

REVIEW

Prolidase

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ABSTRACT

Prolidase (EC.3.4.13.9) or proline dipeptidase, is one of the unique enzyme capable of degrading dipeptides, in which a proline or hydroxyproline residue is located at the C-terminal position. Prolidase has a unique function in all cell types; therefore, the mechanisms and parameters involved in prolidase activity regulation are of special interest. Could prolidase be a good biomarker in different physiologic and pathologic conditions? This is an important question. There is no consensus on the answer to this question. It is of great importance during collagen turnover, inflammation, tissue fibrosis and skeletal abnormalities.

Prolidase itself without other biochemical markers may not provide information to clinicians about disease activity. So, I think it should be evaluated together with other serum biochemical markers.

This review will serve to discuss many in vivo functions of prolidase, as well as level prolidase activity in diagnosis and monitoring of treatment in the various diseases (Ref. 50). Text in PDF www.elis.sk.

KEY WORDS: prolidase, imidodipeptidase, proline dipeptidase.

Introduction

The prolidase (EC 3.4.13.9) is a ubiquitous dipeptidase, which cleavages iminodipeptides containing carboxyterminal proline or hydroxyproline and it plays an important role in collagen metabolism matrix remodelling and cell growth. Glycyl-proline is the best substrate for the prolidase (1). It is a manganese requiring homodimeric enzyme (subunit $M_r \approx 54.3$ kDa). The existence of prolidase has been known for about 75 years. The human prolidase gene is on the short arm of chromosome 19, region 19q12→19q13.2 (PEPD gene), which spans over 130kb and consists of 15 exons (2–4).

Prolidase, also known as Peptidase D, has been found in various mammalian tissues and also in microorganisms. It is a cytosolic enzyme and it was purified from several sources, including human erythrocytes, fibroblasts and different strains of bacteria (1). The enzyme activity is relatively high in kidneys, intestinal mucosa and erythrocytes, while it is low in plasma and liver. The plasma prolidase activity is about 6% as great as in erythrocytes enzyme activity (3).

Boright et al has been reported that human fibroblast subunits and erythrocytes prolidasases are similar in size (2). It has been reported that two forms of prolidase (I and II) have been isolated from normal human erythrocytes, leukocytes and cultured skin fibroblasts (5). Purified from human erythrocytes, prolidase I and II were found with different molecular mass (prolidase I: 56kDa and prolidase II: 95kDa in SDS–PAGE). On the other hand; response to

manganese, substrate specificity and heat stability was detected to be different in those two enzymes (6). Prolidase is a metalloprotease and requires divalent cations such as Mn(II), Zn(II), or Co(II) in their active site for its activity. The human prolidase requires Mn(II) in vitro assay and reducing conditions for activity, although the metal composition of the catalytic centre is still unknown (7).

It was shown that human recombinant prolidase, demonstrated by inductively coupled plasma mass spectrometry (ICP-MS) and by X-ray absorption spectroscopy (XAS), in solution of two different metals, Mn(II) and Zn(II), both could be simultaneously present in the enzyme (8).

Prolidase deficiency

Prolidase deficiency (PD) is an autosomal recessive disorder characterized by massive imidodipeptiduria and elevated proline-containing dipeptides in plasma with variable symptoms, including skin lesions, recurrent infections, mental retardation and abnormalities of collagen tissues. It is a rare disorder with an estimated incidence of 1–2 per 1 million births (9, 10).

Mental retardation has been shown in most cases of prolidase deficiency. The proline concentration is decreased in central nervous system during this disease. Proline has an important role in the modulation of glutamatergic neurons in the central nervous system. Therefore, decreasing the concentration of proline, may disturb the function of glutamatergic neurons in prolidase deficiency (1).

Prolidase deficiency particularly affects the main component of collagen of the connective tissue; therefore skin lesion is one of the clinical symptoms of prolidase deficiency. The pathogenetic mechanism leading to the skin changes is not well understood (1).

Various diagnostic techniques have been developed for the detection of imidodipeptides in the urine in prolidase deficiency.

