

Angiotensin IV [AT II (3-8)] : A Potent Neuropeptide and ACE Inhibitor

Angiotensin IV in the central nervous system

The mammalian brain harbors a renin-angiotensin system (RAS), which is independent from the peripheral RAS. Angiotensin II is a well-studied member of the RAS and exerts most of the known angiotensin-mediated effects on fluid and electrolyte homeostasis, autonomic activity, neuroendocrine regulation, and behavior. This review summarizes a mass of compelling new evidence for the biological role of an active (3-8) fragment of angiotensin II, named angiotensin IV. Angiotensin IV binds to a widely distributed binding site in the brain, but which is different from the known angiotensin II receptors AT1 and AT2. Angiotensin IV has been implicated in a number of physiological actions, including the regulation of blood flow, the modulation of exploratory behavior, and processes attributed to learning and memory. Furthermore, angiotensin IV may also be involved in neuronal development. Collectively, the available evidence suggests that angiotensin IV is a potent neuropeptide, involved in a broad range of brain functions. Von Bohlen Und Halbach O. Cell Tissue Res 2003 Jan;311(1):1-9

AT(4) receptor is insulin-regulated membrane aminopeptidase: potential mechanisms of memory enhancement

Although angiotensin IV (Ang IV) was thought initially to be an inactive product of Ang II degradation, it was subsequently shown that the hexapeptide markedly enhances learning and memory in normal rodents and reverses the memory deficits seen in animal models of amnesia. These central nervous system effects of Ang IV are mediated by binding to a specific site, known as the AT(4) receptor, which is found in appreciable levels throughout the brain and is concentrated particularly in regions involved in cognition. This field of research was redefined by the identification of the AT(4) receptor as the transmembrane enzyme, insulin-regulated membrane aminopeptidase (IRAP). Here, we explore the potential mechanisms by which Ang IV binding to IRAP leads to the facilitation of learning and memory. Albiston AL, et al. Trends Endocrinol Metab 2003 Mar;14(2):72-7

Cellular targets for angiotensin II fragments: pharmacological and molecular evidence

Although angiotensin II has long been considered to represent the end product of the renin-angiotensin system (RAS), there is accumulating evidence that it encompasses additional effector peptides with diverse functions. In this respect, angiotensin IV (Ang IV) formed by deletion of the two N terminal amino acids, has sparked great interest because of its wide range of physiological effects. Among those, its facilitatory role in memory acquisition and retrieval is of special therapeutic relevance. High affinity binding sites for this peptide have been denoted as AT(4)- receptors and, very recently, they have been proposed to correspond to the membrane-associated OTase/ IRAP aminopeptidase. This offers new opportunities for examining physiological roles of Ang IV in the fields of cognition, cardiovascular and renal metabolism and pathophysiological conditions like diabetes and hypertension. Still new recognition sites may be unveiled for this and other angiotensin fragments. Recognition sites for Ang-(1-7) (deletion of the C terminal amino acid) are still elusive and some of the actions of angiotensin III (deletion of the N terminal amino acid) in the CNS are hard to explain on the basis of their interaction with AT(1)-receptors only. A more thorough cross-talk between in vitro investigations on native and transfected cell lines and in vivo investigations on healthy, diseased and transgenic animals may prove to be essential to further unravel the molecular basis of the physiological actions of these small endogenous angiotensin fragments. Vauquelin G, et al. J Renin Angiotensin Aldosterone Syst 2002 Dec;3(4):195-204

Comparative effects of angiotensin IV and two hemorphins on angiotensin-converting enzyme activity

The role of angiotensin IV (AngIV) in the regulation of angiotensin-converting enzyme (ACE) was studied in vitro. This study demonstrates that this active fragment appeared as a novel endogenous ACE inhibitor. Inhibitory kinetic studies revealed that AngIV acts as a purely competitive inhibitor with a $K(i)$ value of 35 μ M. AngIV was found to be quite resistant to ACE hydrolysis opposite to hemorphins which are both ACE inhibitors and substrates. In order to confirm a putative role of AngIV and hemorphins in the Renin-Angiotensin system (RAS) regulation, we studied their influence on AngI conversion. We noticed that 16.7 μ M of both peptides decreased more than 50% of AngI conversion to AngII in vitro. The capacity of hemorphins, particularly LVVH-7, and AngIV to inhibit ACE activity here suggests a synergistic relation between these two peptides and the regulation of RAS. Fruitier-Arnaudin I, et al. Peptides 2002 Aug;23(8):1465-70

