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On the Mechanism of Action of Prolylcarboxypeptidase

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1. Introduction

Many mechanisms are involved in the regulation of blood pressure. Among the molecules, hormones, and factors known to be involved in blood pressure regulation, PRCP can generate the most potent inflammatory vasodilator molecules, including nitric oxide (Zhao et al., 2001c), prostaglandins (Kolte et al., 2011), bradykinin (BK)-(Chajkowski et al., 2010) and angiotensin 1-7 (Ang₁₋₇)-(Mallela et al., 2008) dependent pathways in the endothelium and astrocytes. Experimental evidence suggest that PRCP appears to metabolize its main substrates, des-Arg⁹-bradykinin (des-Arg⁹-BK, BK₁₋₈)(Chajkowski et al., 2010) and alpha-melanocyte stimulating hormone 1-13 (α -MSH₁₋₁₃)(Wallingford et al., 2009), to prevent the production of prostaglandins and NO, indicating that the enzyme may promote anti-inflammatory effects in cardiovascular and cerebrovascular systems. Evidence shows that *Prcp* gene expression is elevated in the developing murine brain vasculature during the intermediate phase of chick chorio-allantoic membrane (CAM)(Javerzat et al., 2009), suggesting that PRCP has a role during the active phase of vascular remodeling. Interestingly, *Prcp* gene is overexpressed in glioblastoma and it is suggested that PRCP also has a role in tumor angiogenesis(Javerzat et al., 2009). Thus, PRCP plays important roles in response to stress and may be an endothelial gate-keeper regulating blood flow, which tightly regulates endothelial barrier function. The historical perspective of knowledge of PRCP and its roles in physiological and cardiovascular diseases such as inflammation, hypertension, thrombosis, and obesity is tabulated in Table 1.

2. Cardiovascular system function

The cardiovascular system is composed of the heart, blood, and a complex network of blood vessels. Humans have a closed cardiovascular system in which the system allows a complete separation of function and blood loss due to having a relatively low blood volume compared to species with open cardiovascular systems. In a closed cardiovascular system, blood flows rapidly from arteries to capillaries and returns through the venous system. The heart sustains the high pressure necessary for the blood to reach the body's tissues.

Year	References
1971	Human PRCP (EC 3.4.16.2) was found in biological fluids (Sorrells and Erdos, 1971)
1978	PRCP was purified from human kidney and its potential substrates was reported. The two substrates were angiotensin II, and angiotensin III (Ody et al., 1978)
1981	A novel and rapid radioassay for PRCP was developed (Skidgel et al., 1981)
1981	PRCP was found in both inflammatory exudates and in cells that appear at sites of inflammation (Kumamoto et al., 1981)
1990	Cultured Madin-Darby canine kidney (MDCK) distal tubular cells was found to contain PRCP (Deddish et al., 1990)
1993	Human PRCP was sequenced and cloned. It was noted that PRCP might have both exopeptidase and endopeptidase activities (Tan et al., 1993)
1994	PRCP was found to have a modulatory role in the angiotensin II-induced pulmonary vasoconstriction (Tamaoki et al., 1994)
1995	PRCP was found in monkey kidney (Suzawa et al., 1995)
1995	PRCP was purified from cell free extracts of <i>Xanthomonas maltophilia</i> , a bacteria species which is normally found in clinical specimens (Suga et al., 1995)
1995	PRCP was found to be highly active in macrophages (Jackman et al., 1995)
1997	Watson and associates described localization of <i>Prpc</i> gene (Watson, Jr. et al., 1997)
2002	PRCP was found to be an endothelial cell prekallikrein activator (Shariat-Madar et al., 2002)
2002	Moreira and associates described the extracellular PRCP that activates prekallikrein (Moreira et al., 2002)
2005	Overexpression of PRCP on Chinese hamster ovary cells was reported (Shariat-Madar et al., 2005)
2006	Wang and associates described the functional significance of PRCP in the etiology of preeclampsia (Wang et al., 2006)
2007	Hooley and associates described a C-terminal extension in the PK serine protease domain as a potential substrate for PRCP. (Hooley et al., 2007)
2009	Wallingford and associates described that <i>Prpc</i> -null mice had elevated levels of alpha-MSH1-13 in the hypothalamus and were leaner and shorter than the wild-type controls on a regular chow diet. <i>Prpc</i> null mice were also resistant to high-fat diet-induced obesity (Wallingford et al., 2009)
2009	Soisson and associates described the crystal structure of human PRCP (Soisson et al., 2010)
2009	E112D polymorphism in the prolylcarboxypeptidase gene was found to be associated with blood pressure response to benazepril in Chinese hypertensive patients (ZHANG Yan et al., 2009)
2009	Javerzat and associates described overexpression of PRCP during the intermediate phase of the chick chorio-allantoic membrane (Javerzat et al., 2009)
2010	Recombinant PRCP (rPRCP) metabolized BK ₁₋₈ to BK ₁₋₇ , whereas rPRCP was ineffective in metabolizing BK 1-9 (Chajkowski et al., 2010)
2010	PRCP was found to be active in human cerebrospinal fluid (Zhao et al., 2010)
2010	Overexpression of angiotensin type 2 (AT2) receptor in mouse coronary artery endothelial cells was found to increase expression of PRCP, which may contribute to kinin release (Zhu et al., 2010)
2011	PRCP is a 4OHTAM resistance factor in estrogen receptor-positive breast cancer cells (Duan et al., 2011)
2011	PRCP ^{gt/gt} mice were found to be hypertensive and prothrombotic (Adams et al., 2011)

Table 1. Historical Perspective

To deal with proper delivery of blood to the tissues as well as many types of insults, including chemical and physical damage as well as infection, the cardiovascular system has evolved an intricate multilayer of specialized biochemical pathways. Multiple feedback mechanisms controlling blood flow with contrasting effects regulate normal vascular function, which have either stimulatory or inhibitory effects. These features enable the cardiovascular system to perform its tasks effectively. Of these regulatory feedback machinery, a few have multiple and redundant control mechanisms that tightly uphold cardiovascular functions. Among these regulatory feedback mechanisms within the mammalian cardiovascular system, we review the renin-angiotensin(Savinetskaia et al., 2008; Hayashi et al., 2010), kallikrein-kinin(Bryant and Shariat-Madar, 2009; Saxena et al., 2011), and pro-opiomelanocortin (POMC) (Wang et al., 2008) systems that communicate with each other. Although within each of these systems are surely a network of molecular interactions with other pathways, their interactions are not either compared or reviewed. However, special attention is given to the role of PRCP in health and disease.

