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· 专家论坛 ·

Interaction Between the Receptors of Angiotensin Ⅱ and Calcitonin Gene-related Peptide: Implication in the Cardiovascular Diseases

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The vascular peptides play a key role in the development of cardiovascular diseases. Angiotensin Ⅱ(AngⅡ), a key effector of the renin-angiotensin system (RAS), induces proliferation and transformation of vascular smooth muscle cells (VSMCs), cardiac hypertrophy and so on, is thought to underlie the cardiovascular diseases, such as hypertension and heart failure. Calcitonin gene-related peptide (CGRP) is a bioactive neuropeptide released from capsaicin sensitive nervous terminal, which extensively distributes in nervous and cardiovascular system. The multiple biological effects of CGRP, such as vasolatation, inhibition of VSMC proliferation, prevention of endothelial cell (EC) apoptosis, promoting ECs proliferation, are suggested to be beneficial to cardiovascular system.

Studies demonstrated that there arebiological interactions between the CGRP and AngⅡ. It has been reported that exogenous and locally converted AngⅡ decreases the function of CGRP nerves (release CGRP) in SHRs with age, which are related to the development of chronic hypertension [1], and activation of the neuronal AT1 receptor by AngⅡ inhibits CGRP synthesis in the dorsal root ganglia[2]. Interestingly, others and our researches showed that CGRP inhibits AngⅡ-induced proliferation [3] and transformation of VSMCs[4]. AngⅡ induces EC apoptosis which is protected by CGRP[5]. These phenomenons suggested that there are interactions between the CGRP and AngⅡ in the receptor and signal pathway levels, which affect the cellular function in different cell type.

1 CGRP Receptor Remodeling

CGRP receptors have been divided into two classes referred to as CGRP1 and CGRP2. Recent data have clarified that the CGRP1 receptor is specific for CGRP [6]. Functional CGRP receptors are composed of a G protein-coupled receptor known as the calcitonin-like receptor (CRLR), a single transmembrane domain protein called receptor activity modifying protein type 1 (RAMP1), and a receptor component protein (RCP) that defines the G-protein to which the receptor couples (Fig 1). Recently, it is reported that CRLR, RAMP1 and RCP are significantly elevated in the myocardium and aorta in SHRs [7], suggesting that the CGRP receptor may be remodeling in hypertensive individual.

RAMP1 functions to traffic mature CRLR proteins to the surface of the cell membrane and plays a critical role for receptor function since it defines the relative potency of ligands for the receptor.

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CGRP-induced vasodilation is selectively enhanced following overexpression of RAMP1 [8], overexpression of human RAMP1 (hRAMP1) in transgenic rats prevented AngⅡ-induced oxidative stress and endothelial dysfunction. These datas suggest that vascular responses to CGRP are normally RAMP1-limited. The latest study founds that fugue CRLR (mfCRLR) could affect the post-translational modification and trafficking pathway of mfRAMP1. In addition, mfCRLRs boosts mfRAMP1 translocation to cell surface [9]. In addition, the CRLR/RAMP1 complex requires a third protein RCP for signaling. Previous studies have demonstrated that depletion of RCP from cells inhibits CRLR signaling, and in vivo studies have demonstrated that expression of RCP correlates with CRLR signaling and CGRP efficacy. RCP regulates CRLR signaling in the cell membrane, and direct interaction between RCP and CRLR is required for CRLR activation [10]. These data demonstrated that there is a remodeling of CGRP receptor in different cardiovascular tissues, which may be related to the development of diseases.

