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Lowered Serum dipeptidyl peptidase IV activity in patients with anorexia and bulimia nervosa

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Abstract The aim of this study was to examine whether anorexia nervosa and bulimia nervosa are accompanied by lower serum activity of dipeptidyl peptidase IV (DPP IV, EC 3.4.14.5), a membrane-bound serine protease that catalyses the cleavage of dipeptides from the amino-terminus of oligo- and polypeptides. Substrates of DPP IV are, amongst others, neuroactive eptides, such as substance P, growth hormone releasing hormone, neuropeptide Y, and peptide YY. DPP IV activity was measured in the serum of 21 women with anorexia nervosa, 21 women with bulimia nervosa and 18 normal women. Serum DPP IV activity was significantly lower in patients with anorexia nervosa and bulimia nervosa than in the normal controls. In the total study group, there were significant and inverse relationships between serum DPP IV activity and the total scores on the Bulimic Investigatory Test, Edinburgh, the Eating Disorder Inventory (EDI) and the Hamilton Depression Rating Scale. In the total study group no significant correlations between DPP IV and age, body weight or body mass index could be found. It is concluded that lowered serum DPP IV activity takes part in the pathophysiology of anorexia and bulimia nervosa. It is hypothesised that a combined dysregulation of DPP IV and neuroactive peptides, which are substrates of DPP IV, e.g. neuropeptide Y and peptide YY, could be an integral component of eating disorders.

Key words Anorexia · Bulimia · Peptidases · Dipeptidyl peptidase IV · Neuropeptides

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Introduction

Dipeptidyl peptidase IV (DPP IV, EC 3.4.14.5) is a membrane-bound serine protease that catalyses the cleavage of dipeptides from the amino-terminus of oligo- and polypeptides under definite structural conditions (De Meester 1992, 1999; Hopsu-Havu and Glenner 1966; Van Hoof et al. 1992). DPP IV is widely distributed among human tissues and body fluids, including serum, the hypophysial portal system and the brain (Hopsu-Havu and Glenner 1966; Kato et al. 1978; Bernstein et al. 1987; Maes et al. 1994; Van Hoof et al. 1992). DPP IV has an important role in the processing of polypeptides and proteins, intestinal assimilation, renal handling of proline containing peptides,and adhesion and modulation of immune reactivity (Yaron and Naider 1993; Morimoto and Schlossman 1998; De Meester et al. 1999). The cleavage of peptides by DPP IV can result in activation, inactivation or in a changed activity of peptides (Heymann and Mentlein 1978). DPP IV can process neuroactive peptides (neuropeptides), such as substance P, growth hormone releasing hormone (GHRH), neuropeptide Y and peptide YY (Conlon and Sheehan 1983; Frohman et al. 1989; Mentlein et al. 1993; Zukowska-Grojec 1997).

On the T cell surface, DPP IV has been proven to be identical with the CD26 molecule and its expression is increased together with that of other activation markers, e.g. HLA-DR (Barton et al. 1990; Iwaki-Egawa et al. 1995; Mattern et al. 1991; Scholz et al. 1985). The origin of plasma DPP IV activity is, in part, determined by peripheral tissues, such as the liver, T lymphocytes, endothelial

cells and platelets (Kasahara et al. 1984; review: Scharpé et al. 1990). Both recombinant sCD26 and plasma sCD26/DPP IV modulate impaired immune responses to recall antigens probably by allowing antigen-specific T cells to exert maximal responses to their specific antigens; CD26 plays an important role in lymphocyte activation and production of cytokines, such as interleukin-2 (IL-2) and interferon-γ (IFNγ) (Ansorge and Schon 1987; Duke-Cohan et al. 1995; Reinhold et al. 1996; Schon et al. 1989; Tanaka et al. 1994; Schmitz et al. 1996; De Meester et al. 1999). Moreover, a number of cytokines, such as interleukin-1β (IL-1β) and IL-6, have a penultimate proline and are possible substrates for DPP IV (Van Hoof et al. 1995). Serum DPP IV activity is significantly decreased in inflammatory and autoimmune disorders, such as rheumatoid arthritis, autoimmune chronic hepatitis and systemic lupus erythematosus (Fujita et al. 1978; De Meester 1992); De Meester et al. 1993). Recently, we reported that serum DPP IV activity is significantly decreased in major depression (Maes et al. 1991, 1994, 1996, 1997). We have hypothesised that lower serum DPP IV activity could play a role in the immune pathophysiology of major depression, e.g. suppression of cell-mediated immunity and activation of the inflammatory response system with an increased production of proinflammatory cytokines, such as IL-1 and IL-6 (Maes et al. 1991, 1997).