2.1 Renin-angiotensin system (RAS)

The systemic RAS is a complex, but fairly well understood pathway(Perret-Guillaume et al., 2009; Molteni, 1982; Brown et al., 1983; Oishi et al., 1996; Renshaw et al., 2001; Hettinger et al., 2002; Volzke et al., 2005; Clerk et al., 2005). Although the physiological importance of the RAS for regulation of blood pressure and water homeostasis has been established(Fukuchi et al., 1973; Bing and Nielsen, 1973), emerging evidence suggests that the components of RAS are important players for maintenance and regulation of many physiological and pathophysiological processes, such as angiogenesis (Abali et al., 2002), inflammation (Akishita et al., 2001), tumorigenesis(Ager et al., 2008), thrombosis (Asselbergs et al., 2008; Asselbergs et al., 2007), vascular hypertrophy (Brede et al., 2001), vascular development (Lasaitiene et al., 2006), and remodeling (Akishita et al., 2000; Alcazar et al., 2009). The molecular mechanisms by which the components of RAS exert their pleiotropic effects are redundant in order to ensure an appropriate balance between the stimulatory and inhibitory signals favoring normal blood delivery. More interestingly, there is also a balance between RAS function and its counter-regulatory hormones, in particular plasma kinins, the main effectors of the plasma Kallikrein-Kinin System (KKS) (Shariat-Madar et al., 2002a). The active metabolites of these two systems regulate each other in an antagonistic manner. In view of the opposing effects of these two systems(Bader, 2001), the complex interplay of RAS and KKS with the local microenvironment of endothelial cells lining blood vessels is responsible for delivering nutrients. The RAS and KKS signaling pathways are also responsible for sustaining the high pressure necessary for the blood to reach all of the tissues of the body while maintaining blood pressure within a narrow range.

The RAS encompasses numerous peptides that act in concert in a cascade triggered by low blood volume or a drop in blood pressure cascades or water-fall(Taquini, Jr. and Taquini, 1961; Nicholls and Robertson, 2000; Shariat-Madar and Schmaier, 2004; Ritz, 2005; Oudart, 2005). These peptides exert their actions, which can be autocrine (Chan and Wong, 1996), paracrine (Haulica et al., 2005), or endocrine(Gohlke et al., 1992), acting through specific cell surface receptors on their target cells to control blood pressure and body fluid homeostasis. In a stepwise enzymatic process, the aspartyl protease renin (a rate-limiting enzyme) cleaves circulating angiotensinogen to the inactive angiotensin I (Ang I) (Helmer, 1965). Subsequently,

Although AT₂ appears to be cell-type specific with a low expression pattern in adult tissues, it is the dominant receptor in fetal tissues (Akishita et al., 1999; Guan et al., 2008). Experimental evidence in support of AT₂-independent G-protein signaling pathway has been demonstrated (Bottari et al., 1991). AT₂ receptors are essential for triggering vasodilation and it can also mediate cell death (Gwathmey et al., 2009). Ang II-induced AT₂ receptor-dependent vasodilation is mediated by activation of nitric oxide/cyclic guanosine 3',5'-monophosphate (cGMP) signaling cascades. On the other hand, AT₂ activation by Ang II may lead to the activation of proapoptotic second messengers, MAPK phosphatase 1 (MKP-1) (Horiuchi et al., 1997), SH2 domain-containing phosphatase 1 (SHIP-1) (Feng et al., 2002), and protein phosphatase 2A (PP2A) (Huang et al., 1996) and subsequent inactivation of MAPKs (Bedecs et al., 1997; Horiuchi et al., 1997), and ERK1/2 (Horiuchi et al., 1997). While identification and characterization of the molecular switch that controls differential activation of distinct downstream signaling pathways by Ang II are poorly understood, our understanding of the downstream events is exponentially mounting.

In the next step of the RAS cascades, angiotensin converting enzyme 2 (ACE2) and PRCP metabolize Ang II (a prothrombotic risk factor) to angiotensin 1-7 (a vasodilator, antithrombotic factor) (Mallela et al., 2008), highlighting the functional significance of these two enzymes. Notably, ACE2 (Gurley et al., 2006) and PRCP (Adams et al., 2011) null mice do not exhibit excessive elevated blood pressure compared to control littermates, suggesting that these enzymes play a critical role in the maintenance of normal vascular physiology, Figure 1. PRCP also metabolizes angiotensin III (Ang III, Ang₂₋₈) to angiotensin 2-7 (Ang₂₋₇) (Mallela et al., 2008). Ang III, like Ang II, is also a pressor agent whose response is mediated by AT₁ receptors (Campbell et al., 1979). Ang III is implicated in cell proliferation and matrix accumulation (Ruiz-Ortega et al., 1998). Ang II- and Ang III-induced AT₁ receptor stimulation mediate vasoconstriction, mitogenic and hypertrophic effects and inflammatory responses (Ishanov et al., 1998; Schluter and Wenzel, 2008; Marshall et al., 2000). Hydrolysis of Ang III by PRCP leads to a decrease in Ang III-mediated effects, further pointing out the importance of PRCP in contributing to regulation of blood pressure.