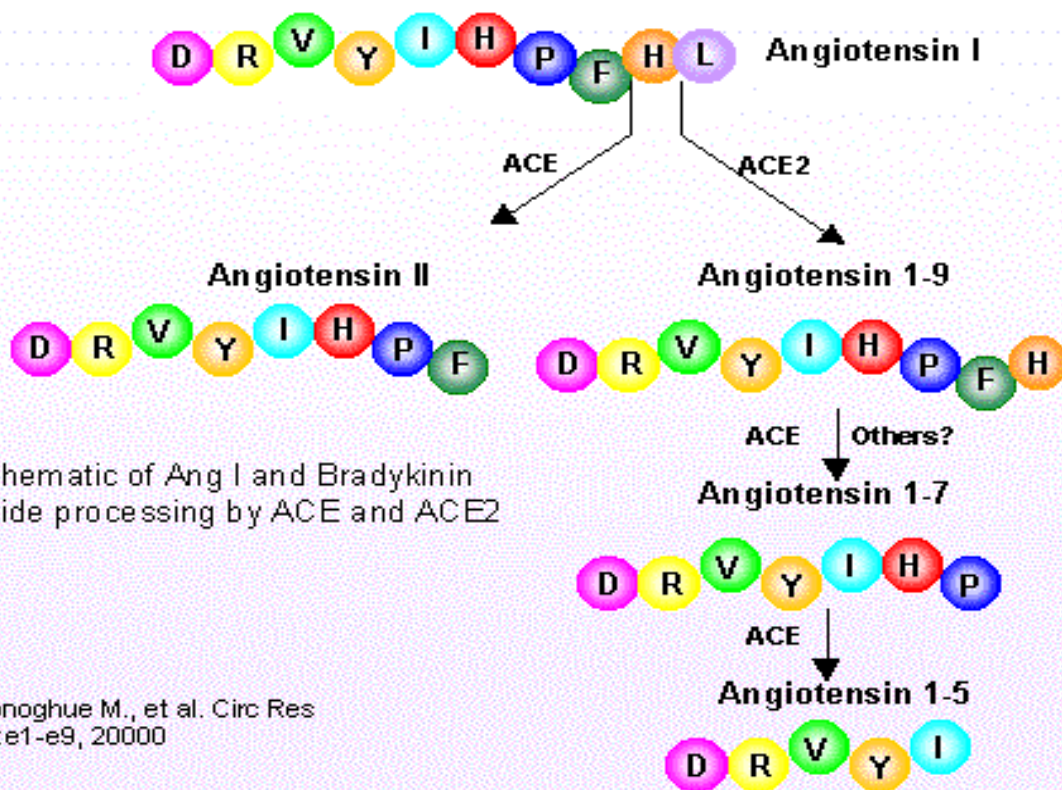
Neuropeptide conversion to bioactive fragments - an important pathway in neuromodulation