The above mentioned findings prompted us to investigate whether serum DPP IV is also lowered in eating disorders, such as anorexia nervosa (AN) and bulimia nervosa (BN), which are accompanied by neuroendocrine and immune abnormalities possibly related to lowered DPP IV activity. Firstly, there is a strong comorbidity between AN or BN and major depression, which is accompanied by lowered serum DPP IV. Second, some of the neuroendocrine changes reported in eating disorders, such as increased cerebrospinal fluid neuropeptide Y concentrations in AN and increased peptide YY concentrations in BN (Kaye et al. 1990; Berrettini et al. 1988), may indicate lowered catabolism by DPP IV. There is also evidence that eating disorder patients have abnormalities in their GHRF-GH axis (review: Vaccarino et al. 1994). In AN, there is an exaggerated response to growth hormone releasing hormone, another substrate of DPP IV (Gianotti et al. 1999). AN patients show abnormalities in growth hormone secretion, such as elevated baseline GH levels and paradoxal GH rise after glucose or thyrotropin releasing hormone (review: Muller and Rolla 1996). Third, some of the immune disorders observed in AN and BN may also be related to lowered serum DPP IV activity. Peripheral blood mononuclear cells (PBMCs) of AN patients produce lower amounts of IL-2 (Bessler et al. 1993; Holden and Pakula 1996; Staurenghi et al. 1997) and interferon-gamma (IFN-γ) Polack et al. 1993; Schattner et al. 1990 b, 1992) than those of control subjects. When analysing lymphocyte subsets, slightly decreased CD4+ counts in patients anorexia and bulimia (Do Carmo et al. 1997; Fink et al. 1996; Marcos et al. 1997; Mustafa et al. 1997; Pirke et al. 1992; Allende et al. 1998) and significantly lower percentage and number of CD8+ lymphocytes (Fink et al. 1996; Marcos et al. 1997; Mustafa et al. 1997; Pirke et al. 1992) were found.

Based on the above, we anticipated to find lowered serum DPP IV activity in AN and BN and inverse correlations between serum DPP IV activity and the severity of eating disorders and depression in eating disorder patients. The specific aims of the present study were to determine whether lowered serum DPP IV occurs in AN and BN patients and whether serum DPP IV is inversely related to the Bulimic Investigatory Test, Edinburgh (BITE), the Eating Disorder Inventory (EDI) or to the Hamilton Depression Rating Scale (HDRS).

Materials and methods

Subjects

The subjects were 18 normal volunteers, 21 AN and 21 BN female outpatients with no history of previous hsopitalisation for an eating disorder. All patients met the DSM-IV diagnostic criteria for AN and BN (American Psychiatric Association 1994). The AN patients were classified in two subtypes: the «restricting» type who only lost weight through fasting and eventually rigorous physical exercises (n = 13) and the «binging» type of anorectics who (intermittently) showed episodes of binge-eating and/or self-induced vomitting and/or laxative use (n = 8). They were selected from consecutive clinic outpatients who came to the psychiatric ward of the University Hospital between June 1996 and January 1998. Table 1 shows the demographic data of patients and controls. Patients with other axis-I diagnoses beside AN and BN were excluded from this study. Not one of the subjects was taking oestrogens or other hormonal therapy. Not one of the patients or controls was a regular drinker or had ever been taking psychotropic drugs. Controls were screened for present, past and family history of psychiatric disorder by means of the Composite International Diagnostic Interview (CIDI, WHO 1987) and the Family History Re-

