

Prolylcarboxypeptidase in Cardiovascular Physiology and Pathophysiology

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Abstract

Prolylcarboxypeptidase (PRCP), a serine protease, is highly expressed by vascular endothelial cells and kidney, the two tissues responsible for regulating blood pressure and cardiovascular functioning. In addition to its effect on angiotensin and kinin molecules, as well as alpha Melanocyte Stimulating Hormone (α -MSH), PRCP has been found to regulate various fundamental cell functions such as proliferation, autophagy and host defense, and appears to be influenced by several critical cellular processes. Abnormal activation or upregulation of PRCP has been observed in major cardiovascular disorders such as hypertension, inflammation, rheumatoid arthritis, diabetes, and tumorigenesis. We discuss major challenges on which the physiological importance of PRCP depends, serving as an argument to divulge the importance of PRCP for living beings under many pathological conditions.

Keywords: Melanocortin system; Pain; Renin-Angiotensin System (RAS); Diabetes; Autophagy

Introduction

PRCP is one of the two members of the S28 exopeptidase [1] that, in addition to its effects on neuronal [2] and non-neuronal hormones [3], regulates a wide range of cell functions such as proliferation, autophagy [4], and the maintenance of vascular homeostasis (Figure 1).

PRCP appears to favor vasorelaxation, which contributes to normal blood flow. Impaired PRCP function is associated with cardiovascular diseases including diabetes, obesity, thrombosis and hypertension.

The biochemical aspects of PRCP were reported slightly over

forty years ago [5]; however, the wide spectrum of physiological and pharmacological properties of PRCP is gradually being broadened. PRCP metabolizes Ang II to angiotensin 1-7 (Ang 1-7), stimulating the synthesis and release of the two well-known vasodilators, prostaglandin and nitric oxide (Figure 1). While much research remains to be done, studies show that PRCP metabolizes Ang III (a vasopressin peptide) to angiotensin 2-7 (Ang 2-7). Although its half-life (17 sec) is short, studies are needed to determine whether Ang 2-7 mimics Ang 1-7 as an alternative physiological adaptation. PRCP metabolizes both des-Arg⁹-bradykinin [6] des-Arg⁹-BK, also known as BK1-8 [7], a potent proinflammatory peptide) and alpha melanocyte stimulating hormone (α -MSH, an anti-inflammatory hormone, energy metabolism) [2,8] suggesting that PRCP inherently protects cardiovascular functioning (Figure 1).

The plasma Kallikrein-Kinin System (KKS) plays a role in the activation of blood coagulation cascade by acting as co-stimulator of tenase complex on activation of the blood clotting pathway through a unique proteolytic cascade. A major downstream effector of the KKS in activating tenase is activated factor IX (FIXa), which forms tenase complex in the presence of activated factor VIII. Prekallikrein, a key component of the KKS can be activated by a wide variety of different stimuli, including PRCP in vitro and in vivo. However, the mechanism by which PRCP-dependent PK activation occurs has not been identified. The second major effector of KKS on the surface of endothelium is bradykinin, a potent inflammatory peptide.

Activation of bradykinin 2 (B_2) receptors by BK mediates release of nitric oxide (NO), prostacyclin (PGI₂), and tissue plasminogen

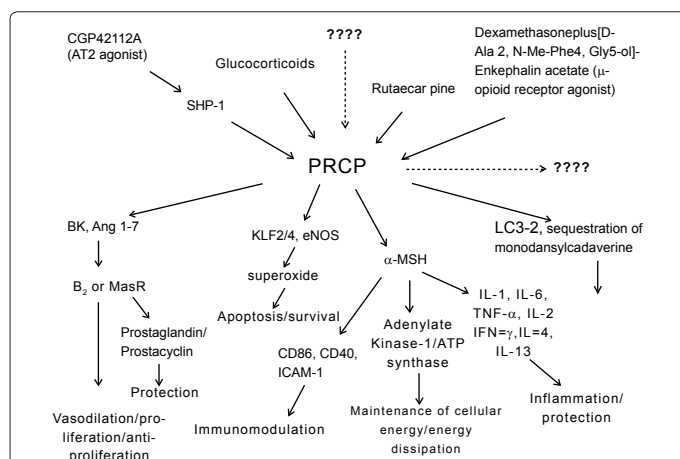


Figure 1: Schematic presentation of PRCP roles in mammals

This schematic presentation highlights major cell functions, which are regulated by PRCP following stimulation by hormones, neuromediators, or drugs. It appears that PRCP is highly regulated and the target of pharmaceutical intervention. AT2; angiotensin II type 2 receptor, SHP-1; sarcoma homology region 2 domain-containing phosphatase 1 (also known as tyrosin protein phosphatase type 6), LC3-2; microtubule-associated protein 1 light chain 3 type 2, BK; bradykinin, KLF2; Krueppel-like factor 2, eNOS; endothelial nitric oxide synthase, B2; bradykinin B2 receptor, MasR; Mas 1 oncogene, α -MSH; alpha melanocyte stimulating hormone, IL; interleukin, TNF- α ; tumor necrosis factor alpha, IFN- γ ; interferon gamma, and ICAM-1; intracellular Adhesion molecule 1.