2.2 RAS and angiogenesis

Ang II is a proangiogenic hormone and AT₁ mediates its proangiogenic actions (Wilop et al., 2009). The proangiogenic effect of Ang II leads to upregulation of EGF (Friedlander and Terzi, 2006; Lautrette et al., 2005), β FGF (Liu et al., 2009), PDGF (Blaschke et al., 2002; Li et al., 2005), IGF-1 (Kajstura et al., 2001; Song et al., 2005; Jia et al., 2011), hepatocytes growth factor (Bataller et al., 2003), and NO (Abassi et al., 1997). Ang II-induced AT₁ mediated signaling pathway cause an activation of mitogen-activated protein kinases (MAPK) (Guo et al., 2006; Morrell et al., 1999; Taniyama et al., 2004).

The MAPK pathway induces cellular protein synthesis, volume regulation, gene expression, and growth (Morrell et al., 1999). In contrast, activation of AT₁-independent G-protein signaling pathway by Ang II can also cause endothelial cell proliferation through non-receptor tyrosine kinase Src-mediated increase of NADP oxidase activation, phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2), P38 MAP kinase, and a decrease in phosphorylation of Src homology 2 (SH2)-containing inositol phosphatase 2 (SHIP2) (Ali et al., 1997b; Feng et al., 2002; Bedecs et al., 1997). These experimental observations suggest that Ang

II is proangiogenic. However, evidence suggests that Ang II may inhibit angiogenesis under certain conditions by activating AT₂-receptors, suggesting that AT₁ mediates effects that counteract those mediated by AT₂ receptors (Chung et al., 1996).

2.3 RAS in cardiovascular disease

Since Ang II, Ang III, Ang IV, and Ang 1-7 can act systemically and locally to control blood pressure and body fluid homeostasis, components of RAS have become therapeutic targets for diseases such as hypertension (Farmer, 2000), cardiac hypertrophy (Brasier et al., 2000; Billet et al., 2008), congestive heart failure (Volpe and De, 2000; Yang et al., 1998), ischemic heart disease (Burrell et al., 2005), coronary heart disease (Farmer and Torre-Amione, 2001), and renal diseases.

3. Plasma kallikrein kinin system (KKS)

The primary functions of plasma KKS are to 1) assist hemostasis and limit blood loss, 2) increase capillary permeability and dilate arterioles, 3) promote antiatherogenic and antithrombogenic properties of endothelium by maintaining or increasing antiatherogenic agents including nitric oxide, prostaglandins, and tissue plasminogen activator, and 4) induce acute vascular pain. In addition to its hemodynamic actions, antifibrotic and renoprotective effects of kallikrein have been reported (Pawluczyk et al., 2008). Although the expression and activity of components of plasma KKS are known to be age-dependent (Gordon et al., 1980) for three decades, the mechanism underlying this phenomenon is yet to be unravelled.

The components of KKS, also called the contact activation pathway, consist of three serine zymogens (prekallikrein, factor XII, and factor XI) as well as a kinin and antiangiogenic precursor (high molecular weight kininogen) (Figure 2) (Ratnoff and Saito, 1979). Plasma kallikrein, a serine protease, is synthesized in the liver. It is predominantly secreted by hepatocytes as an inactive molecule called prekallikrein (PK) that circulates in plasma as a heterodimer complex bound to high molecular weight kininogen (HK) with 1:1 molar stoichiometry. PK is a single chain α -globulin that is present in the plasma of humans and of other animal species. About 80-90% of PK is normally in complexed with HK.

HK is a single-chained glycoprotein synthesised by liver and secreted into the circulation (Sueyoshi et al., 1987). HK consists of three domains: an amino acid-terminal heavy chain, a carboxyl-terminal light chain, and bradykinin moiety (Figure 3) (Kleniewski et al., 1988). The heavy chain linked to the light chain by a single disulfide bond (Kleniewski et al., 1988). Domain 6 of HK has a PK and FXI-binding site (Reddigari and Kaplan, 1989). HK binding to cell surface proteins or artificial surfaces is vital for activation of the plasma KKS (Pixley et al., 2011; Joseph et al., 2001; Zhao et al., 2001). The procoagulant activity of HK is dependent on whether it is in complexed with PK or FXI (Gailani and Broze, Jr., 1991). The proteolytic cleavage of HK by kallikrein results in the production of BK and cleaved HK (HKa). HK could be metabolized by activated factor XI into three peptide fragments, yet its physiological significance has been unclear. HK is involved in angiogenesis and in cell adhesion and the matrix of various endothelial cells (Motta et al., 2001).

Unlike PK, factor XI (FXI) is involved in normal hemostasis *in vivo*. FXI synthesis is primarily in the liver. Factor XI activity is age-dependent (Andrew et al., 1987). While its activity is low at

birth, FXI levels are reached to normal adult plasma levels by six months of age. FXI circulates in the plasma as a disulfide bond-linked dimer complexed with HK. It is important for propagation of blood coagulation (Walsh and Griffin, 1981). FXI can be activated to activated FXI (FXIa) by FXIIa-mediated activation on the negatively charged surfaces or thrombin-mediated activation on the platelet surface (Baglia et al., 2004), Figure 2. FXIa augments thrombin generation via interaction with a coagulation factor of the extrinsic pathway, factor IX (Baglia and Walsh, 1998; Taketomi et al., 2008). It appears that FXI along with activated platelet are a prerequisite for optimum thrombin generation in which the procoagulant activity of KKS is so just below the threshold point (Keularts et al., 2001).

Plasma KKS activation has been demonstrated under physiological conditions and in numerous inflammatory human diseases. Under pathological conditions, conversion of plasma factor XII (FXII) to its active form (FXIIa) is concomitant with the appearance of hematologic responses including coagulation, fibrinolytic, and inflammation. FXIIa initiates propagation of the intrinsic pathway (IP) of blood coagulation via factor XI activation, Fig. 2 (1; Pathway 1). In the presence of HK, FXIIa converts plasma prekallikrein (PK) to kallikrein, Fig. 2 (2; Pathway 2). In a reciprocal feedback mechanism, kallikrein accelerates FXII activation. Kallikrein causes the release of tissue plasminogen activator (tPA) via a bradykinin-dependent pathway. Kallikrein causes the release of tissue plasminogen activator (tPA) via a bradykinin-dependent pathway.