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However, confirmation of the diagnosis requires the measurement of the enzyme activity in erythrocytes, leukocytes or fibroblasts in culture and/or sequence analysis of the PEPD gene (11).

Endo et al had compared the biochemical and clinical phenotypes in eighth patients with clinical symptoms of prolidase deficiency. They had shown that no apparent relation between the clinical symptoms and the biochemical phenotypes except that mental retardation was present in the polypeptide negative patients (10).

The molecular basis in prolidase deficiency are mutations. Several mutated alleles were found in the prolidase gene. That mutated alleles products cannot be to active form or expose rapid degradation (12).

Mitsubichi et al analyzed PEPD in the patients with prolidase deficiency and they have noted that an abnormal mRNA with the skipping of a 192-bp sequence corresponding to exon 14 lymphoblastoid cells was taken from these patients. This mutant prolidase was enzymatically inactive (13).

It has been found that there was an increase in rapidly degraded collagen in fibroblast cultures from prolidase deficient patients and decrease in proline pool in comparison to control cells (14).

It has been reported that an association might have been between prolidase deficiency and systemic lupus erythematosus (SLE) in literature (9, 15). Prolidase deficiency could be a risk factor for the development of SLE. Both of them are associated with disturbances in immune function and have many clinical features in common (16). Additionally, in one case, the association between an enzyme deficiency and a multisystemic hereditary disorder such as lupus and rhus had been illustrated (17).

The kinetics of the activities of healthy subject's prolidase I, II and patient enzyme with prolidase deficiency were analysed. It had been detected that Km values were changed by adding sulfur containing amino acids, however, Vmax values were unchanged (5).

Much of the work has to be done before the role of prolidase in metabolism of various tissues will be understood and before an effective treatment of prolidase deficiency will be developed.

The relationship between prolidase activity and collagen metabolism

Extracellular collagenases initiate the breakdown of collagen, but the final step of its degradation is mediated by prolidase. This cytosolic enzyme specifically splits imidodipeptides with C terminal proline or hydroxyproline, which together contribute to 21% of collagen. Therefore, an increase in the enzyme activity is believed to be correlated with the increased intensity of collagen degradation. On the other hand, prolidase activity may be a step-limiting factor in the regulation of collagen biosynthesis.

The relationship between prolidase activity and collagen metabolism was investigated in various studies.

Increased levels of the prolidase activity has been shown in some disorders, which are characterized by excessive collagen turnover. High levels of the prolidase activity were detected in both hypertension and erectile dysfunction. An increased collagen deposition in the blood vessels of these patients is leading to the side effects (18, 19).

Hip dysplasia is a common congenital abnormality that affects the development of the hip joint in newborns. The prolidase activity in patients with hip dysplasia was found significantly higher than the control group. In addition, a positive correlation was detected between the prolidase activity and dysplasia level (20).

It was hypothesized that the increased prolidase activity related to collagen turnover may be associated with etiopathogenesis and/or the progression of these diseases.

Serum prolidase activity (SPA) has been compared in ankylosing spondylitis (AS), rheumatoid arthritis (RA) and control groups. The SPA of AS patients were statistically significantly lower than in the RA and control groups ($p < 0.05$). On the other hand, the enzyme activity in the RA group was not statistically significantly different than in control group ($p > 0.05$). According to the results of this study, the following comment can be made; lower SPA is probably associated with a decreased collagen turnover and fibrosis, which is related to the decreased physical functions in both of these chronic inflammatory musculoskeletal diseases (21).

Prolidase activity is known to be positively correlated with the turnover of collagen. We investigated the serum and erythrocytes prolidase activity in healthy mothers, in the cord blood of their newborn babies and non-pregnant controls. There was no significant difference in the enzyme activities between healthy mothers and the control group ($p > 0.05$). However, the enzyme activities in cord blood were significantly lower than in the control group ($p < 0.001$). Additionally, there was a significant correlation between maternal and cord blood serum prolidase activity. Otherwise, cord blood enzyme activity was positively correlated with birth weight. It was concluded that prolidase activity may reflect foetal growth (22).

