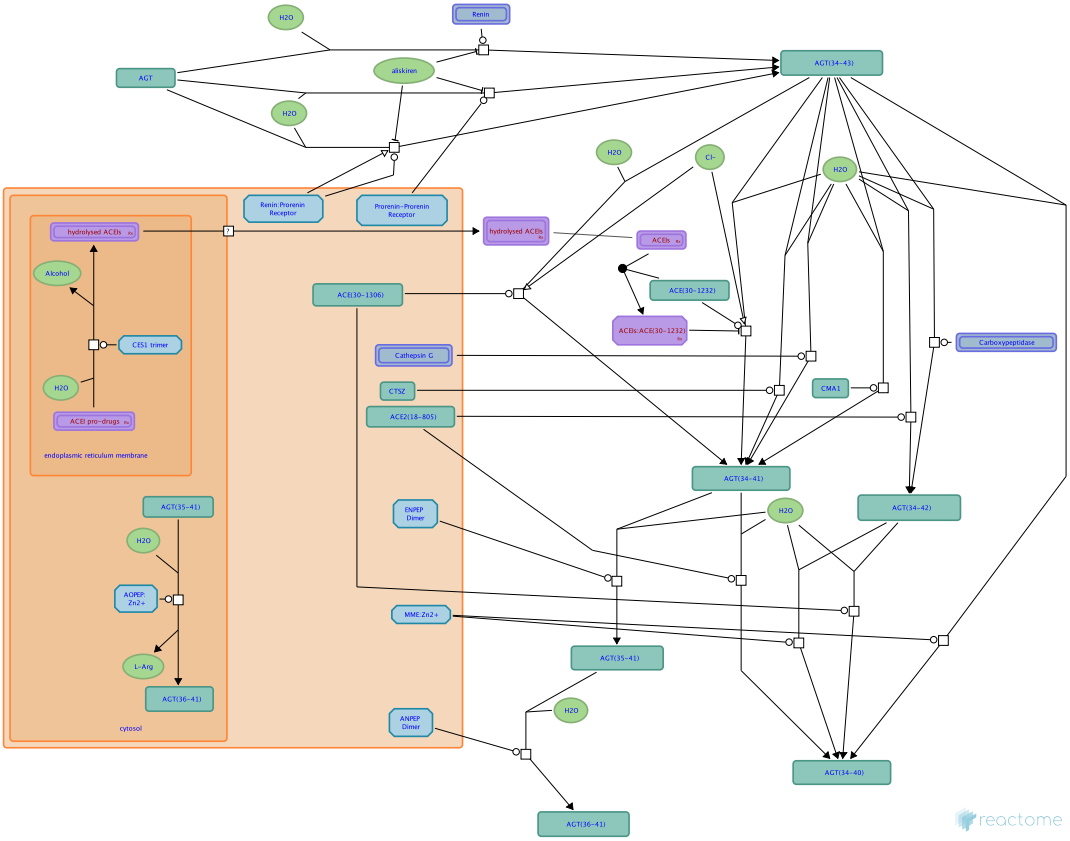
Metabolism of Angiotensinogen to Angiotensins



