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SUBCHAPTER 29C

Other Angiotensins

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Additional names/abbreviations: Angiotensin III or angiotensin (2−8) (Ang III, AIII, Ang(2−8)); angiotensin IV or angiotensin (3−8) (Ang IV, AIV, Ang(3−8)); angiotensin (1−7) (Ang(1−7))

Originally thought to be inactive metabolites of the renin-angiotensin system, but these peptides were recently shown to possess different receptors and the functions are often antagonistic to those of Ang II. Drug targets for hypertension and Ang II-induced cardiovascular and renal diseases.

Discovery

Originally thought to be biological inactive, these angiotensin peptide subtypes were found to have physiological roles and some possess specific receptors and signaling pathways [1].

Structure

Structural Features

Ang III, Ang IV, and Ang(1−7) are linear peptides with no known secondary modification (Table 29C.1).

Primary Structure

Ang III is produced by subsequent cleavage of Ang II by aminopeptidase A. Ang IV is produced by cleavage of Ang III by aminopeptidase N. Ang(1−7) is produced by various pathways involving ACE2 (See Chapter 29, Renin-Angiotensin System).

Synthesis and Release

Gene and mRNA

See Chapter 29B, Angiotensin II.

Distribution of mRNA

See Chapter 29B, Angiotensin II.

Tissue and Plasma Concentrations

Ang III and Ang IV are short-lived peptides, and their concentrations in human plasma are kept at undetectable levels. Plasma Ang(1−7) baseline concentration in humans is 4.7 ± 0.9 fmol/ml. In eels, plasma Ang III and Ang IV are present in plasma but their levels are low compared to Ang II (Table 29C.2) [2]. In trout brain, Ang III is not detectable but Ang IV is present [3].

Regulation of Synthesis and Release

The regulation of synthesis and release of Ang III and Ang IV is not clear. Ang(1−7) synthesis and release are regulated by the activity of ACE2 (see Chapter 29, Renin-Angiotensin System).

Receptors

Structure and Subtypes

Ang III binds to AT1 and AT2. Ang IV binds to the angiotensin type-4 receptor (AT4), also known as insulin-regulated aminopeptidase (IRAP). Ang(1−7) binds to the Mas receptor (*Mas1*).

Signal Transduction Pathway

Ang III stimulates AT1 and AT2 receptors and its signaling pathway is similar to that of Ang II. Ang III has preferential binding on the AT2 receptor. The Mas receptor is activated by Ang(1−7) but the intracellular signaling pathway is not well understood. The receptor function is usually associated with Ang II-dependent effects and is known to counter the AT1-dependent signaling. Ang(1−7)/Mas activation inhibits the AT1-dependent activation of MAPK kinase in the epithelial cells of proximal tubules. In cardiovascular epithelium of mammals, Mas receptor activation stimulates phosphorylation of AKT and increases endothelial NO synthesis, leading to vasorelaxation that counters the vasoconstriction effects of Ang II. A combination of angiotensin signaling has been recently noticed, which states that the physiological effect depends not only on a single pathway, but is a result of a specific ratio among various angiotensins, acting through their own receptor pathways. Renal mesangial cell proliferation was stimulated by Ang II and Ang(1−7) independently via AT1 and Mas receptors respectively [4]. However, a combination of stimulatory concentration of Ang II and Ang(1−7) counters the stimulation, indicating the complex interaction within RAS signaling. AT4/IRAP activates intracellular signals including an increase in intracellular Ca concentration, modulation of MAPK kinases, activation of NF-κB signaling, and production of cGMP. However, the effects are largely dependent on the cell types and, in some cases, no classical signaling could be demonstrated despite the presence of AT4 binding sites.

Agonist

AVE 0991 is a non-peptide Ang(1−7) agonist and it stimulates the Mas receptor to produce cardiovascular protective effects to counter the pathophysiological effects of AT1 [5].