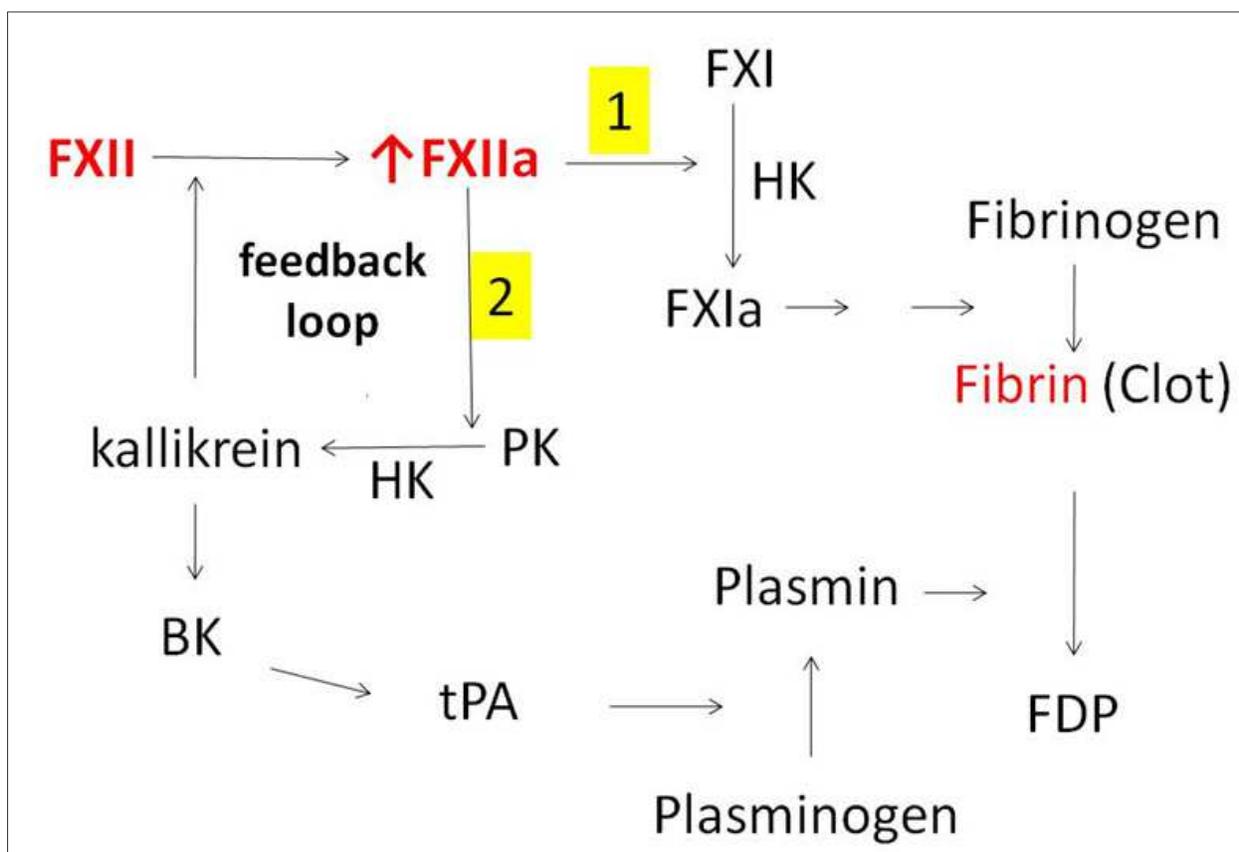


Fig. 2. A schematic representation of factor XII (FXII) activation during pathological plasma proteolytic states. **FXIIa**; activated factor XII, 1; pathway 1, **FXI**; factor XI, **FXIa**; activated factor XI, 2; pathway 2, **HK**; high molecular weight kininogen, **PK**; prekallikrein, **BK**; bradykinin, **tPA**; tissue plasminogen activator, **FDP**; Fibrin degradation Products.

Fibrinolysis is the process by which plasmin digests fibrin, Fig. 2. This aids in thrombus (clot) dissolution and limits the promotion of coagulation (clot formation). tPA converts plasma plasminogen to plasmin, which in turn remodels the thrombus. Plasmin breaks down the clot fibrin to fibrin degradation products (FDP). Consequently, FDP blocks thrombin-induced fibrin (clot) formation, Figure 2. Notably, plasmin triggers a positive feedback amplification by accelerating conversion of PK to kallikrein.

Kallikrein acts on HK to generate HKa (cleaved HK) and bradykinin (BK), Figure 3. BK-induced activation of the B₂ (B₂) receptor leads to the formation of tissue plasminogen activator (tPA, a potent fibrinolytic molecule)(Czokalo-Plichta et al., 2001), Fig. 3. BK upon activation of its constitutive B₂ receptors on endothelial cells leads to an increase in intracellular Ca²⁺ levels and subsequent production of nitric oxide (NO, a vasodilator) and prostacyclin (PGI₂, a platelet activation inhibitor), ultimately leading to vasodilation, increased vascular permeability and edema (Zhao et al., 2001b; Hong, 1980; Palmer et al., 1987). Whereas B₂ receptors are constitutively expressed, the expression of bradykinin B₁ (B₁) receptors is induced during inflammation (Marceau, 1995). Metabolism of BK by carboxypeptidase N (CPN) in plasma or carboxypeptidase M (CPM) on endothelial cells yields des-Arg⁹-BK which interacts with B₁ receptors to potentiate and/or perpetuate the inflammatory response (Figure 3)(Marceau et al., 1981).

