EDI-2 score and levels of autoAbs directed against α-MSH, but not against other neuropeptides, were found in patients with AN and with BN, and this correlation was positive in AN but negative in BN [19]. Within the EDI-2, the subscale values for "drive for thinness," "bulimia," and "ineffectiveness" also significantly correlated with levels of α-MSH autoAbs, suggesting that these autoAbs might be associated with the appearance of the core psychopathologic traits characteristic for eating disorders. Importantly, levels of IgM α-MSH autoAbs also showed correlations with the EDI-2 values, but these correlations were opposite in patients with AN versus those with BN, suggesting that the IgG and IgM classes of these autoAbs might have opposite properties with regard to α-MSH signaling. Furthermore, serum levels of α-MSH IgM, but not of IgG autoAbs, were elevated in restrictive AN, pointing to their pathogenic role in the reduction of appetite. Interestingly, levels of autoAbs directed against different neuropeptides displayed correlations between each other (Fig. 2), suggesting that changes in levels of these autoAbs could be triggered by a common factor.

Furthermore, in contrast to the immunohistochemical detection, the serum presence of autoAbs directed against α-MSH, ACTH, OT, or VP was readily detected by enzyme-linked immunosorbent assay in healthy controls. This may signify that these autoAbs participate in thus far unknown physiologic mechanisms characteristic for peptidergic transmission. In fact, the phenomenon of autoAbs directed