Y. Takei, H. Ando, & K. Tsutsui (Eds): Handbook of Hormones. DOI: http://dx.doi.org/10.1016/B978-0-12-801028-0.00178-1

Table 29C.1 Peptide Sequences of Ang III, Ang IV, and Ang(1−7) in Human

Ang III	RVYIHPF
Ang IV	VYIHPF
Ang (1−7)	DRVYIHP

Table 29C.2 Plasma Concentrations of Ang III and Ang IV in Eel

	Ang III	Ang IV
FW	28.3 ± 3.8	26.5 ± 3.6 fmol/ml
SW	56.3 ± 11.9	60.1 ± 13.3 fmol/ml

[Nle^1]-angiotensin IV has been suggested as a specific Ang IV agonist that constitutively activates AT4/IRAP.

Antagonist

A779 is a non-peptide Ang(1−7) agonist and it inhibits the signaling of Mas receptors and attenuates the cardiovascular effects of Ang(1−7) [6].

Biological Functions

Target Cells/Tissues and Functions

Ang III has preferential stimulation to release aldosterone in adrenal cortex, which is partially via AT2 but not AT1 [7]. Intra-arterial injection of Ang III or Ang IV increases blood pressure in teleosts but Ang III has a higher potency than Ang IV. Intracerebroventricular (ICV) injection of Ang III increases the heart rate without affecting the blood pressure and ventilation rate in trout, in contrast to the effect of Ang II, which increases all three parameters [3]. ICV injection of Ang IV does not affect blood pressure, heart rate, and ventilation rate even though it is detected in the brain by immunoassays. This suggested that a specific receptor for Ang III (and Ang II) could be present to elicit the preferential effect of heart rate control in trout [8]. The Mas receptor expresses in brain, testis, ovary, and endothelial cells of blood vessels. Besides AT2, the Ang(1−7)/Mas receptor axis is also known to antagonize the effects of the AT1 axis. These antagonistic effects include anti-hypertrophic action, anti-thrombotic and anti-fibrotic effects, and vasodilation via stimulation of NO synthesis in endothelium and potentiation of the bradykinin effect. The localization and physiological effects of the Mas receptor are not clear in non-mammalian vertebrates. AT4/IRAP is broadly distributed in kidney, aorta, heart, liver, lung, uterus, adrenal gland, and brain, especially in neurons associated with memory function [9]. The Ang IV/AT4 axis is involved in facilitation of memory and can reverse memory deficits caused by alcohol abuse and ischemia. AT4 antagonist decreases renal blood flow and increases urinary sodium excretion, and these effects are independent of the AT1 pathway. The large variation in signaling and function of AT4 poses difficulties for researchers. Ang IV was detected in considerable amounts in the brain of trout, indicating a possible role of memory function as in the case of mammals. There is so far no information on AT4/IRAP in non-mammalian vertebrates.

Phenotype in Gene-Modified Animals

ACE-deleted human patients exhibit hypertension and this is related to a low plasma Ang(1−7) concentration. Baroreflex bradycardia was lowered but vascular responsiveness to Ang II was enhanced in Mas-knockout mice. Mas-knockout also impaired post-ischemic neovascularization and endothelial NO formation.

Pathophysiological Implications

Clinical Implications

Ang(1−7) reduces mechanical stretch-induced cardiac hypertrophy through downregulation of AT1. ACE2 was found to function as a receptor for the coronavirus that caused the infamous severe acute respiratory syndrome (SARS) in 2002−2003. The SARS virus attaches to ACE2 and diminishes the expression and thus the production of Ang(1−7), leading to an intensified activation of AT1. Injection of recombinant ACE2 into mice protected the lung from sepsis and thus ACE can be a target treatment in lung injury associated with SARS.

Use for Diagnosis and Treatment

A low Ang(1−7) is associated with hypertension and cardiac hypertrophy. Agonists for the Mas receptor have been targets to control cardiovascular diseases caused by hyperactive AT1. AngIV/AT4 is involved in memory and is a treatment target of Alzheimer's and Parkinson's diseases.