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10/09/2021

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

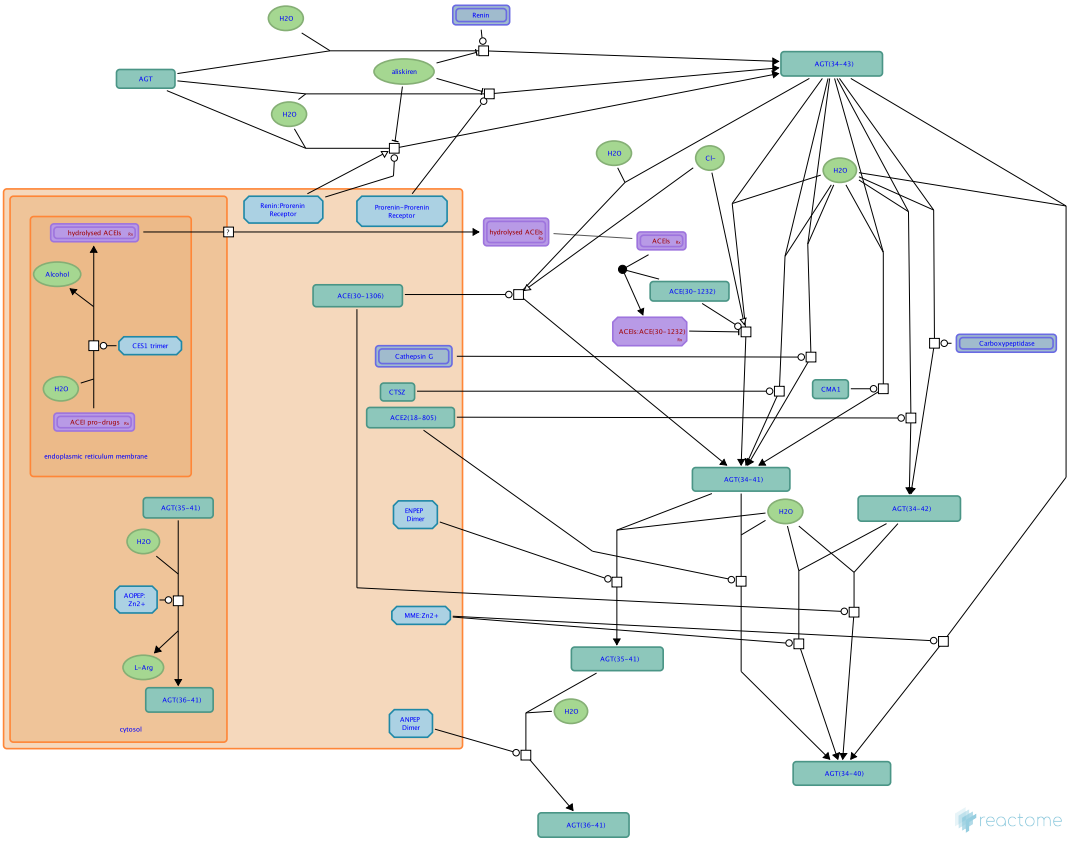
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Metabolism of Angiotensinogen to Angiotensins ↗

Stable identifier: R-HSA-2022377

Compartments: extracellular region, plasma membrane



Angiotensinogen, a prohormone, is synthesized and secreted mainly by the liver but also from other tissues (reviewed in Fyhrquist and Saijonmaa 2008, Cat and Touyz 2011). Renin, an aspartyl protease specific for angiotensinogen, is secreted into the bloodstream by juxtaglomerular cells of the kidney in response to a drop in blood pressure. Renin cleaves angiotensinogen to yield a decapaptide, angiotensin I (angiotensin-1, angiotensin-(1-10)). Circulating renin can also bind the membrane-localized (pro)renin receptor (ATP6AP2) which increases its catalytic activity. After cleavage of angiotensinogen to angiotensin I by renin, two C-terminal amino acid residues of angiotensin I are removed by angiotensin-converting enzyme (ACE), located on the surface of endothelial cells, to yield angiotensin II (angiotensin-2, angiotensin-(1-8)), the active peptide that causes vasoconstriction, resorption of sodium and chloride, excretion of potassium, water retention, and aldosterone secretion.

More recently other, more tissue-localized pathways leading to angiotensin II and alternative derivatives of angiotensinogen have been identified (reviewed in Kramkowski et al. 2006, Kumar et al. 2007, Fyhrquist and Saijonmaa 2008, Becari et al. 2011). Chymase, cathepsin G, and cathepsin X (cathepsin Z) can each cleave angiotensin I to yield angiotensin II. Angiotensin-converting enzyme 2 (ACE2) cleaves 1 amino acid residue from angiotensin I (angiotensin-(1-10)) to yield angiotensin-(1-9), which can be cleaved by ACE to yield angiotensin-(1-7). ACE2 can also cleave angiotensin II to yield angiotensin-(1-7). Neprilysin can cleave either angiotensin-(1-9) or angiotensin I to yield angiotensin-(1-7). Angiotensin-(1-7) binds the MAS receptor (MAS1, MAS proto-oncogene) and, interestingly, produces effects opposite to those produced by angiotensin II.

Aminopeptidase A (APA, ENPEP) cleaves angiotensin II to yield angiotensin III (angiotensin-(2-8)), which is then cleaved by aminopeptidase N (APN, ANPEP) yielding angiotensin IV (angiotensin-(3-8)). An-

giotensin IV binds the AT4 receptor (AT4R, IRAP, LNPEP, oxytocinase).