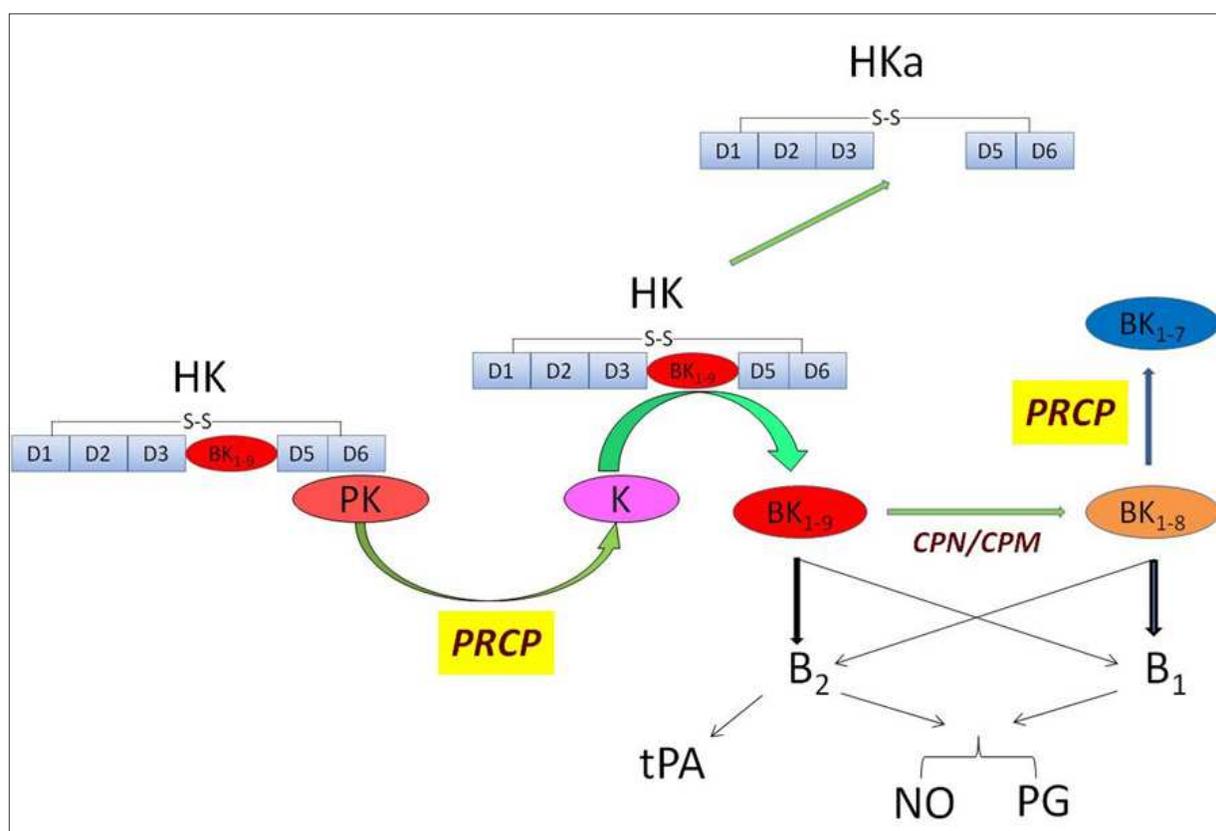


Fig. 3. A schematic representation of PRCP-dependent prekallikrein activation. **HK**; high molecular weight kininogen, **PK**; prekallikrein, **PRCP**; prolylcarboxypeptidase, **K**; kallikrein, **BK₁₋₉**; bradykinin, **HKa**; cleaved HK, **BK**; bradykinin, **NO**; nitric oxide, **PGI₂**; prostacyclin, **tPA**; tissue plasminogen activator, **CPN**; carbox peptidase N, **CPM**; Carboxypeptidase M, **BK₁₋₈**; bradykinin 1-8 (des-Arg⁹-bradykinin), **BK₁₋₇**; bradykinin 1-7.

Under physiological conditions, PK bound to HK on endothelial cells can lead to PK activation through a FXIIa-independent mechanism, which in turn leads to BK generation. While assembly and activation of the plasma KKS is regulated by PRCP on several cultured cell lines, heat shock protein 90 (HSP90) is the main activator of the plasma PK in mesothelium-derived cell lines (Varano, V et al., 2011). Thus, the plasma KKS participates in both surface-dependent activation of blood clotting and inflammatory process. Further, PRCP participates in cell surface - dependent activation of PK and its dependent pathways. The question remains how PRCP-dependent PK signaling pathway is assembled, activated, and regulated in response to plasma levels of Ang II and/or Ang III. However, in an elegant study, the authors find evidence for a cross-talk among the kinin, PRCP, and angiotensin signaling pathways (Zhu et al., 2010).

3.1 The plasma KKS and cardiovascular diseases

Whereas the normally functioning KKS can successfully counteract blood pressure, promote smooth blood flow, modulates neovascularisation and eliminates pathogens by promoting the recruitment of neutrophils to the site of injury, inappropriate responses can lead to extensive tissue damage. KKS has been implicated in the pathogenesis of inflammation, hypertension, endotoxemia, and coagulopathy. Increased BK levels is a hallmark in all of these cases. In some cases, the persistent production of BK due to the deficiency of the blood protein C1-inhibitor, which controls kallikrein and activated FXII, is detrimental to the survival of the patients with hereditary angioedema (HAE). In others, the inability of angiotensin converting enzyme (ACE) to degrade BK leads to elevated BK levels and edema in patients on ACE inhibitors.

3.2 The importance of KKS for angiogenesis

Various cancers exhibit upregulation of either epidermal growth factor or urokinase receptor or both, which leads to poor prognosis. On studies done on human prostate cancer cells (DU145) the cleaved fragment of HK, HKa and also domain 5 prevented colocalization of uPAR and EGFR, decreased downstream extracellular signal-regulated kinase (ERK) and AKT-mediated signal transduction at EGFR (Wuepper and Cochrane, 1972). This indicates therapeutic potential of HKa and D5 to inhibit metastasis involving migration and invasion of human prostate cancer cells.