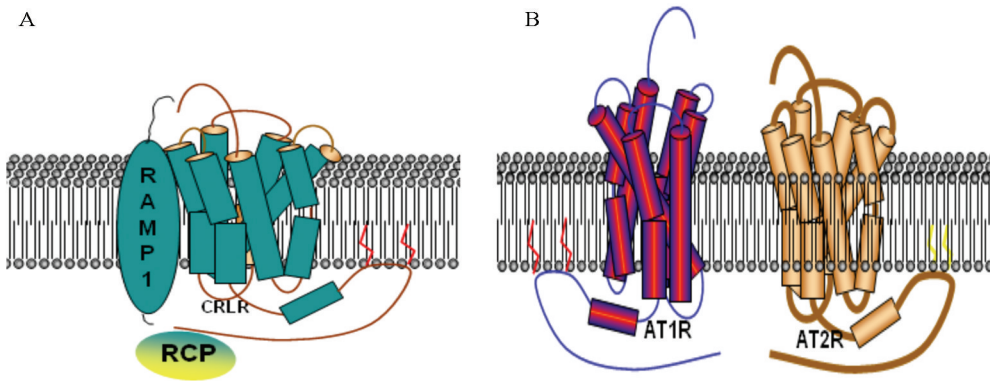

Fig. 1 Structures of the CGRP and AngII receptor A. The functional CGRP receptors are composed of calcitonin-like receptor (CRLR), receptor activity modifying protein type 1 (RAMP1), and a receptor component protein (RCP). CRLR is a G protein-coupled 7-transmembrane receptor. RAMP1 is a single transmembrane domain protein. The active receptor is a functional heterodimer of CRLR complexes with RAMP1, at the cell membrane. RCP is suggested to allow coupling to intracellular signaling pathways, and required for CRLR activation. B. AngII receptors (AT1R and AT2R) are G protein 7-transmembrane proteins, distribute in the cell membrane

2 Angiotensin Ⅱ Receptor

Angiotensin Ⅱ receptors (ATRs) widely distribute in the cardiovascular system. Two distinct ATR subtypes, the AngⅡ type1 receptor (AT1R) and type2 receptor (AT2R), have been characterized as G-protein 7-transmembrane proteins (Fig 1B). AngⅡ exerts many physiological and pathophysiological effects via AT1R, such as vasoconstriction, cardiac and vascular remodeling[11]. AT2R are significantly expressed during fetus development, but decline in the adulthood. Evidences support that AT2R became functional in response to stress and oppose the effect of AT1R under certain pathophysiological condition[12].

3 The Interactional Regulation Between the Receptors of CGRP and AngⅡ

CRLR and RAMP1 could be regulated by AngⅡ. It is reported that long-term (10 days) AngⅡ infusion increases expression of CRLR and RAMP1 in mesenteric arteries but not CGRP levels in plasma and dorsal root ganglion [13]. The increase in mesenteric CGRP receptor expression appears to be pressure dependent and to enhance the blood pressure response to CGRP[13]. while AngⅡ reduces the membrane distribution of RAMP1 but has no effect on the expression of RAMP1 in Human Umbilical Vein Endothelial Cells (HUVECs). In rat cardiomyocytes, AngⅡ significantly elevates the mRNA levels of RAMP1 without a change of CRLR[14]. RAMP1 attenuates AngⅡ-induced hypertension and increases baroreflex sensitivity in turn [15]. Our study also finds that overexpression of RAMP1 significantly enhances the inhibitory effect of CGRP on the proliferation of VSMC induced by AngⅡ [16]. In addition, AngⅡ increases the gene expression of left ventricular CRLR in different types of cardiac overload including pressure overload (POL) and volume overload (VOL) [17]. All these datas indicate that the irritating receptor remodel of AngⅡ or CGRP can be regulated by the opposing ligands, respectively.

4 The Key Proteins in the SignalPathways Cross Talking Between the Receptors of CGRP and AngⅡ

4.1 Caveloae/Caveolin-1

Caveolae are unique flask-shaped nonclathrin-coated plasma membrane microdomains. It has been demonstrated that many signaling molecules dockes within caceolae, such as BK channels, AT_1R, $G_{\alpha q/11}$, non-phagocytic NADPH oxidases (NOX) and c-Src kinases (c-Src) [18]. Alterations in components of the caveolae have been shown to have profound effects both on caveolae formation and on a multitude of intracellular signaling pathways. The main component of caveolae in vascular tissues, caveolin-1, has also been shown to associate with important modulators of cardiovascular homeostasis, such as the endothelial nitric oxide synthase (eNOS) and AT1R. Recent studies showed that the expression and/or phosphorylation of caveoin-1 is regulated by CGRP and/or AngⅡ. AngⅡ

significantly decreases the caveolin-1 protein expression, which is significantly increased by AT1R antagonist, CV-116 in rats[19]. Ang Ⅱ causes tyrosine 14 phosphorylation of caveoin-1 through AT1R→Gβγ→c-Src→c-Abl signaling and facilities the AT1R translocation into caveolae to regulate cardiovascular homeostasis [20-21]. In addition, CGRP activates G-protein βγ subunits in VSMC[22]. $G_{\beta\gamma}$ activates c-Src kinase (c-Src), which in turn activates c-Abl tyrosine kinase, causes phosphorylation of caveoin-1, CRLR interacts with caveoin-1 in caveolae (unpublished). These datas indicate that CGRP may regulate caveoin-1 phosphorylation via Gβγ→c-Src→c-Abl axis.

