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ScienceDirect
Regulatory Peptides 143 (2007) 15–27
REGULATORY PEPTIDES
www.elsevier.com/locate/regpep

Review

Enzymatic pathways of the brain renin–angiotensin system: Unsolved problems and continuing challenges

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Received 15 February 2007; received in revised form 18 March 2007; accepted 19 March 2007
Available online 30 March 2007

Abstract

The brain renin–angiotensin system continues to be enigmatic more than 40 years after the brain was first recognized to be a site of action of angiotensin II. This review focuses on the enzymatic pathways for the formation and degradation of the growing number of active angiotensins in the brain. A brief description and nomenclature of the peptidases involved in the processing of angiotensin peptides in the brain is given. Of primary interest is the array of enzymes that degrade radiolabeled angiotensins in receptor binding assays. This poses major challenges to studies of brain angiotensin receptors and it is debatable whether an accurate determination of brain angiotensin receptor binding kinetics has yet been made. The quandary facing the investigator of brain angiotensin receptors is the need to protect the radioligand from metabolic alteration while maintaining the characteristics of the receptors *in situ*. It is the tenet of this review that we have yet to fully understand the binding characteristics of brain angiotensin receptors and the extent of their distribution in the brain because of our inability to fully protect the angiotensins from metabolic alteration until equilibrium binding conditions can be attained.

Keywords: Angiotensin receptors; Metabolism; Radioligand binding assays; Angiotensinases; Peptidases

Contents

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0167-0115/$ - see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.regpep.2007.03.006

1. Introduction

The first definitive demonstration of an effect of angiotensin II (Ang II) in the brain was the cross perfusion study of Bickerton and Buckley [1]. However, this effect was produced by blood-borne Ang II later recognized to be mediated by the circumventricular organs of the brain which are outside of the blood–brain-barrier. A subsequent casual observation by Booth [2] revealed that Ang II acts within the brain which initiated an interest in the possible existence of a brain renin–angiotensin system (RAS). A few years later, Ganten et al. [3] reported the existence of renin-like activity in the brain and research on the brain RAS began in earnest.

1.1. Roles of the brain renin–angiotensin system

The influence of the brain RAS on hydromineral balance, arterial blood pressure, neurosecretory functions and overall body homeostasis is well documented. There are several excellent review articles covering early studies of the brain RAS [4–6].

While these 'traditional' functions of angiotensins in the brain have been established for some time, the recognition of the presence of multiple receptor subtypes for angiotensins in the brain as well as novel functions for metabolites of the octa- and heptapeptide angiotensins has greatly extended the range of activities attributed to the brain RAS. More recent reviews cover these aspects of the brain RAS [7–12].

1.2. Generation and degradation of angiotensin peptides in the brain

The rate of synthesis as well as the rate of degradation of neurotransmitters and neuromodulators is an important factor in initiating and terminating their biological effects. This principle applies to peptide hormones as well. They are regulated by proteases (otherwise called peptidases, proteinases or proteolytic enzymes) that generate and metabolize them [13–15]. The human genome encodes several hundred proteases, of which the function of many has not yet been determined. Peptidases involved in processing of angiotensin peptides have been collectively termed "angiotensinases". While the term has largely been used to infer degradation, it is now know that these enzymes can generate active angiotensins. Angiotensinases are comprised of three groups of peptidases: amino-, endo- and carboxypeptidases. Aminopeptidases have traditionally been viewed as the most important group, accounting for 60–90% of angiotensinase activity in various tissues [16] however, it is now known that angiotensin peptides are processed by a broad variety of peptidases.

2. Angiotensin-forming enzymes

The formation of the primary active angiotensin, Ang II is considered to occur via a cascade of enzymatic reactions, starting with a large protein precursor. The fact that the enzyme renin was the first component of the RAS to be discovered has led to the naming of this hormonal system as the renin–angiotensin system. However, as will be seen, renin is certainly not the only angiotensin-forming enzyme. However, out of respect for the discovery of renin by Tigerstedt and Bergstrom [17], use of the term renin–angiotensin system likely will continue. In Section 2 the primary focus will be on formation of Ang II and Ang III from angiotensinogen and Ang I, as they are the angiotensins that act on the classical AT1 and AT2 receptors. The formation of the other active angiotensins from Ang I, Ang II and Ang III, which act on receptors other than AT1 and AT2, are pirmarily addressed in Section 3.

2.1. Renin

The only known substrate for renin is angiotensinogen, which is the only known precursor for the active octapeptide