Rev Port Cardiol. 2014;33(7–8):439–449

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

REVIEW ARTICLE

Cardiovascular effects of the angiotensin type 2 receptor☆

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Received 20 December 2013; accepted 2 February 2014
Available online 26 August 2014

KEYWORDS
Angiotensin type 2 receptor;
Renin–angiotensin system;
Cardiovascular system;
Hypertension;
Myocardial infarction

Abstract The angiotensin type 2 receptor, AT_2R, has been described as having opposite effects to the angiotensin type 1 receptor, AT_1R. Although the quantities of the AT_2R found in the adult are low, its expression rises in pathological situations. The AT_2R has three major signaling pathways: activation of serine/threonine phosphatases (promoting apoptosis and antioxidant effects), activation of the bradykinin/NO/cGMP pathway (promoting vasodilation), and activation of phospholipase A2 (associated with regulation of potassium currents). The AT_2R appears to have effects in vascular remodeling, atherosclerosis prevention and blood pressure lowering (when associated with an AT_1R inhibitor). After myocardial infarction, the AT_2R appears to decrease infarct size, cardiac hypertrophy and fibrosis, and to improve cardiac function. However, its role in the heart is controversial. In the kidney, the AT_2R promotes natriuresis. Until now, treatment directed at the renin–angiotensin–aldosterone system has been based on angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers. The study of the AT_2R has been revolutionized by the discovery of a direct agonist, C21, which promises to become part of the treatment of cardiovascular disease.

PALAVRAS-CHAVE
Recetor da angiotensina tipo 2;
Sistema renina-angiotensina-aldosterona;

Efeitos cardiovasculares do receptor tipo 2 da angiotensina

Resumo O recetor da angiotensina do tipo 2, AT_2R, tem vindo a ser descrito como tendo ações opostas ao recetor da angiotensina do tipo 1, AT_1R. Apesar do AT_2R existir em baixas quantidades no adulto, a sua expressão sobe bastante em situações patológicas. O AT_2R tem três grandes vias de sinalização: a ativação fosfátases de serina/treonina (promoção da apoptose celular e

☆ Please cite this article as: Faria-Costa G, Leite-Moreira A, Henriques-Coelho T. Efeitos cardiovasculares do receptor tipo 2 da angiotensina. Rev Port Cardiol. 2014;33:439–449.

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Sistema cardiovascular;
Hipertensão;
Enfarte agudo do miocárdio

efeitos antioxidantes); ativação da via bradiquinina/NO/cGMP (promoção de vasodilatação) e ativação da fosfolípase A_2 (associada ao controlo das correntes de potássio). O AT_2R parece ter um efeito na remodelação vascular, na prevenção da aterosclerose e na descida da pressão sanguínea (quando associada a um inibidor do AT_1R). Após enfarte do miocárdio, o AT_2R parece diminuir o tamanho do enfarte, a hipertrofia cardíaca, a fibrose e aumentar a função cardíaca. Contudo, o seu papel a nível cardíaco é o mais controverso. A nível renal o AT_2R promove a natriurese. Até agora, a terapêutica direcionada para o sistema renina-angiotensina-aldosterona é à base de inibidores da enzima de conversão da angiotensina (IECA) ou de inibidores do recetor da angiotensina tipo 1 (ARA). O estudo do AT_2R foi revolucionado pela descoberta de um agonista direto, o C21, que promete integrar parte da terapêutica das doenças cardiovasculares.

