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Lower serum activity of prolyl endopeptidase in anorexia and bulimia nervosa

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Abstract

The aim of this study was to examine whether anorexia and bulimia nervosa are accompanied by lower serum activity of prolyl endopeptidase (PEP;EC 3.4.21.26; post-proline cleaving enzyme), a cytosolic endopeptidase which cleaves peptide bonds on the carboxyl side of proline in proteins of relatively small molecular mass. Substrates of PEP are, amongst others, neuroactive peptides, such as arginine vasopressin, luteinizing hormone-releasing hormone, thyrotropin releasing hormone,α-melanocyte secreting hormone, substance P, oxytocin, bradykinin, neurotensin and angiotensin (Ag) I and II. Serum PEP activity was measured in the serum of 18 normal women, 21 anorexia nervosa and 21 bulimia nervosa women by means of a fluoremetric method. The Bulimic Investigatory Test, Edinburgh (BITE), the Eating Disorder Inventory (EDI) and the Hamilton Depression Rating Scale (HDRS) were scored. Serum PEP activity was significantly lower in patients with bulimia nervosa and anorexia nervosa, irrespective of the restricted or binging subtype, than in normal controls. There were significant and inverse correlations between serum PEP activity and the HDRS and BITE. In anorectic patients, but not in normal or bulimic patients, there was a significant correlation between serum PEP and body mass index. In bulimic patients, but not in normal or anorectic

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patients, there was a significant correlation between serum PEP and duration of illness. It is concluded that lowered serum PEP activity takes part in the pathophysiology of anorexia and bulimia nervosa. It is hypothesized that a combined dysregulation of PEP and neuroactive peptides, which are substrates of PEP, could be an integral component of eating disorders.

Keywords: Anorexia and bulimia nervosa; Peptidases; Prolyl endopeptidase; Peptides

1. Introduction

Prolyl endopeptidase (PEP; EC 3.4.21.26; post-proline cleaving enzyme) is a cytosolic endopeptidase which cleaves peptide bonds on the carboxyl side of proline in proteins of relatively small molecular mass (Walter et al., 1971; Kato et al., 1980a; Wilk, 1983; Moriyama et al., 1988; Goossens et al., 1996). PEP is widely distributed among different tissues and body fluids (Kato et al., 1980a; Wilk, 1983). High PEP activity is observed in muscle, testes, kidney and submandibular gland, and intermediate PEP activity in liver, thyroid gland, thymus and adrenal gland (Kato et al., 1980a). Several brain areas, and in particular the frontal cortex, show a relatively high PEP activity (Kato et al., 1980a; Wilk, 1983). PEP is suggested to be functionally involved in the regulation of intracellular protein turnover and in the degradation and processing of mature peptide hormones and neuropeptides (Mentlein et al., 1990; Welches et al., 1993). In this respect, PEP may modulate many neuropeptides which control the secretory function of the pituitary. Several behaviorally active peptides are substrates for PEP, e.g. arginine vasopressin (AVP), luteinizing hormone-releasing hormone (LH–RH), thyrotropin releasing hormone (TRH), α-melanocyte secreting hormone (α-MSH), substance P, oxytocin, bradykinin, neurotensin (NT), and angiotensin (Ag) I and II and maybe corticotropin releasing hormone (CRH) (Camargo et al., 1983; Lopez-Jaramillo et al., 1984; Nagaoka and Yamashita, 1985; Ward et al., 1987; Welches et al., 1993; Maes et al., 1994a).

As discussed previously (Maes et al. 1994a, 1995), PEP activity in the peripheral blood may be relevant to PEP peptidase activity in the brain. First, high PEP activity is observed in the central cortex (Kato et al., 1980b; Wilk, 1983) and in the hypophysial-portal plasma and median eminence (Lawrence et al., 1992). Second, in sheep, PEP is released from the vascular bed of the head and it is thought that the brain is a major source of PEP in the peripheral blood (Lawrence et al., 1992).

The above literature and findings, prompted us to investigate whether serum PEP is also lowered in eating disorders, such as anorexia and bulimia nervosa. First, there is a strong comorbidity between eating disorders and major depression. The latter is characterized by lowered serum PEP activity (Maes et al., 1994a). Second, eating disorders are accompanied by neuropeptide abnormalities which may indicate lowered serum PEP activity: (1) increased cerebrospinal fluid (CSF) vasopressin concentrations in bulimia nervosa and defects in the response of plasma vasopressin to intravenous hypertonic saline in anorexia nervosa (Gold et al., 1983; Demitrack et al., 1989); and (2) increased CSF CRH concentrations in anorexia nervosa and indi-