References

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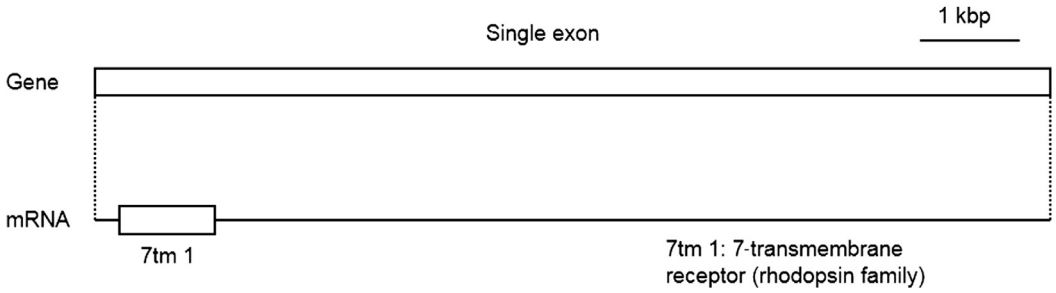
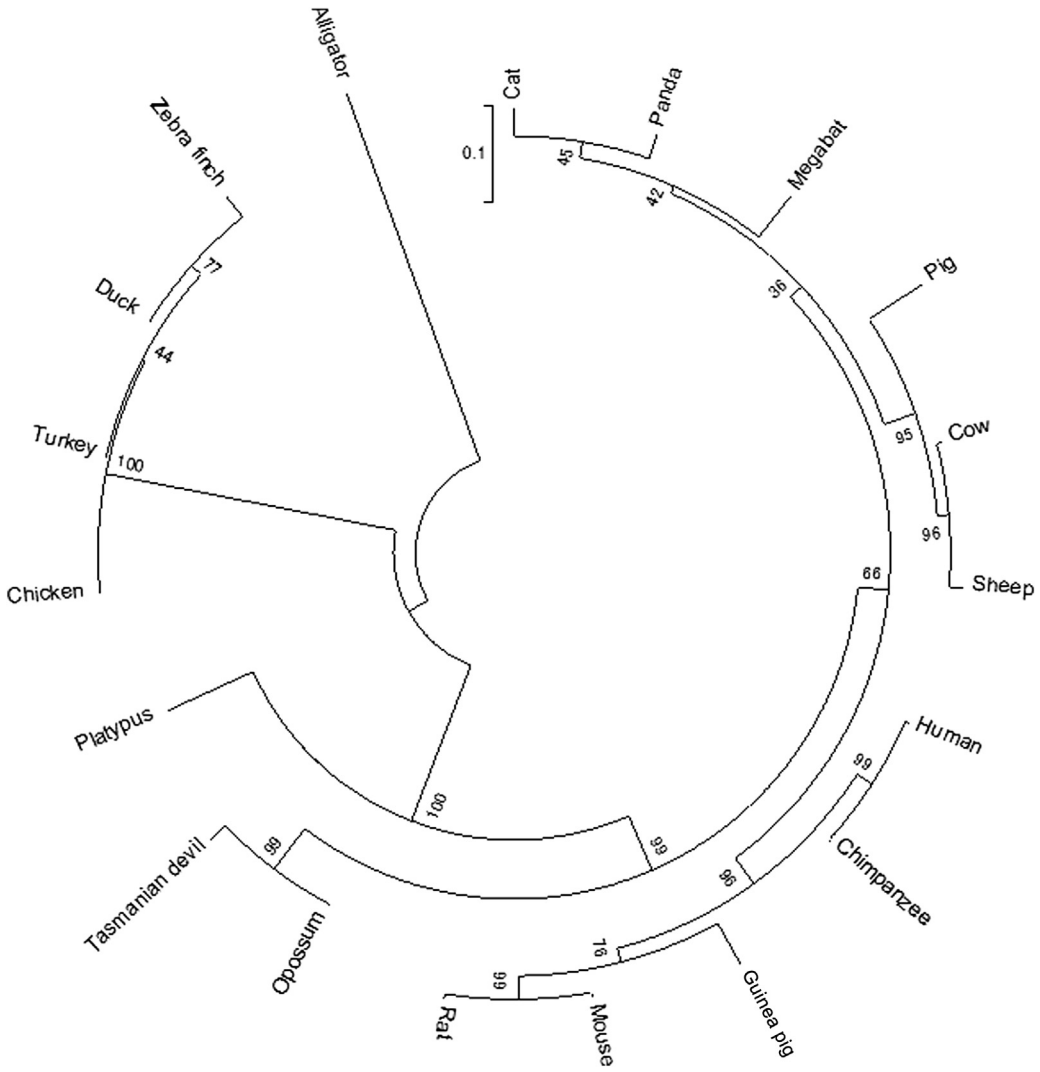
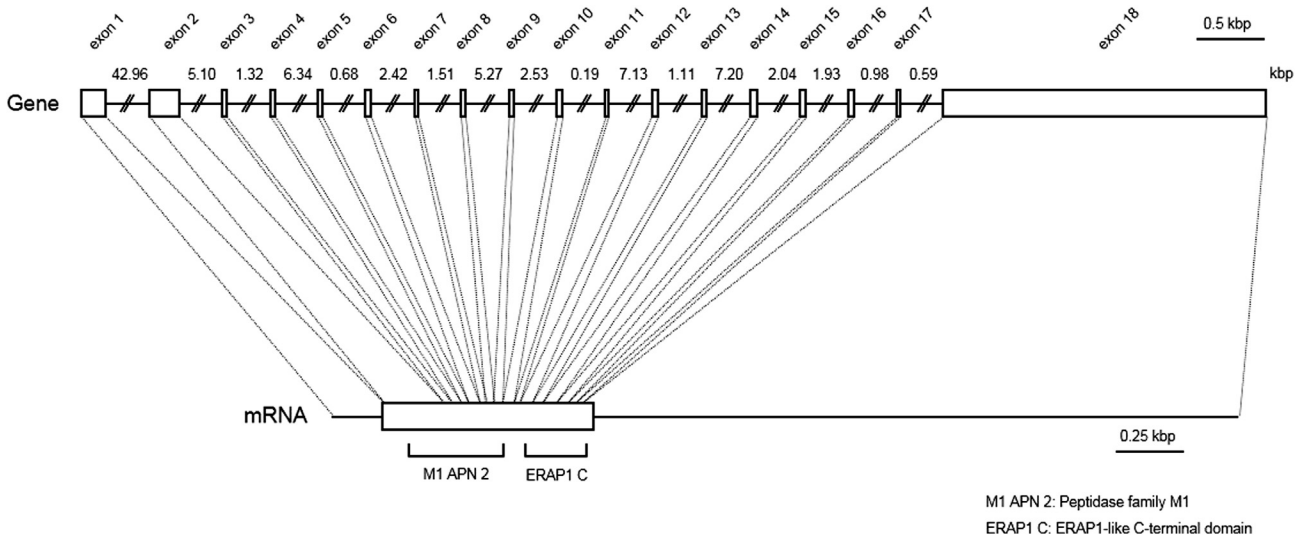
Supplemental Information