Introduction

In the renin–angiotensin–aldosterone system (RAAS), the most widely studied angiotensin (Ang) II receptor is the type 1 receptor, AT_1R. This receptor is responsible for most of the effects of RAAS activation, including vasoconstriction, sodium retention, aldosterone release, cell proliferation, cardiac and vascular hypertrophy, and modulation of oxidative stress and inflammation. Ang II also binds to another receptor, AT_2R, which was discovered over 20 years ago.[1] However, its functions are still not fully understood. Activation of the AT_2R has been reported as having opposite effects to that of the AT_1R,[2–5] and thus appears to have a protective effect in conditions such as hypertension, atherosclerosis and myocardial infarction (MI). Both the AT_1R and the AT_2R are G protein-coupled receptors (GPCRs)[6] with 34% sequence homology.[7] Various GPCR-interacting proteins (GIPs) also interact with these receptors, binding to the C-terminus.[8,9] In adults, the AT_1R is expressed ubiquitously, while the AT_2R is found in low quantities, mainly in the blood vessels, kidneys, adrenal medulla, uterus and ovaries, heart, and certain brain nuclei.[2,10] However, its expression rises in the above pathological situations. The physiological role of the AT_2R in adults is thus insignificant, but in the fetus, the opposite is seen: the AT_2R is more abundant, which may be related to its function in general physiological development.

The aim of this review is to describe the functions of the AT_2R in the cardiovascular system and to investigate their role in possible treatments.

Signal transduction pathways of the AT_2R

The Ang II receptors form homodimers and heterodimers between each other. The homodimers AT_1R/AT_1R and AT_2R/AT_2R strengthen the effects of their respective receptors.[9] Formation of the heterodimer AT_1R/AT_2R reduces the signaling of the AT_1R, one way in which the AT_2R directly inhibits the effects of the AT_1R.[11] The AT_2R also forms heterodimers with the bradykinin B2 receptor (B_2R), increasing production of nitric oxide (NO).[12] This interaction is important in the kinin/NO/cGMP system.

Once activated, the AT_2R has three main signaling pathways: activation of serine/threonine phosphatases, activation of the bradykinin/NO/cGMP pathway, and activation of phospholipase A2[13] (Figure 1).

With regard to phosphatases, the role of the AT_2R has been studied in the activation of MAP kinase phosphatase (MKP-1), protein phosphatase 2 (PP2A) and SH2 domain-containing tyrosine phosphatase (SHP-1).[3,13]

Activation of MKP-1 and PP2A by the AT_2R results in inhibition of ERK1/2 (ERK1/2), inducing apoptosis. When activated, SHP-1 inhibits ERK1/2 and NAD(P)H oxidase (stimulated by the AT_1R[14]), and is thus part of the endothelium's oxidative stress defense.[15]

Activation of the bradykinin/NO/cGMP pathway is associated with vasodilation.[4,16] When activated, the AT_2R stimulates the B_2R receptor, which in turn induces phosphorylation of endothelial nitric oxide synthase (eNOS) at Ser^{633} and Ser^{1177} via a PKA-mediated signaling pathway.[17] NO production is thus increased, activating guanylate cyclase (sGC), which synthesizes cGMP from GTP, in turn promoting vasodilation. Although these mechanisms have been described before,[16,18] the role of the AT_2R in regulation of blood pressure (BP) is still the subject of debate.[1]

The AT_2R also stimulates phospholipase A_2 (PLA_2) activity and arachidonic acid (AA) formation; the latter regulates potassium currents and can lead to cell hyperpolarization and reduced excitability.[3,19] This effect appears to be particularly important in reducing sympathetic activity.[20]

Guilluy et al.[21] described an alternative signaling pathway to the bradykinin/NO/cGMP system in vascular smooth muscle cells that culminates in phosphorylation and inactivation of RhoA on Ser^{188}, leading to vasodilation (Figure 2). Ste20-related kinase (SLK) is responsible for this phosphorylation, which is independent of eNOS, PKA and PKG. The effect is weakened when SLK is phosphorylated, hence SLK phosphorylates RhoA when in the dephosphorylated state. Meanwhile, casein kinase 2 (CK2) is responsible for the basal phosphorylation of SLK. The role of the AT_2R in this pathway is thus to reduce the activity of CK2 in order to increase the quantity of dephosphorylated SLK. Since CK2 is active when phosphorylated, the AT_2R achieves its