Table 1 Demographic data and serum dipeptidyl peptidase activity (DPP-IV) in women with anorexia nervosa (AN) or bulimia nervosa (BN) and in healthy controls

Groups	Age (yrs)	BW (kg)	Height (cm)	BMI (kg/m^2)	Duration of illness (yrs)	DPP-IV (U/l)	EDI Total Score	BITE Total Score	HDRS Total Score
Controls (n = 19)	22.8 (2.6)	59.1 (5.0)	163.2 (5.4)	22.2 (2.0)	–	34.4 (7.8)	23.6 (9.3)	4.3 (3.2)	1.1 (1.2)
AN (n = 21)	24.8 (6.7)	43.9 (6.1)	162.1 (6.9)	16.7 (1.9)	5.7 (5.9)	27.3 (14.7)	80.1 (22.3)	23.5 (9.6)	18.1 (7.8)
BN (n = 21)	23.1 (3.0)	54.2 (7.4)	158.8 (7.5)	21.6 (3.3)	5.1 (2.4)	22.7 (11.4)	99 (24.9)	38.1 (7.6)	15.0 (6.8)

All results are shown as mean (± S.D.)
See Results section for results of statistical tests

BW body weight; *BMI* body mass index; *EDI* the Eating Disorder Inventory; *BITE* the Bulimic Investigatory Test, Edinburgh; *HDRS* the Hamilton Depression Rating Scale

search Diagnostic Criteria (Andreasen et al. 1977). Controls with current or past history of psychiatric disorder and those with family history in first degree relatives were excluded from this study. All controls were medically healthy. Patients and controls had normal physical examinations, normal electrocardiograms, normal radiographs of lungs, normal values of blood and urine tests, such as SGOT, SGPT, GGT, hematocrit, serum electrolytes, thyroid function (e.g. basal TSH) and renal function tests (e.g. blood urea and creatinine). All subjects were free of i) drugs known to affect immune or endocrine function; and ii) chronic medical illness known to affect the immune or endocrine systems; iii) acute infectious, allergic or inflammatory reactions for at least 4 weeks prior to the study.

All subjects completed two self-report questionnaires. Firstly, the EDI is a 64-item, multiscale measure designed for the assessment of psychological and behavioural traits common in anorexia nervosa and bulimia (Garner et al. 1983). The EDI consists of 8 subscales measuring drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionsim, interpersonal distrust, interoceptive awareness and maturity fears (Garner et al. 1983). The 17-item HDRS was used to measure depressive symptomatology (Hamilton 1960). Second, also the BITE was completed as a self-rating scale for bulimia and binge-eating. The BITE is a 33-item self-report questionnaire, which is designed as an objective screening test for use in a wide variety of settings to identify subjects with symptoms of bulimia or binge-eating (Henderson and Freeman 1987). The questionnaire is divided into two subscales. The 'Symptom' subscale is made up of 30 items relating to symptoms, behaviour and dieting. The 'Severity' subscale contains six items measuring the severity of binging and purging behaviour as defined by its frequency, with a maximum possible score of 39. Threshold scores for clinical significance are a symptom score of 20 or more, a severity score of 5 or more and a combined symptom and severity score of 25 or above (Henderson and Freeman 1987).

Methods

Blood samples were collected in the morning between 8:00 and 10:00 a.m. Sera were separated from fasting blood samples and stored at –80 °C until thawed for enzyme activies. Serum DPP IV is determined by means of a colorimetric method using the chromogenig substrate glycyl-L-proline-p-nitroanilide tosylate (Gly-Pro-p-NA) (Nagatsu et al. 1976). The method was adapted for direct continuous measurement on the centrifugal analyser Cobas Bio (Roche Diagnostics, FRG). The sensitivity of the assay was 3.0 U/l. The conversion factors to transform the units (U) employed in this study to the SI units are as follows: 1 U/l corresponds to 16.67×10^{-9} kat/l, and 1×10^{-9} kat/l corresponds to 0.06 U/l. The sera of controls and patients were all assayed on the same day and in one and the same run. The analytical imprecision (i.e. the coefficient of variation, expressed as a percentage, CV%) of our DPP IV assay was CV = 2.2% (Maes et al. 1994).