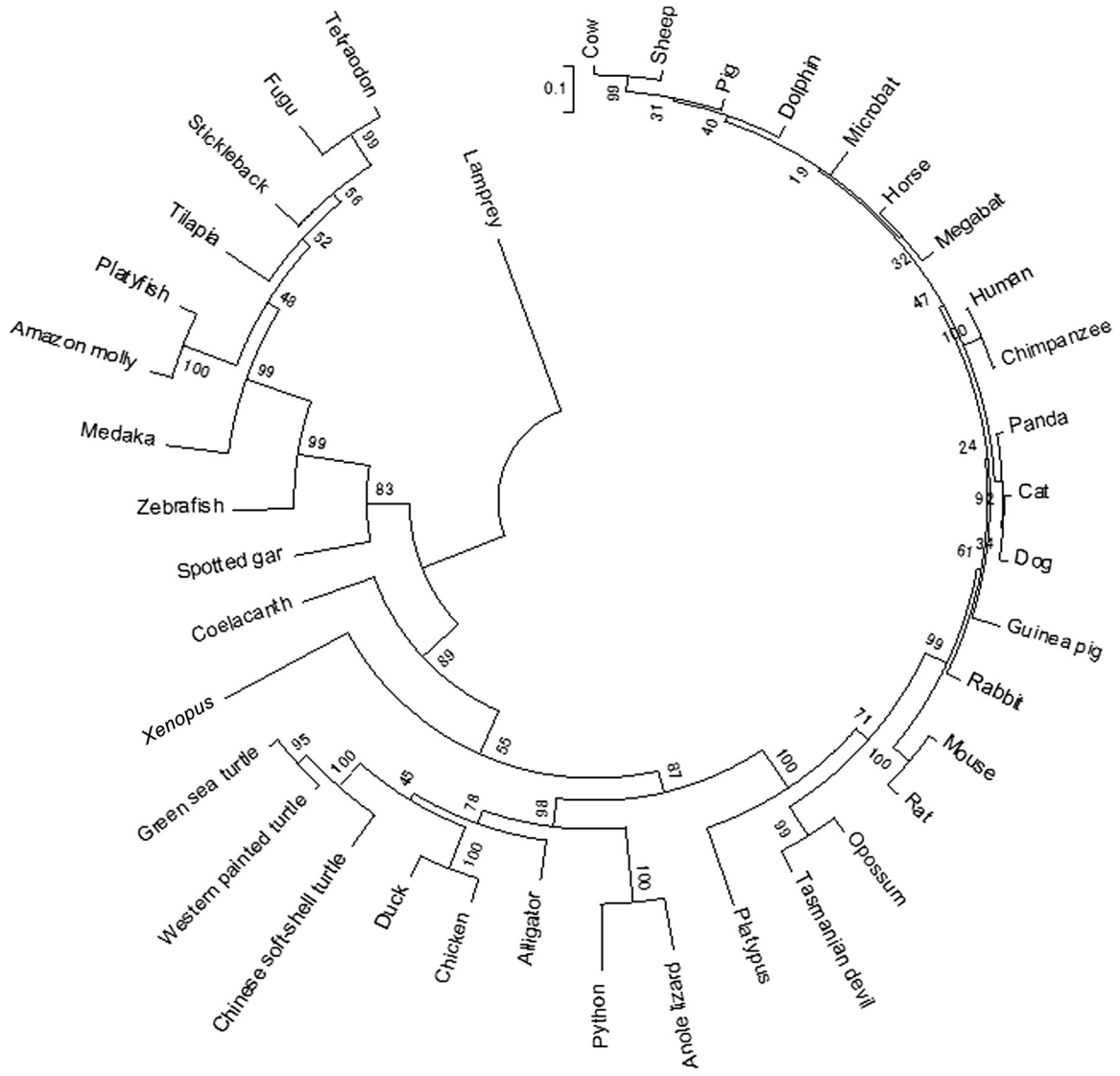
E-Figure 29C.1 Gene, mRNA, and domain structure of the human Mas-1 receptor. Human Mas-1 oncogene: *Mas1*, location 6q25.3–q26.