Infection of adenovirus encoding caveoin-1 markedly inhibites AngⅡ-induced ERK activation in ECs . CGRP up-regulates ERK2 expression to antagonize high glucose-induced HUVECs apoptosis [23] and decreases the expression of caveoin-1 to have a protective effect on HUVECs injured by H_2O_2 which is enhanced after the destruction of caveolae by β-cyclodextrin [24]. The results show that CGRP inhibits AngⅡ-induced proliferation via CGRP1→caveoin-1→ERK pathway possibly. However, CGRP increases the expression of caveoin-1 in hypertrophic VSMCs, which is contributed to the inhibitions of hypertrophic VSMCs proliferation induced by AngⅡ[25]. In the same way, the NOX and eNOS signaling pathways also are regulated by caveolae / caveolin-1 in the presence of CGRP and AngⅡ through mechanisms including caveolin phosphorylation [21, 26-27] (Fig 2).

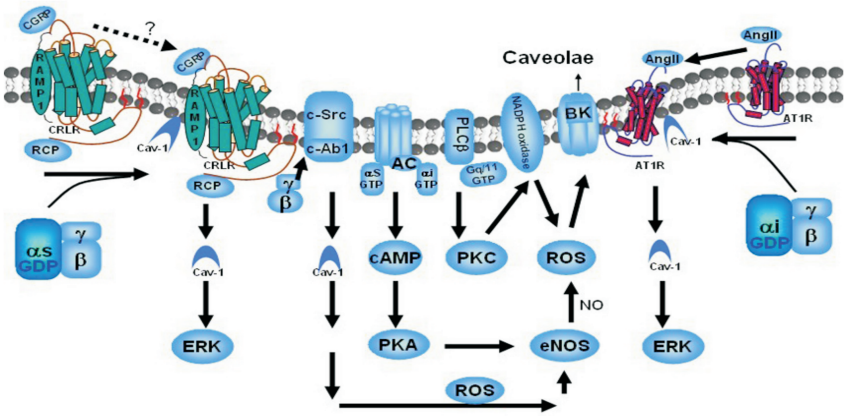

Fig. 2 Cross talking at the caveolae/caveolin－1 level between the receptors of CGRP and Ang Ⅱ

4.2 G Proteins

G proteins (guanine nucleotide-binding proteins) are a family of proteins involved in transmitting chemical signals outside the cell and changing the activity of enzymes inside the cell. Receptor-activated G proteins consist of the Gα and the tightly associated Gβγ subunits. There are many classes of Gα subunits including Gsα (G stimulatory), Giα (G inhibitory), Goα (G other), Gαq/11, and Gα12/13. They behave differently in the recognition of the effectors, but share a similar mechanism of activation. Gsα and Giα activate the cAMP-dependent pathway. Gα12/13, Gβγ and Gαq/11 activate the Inositol Phospholipid dependent pathway (Fig 2).

G proteins communicate signals from many hormones, neurotransmitters, and other signaling factors. AngⅡ activates several signaling pathways to exert its physiological and pathological effects depending on G protein activation: Giα for the cAMP pathway and Gαq/11 for the PLC pathway, Gβγ/Gα12 for the PLD pathway, additionally AngⅡ also activates Gαq/11→Ca^{2+}→AC→cAMP pathway. In VSMCs, AngⅡ enhances the expression of Giα proteins[28] and activates Giα / MAP kinase / PI3K / Akt pathways [29] contributing to the proliferation. Additionally, Gαq/11 or Gα12 combines with Gβγ irriates PLCβ→IP3→Ca^{2+}, PLCβ→DAG→PKC and Src→ PLD signal pathways which are activated by AngⅡ [20, 30]. AngⅡ contributes to VSMC hypertrophy via Gq→Ca^{2+}→EGF-R→Ras signaling pathway [31].

Like manyG proteins coupled receptors (GPCRs), the CGRP receptor appears to be promiscuous, potentially coupling to several G proteins and intracellular pathways. Although the main second messenger produced in response to CGRP remains cAMP in various cell types, probably via Gαs-protein, there are also more data strongly suggest that the signaling of CGRP is due to the activation of more than one G-protein: Gsα for the AC→cAMP→PKA[32] and GC→cGMP→PKG pathways [33]; Gαq/11 for the PLCβ1→IP3→Ca^{2+} pathway [32] and Gβγ for the PLD pathway. In addition, CGRP receptors in the gerbil spiral modular artery mediate a sustained vasodilation via a transient cAMP-mediated Ca^{2+}-decrease[34] (Fig3).