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activator (tPA), which are involved in intracellular signaling pathway protecting cells from overstretching and thrombus formation (Figure 1). PRCP induces cytoprotection through dampening reactive oxygen species (ROS) signaling (Figure 1) [9]. Although both PGI₁ and NO play roles in the maintenance of vascular homeostasis, PGI₂ has been found to be the major mediator of acetylcholine-induced vasodilatation in the isolated mouse heart [6]. Muscle velocity is reduced in mice with PRCP deficiency [9]. Does PRCP reduce a burden on the heart?

Peptidomic profiling of human cerebrospinal fluid and knockout mice studies have uncovered new functions for the PRCP-dependent pathway in central nervous system. Recently, YPRPIHPA (the extracellular portion of endothelin B receptor-like protein 2), a novel substrate for PRCP is found in human cerebrospinal fluid [10]. Understanding this process can provide insight into how PRCP functions in human cerebrospinal fluid. α -MSH appears to be a multifunctional neurohormone [11], which regulates a variety of physiological processes including energy balance regulation through centrally pathway and lipolysis in adipocytes [12]. PRCP metabolizes the anorexigenic α -MSH, leading to an activation of an orexigenic pathway.

Although a number of synthetic PRCP inhibitors have been developed in recent years, the endogenous inhibitor of PRCP has not yet been identified. Studies into identification of the endogenous inhibitor of PRCP may allow a better understanding of PRCP contributions to central and peripheral systems. Needless to say, a potential endogenous inhibitor of PRCP was found to be angiotensin I (Ang I) in vitro [13]. The physiological significance of this inhibition by Ang I is not fully understood. Since PRCP has a role in blood flow along with the fact that the concentration of Ang I is 45 times higher than that of Ang II in the renal vein [14], Ang I might be a major inhibitor of PRCP in kidney. Further investigations are necessary to determine if there is an association.

Emerging evidence provides support the idea that non-biological and biological molecules, hormones and neurotransmitters known to regulate blood pressure, inflammation and pain also regulate PRCP expression and functions (Figure 1). CGP42112A is an angiotensin type 2 (AT₂) receptor agonist. More recently, it has been reported that CGP42112A enhances PRCP expression and function [15]. Thus, this evidence positions PRCP downstream in AT₂ signaling pathway. AT₂ is upregulated in resistance arteries of hypertensive diabetic patients treated with AT₁ blocker. It is reasonable to assume that PRCP expression can be influenced in diabetic patients. However, investigations are needed to validate this association.

Rutaecarpine is an alkaloid found in *Evodia rutaecarpa* herbs, which blocks elevated blood pressure and prevents vascular hypertrophy, also enhances expression of PRCP in the circulation and small arteries in renovascular hypertensive rats. The implications of this study for hypertensive patients are not known. However, the study may highlight a possible mechanism by which PRCP is regulated in response to the external stimuli, which will have fundamental importance for characterizing PRCP regulation under physiological condition. Glucocorticoid or its synthetic analog, dexamethasone plus [D-Ala², N-Me-Phe⁴, Gly⁵-ol]-Enkephalin acetate increases PRCP gene in human SH-SY5Y neuroblastoma cells [16]. However, it is not known whether PRCP-dependent pathways contribute to neuronal functions and perhaps pain sensitivity.

In summary, it appears to be ubiquitous, suggesting that PRCP

might have many different physiological roles. It would be an important step to definitely unravel the true extent of PRCP biological function. A protease with the ability to regulate autophagy and proliferation in addition to the inflammation, diabetes and feeding behavior proves to be extreme versatile. What are some questions that need to be answered? What other processes does PRCP affect? What controls PRCP expression? A number of intriguing clinical observations suggest that PRCP expression and function is altered in hypertension, rheumatoid arthritis, and diabetes. How exactly does altered PRCP activity contribute to diseases such as rheumatoid arthritis and diabetes? Given these provocative findings, it is not clear whether aberrant PRCP activity actually affects patients' chance of getting these diseases. However, the results of these studies suggest that the fine-tuned PRCP-dependent pathway becomes altered with the status of cell function that in part may be utilized to determine the onset and progression of cell abnormality. The emerging evidence offers a new paradigm in understanding the function of PRCP and providing implications for the pathogenesis and treatment of cardiovascular disease.

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