Inhibitors of renin (e.g. aliskiren) and ACE (e.g. lisinopril, ramipril) are currently used to treat hypertension (reviewed in Gerc et al. 2009, Verdecchia et al. 2010, Alreja and Joseph 2011).

Literature references

Cat, AN., Touyz, RM. (2011). A new look at the renin-angiotensin system--focusing on the vascular system. *Peptides, 32*, 2141-50. ↗

Gerc, V., Buksa, M., Loza, V., Kulic, M. (2009). Is aliskiren superior to inhibitors of angiotensin-converting enzyme and angiotensin receptor blockers in renin-angiotensin system blockade?. *Med Arh, 63*, 343-9. ↗

Kramkowski, K., Mogielnicki, A., Buczko, W. (2006). The physiological significance of the alternative pathways of angiotensin II production. *J Physiol Pharmacol, 57*, 529-39. ↗

Fyhrquist, F., Saijonmaa, O. (2008). Renin-angiotensin system revisited. *J Intern Med, 264*, 224-36. ↗

Kumar, R., Singh, VP., Baker, KM. (2007). The intracellular renin-angiotensin system: a new paradigm. *Trends Endocrinol Metab, 18*, 208-14. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

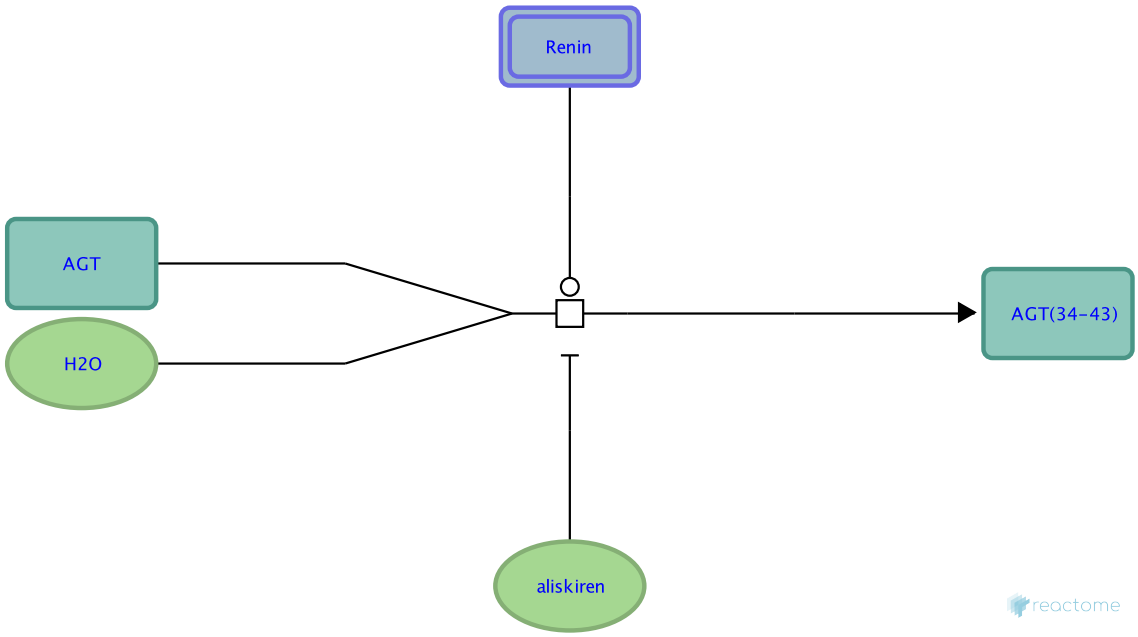
Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022412

Type: transition

Compartments: extracellular region



Renin in the bloodstream hydrolyzes angiotensinogen to yield angiotensin-(1-10) (angiotensin I). Renin is produced in the juxtaglomerular cells of the kidney in response to reduced blood pressure. Aliskiren, a drug used clinically to treat hypertension, inhibits this reaction (Gossas et al. 2011, Wood et al. 2003, reviewed in Gerc et al. 2009).

Followed by: ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Secreted ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Mast Cell Carboxypeptidase hydrolyzes Angiotensin-(1-10) to Yield Angiotensin-(1-9), MME:Zn2+ hydrolyses AGT(34-43), Cathepsin G hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Chymase hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Cathepsin Z (Cathepsin X) hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), ACE2 hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-9)

Literature references

Rosenthal, J., Wolff, HP., Weber, P., Dahlheim, H. (1971). Enzyme kinetic studies on human renin and its purified homologous substrate. *Am J Physiol, 221*, 1292-6.