4.3 NADPH Oxidases

Noxs, major sources of produce reactive oxygen species (ROS) in non-phagocytic cells, are increasingly recognized as important mediators and modulators of intracellular signal transduction pathways involved in atherosclerosis, VSMCs and cardiac hypertrophy, endothelial activation, and other conditions. Each Nox family member contains a distinct NOX subunit (NOX1-5). In cardiovascular system, NOX1 is expressed mainly in VSMCs; Nox2 in ECs, cardiomyocytes, fibroblasts, and some VSMCs; Nox4 in ECs, VSMCs, cardiomyocytes, and fibroblasts, and Nox5 in human endothelial cells. MAPKs, tyrosine kinases, NF-kB and the Akt / GSK3β pathways are among the redox-sensitive kinases that may be activated by NOXs, depending on cell type and agonist.

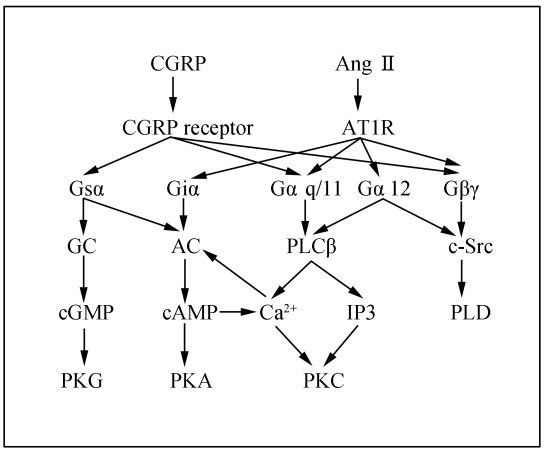

Fig. 3 Cross talking in G-protein dependent signal pathways between the receptors of CGRP and Ang Ⅱ

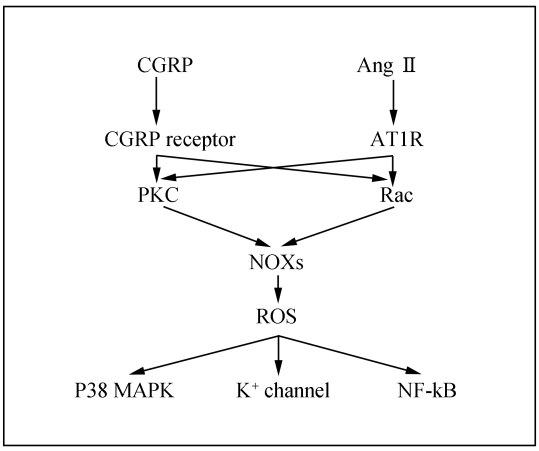

Fig. 4 Cross talking in signal pathways of NADPH oxdiases activation between the receptors of CGRP and Ang Ⅱ

AngⅡ is a potent stimulator for vascular and renal Noxs, which has been functionally linked to Nox1, Nox2 and variably to Nox4 in the vasculature. In VSMCs, Ang Ⅱ increases Noxs activity and Nox1/ Nox4 mRNA [35-36]. Moreover, AngⅡ induces an upregulation of NOX1 [35] and uncouples eNOS [37] through PKC activation, thus increasing ROS production in a positive feedback fashion. It is reported that CGRP counteracts AngⅡ-induced endothelial progenitor cells (EPCs) senescence through down-regulating the expression of NOXs and ROS production [38].

AngⅡ-stimulated ROS production is biphasic. The first phase occurs rapidly (peak at 30 s) depending on PKC activation. The larger second phase of ROS generation (peak at 30 min) requires Rac and Src activation. We find that CGRP inhibits AngⅡ-induced cell proliferation via Nox1/ p38MAPK pathway[3]. Exogenous H_2O_2 increases the expression of NOX4 and p38MAPK phosphorylation, CGRP reverses this effect, this data indicates that CGRP protects HUVEC injury induced by H_2O_2 via Nox4/ p38 MAPK pathway [5]. The cross talking in Noxs level between the receptors of CGRP and AngⅡ is summarized in Fig 4.

4.4 MAPKs

Mammalian mitogen-activated proteinkinases (MAPKs) family are important enzymes that connect the activation of cell surface receptors to key regulatory events within the cell via a series of reversible phosphorylation events. MAPKs include extracellular signal-regulated kinase (ERKs), c-Jun amino-terminal kinase (JNK), and p38 MAP kinase. The phosphorylation of ERKs regulated by Ras proteins and G-proteins leads to the activation of the Raf-1→MEK1/2→ERK1/2 signaling pathway. Activation of MAPK phosphorylates the kinase Rsk, the nuclear proteins c-Fos, Elk-1, c-Myc and perhaps other proteins which collectively contribute to mitogenesis. The other two activated MAPKs translocate to nucleus, at least in part, regulating the activity of transcription factors: p38MAPK for ATF1 and -2, MEF2A, Sap-1, Elk-1, NF-kB, Ets-1, and p53; JNKs for c-Jun , ATF2 and Elk-1.