Biosynthetic pathways for the formation of neuroactive peptides and the processes for their inactivation include several enzymatic steps. In addition to enzymatic processing and degradation, several neuropeptides have been shown to undergo enzymatic conversion to fragments with retained or modified biological activity. This has most clearly been demonstrated for e.g. opioid peptides, tachykinins, calcitonin gene-related peptide (CGRP) as well as for peptides belonging to the renin-angiotensin system. Sometimes the released fragment shares the activity of the parent compound. However, in many cases the conversion reaction is linked to a change in the receptor activation profile, i.e. the generated fragment acts on and stimulates a receptor not recognized by the parent peptide. This review will describe the characteristics of certain neuropeptide fragments having the ability to modify the biological action of the peptide from which they are derived. Focus will be directed to the tachykinins, the opioid peptides, angiotensins as well as to CGRP, bradykinin and nociceptin. The kappa opioid receptor selective opioid peptide, dynorphin, recognized for its ability to produce dysphoria, is converted to the delta opioid receptor agonist Leu-enkephalin, with euphoric properties. The tachykinins, typified by substance P (SP), is converted to the bioactive fragment SP(1-7), a heptapeptide mimicking some but opposing other effects of the parent peptide. The bioactive angiotensin II, known to bind to and stimulate the AT-1 and AT-2 receptors, is converted to angiotensin IV (i.e. angiotensin 3-8) with preference for the AT-4 sites or to angiotensin (1-7), not recognized by any of these receptors. Both angiotensin IV and angiotensin (1-7) are biologically active. For example angiotensin (1-7) retains some of the actions ascribed for angiotensin II but is shown to counteract others. Thus, it is obvious that the activity of many neuroactive peptides is modulated by bioactive fragments, which are formed by the action of a variety of peptidases. This phenomenon appears to represent an important regulatory mechanism that modulates many neuropeptide systems but is generally not acknowledged. Hallberg M, Nyberg F. *Curr Protein Pept Sci* 2003 Feb;4(1):31-44

Effects of angiotensins II and IV on blood pressure, renal function, and PAI-1 expression in the heart and kidney of the rat

The role of angiotensin II (AII) and angiotensin IV (AIV) as inducers of PAI-1 expression during hypertension was studied in vivo. A 2-week infusion of AII (300 ng/kg/min) via an osmotic pump increased systolic blood pressure (171.2 vs. 138.6 mm Hg), urinary protein excretion (32.6 vs. 14.2 mg/day), and renal (2.2 0.5 vs. 1.0 0.1) and cardiac (1.8 0.3 vs. 1.0 0.1) gene expression of plasminogen activator inhibitor 1 (PAI-1). AIV infusion did not affect any of the above with the exception of PAI-1 gene expression which was increased in the left ventricles (1.7 0.3 vs. 1.0 0.1). AII-infused rats displayed a decreased creatinine clearance (538.75 vs. 898.96 ml/min) and hypertrophic left ventricles (0.275 0.006 vs. 0.220 0.011 g/100 g). Our results demonstrate that AII but not AIV infusion is associated with increased renal PAI-1 gene expression. Abrahamsen CT, et al. *Pharmacology* 2002 Sep;66(1):26-30

Angiotensin IV is a potent agonist for constitutive active human AT1 receptors. Distinct roles of the N- and C-terminal residues of angiotensin II during AT1 receptor activation. The octapeptide hormone, angiotensin II (Ang II), exerts its major physiological effects by activating AT(1) receptors. In vivo Ang II is degraded to bioactive peptides, including Ang III (angiotensin-(2-8)) and Ang IV (angiotensin-(3-8)). These peptides stimulate inositol phosphate generation in human AT(1) receptor expressing CHO-K1 cells, but the potency of Ang IV is very low. Substitution of Asn(111) with glycine, which is known to cause constitutive receptor activation by disrupting its interaction with the seventh transmembrane helix (TM VII), selectively increased the potency of Ang IV (900-fold) and angiotensin-(4-8), and leads to partial agonism of angiotensin-(5-8). Consistent with the need for the interaction between Arg(2) of Ang II and Ang III with Asp(281), substitution of this residue with alanine (D281A) decreased the peptide's potency without affecting that of Ang IV. All effects of the D281A mutation were superseded by the N111G mutation. The increased affinity of Ang IV to the N111G mutant was also demonstrated by binding studies. A model is proposed in which the Arg(2)-Asp(281) interaction causes a conformational change in TM VII of the receptor, which, similar to the N111G mutation, eliminates the constraining intramolecular interaction between Asn(111) and TM VII. The receptor adopts a more relaxed conformation, allowing the binding of the C-terminal five residues of Ang II that switches this "preactivated" receptor into the fully active conformation. Le MT, et al. *J Biol Chem* 2002 Jun 28;277(26):23107-10



Schematic of Ang I and Bradykinin peptide processing by ACE and ACE2

Donoghue M., et al. Circ Res
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