Haas, E., Goldblatt, H. (1967). Kinetic constants of the human renin and human angiotensinogen reaction. *Circ Res, 20*, 45-55.

Gould, AB., Green, D. (1971). Kinetics of the human renin and human substrate reaction. *Cardiovasc Res, 5*, 86-9.

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Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

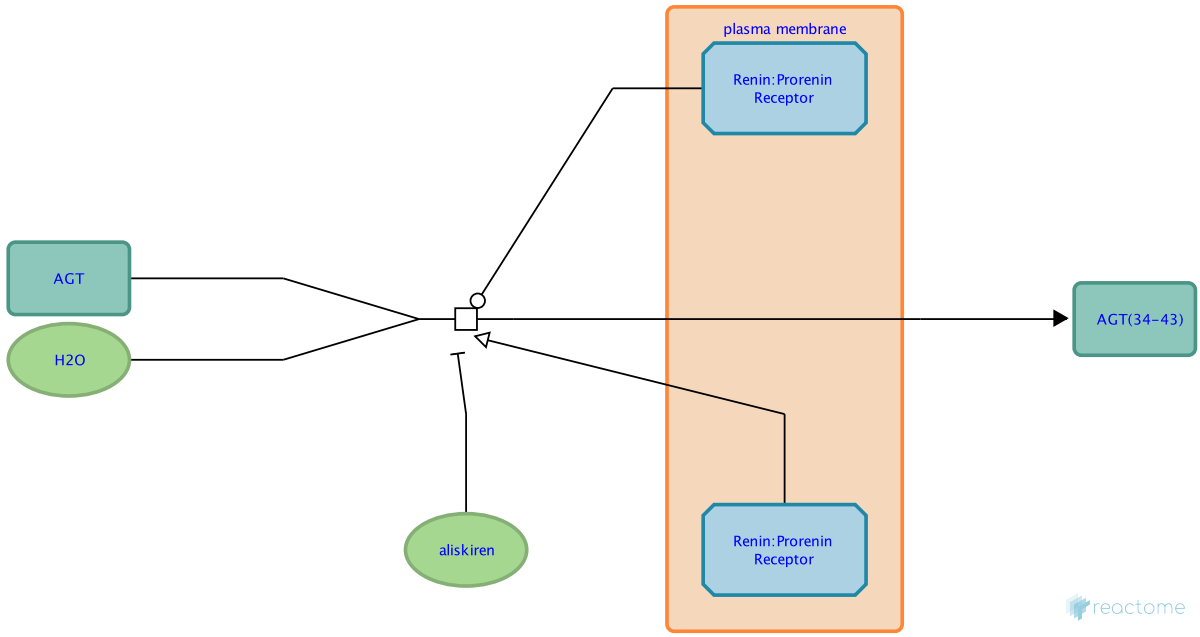
Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022403

Type: transition

Compartments: extracellular region, plasma membrane



Renin bound to the (pro)renin receptor (ATP6AP2) hydrolyzes angiotensinogen to yield angiotensin-(1-10) (angiotensin I) (Nguyen et al. 2002). Binding to the (pro)renin receptor increases the catalytic efficiency of renin 4-fold (Nguyen et al. 2002). Aliskiren, a drug used clinically to treat hypertension, inhibits cleavage of angiotensinogen by renin (Gossas et al. 2011, Wood et al. 2003, reviewed in Gerc et al. 2009).

Followed by: Mast Cell Carboxypeptidase hydrolyzes Angiotensin-(1-10) to Yield Angiotensin-(1-9), MME:Zn2+ hydrolyses AGT(34-43), Cathepsin G hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Chymase hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Cathepsin Z (Cathepsin X) hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), ACE2 hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-9), ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Secreted ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8)

Literature references

Nguyen, G., Delarue, F., Burcklé, C., Bouzhir, L., Giller, T., Sraer, JD. (2002). Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest, 109*, 1417-27. ↗

Gossas, T., Vrang, L., Henderson, I., Sedig, S., Sahlberg, C., Lindström, E. et al. (2011). Aliskiren displays long-lasting interactions with human renin. *Naunyn Schmiedebergs Arch Pharmacol.* ↗