Both HK and LK are proangiogenic as demonstrated by induction of vascularization on chorioallantoic membrane. Monoclonal antibody directed against HK has been shown to inhibit HK-induced neovascularization on chorioallantoic membrane as well as HK-induced fibrosarcoma formation. Domain 5 of HK, also called kininostatin, is antiangiogenic (Colman et al., 2000). There are reports that peptides derived from domain 3 and domain 5 inhibit angiogenesis in Zn²⁺ independent and dependent manner (Zhang et al., 2002). Antibody directed against domain 5 also prevents neovascularization (Song et al., 2004).

Like HK, BK also is proangiogenic and a reduction in its levels may be associated with impaired neovascularization (Krankel et al., 2008). But HKa is antiangiogenic as it prevents VEGF and FGF2 induced vascularization. HKa through its D5 domain has been shown to inhibit sphingosine 1-phosphate (S1P) and vascular endothelial growth factor (VEGF) mediated endothelial cell migration by modifying PI3 kinase-Akt signaling (Katkade et al.,

2005). HKa acting through uPAR can also bring about apoptosis in endothelial cells, which is due to inhibition of uPA binding to uPAR thus preventing subsequent uPAR internalization and regeneration to the cell surface (Cao et al., 2004). This results in interference with all aspects of angiogenesis such as cell migration, proliferation, and survival.

Histidine proline rich glycoprotein (HPRG) is present in plasma abundantly and might be the predecessor of HK (Koide and Odani, 1987). HPRG is similar in sequence and function to HKa and is shown to bind to tropomyosin and inhibit angiogenesis through apoptosis (Donate et al., 2004).

4. Pro-opiomelanocortin (POMC)

POMC is expressed in numerous mammalian tissues (Tatro et al., 1992; Tatro and Reichlin, 1987). It undergoes extensive posttranslational modification by a family of serine proteases and the prohormone convertases (PCs). The metabolism of POMC results in the generation of alpha-melanocyte stimulating hormone (α -MSH, α -MSH₁₋₁₃) along with β -MSH, γ -MSH, and β -endorphin (Shariat-Madar et al., 2010). Although all four of these hormones are important, only α -MSH₁₋₁₃ will be discussed here. The synthesis of α -MSH₁₋₁₃ from POMC involves numerous specific enzymes in addition to PC1 and PC2. It appears that PRCP plays an important role in regulating α -MSH.

5. The interactions among KKS, RAS, and POMC

The participation of the components of the plasma kallikrein-kinin system in some pathological processes like hypertension and cardiovascular diseases is still a matter of controversy. The availability of transgenic and knock-out mice for B2 and B1 receptors and angiotensinogen and angiotensin II receptors have advanced our understanding about the roles of KKS and specifically these receptors in cardiovascular regulation and inflammatory processes.

Bradykinin (BK) is the natural hypotensive agent that causes vasodilatation by stimulation of endothelial B2 receptors of arteries and arterioles, and the subsequent endothelial release of nitric oxide and prostaglandins (Sharma, 2009). BK influences the kidneys to produce diuresis and natriuresis (Katori and Majima, 2008; Katori and Majima, 2003). The diuretic effect of the exogenous BK administered by the renal artery is by B₂ receptors (Boric et al., 1998; Croxatto et al., 1999), whereas the BK-induced natriuresis and increase in renal blood flow are due to both B₁ and B₂, Figure 3 (Lortie et al., 1992). Tissue injury such as myocardial ischemia and inflammation can cause the expression of B1 receptors on their surfaces (Foucart et al., 1997b; Foucart et al., 1997a). In addition, elevated concentrations of BK have been observed in ischemic myocardium (Burch and DePasquale, 1962; Burch and DePasquale, 1963). Occlusion of the proximal left anterior coronary artery causes a change in BK (Hashimoto et al., 1979; Kimura et al., 1973; Hashimoto et al., 1977). Exposure of the epicardium of anesthetized dogs to BK leads to stimulation of sympathetic afferent fibers protruding into the left ventricle (Uchida and Murao, 1974). Inhibition of the B₂ receptor inhibitor resulted in increased kallikrein activity, but not kallikrein mRNA levels, in kidney of adult rats. There is a direct correlation between increased renal interstitial BK levels in dogs in low-sodium balance and the presence of B₂ receptors (Siragy et al., 1997). There is

also evidence that kinin or B₂-receptor inhibitor administration increases renin secretion or decrease plasma renin levels in anesthetized rabbits, respectively (Chiu and Reid, 1997). This data plus the location of B₂ receptors in different parts of the kidney and vascular endothelium suggests a role for the plasma KKS in the cardiovascular system (Schricker et al., 1995).

There have been numerous suggestions that kallikrein converts prorenin to renin and a few results suggest that RAS and KKS are interdependent and KKS regulates RAS activity (Sealey et al., 1979). In this report, the plasma prorenin was activated to renin *in vitro* by kallikrein when plasma acidity increased (Sealey et al., 1979). Later, Purdon and colleagues evaluated the effect of kallikrein converting prorenin to renin in plasma deficient in C1 inhibitor (hereditary angioedema) at neutral pH (Purdon et al., 1985). Although PK was completely activated to kallikrein and despite normal prorenin concentration, prorenin was not converted to an active enzyme. Regardless of kallikrein metabolic capability in converting prorenin to renin, studies suggest the presence of a crosstalk between the vasoconstricting RAS and the vasodilating KKS (Yokosawa et al., 1979).

In summary, the increased activity of RAS could be responsible both for arterial wall constriction and KKS activation and subsequent BK production to relief vasoconstriction. This explains the previous finding when the pressure is raised in the perfused heart muscle and brain, the flow can be held constant independently of any external neurogenic control (Mosher et al., 1964). The regulation of tissue flow as perfusion pressure changes can be affected by the rate of delivery or removal of BK and Ang II to the perfused region, influencing the state of contraction of the smooth muscle cells of the blocked vessels directly. This signifies the importance of the feedback mechanism between KKS and RAS. These systems may serve as a "on-off" biological switch impacting the risk of thrombosis/bleeding and those of low/high blood pressure.