E-Figure 29C.2 Phylogenetic tree of the Mas-1 oncogene receptors in vertebrates. The unrooted phylogenetic tree of the Mas-1 oncogene receptors (Mas1) was constructed with the maximum likelihood method using full-length sequences from representative vertebrate species. The Mas receptor is specific to Ang(1–7) in mammals but specificity has not been demonstrated in non-mammalian species. The numbers on the branches indicate the bootstrap values from 1,000 replicates. Mas1 was not identified in reptiles, amphibians, and fishes.



E-Figure 29C.3 Gene, mRNA, and domain structure of the human AT4 receptor/IRAP. Human IRAP: *lnpep*, location 5q15.



E-Figure 29C.4 Phylogenetic tree of the angiotensin type-4 receptors in vertebrates. The phylogenetic tree of the angiotensin type-4 receptors (AT4/IRAP) was constructed with the maximum likelihood method using full-length sequences from representative vertebrate species. Lamprey AT4 was used as the root to indicate the origin of the tree. The numbers on the branches indicate the bootstrap values from 1,000 replicates.

E-Table 29C.1 Accession Numbers of Vertebrate Mas-1 Oncogene (MAS1) for Angiotensin(1−7)

	Accession Number
Species	**Mas1**
Alligator	XM_006021927
Cat	ENSFCAG00000002849
Chicken	ENSGALG00000011622
Chimpanzee	ENSPTRG00000018763
Cow	ENSBTAG00000031724
Duck	ENSAPLG00000000729
Guinea Pig	ENSCPOG00000000027
Human	ENSG00000130368
Megabat	ENSPVAG00000005330
Mouse	ENSMUSG00000068037
Opossum	ENSMODG00000007377
Panda	ENSAMEG00000019584
Pig	ENSSSCG00000004045
Platypus	ENSOANG00000012996
Rat	ENSRNOG00000014971
Sheep	ENSOARG00000002781
Spotted gar	ENSLOCG00000010437
Tasmanian devil	ENSSHAG00000001441
Turkey	ENSMGAG00000015847
Xenopus	ENSXETG00000023891
Zebra finch	ENSTGUG00000011427

E-Table 29C.2 Accession Numbers of Vertebrate AT4 Receptor/IRAP Gene (*Inpep*) for Angiotensin IV

	Accession Number
Species	**AT4/IRAP (LNPEP)**
Alligator	XM_006261603
Amazon molly	ENSPFOG00000017275
Anole lizard	ENSACAG00000012000
Cat	ENSFCAG00000004970
Chicken	ENSGALG00000015301
Chimpanzee	ENSPTRG00000017097
Chinese soft-shell turtle	XM_006130447
Coelacanth	ENSLACG00000004747
Cow	ENSBTAG00000019900
Dog	ENSCAFG00000007770
Dolphin	ENSTTRG00000002967
Duck	ENSAPLG00000014098
Fugu	ENSTRUG00000010651
Green sea turtle	XM_007054086
Guinea pig	ENSCPOG00000013399
Horse	ENSECAG00000021790
Human	ENSG00000113441
Lamprey	ENSPMAG00000002128
Medaka	ENSORLG00000008772
Megabat	ENSPVAG00000016654
Microbat	ENSMLUG00000016096
Mouse	ENSMUSG00000023845
Opossum	ENSMODG00000015542
Panda	ENSAMEG00000014548
Pig	ENSSSCG00000014173
Platyfish	ENSXMAG00000007345
Platypus	ENSOANG00000001221
Python	XM_007430066
Rabbit	ENSOCUG00000001651
Rat	ENSRNOG00000013082
Sheep	ENSOARG00000017994
Spotted gar	ENSLOCG00000006318
Stickleback	ENSGACG00000009799
Tasmanian devil	ENSSHAG00000000919
Tetraodon	ENSTNIG00000015404
Tilapia	ENSONIG00000013699
Turkey	ENSMGAG00000007011
Western painted turtle	XM_005284045
Xenopus	ENSXETG00000013199
Zebrafish	ENSDARG00000014403