Vural et al compared the maternal serum and placental tissue levels of prolidase enzyme activity in women with early pregnancy loss with those women, who underwent elective dilatation and curettage. An inverse relationship of serum and placental levels of prolidase activity was demonstrated. Placental utilization of the enzyme may explain the low prolidase activity. They concluded that collagen turnover was increased in patients with early pregnancy loss and might be an etiopathological factor of this disease (23).

Because prolidase activity would need to increase in order for collagen degradation and synthesis to increase, monitoring of prolidase activity levels could be a way to achieve an earlier and more definitive diagnosis in some of these conditions. The connection between prolidase and collagen metabolism can be better understood by studying prolidase deficiency.

Fibrosis and prolidase

Hepatic fibrosis or cirrhosis is caused by an increased synthesis and storage or decreased breakdown of extracellular matrix elements, especially collagen. Prolidase is required for collagen breakdown and re-synthesis. It has an important role in the breakdown of intracellular protein as well, and at this time it is activity is increased.

The measurement of prolidase in serum may reflect the activity of liver fibrogenesis. It may be a marker with the potential for

diagnosis and therapeutic control. However, it is very important to note that circulating biochemical markers of fibrogenesis, fibrolysis or both may not reflect hepatic fibrosis or cirrhosis, since they are not liver-specific. Thus, the best diagnostic approach would be the identification and measurement in serum of the driving force of fibrogenic process.

Liver biopsy is a gold standard method to show changes in the liver. However, it is an invasive method. Measurements of serum connective tissue proteins and some enzymes can reflect the fibrosis in liver by showing progression of disease and efficiency of treatment on fibrosis. It has been suggested that plasma prolydase activity might be useful in evaluating fibrotic processes in chronic liver disease in humans. However, studies on this subject could not support this hypothesis.

Myara et al did not find any correlation between prolydase activity and some routine laboratory test results of liver function. On the other hand, plasma prolydase activity and liver histology were not correlated in cirrhotic patients. It was detected in the early stage of fibrosis, plasma prolydase activity might be high and might subsequently drop in advanced fibrosis. Therefore plasma prolydase activity did not seem to be a good marker for chronic liver dysfunction (3).

Increased prolydase activity was observed in chronic hepatitis infection, in which increased collagen turnover has already been known. Results have indicated that prolydase levels are higher in inactive hepatitis B infection than those in CHB. But there was no correlation between histopathological evaluations of liver biopsies of CHB patients and the prolydase activity (24).

Studies have shown decreased prolydase activity in fibrosis. Sezen et al has detected lower prolydase activity than in control group in idiopathic and ischemic dilated cardiomyopathy patients groups. These patient groups exhibit the same histopathological feature of fibrosis (25). A decreased prolydase activity was shown in advanced chronic obstructive pulmonary disease. The airway tissue gradually becomes fibrotic during which collagen turnover slows in this disease (26).

In conclusion, serum prolydase activity was not shown to be a noninvasive biochemical marker to fibrosis in clinical practice because it can be affected by many factors.

Osteoporosis and prolydase

The alteration in prolydase enzyme activity is believed to be correlated to an increased intensity of collagen degradation and may be a useful tool in diagnosis and / or monitoring osteoporosis.

We detected that the serum prolydase activity was neither significantly different in postmenopausal osteoporotic group nor correlated to other bone turnover markers. In addition, urinary Dpd/creatinine and serum Pi levels of postmenopausal osteoporotic group were significantly higher than in the control group (27).

In addition, we observed that a significant decrease was in SPA in non osteoporotic diabetic patients, compared to osteoporotic diabetic patients and healthy controls, which may be interpreted as evidence of decreased bone resorption. Urinary Dpy excretion was not different between osteoporotic and nonosteoporotic diabetic pa-

tients. Our data also suggested that serum prolydase activity might be a better marker of osteoporosis in diabetic state than Dpy (28).

In Verit's study, it was found that there was no statistically significant difference in SPA in the postmenopausal osteoporotic women when compared to postmenopausal nonosteoporotic and premenopausal nonosteoporotic controls (29).