Statistics

Group mean differences were examined by means of analysis of variance (ANOVA). Multiple comparisons between group means were checked by means of the Scheffe's test. Non-parametric tests, i.e. the Kruskal Wallis test and the Wilcoxon rank sum test, were employed when assessing the differences in serum DPP IV activity between the study groups. Relationships between variables were ascertained by means of Pearson's product moment or Spearman's rank order correlation coefficients. The level of significance was set at $P = 0.05$ (two-tailed).

Results

Table 1 shows that there were no significant differences in age between the three study groups (F = 1.0, df = 2/57, $P = 0.4$). There were significant differences in body weight between the study groups (F = 29.6, df = 2/57, $P < 10^{-3}$). Scheffe's test showed a significantly lower body weight in AN women than in normal ($P < 10^{-3}$) and BN ($P < 10^{-3}$) women. There were no significant differences in body weight between BN and normal women (Scheffe's test: $P = 0.07$). There were no significant differences in body height between the study groups (F = 2.7, df = 2/37, $P = 0.07$). BMI was significantly lower (F = 28.2, df = 2/57, $P < 10^{-3}$) in AN women than in controls (Scheffe's test: $P < 10^{-3}$) and BN (Scheffe's test: $P < 10^{-3}$) women. There were no significant differences (Scheffe's test: $P = 0.8$) in BMI between controls and BN patients.

In the total study group no significant correlations between DPP IV and age ($r = 0.06$, $P = 0.63$), body weight ($r = 0.03$, $P = 0.85$), body height ($r = 0.06$, $P = 0.6$) and BMI ($r = 0.03$, $P = 0.8$) could be found (intra-class correlations pooled over the three study groups). In AN women, there was a significant and inverse correlation between serum DPP IV and body weight ($r = -0.48$, $P = 0.02$) and BMI ($r = 0.57$, $P = 0.007$). In BN patients no significant correlations between serum DPP IV activity and body weight, body height or BMI could be detected. Table 1 shows also the duration of illness in both AN and BN patients. In AN and BN patients, no sognificant correlation could be found between serum DPP IV and duration of illness and age of onset of AN or BN.

Table 1 shows the serum DPP IV values in the three study groups. Kruskal-Wallis test showed significant differences in serum DPP IV between the study groups (Kruskal Wallis test or H statistic, H = 10.2, $P = 0.006$). There were significant differences between normal women and either AN ($P = 0.032$) or BN women ($P = 0.002$). Wilcoxon's rank sum test showed no significant differences in serum DPP IV between BN and AN patients. Figure 1 shows the scatter plot (with mean and SEM values) of the serum DPP IV values in the normal, BN and the two subgroups of AN women. There were significant differences in serum DPP IV between the four

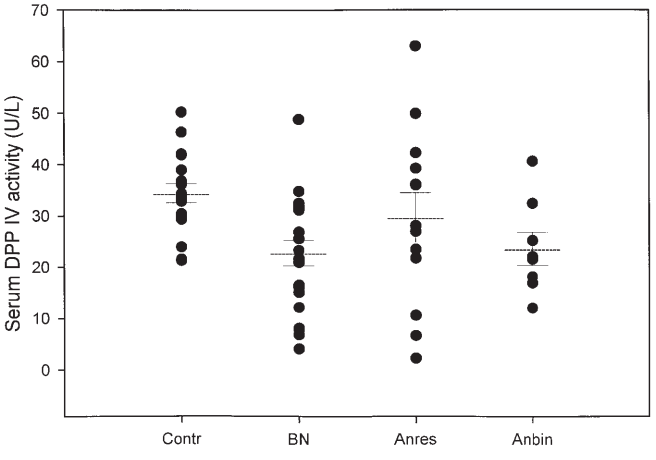

Fig. 1 Scatterplot (with mean and SEM) of serum DPP IV activity in normal women (Contr), women with bulimia nervosa (BN), anorexia nervosa restricting (Anres) and binging (Anbin) type

study groups (Kruskal Wallis Test statistic, H = 11.6, P = 0.009). Serum DPP IV was significantly lower in patients with AN binging type (P = 0.009), but not restricting type (P = 0.4), than in normal controls.