6. Prolylcarboxypeptidase or angiotensinase C

PRCP has a subtle role in preserving the blood flow through the endothelial lining of blood vessels so that the tissues can maintain cellular function. PRCP exerts this effect through regulation of local levels of autocrine-paracrine hormones such as angiotensin II (Ang II), angiotensin III (Ang III), and bradykinin generation via kallikrein-kinin pathway. Subsequently, the modification of these vasoactive substances influences the secretion or expression of a diverse group of endothelium mediators that are involved in the contraction and relaxation of smooth muscles, regulating blood flow, blood clotting, inhibition of platelet aggregation, and electrolyte homeostasis. It is well-established that dysfunction of endothelium significantly contributes to the development of thrombosis.

6.1 Physiology

PRCP is a serine peptidase that cleaves peptides at C-terminal amino acids linked to a proline residue. The first evidence that PRCP might play a role in the cardiovascular system was provided by catalytic activity analysis, which showed the metabolism of angiotensin II (Ang II) to angiotensin 1-7 (Ang 1-7) (Ody et al., 1978b). The mere inactivation of Ang II results in two events that broaden the functional spectrum of PRCP. First, it is a negative regulator of the pressor actions of the renin-angiotensin system (RAS). Second, PRCP

activity provides a measure of endothelium relaxation due to its ability to initiate nitric oxide generation through Mas receptor activation (Silva et al., 2007). PRCP metabolizes angiotensin III (Ang III) to angiotensin 2-7 (Ang 2-7)(Ody et al., 1978c). Ang III is a pressor agent whose response, like that of Ang II, is mediated by AT₁ receptors(Felix et al., 1991a; Gammelgaard et al., 2006b). We described that when the complex of high molecular weight kininogen (HK) and prekallikrein (PK, Fletcher factor) binds to endothelium membrane, PK is rapidly converted to kallikrein by PRCP, Figure 3(Shariat-Madar et al., 2002b). The formed kallikrein then cleaves HK to liberate bradykinin (BK), which leads to vasodilation and subsequent nitric oxide and PGI₂ formation by activating constitutive bradykinin B₂ and inducible bradykinin B₁ receptors (Zhao et al., 2001a; Colman and Schmaier, 1997). BK also causes release of tissue plasminogen activator (tPA, a profibrinolytic factor) to convert plasminogen to plasmin, which inhibits platelet aggregation, thrombus formation and promotes fibrinolysis, Figure 2(Pawluczyk et al., 2006). Thus, PRCP locally regulates nitric oxide-dependent vasodilation and indirectly modulates fibrinolysis within the vascular wall.

6.2 Protein structure and molecular biology

The human *Prcp* gene has been mapped to 11q14 and the gene is more than 147 kb in length and has 9 exons (Watson, Jr. et al., 1997). More recently, a new *Prcp*-like gene (*Prcp2*) has been discovered. The human *Prcp* gene family contains at least 2 genes. Both genes share important similarities including significant homology at the nucleotide level. Both genes encode for putative serine proteases. However, the functional role of *Prcp2* gene has not been characterized.

PRCP belongs to the single chain serine peptidase S28 family. It is derived from a larger precursor, prepro-PRCP, whose primary nucleotide structure was first described in a human cDNA clone by Tan et al., 1993. It appears that the precursor is homodimer polypeptides containing a secretory signal sequence. PRCP regulates the activity of bradykinin, Ang II, Ang III, prekallikrein, and α -MSH(Ody et al., 1978a; Shariat-Madar et al., 2002c; Moreira et al., 2002; Wallingford et al., 2009), suggesting that PRCP has versatile roles in influencing cardiovascular system. The enzyme is ubiquitously present in all major areas of the vascular bed as well as in the kidney, heart, placenta, and hypothalamus (Jackman et al., 1995b; Skidgel et al., 1981; Rosenblum and Kozarich, 2003; Schmaier, 2003; Shariat-Madar et al., 2010). However, PRCP is highly produced in endothelial cells, which is one cell type involved in the release of vasodilators and antithrombotic mediators.

6.3 PRCP in cardiovascular diseases

PRCP and angiotensin converting enzyme 2 (ACE2) are exopeptidases, which convert Ang II to Ang 1-7. ACE2 metabolizes AngII at a much faster rate than PRCP (Rice et al., 2004), suggesting that Ang II is a poor substrate for PRCP. Clinical studies have provided reliable evidence that ACE2 is an essential regulator of angiotensin I (Ang I), Ang II and angiotensin-induced cardiac hypertrophy (Huentelman et al., 2005). Increased myocardial levels of Ang II concomitant with a significant decrease in Ang 1-7 in ACE2 deficient hearts has been reported (Kassiri et al., 2009). These data suggest that PRCP may indeed be important in metabolizing Ang II in the absence of ACE2. These observations suggest that PRCP is a redundant catalyst contributing to alternate pathways for Ang II metabolism.

Over thirty years ago, Ody et al (Ody et al., 1978d) showed that PRCP can metabolize Ang III to Ang 2-7. Evidence indicates that Ang 2-7 excites some neurons in the paraventricular nucleus (Ambuhl et al., 1992). Differential regulation of Ang 2-7 during ACE inhibitor treatment suggests a cardiovascular role for this peptide (Campbell et al., 1991). Because of the significance of Ang 2-7, AngIII regulation and metabolism are important. Results from several studies show that Ang III is a pressor agent. It exerts its hypertensive effects via AT₁ receptors (Felix et al., 1991b; Gammelgaard et al., 2006a). Ang III can enhance renal disease through the overproduction of aldosterone and subsequent development of arterial hypertension and/or to atrial fibrillation (Al-Aloul et al., 2006). Aldosterone which is produced by adrenal cortex maintains blood volume, pressure, and electrolyte balance. It is tightly regulated by renin, an enzyme produced in the juxtaglomerular apparatus of the kidneys. Renin production is elevated by low blood pressure, decreased blood flow to the kidneys or sodium deficiency. In theory, inactivation of Ang III by PRCP might lead to a decrease in blood pressure. However, further studies are needed before claims can be made of a beneficial effect of PRCP on hypertension.

