Available online at www.sciencedirect.com
SCIENCE DIRECT®
PEPTIDES
Peptides 26 (2005) 1676–1685
www.elsevier.com/locate/peptides

Review

Calcitonin gene-related peptide and hypertension

Pan-Yue Deng, Yuan-Jian Li *

Department of Pharmacology, School of Pharmaceutical Sciences, Central South University, Xiang-Ya Road #90, Changsha, Hunan 410078, China

Received 8 December 2004; received in revised form 31 January 2005; accepted 1 February 2005
Available online 2 March 2005

Abstract

Capsaicin-sensitive sensory nerves participate in the regulation of cardiovascular functions both in the normal state and the pathophysiology of hypertension through the actions of potent vasodilator neuropeptides, including calcitonin gene-related peptide (CGRP). CGRP, a very potent vasodilator, is the predominant neurotransmitter in capsaicin-sensitive sensory nerves, and plays an important role in the initiation, progression and maintenance of hypertension via: (1) the alterations in its synthesis and release and/or in vascular sensitivity response to it; (2) interactions with pro-hypertensive systems, including renin–angiotensin–aldosterone system, sympathetic nervous system and endothelin system; and (3) anti-hypertrophy and anti-proliferation of vascular smooth muscle cells. The decrease in CGRP synthesis and release contributes to the elevated blood pressure, as shown in the spontaneously hypertensive rats, α-CGRP knockout mice, Dahl-salt or phenol-induced hypertensive rats. In contrast, the increase in CGRP levels or the enhancement of vascular sensitivity response to CGRP plays a beneficial compensatory depressor role in the development of hypertension, as shown in deoxycorticosterone-salt, sub-total nephrectomy-salt, N^{ω}-nitro-L-arginine methyl ester or two-kidney, one-clip models of hypertension in rats. We found that rutaecarpine causes a sustained depressor action by stimulation of CGRP synthesis and release via activation of vanilloid receptor subtype 1 (VR1) in hypertensive rats, which reveals the therapeutic implications of VR1 agonists for treatment of hypertension.

Keywords: Calcitonin gene-related peptide (CGRP); Hypertension; Sensory nerve; Renin–angiotensin–aldosterone system; Sympathetic nervous system; Endothelin

Contents

* Corresponding author. Tel.: +86 731 235 5076; fax: +86 731 235 5078.
E-mail address: yuan_jianli@yahoo.com (Y.-J. Li).

0196-9781/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.peptides.2005.02.002

1. Introduction

Hypertension is the most common cardiovascular disease in humans. Hypertensives often have other cardiovascular risk factors, including left ventricular hypertrophy, obesity, diabetes, elevated cholesterol levels, and reduced high-density lipoproteins [81]. The severe consequences of hypertension involve stroke, heart failure, myocardial infarction and renal failure. Most patients with essential hypertension have abnormalities in myocardium, vascular smooth muscle or endothelium, and in physiological regulatory system for blood pressure (BP), including neurotransmitters and humoral factors. Although it is often unclear that the abnormalities are causes or consequences of hypertension [6], these changes are the characteristics of human hypertension that animal models should mimic. Many studies have been undertaken using animal models of hypertension to elucidate the mechanisms underlying the pathogenesis, development and maintenance of hypertension, which may greatly contribute to the prevention from and therapy for hypertension.

Increased peripheral vascular resistance maintains the elevated BP in hypertension [52,88], so impairment of its control might be causative of hypertension [26]. The cardiovascular system is widely innervated both by sympathetic and capsaicin-sensitive sensory nerves [5], which play significant roles in controlling the resistance vascular tone through the release of two classes of vasoactive neurotransmitters, vasoconstrictors and vasodilators. Calcitonin gene-related peptide (CGRP), a very potent vasodilator, is the prominent neurotransmitter in the capsaicin-sensitive sensory (CGRPergic) nerves [3], and plays an important role in modulating the total peripheral resistance of the systemic circulation [48]. In addition to CGRP, there are two members in the CGRP superfamily: adrenomedullin and amylin. They can decrease BP and may be playing a role in the development of hypertension, which have been discussed by others [4,32,33,40,41,54,83,84]. The present review mainly focused on the evidence for the role of CGRP in the regulation of BP and in the initiation, development and maintenance of hypertension, and the potential therapeutic implications related to CGRP in hypertension.

CGRP is a 37-amino acid residue vasoactive neuropeptide. There are two CGRP genes, α and β. The α-CGRP is produced by the tissue-specific splicing of the primary RNA transcript of the calcitonin/CGRP gene in nervous system [60]. The β-CGRP also mainly occurs in neuronal tissues [8,82]. The two CGRP isoforms, α and β in rats and I and II in humans, differ in their peptide sequences by one and three amino acids, respectively, and the biological activities of the two peptides are quite similar in most vascular beds [3].

2. Distribution of CGRP

CGRP is widely distributed in the nervous and cardiovascular systems and often coexists with substance P (SP)

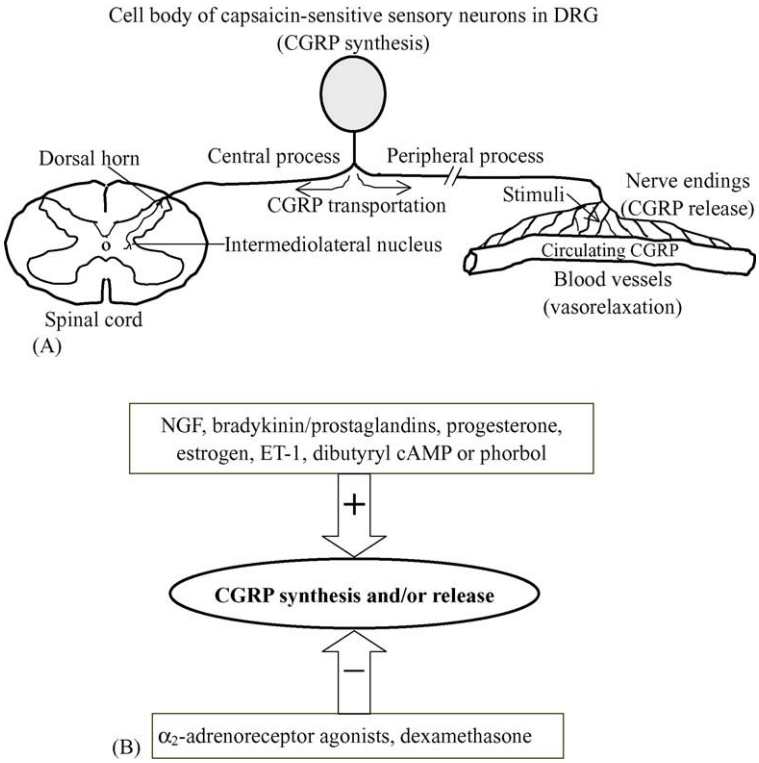

Fig. 1. (A) Schematic illustration of the functional anatomy of the capsaicin-sensitive sensory neurons, indicating the pathway of CGRP synthesis, release and action. (B) Factors those modulating CGRP synthesis and release.