Wood, JM., Maibaum, J., Rahuel, J., Grütter, MG., Cohen, NC., Rasetti, V. et al. (2003). Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun, 308*, 698-705. ↗

Editions

2011-11-19	Authored, Edited	May, B.
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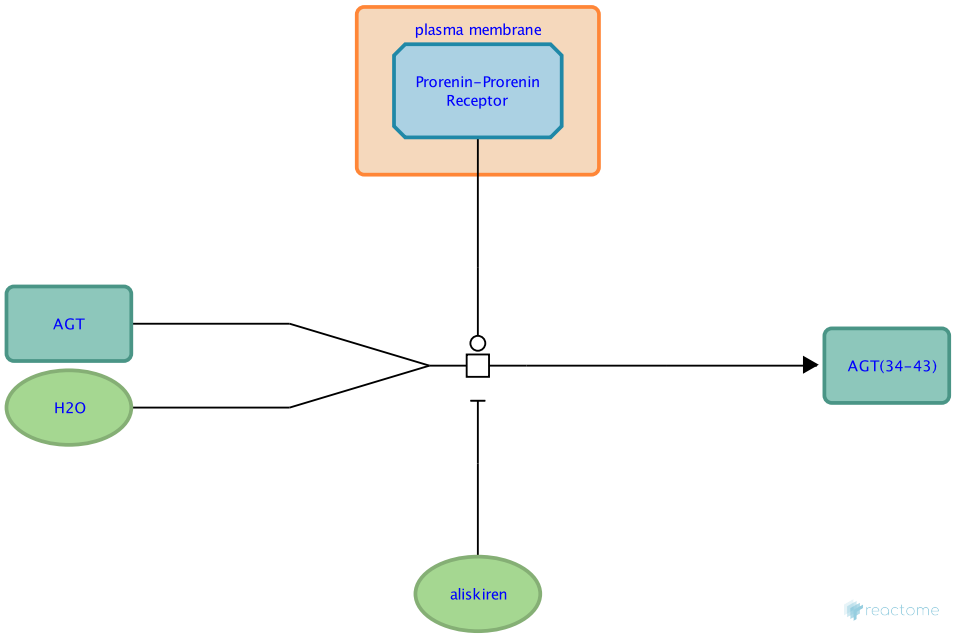
Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2065357

Type: transition

Compartments: extracellular region, plasma membrane



The binding of prorenin to the (pro)renin receptor activates the protease activity of prorenin, which can then hydrolyze angiotensinogen to yield angiotensin-(1-10) (angiotensin I) (Nguyen et al. 2002). Prorenin is inactive when not bound to the (pro)renin receptor. Aliskiren, a drug used clinically to treat hypertension, inhibits the cleavage of angiotensinogen by renin (Gossas et al. 2011, Wood et al. 2003, reviewed in Gerc et al. 2009).

Followed by: Mast Cell Carboxypeptidase hydrolyzes Angiotensin-(1-10) to Yield Angiotensin-(1-9), MME:Zn2+ hydrolyses AGT(34-43), Cathepsin G hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Chymase hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Cathepsin Z (Cathepsin X) hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), ACE2 hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-9), ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Secreted ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8)

Literature references

Nguyen, G., Delarue, F., Burcklé, C., Bouzhir, L., Giller, T., Sraer, JD. (2002). Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest, 109*, 1417-27.

Gossas, T., Vrang, L., Henderson, I., Sedig, S., Sahlberg, C., Lindström, E. et al. (2011). Aliskiren displays long-lasting interactions with human renin. *Naunyn Schmiedebergs Arch Pharmacol.*

Wood, JM., Maibaum, J., Rahuel, J., Grütter, MG., Cohen, NC., Rasetti, V. et al. (2003). Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun, 308*, 698-705.