Toker et al reported that serum prolydase activity was slightly decreased in the postmenopausal osteoporotic group but it was not statistically significantly different from the nonosteoporotic group (30).

As the result, prolydase is a marker of bone turnover, but SPA was not correlated with the bone turnover markers and bone mineral density in postmenopausal osteoporotic women, for that reason SPA may not reflect bone turnover alteration in the menopause patients. Prolydase itself without other biochemical markers may not provide information to clinicians about osteoporosis. So, we think that it should be evaluated together with other serum biochemical markers.

Oxidative stress and prolydase

It was detected that NO has an important role in the regulation of collagen metabolism, but the mechanism linking collagen and NO was not understood well (31).

It was believed that prolydase may also be regulated by NO in enhanced collagen turnover, such as bladder cancer. Serum prolydase activity and oxidative stress parameters NO, MDA levels were detected significantly higher in bladder cancer than in controls, while TAS levels were found significantly lower (32).

It has been detected that a positive correlation was present between serum prolydase activity and total antioxidant capacity in the asthma patients. Furthermore, no correlation was found between enzyme activity and oxidative levels. At the same time, serum prolydase activity was determined as a statistically significant difference in the asthma patients compared to the control group (33).

Prolydase activity was determined significantly higher in intrauterine foetal growth restriction (FGR) subjects compared to the control group. On the other hand, serum prolydase activity and oxidative stress were significantly associated with the presence of FGR (34).

Duygu et al suggested that the values of prolydase and the oxidative stress are increased while the antioxidant levels are decreased in chronic hepatitis C and they proposed that prolydase enzyme and oxidative damage might have an association with the HCV infection becoming chronic (35).

Diabetic neuropathy (DN) is a common and debilitating complication of diabetes mellitus associated with multiple connective tissue changes in many organs. Uzar et al investigated prolydase activity in DN patients with the idea that collagen deposition might be increased in microvascular disease in these patients. They found that an increase in prolydase activity was at a highly significant level in the DN patients, in comparison with both diabetics without neuropathy and the control group. However, serum TOS levels were significantly higher in diabetic patients with or without neuropathy than in controls. In addition, a relationship between

prolidase activity and electrophysiological abnormalities in DN patients has been found and it may be interpreted as an evidence of increased collagen turnover in the DN (36).

On the other hand, Sayin et al determined a significantly lower prolidase activity in the DN patients than in controls while serum MDA and NO levels were significantly higher. Prolidase activity was found negatively correlated with NO and MDA, but positively correlated with TAS in the DN patient group (37).

Collagen and glycosaminoglycans, elastin, a hydrophobic ECM protein is an important component of the uterus. Vural et al has investigated oxidative stress markers and prolidase activity in serum and tissue samples of women with uterine fibroids. Ceruloplasmin, catalase, arylesterase, free sulfhydryl group and prolidase activities were detected higher in fibroid tissue than those in myometrial tissue. In addition, serum levels of catalase and prolidase were found lower, and arylesterase and free sulfhydryl groups were higher in the fibroid group than those in the control group (38).

Fitowska et al demonstrated a significantly higher SOD and glutamate dehydrogenase activity in patients with hip osteoarthritis, also prolidase activity had been increased in this patients group compared with the control one (39).

Psoriasis is a chronic, systemic and an inflammatory disorder of the skin. Güven et al concluded that patients with psoriasis exhibit higher serum prolidase activity independent of gender, BMI, disease severity or duration, type of treatments or NO level (40).

In renal cancer patient's serum, prolidase activity and MDA levels were detected significantly higher than in controls (all, $p < 0.05$), while SOD, GSHPx, and GST levels were found significantly lower ($p < 0.05$). The results indicated that an increased prolidase activity might be related to increased oxidative stress along with decreased antioxidant levels in renal cancer (41).

Hilali et al detected that serum prolidase activity, TOS and OSI were significantly higher in patients with polycystic ovary syndrome (PCOS) than controls. It has been found that prolidase activity was positively correlated with TOS, follicle number and prolactin levels in the patients. It has been known that women with PCOS have increased cardiovascular risk. It might be hypothesized that elevated serum prolidase activity and oxidative stress might be associated with an increased cardiovascular risk in that patients (42).