Table 1 shows also the mean EDI, BITE and HDRS values. Kruskal Wallis test showed significant differences in the EDI (H = 40.5, $P < 10^{-3}$), BITE (H = 45.2, $P < 10^{-3}$) and HDRS (H = 38.2, $P < 10^{-3}$) between the three groups. The EDI and BITE scores were significantly higher in AN ($P < 10^{-3}$) and BN ($P < 10^{-3}$) women than in normal controls and significantly higher in BN than AN women. The HDRS score was significantly higher in BN ($P < 10^{-3}$) and AN ($P < 10^{-3}$) women than in normal controls. In the subgroups of BN and AN women, no significant correlations between serum DPP IV and any of the rating scales could be found. In the total study group, there were significant and inverse relationships between serum DPP IV and the EDI (r = 0.26, P = 0.04), BITE (r = –0.40, P = 0.002) and HDRS (r = –0.38, P = 0.003) scores.

Discussion

To the best of our knowledge, this is the first report on decreased serum DPP IV activity in the serum of patients with AN or BN as compared with healthy controls. In addition, serum DPP IV activity was inversely related to measurements of disturbed eating behavior, such as the EDI and BITE. The lowered serum DPP IV activity in AN patients was attributable to significant decreased serum DPP IV activity in the binging, but not restricting, subtype of AN. There was also a significant inverse relationship between serum DPP IV and the HDRS score. This suggests an inverse relationship between serum DPP IV and the presence of mild depressive symptoms in both eating disordered patient groups. These results extend those of Maes et al. (1991) who found decreased serum DPP IV activity in major depressed patients. Previously, significant relationships between depressive symptoms and starvation, reflected by amongst other things body weight, were found in patients with anorexia nervosa or bulimia. Thus, Laessle et al. (1988) observed significant effects of body weight on depressive symptoms, such as depressed or dysphoric mood when controlling for severity of psychopathology of the eating disorder. We found that in AN women, there was a significant and inverse correlation between serum DPP IV and body weight and BMI. Since in our anorexia nervosa study group the BMI was relatively high, i.e. 16.7, a much lower serum DPP IV activity may be expected in more severely underweight anorectic patients. On the other hand, the negative correlations between serum DPP IV activity and body weight/BMI in anorectic patients could suggest that lowered serum DPP IV may be related to the effects of starvation. There is a considerable body of literature that weight loss in the previous hours, days or weeks causes considerable changes in neurotransmitters and neuroendocrinology (Pirke et al. 1993). Thus, it is possible that lowered serum DPP IV is not a cause but rather a consequence of an eating disorder. This could have been assessed by measuring free fatty acids and beta-hydroxybutyric acid in the subjects. On the other hand, lowered serum DPP IV was also detected in our BN patients, who had a normal BMI.

The possible causes for the decreased DPP IV activity in AN and BN have remained elusive. There are at least two different factors which could be related to lowered serum DPP IV activity in eating disorders. The production rates of both transforming growth-factor-β (TGF-β) and tumor necrosis factor-alpha (TNFα) are significantly increased in AN and BN (Mc Murray et al. 1981; Pomeroy et al. 1994; Schattner et al. 1990a, 1990b, 1992; Vaisman et al. 1990). Both these cytokines may inhibit DPP IV mRNA expression in renal tubular epithelial and carcinoma cells or the expression of DPP IV enzyme activity (Kehlen et al. 1998; Riemann et al. 1995). In AN, serum concentrations of TGF-β are significantly elevated during starvation and return to levels comparable to those of normal-weight controls by the end of therapy (Pomeroy et al. 1994). TGF-β is an antiinflammatory cytokine which halts immune responses (Ruscetti and Palladino 1991; Sporn and Robert 1989). Some (Vaisman and Hahn 1991; Schattner et al. 1992), but not all, authors (Brambilla et al. 1998) found significant increases in serum levels, and the spontaneous or stimulated production of TNFα in eating disorder patients. Following refeeding and nutritional rehabilitation of AN patients, TNFα production normalised concomitantly with weight gain (Vaisman and Hahn 1991). TNFα is a proinflammatory cytokine that has been implicated as mediator of cancer-associated cachexia (Grimble 1989; Vassalli 1992). Because of the physical similarities between the cachexia observed in many patients with cancer and the weight loss seen in AN, it has been assumed that TNFα might contribute to the aetiology of AN. It is also thought that increased TNFα production may be secondary to hyponutrition, but that increased TNFα production may further suppress food intake and enhance tissue catabolism (Schattner et al. 1992). Thus, one hypothesis is that lowered DPP IV activity in eating disorder patients may be related to the increased production rate of TGF-β and TNFα in that illness.