It is well known that cells produce and secrete a large variety of proteases either as proenzymes or activated proteases. Although PRCP can be viewed as a proenzyme based on its primary structure, its post-translational regulation has not been characterized. PRCP is distributed throughout endothelial cells, including lysosome, cytoplasm, and plasma membrane. The membrane bound PRCP activates plasma PK to kallikrein in endothelial cells. The activation of PK is characterized by elevated kallikrein expression along with increased local BK production. Kallikrein-induced BK production causes endothelial cells to produce proinflammatory prostaglandins and vasodilatory nitric oxide (Ngo et al., 2009). Thus, the PRCP-dependent PK activation pathway might be considered as an additional mechanism to counteract the hypertensive activities of both Ang II and Ang III.

Local skeletal muscle ischemia and acidosis are shown to increase the generation of BK and prostaglandins, the two circulating end-products of the PRCP-dependent pathways, Figure 3 (Piepoli et al., 2001). The increased acidotic response during exercise and inflammatory mediators such as BK and prostacyclin have been shown to cause the abnormal exercise-related symptoms and autonomic responses in congestive heart failure syndrome (Scott et al., 2003). Emerging evidence suggest that the long-term elevated concentrations of NO and prostacyclin may be detrimental and eventually responsible for cardiovascular diseases such as congestive heart disease (Kai C.Wollert and Helmut Drexler, 2004). Needless to say, the reduction of endogenous PGI₂ synthesis is associated with the occurrence of cyclic reduction of coronary flow (Tada et al., 1984). Thus, PRCP-dependent Ang₁₋₇ and PRCP-dependent BK pathways have important biological activities. Altered PRCP expression levels mediates pathophysiological changes in the cardiovascular system.

PK is markedly elevated during pregnancy (Maki and Soga, 1981). Among proteases that metabolize neuropeptide Y 3-36 (NPY₃₋₃₆, anorexigenic hormone), plasma kallikrein metabolizes NPY₃₋₃₆ to NPY₃₋₃₅ (Abid et al., 2009). In addition, specific inhibitor of plasma kallikrein prevents the production of NPY₃₋₃₅. We find these studies intriguing because elevation of kallikrein should provoke anorectic effect via accelerated inactivation of NPY₃₋₃₆. Recent evidence suggests that there is a link between severe prekallikrein deficiency and pregnancy loss (Dasanu and Alexandrescu, 2009). As mentioned earlier, PRCP activates PK to kallikrein. If PRCP is inhibited/down-regulated, kallikrein levels are lower. Thus,

disruption of PRCP-dependent PK activation may be a risk factor for pregnancy losses. The inhibitors of both kallikrein and PRCP may be contraindicated during pregnancy. However, further investigations are required to define the safety of these inhibitors.

The activation of POMC is characterized by elevated α -MSH₁₋₁₃ production. α -MSH₁₋₁₃ regulates inflammation and food intake, suggesting that it may contribute to tissue damage production. Recently, experimental evidence indicated that PRCP metabolizes α -MSH₁₋₁₃ to α -MSH₁₋₁₂ (Wallingford et al., 2009). Mice deficient for PRCP present high blood pressure (Adams G.N et al., 2009), a sustained long-term reduction in food intake, and increased energy expenditure (Wallingford et al., 2009). In humans, hypertension is considered to be a multifactorial disorder. *Prpc* gene and its variants contribute to hypertension (Wang et al., 2006c; Zhang et al., 2009; Zhu et al., 2010). Rutaecarpine stimulates expression of PRCP in the circulation and small arteries in renovascular hypertensive rats (Qin et al., 2009). Since PRCP variant promotes disease progression (Zhang et al., 2009) in Chinese hypertensive patients and risk of preeclampsia in black and non-black women (Wang et al., 2006b), it is a candidate for pharmacological intervention.

7. Conclusions and future directions

In conclusion, PRCP is one of the conserved proteases throughout evolution in vertebrates. In-vitro and in-vivo studies of PRCP, this enzyme serves to generate nitric oxide and prostaglandins. Notably, bradykinin and bradykinin 1-8 are important mediators of pain (Argent et al., 1954) and endotoxin-induced vascular permeability {Ueno, 1995 783 /id}. BK production is increased in ischemic myocardial tissue (Dell'Italia and Oparil, 1999). They are involved in the control of local blood flow. Although PRCP is less efficient than ACE2-induced NO and prostaglandin generation under pathophysiological conditions, this redundant mechanism has presumably evolved for ischemic remodeling and smooth blood flow (Figure 1 and Figure 3). Overactivation of this mechanism may contribute to myocardial tissue damage or endothelial dysfunction. It inactivates BK₁₋₈, suggesting that PRCP may also reduce marked inflammatory response. It appears that PRCP is fine-tuned to discriminate between physiological and pathophysiological changes. Since cardiomyocytes are unable to proliferate (Lagrang et al., 2000), inactivation of BK₁₋₈ by PRCP may contribute to prevention of tissue damage. Further studies are warranted to evaluate the role of PRCP in cardiovascular system, in particular the heart.

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9. References

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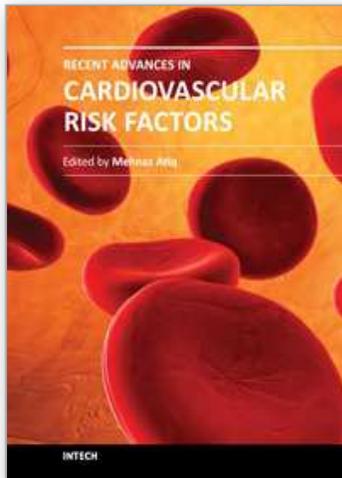
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Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

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