It was shown that prolidase activity was lower in the cholesteatomatous group compared with the noncholesteatomatous group while serum TOS and OSI levels were significantly higher in both the cholesteatomatous and noncholesteatomatous patient groups compared with the control group (43).

It is known that glutamate excitotoxicity and oxidative stress have a critical roles on the pathogenesis of Alzheimer's disease (AD). Prolidase is an essential cytosolic enzyme, specifically in the recycling of proline for collagen synthesis and it has been shown that elevated proline levels increased glutamate concentration. The prolidase activity and the TOS levels were found statistically significantly higher in the AD group as compared to the control group. Total antioxidant status level was detected significantly lower in the dementia group than in the control group. In addition,

a negative correlation has been shown with prolidase and the TOS levels while a positive correlation with the TAS levels (44).

A cross-sectional study showed that joint hypermobility syndrome was associated with inguinal hernia in children and that increased prolidase activity and oxidative stress in tissue samples from patients with joint hypermobility syndrome were related to collagen tissue damage and turnover (45).

Prolidase activity was detected significantly lower in the systemic sclerosis (SSc) patients than controls. In addition, oxidative stress was increased in SSc. TAS was decreased in the patients with lung and gastrointestinal tract involvement. According to these results, the TAS may be a marker that predicts the risk of involvement of a specific organ and prolidase may be a marker of SSc and antioxidant treatment may be useful and it may also prevent organ involvement in SSc (46).

In acute hemorrhagic stroke, patient's significantly lower serum TAC levels and catalase activity than controls were found. However, the NO, TOS levels and prolidase activity were significantly higher compared with controls (47).

Vural et al evaluated oxidative stress markers and prolidase activity in the amniotic fluid of fetuses with a neural tube defect (NTD) compared to the amniotic fluid of normal fetuses. Prolidase activity, TOS and OSI of amniotic fluid from fetuses with the NTD were significantly higher compared to controls, whereas TAS was significantly lower. Levels of the prolidase activity and oxidative stress were increased in the amniotic fluid of fetuses with NTD. It was concluded that these indicators may be as useful as biomarkers for the diagnosis of this disease (48).

Behçet's disease (BD) is characterized by recurrent oral aphthae, skin lesions, eye lesions, and genital ulceration. Serum prolidase activity has been detected significantly higher in the BD patients with active disease compared with the inactive and control group. Serum TAS levels were significantly lower in BD patients in comparison with healthy controls while MDA, TOS, and OSI levels were all significantly higher in the BD group when compared with the healthy controls (49).

Although prolidase and ROS were found to play an important role in the pathogenesis of various diseases separately, most basic questions still remain unanswered: What factors are involved in prolidase activity regulation? Is there a relationship between the prolidase activity with production of the ROS?

It was showed that prolidase activity and collagen biosynthesis were stimulated by NO in fibroblasts. This effect of NO on enzyme activity was detected at post-translation modification level of prolidase. Increase in the prolidase activity was due to increase phosphorylation on serine/threonine residue in the enzyme (31).

Recently, it was determined that in the presence of NO, the prolidase activity increases but prolidase expression remains unchanged (50).

Conclusion

Prolidase is a cytosolic imidodipeptidase, which specifically cleaves imidodipeptides with C-terminal proline or hydroxyproline. The imidodipeptides are derived from intracellular degra-

dation of collagen, other proline-containing proteins and dietary proteins. Intestinal hydrolases cannot split the inherent tertiary amide bonds, therefore, termination of ingested protein degradation take place intracellularly.

It has been documented that prolidase activity changes in several diseases. An increase or decrease in prolidase activity can indicate not only the presence of a disease state, but also progression of the condition.

Although the role of prolidase in pathobiochemistry of the disorders is not well understood, it seems that prolidase-dependent regulation of transcription factors activity may be an underlying mechanism.

I believe that these findings will evaluate further studies about prolidase activity in different physiologic and pathologic conditions.

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