In theory, lower DPP IV activity may play a role in the immune alterations and in the neuroendocrine disorders in AN and BN. Firstly, the diminished production of the Th-1-like cytokines, IL-2 and IFN-γ, in AN and BN may be the consequence of reduced DPP IV/CD26 activity. Indeed, serum sCD26/DPP IV is apotent T cell costimulator, which plays an important role in lymphocyte activation as well as in the production of Th-1-like cytokines, such as IL-2 (Ansorge and Schon 1987; Duke-Cohan et al. 1995; Reinhold et al. 1996; Schon et al. 1989; Tanaka et al. 1994). Thus, at least three factors may play a role in the defects in Th-1-like cytokine production, i.e. the deficiency in nutritional factors necessary for a normal immune response, neuroendocrine disorders, such as increased cortisol production (Armstrong-Esther et al. 1978; Cason et al. 1986; Herzog 1984) and lower serum DPP IV activity. Pomeroy et al. (1994) showed that the serum concentrations of IL-6 are increased in untreated AN patients.

These findings may also be explained by lowered DPP IV activity since IL-6 is another possible substrate for DPP IV (Van Hoof et al. 1995).

Second, lowered serum DPP IV activity may also explain the increases in the concentrations of neuropeptide Y and peptide YY in eating disorders (Kaye et al. 1990). Neuropeptide Y has been implicated in the regulation of food intake and body weight (review: Marsh et al. 1998). Neuropeptide Y has a physiological role as an integrator of different adaptive behaviors such as diet restriction, extending its action to inhibition of sexual functions and anabolic processes (Catzeflis et al. 1993). Injections of neuropeptide Y into the hypothalamus promotes feeding behavior and enhances locomotor activity (Ruffin et al. 1997). Thus, increased neuropeptide Y activity in AN may contribute to several characteristic disturbances in AN, such as menstrual dysregulation (Kaye et al. 1990) and locomotor activity. Central injection of peptide YY produces one of the most powerful stimulating effects on food intake in rats (Hagan et al. 1998). It has been suggested that increased brain peptide YY activity could contribute to bulimic binge-eating (Hagan and Moss 1995). Increased growth hormone (GH) in AN and BN (Kiriki et al. 1987; Levy 1989; Maeda et al. 1987; Travaglini et al. 1976) can also be explained by decreased DPP IV activity, since the latter is responsible for the plasma degradation of growth hormone releasing hormone (GHRH) (Van Hoof et al. 1992). Thus, decreased DPP IV activity in eating disorder patients may contribute to the neuroendocrine and subsequent behavioural alterations in those patients through diminished breakdown of neuroactive peptides, such as neuropeptide Y and peptide YY.

Some limitations of the present study are the following: 1) the sample size of the three study groups is rather low and, therefore, some of the conclusions are restricted; and 2) some variables have a high variability, e.g. BMI in the anorectic patients. Nevertheless, the results of the present study be consistent with the hypothesis of a combined dysregulation of neuroactive peptides, such as neuropeptide Y and peptide YY, cytokines and DPP IV as an integral component of eating disorders. Future research should focus on the consequences, if any, and causes of lowered serum DPP IV activity in AN and BN. More specifically, the putative causal relationships should be explored between DPP IV and (1) the production rate of TNFα and TGF-β, (2) the production of IL-2 and IFNγ; and (3) the levels of neuroactive peptides related to the pathophysiology of eating disorders, such as neuropeptide Y and peptide YY.

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