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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].
agonist that constitutively activates AT4/IRAP. The Ang IV/AT4 axis is involved in facilitation of memory [9]. The Ang IV/AT4 axis is involved in facilitation of memory in the brain, especially in neurons associated with memory function [9]. The Ang IV/AT4 axis is involved in facilitation of memory.

The localization and physiological effects of the Mas receptor 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.

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.

**References**

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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: Inpep, 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)

| Species                  | Accession Number        |
|--------------------------|-------------------------|
| Alligator                | XM_006021927             |
| Cat                      | ENSFCAG00000011622      |
| Chicken                  | ENSGALG00000011622      |
| Chimpanzee               | ENSPTRG00000018763      |
| Cow                      | ENSBTAG00000031724      |
| Duck                     | ENSAPLG00000000729      |
| Guinea Pig               | ENSPCOG000000000027     |
| Human                    | ENSG0000010368           |
| Megabat                  | ENSPVAG00000005330      |
| Mouse                    | ENSMUSG00000008907      |
| Opossum                  | ENSMODG00000007577      |
| Panda                    | ENSAMEG00000019584      |
| Pig                      | ENSSSCG00000004045      |
| Platypus                 | ENSOANG00000012956      |
| Rat                      | ENSRNOG000000014971     |
| Sheep                    | ENSOARG00000002781      |
| Spotted gar              | ENSLOCQ00000000437      |
| Tasmanian devil          | ENSHAG000000001441      |
| Turkey                   | ENSMGAG000000015847     |
| Xenopus                  | ENSXETG000000023891     |
| Zebra finch              | ENSXEGU00000011427      |

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

| Species                  | Accession Number   |
|--------------------------|--------------------|
| Alligator                | XM_00626103        |
| Amazon molly             | ENSPFOG000000017275|
| Anole lizard             | ENSSACG000000012200|
| Cat                      | ENSFCAG00000004970 |
| Chicken                  | ENSGALG000000015301|
| Chimpanzee               | ENSPTRG000000017907|
| Chinese soft-shell turtle| XM_00613047         |
| Coelacanth               | ENSLACG00000004747 |
| Cow                      | ENSBTAG00000019900 |
| Dog                      | ENSAFAG00000007770 |
| Dolphin                  | ENSTTRG00000002967 |
| Duck                     | ENSAPLG000000014908|
| Fugu                     | ENSBUXG00000010651 |
| Green sea turtle         | XM_007054086       |
| Guinea pig               | ENSCPOG00000001399 |
| Horse                    | ENSCEAG000000021790|
| Human                    | ENSG00000113441    |
| Lampreedy                | ENSPMAG000000002128|
| Medalka                  | ENSDRLG00000008772 |
| Megabat                  | ENSPVAG000000016654|
| Microbat                 | ENSMLUG000000016096|
| Mouse                    | ENSMUSG00000027945 |
| Opossum                  | ENSMODG00000015542 |
| Panda                    | ENSAMLIB00000014548|
| Pig                      | ENSSSCG00000014713 |
| Platypus                 | ENSMAG000000007545 |
| Platypus                 | ENSANG00000001221  |
| Python                   | XM_007430066       |
| Rabbit                   | ENSOCR00000001651  |
| Rat                      | ENSRNOG00000001082 |
| Sheep                    | ENSOARG000000017994|
| Spotted gar              | ENSLOCQ000000006318|
| Stickleback              | ENSGAG000000009799 |
| Tasmanian devil          | ENSHAG00000000919  |
| Tetraodon                | ENSNTRC00000015404 |
| Tilapia                  | ENSOINC00000013599 |
| Turkey                   | ENSMGAG000000007011|
| Western painted turtle   | XM_005284045        |
| Xenopus                  | ENSXETG00000001399  |
| Zebrafish                | ENSJABG000000014405|

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**SUBCHAPTER 29C Other Angiotensins**