Editions

2011-11-19	Authored, Edited	May, B.
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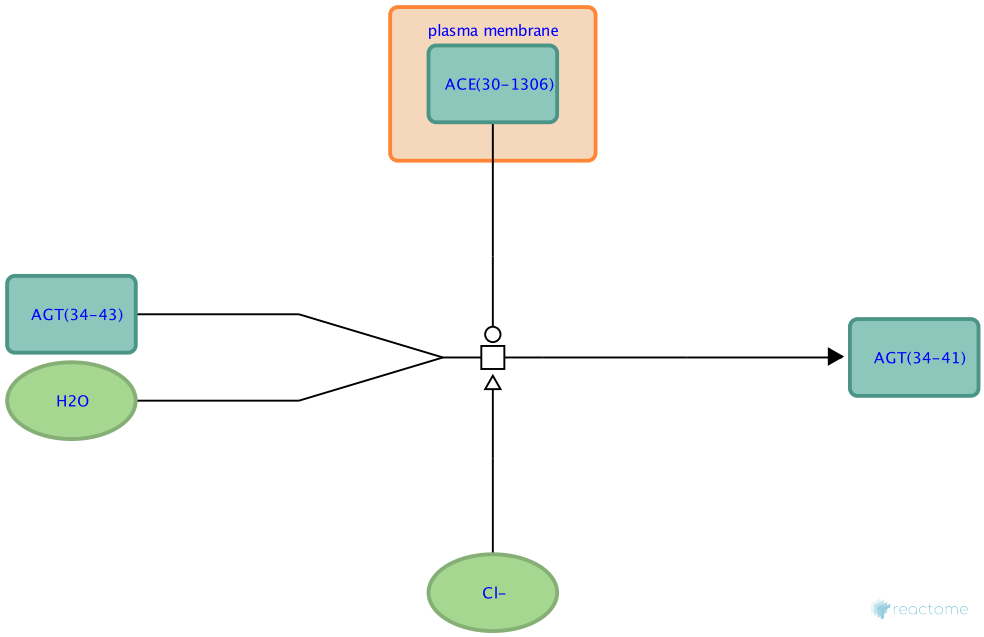
ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022405

Type: transition

Compartments: extracellular region, plasma membrane



Angiotensin-converting enzyme (ACE) hydrolyzes angiotensin-(1-10) (angiotensin I) to yield angiotensin-(1-8) (angiotensin II) (Ehlers and Kirsch 1988). ACE is found at the plasma membrane of endothelial cells. This reaction is inhibited by drugs used to treat hypertension (angiotensin converting enzyme inhibitors, ACEI) including captopril (Gronhagen-Riska and Fyhrquist 1980, Stewart et al. 1981, Ehlers et al. 1986, Hayakari et al. 1989, Wei et al. 1991, Baudin and Beneteau-Burnat 1999), enalaprilat (metablized from the prodrug enalapril, Wei et al. 1991, Baudin and Beneteau-Burnat 1999), lisinopril (Ehlers et al. 1991, Natesh et al. 2003), and ramiprilat (metabolized from the prodrug ramipril, Baudin and Beneteau-Burnat 1999).

Preceded by: Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10), Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10), Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Followed by: ACE2 hydrolyzes Angiotensin-(1-8) to Angiotensin-(1-7), ENPEP hydrolyzes Angiotensin-(1-8) to Angiotensin-(2-8)

Literature references

Ehlers, MR., Kirsch, RE. (1988). Catalysis of angiotensin I hydrolysis by human angiotensin-converting enzyme: effect of chloride and pH. *Biochemistry, 27*, 5538-44. ↗

Wei, L., Alhenc-Gelas, F., Corvol, P., Clauser, E. (1991). The two homologous domains of human angiotensin I-converting enzyme are both catalytically active. *J Biol Chem, 266*, 9002-8. ↗

Wei, L., Alhenc-Gelas, F., Soubrier, F., Michaud, A., Corvol, P., Clauser, E. (1991). Expression and characterization of recombinant human angiotensin I-converting enzyme. Evidence for a C-terminal transmembrane anchor and for a proteolytic processing of the secreted recombinant and plasma enzymes. *J Biol Chem, 266*, 5540-6. ↗

Hayakari, M., Amano, K., Izumi, H., Murakami, S. (1989). Purification of angiotensin-converting enzyme from human intestine. *Adv Exp Med Biol, 247*, 365-70. ↗

Grönhagen-Riska, C., Fyhrquist, F. (1980). Purification of human lung angiotensin-converting enzyme. *Scand J Clin Lab Invest, 40*, 711-9. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