Activation of CGRP receptors increases cAMP and cGMP levels in a number of different cell types. However, CGRP receptors have also been reported to activate MAPKs signaling. Recently, studies show that CGRP increases ERK1/2 and P38 MAPK, JNK activities in a time- and concentration-dependent fashion in Human keratinocyte and neuroblastoma cells [39-41], which are related to the cell proliferation and inflammation. Our research also suggest that CGRP increase the p-ERK1/2 expression in quiescent cells but decreased in proliferation cells induced by AngⅡ or FSB[42-43], and increases p53 and p21 expression in aortic smooth muscle cell [33].

Studies show that AngⅡ evokes Ras→ERK1/2→p70S6K and Ras→PI3K→Akt/PKB→mTOR→p70S6K signal pathways [44], and increases phosphorylation of p38MAPK [3]. Further more, AngⅡ-induced VSMC migration by ERK1/2 activation has been reported to be mediated by c-Src and AngⅡ via c-Src stimulates Ca^{2+}-dependent protein-kinase related protein kinase associated substrate that promotes VSMC migration by activating c-JNK[45]. AngⅡ can also mediate activation of transcription factors, such as c-fos, c-Myc, NF-kB, ATF-2, c-Jun, MEF-2, HIF-1alpha, Ets-1, p53, p16 and AP-1 [46-48], which are the targets of MAPKs in nucleus. All these studies suggest that at the level of MAPKs there is a cross talk which is regulated by CGRP and AngⅡ via their receptors respectively (Fig 5).

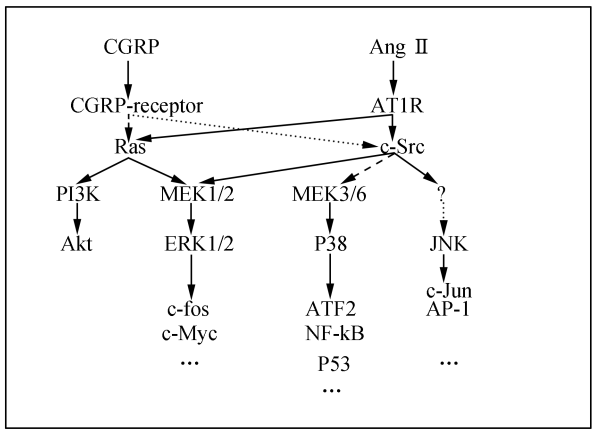

Fig. 5 Cross talking in MAPKs-dependent pathways between the receptors of CGRP and Ang Ⅱ

5 Summary

Interaction of receptors occurs at cell membrane, cytoplasm and nucleus, which involves cell signal transduction, signal integration and genetic transcription. Over expression of AngⅡ not only decreasing the synthesis and release of CGRP but also decreasing the sensitivity of CGRP receptor, which may be related to the development of cardiovascular diseases, such as hypertension, arthrosclerosis, and heart failure. Further understanding the regulatory factors, such as microRNA, in the interaction between the receptors of CGRP and AngⅡ would be reveal the multiple biological effects of CGRP on the different type cells and the development of cardiovascular diseases.

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血管紧张素Ⅱ受体与降钙素基因相关肽受体间相互调节在心血管疾病中的意义

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摘 要: 血管紧张素Ⅱ受体(ANGⅡR)和降钙素基因相关肽受体(CGRPR)同属于 G 蛋白藕联受体家族。研究发现,单独激活 ANGⅡR 或 CGRPR 和同时激活两受体对细胞的命运表现出不同甚至相反的作用。目前已知,CGRP 受体是由降钙素受体样受体(CRLR)、受体活性修饰蛋白-1(RAMP1)、受体组分蛋白(RCP)3 个组分组成。ANGⅡR 和 CGRPR 间的相互作用可能发生在细胞膜的信号转导、细胞浆信号通路以及核内的基因转录等水平。本文综述了 ANGⅡR 和 CGRPR 在跨膜信号蛋白(如 G 蛋白及 caveolae/caveoilins)、胞浆-胞核内信号蛋白(如 NADPH 氧化酶、MAPK 家族)水平的相互作用,可望从心血管受体间信号整合改变的新视角来解释心血管疾病的发病机制。

关键词: 血管紧张素Ⅱ; 降钙素基因相关肽; 受体; 信号通路; 相互作用

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