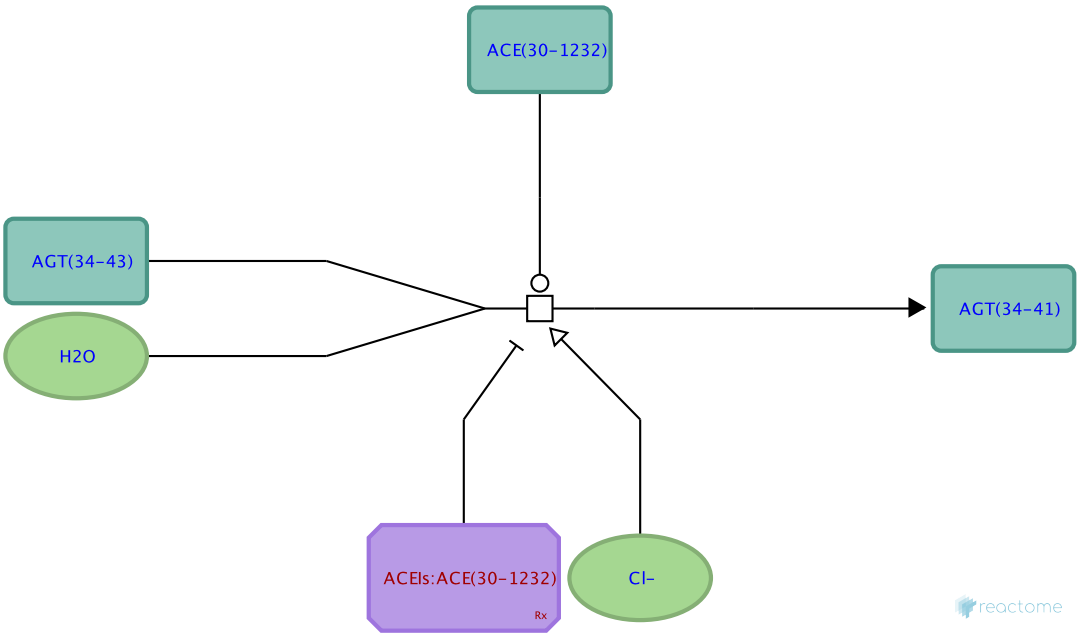
Secreted ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2065355

Type: transition

Compartments: extracellular region



Secreted angiotensin-converting enzyme (ACE) cleaves 2 amino acid residues from the C-terminus of angiotensin-(1-10) (angiotensin I) to yield angiotensin-(1-8) (angiotensin II) (Wei et al. 1991). This reaction is inhibited by drugs used to treat hypertension (angiotensin converting enzyme inhibitors, ACEI) including captopril (Gronhagen-Riska and Fyhrquist 1980, Stewart et al. 1981, Ehlers et al. 1986, Hayakari et al. 1989, Wei et al. 1991, Baudin and Beneteau-Burnat 1999), enalaprilat (metablized from the prodrug enalapril, Wei et al. 1991, Baudin and Beneteau-Burnat 1999), lisinopril (Ehlers et al. 1991, Natesh et al. 2003), and ramiprilat (metabolized from the prodrug ramipril, Baudin and Beneteau-Burnat 1999). ACE is secreted ("shed") from membranes of endothelial cells by cleavage in the C-terminal region that removes the membrane anchor.

Preceded by: Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10), Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10), Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Followed by: ACE2 hydrolyzes Angiotensin-(1-8) to Angiotensin-(1-7), ENPEP hydrolyzes Angiotensin-(1-8) to Angiotensin-(2-8)

Literature references

Wei, L., Alhenc-Gelas, F., Soubrier, F., Michaud, A., Corvol, P., Clauser, E. (1991). Expression and characterization of recombinant human angiotensin I-converting enzyme. Evidence for a C-terminal transmembrane anchor and for a proteolytic processing of the secreted recombinant and plasma enzymes. *J Biol Chem, 266*, 5540-6. ↗

Wei, L., Alhenc-Gelas, F., Corvol, P., Clauser, E. (1991). The two homologous domains of human angiotensin I-converting enzyme are both catalytically active. *J Biol Chem, 266*, 9002-8. ↗

Hayakari, M., Amano, K., Izumi, H., Murakami, S. (1989). Purification of angiotensin-converting enzyme from human intestine. *Adv Exp Med Biol, 247*, 365-70. ↗

Grönhagen-Riska, C., Fyhrquist, F. (1980). Purification of human lung angiotensin-converting enzyme. *Scand J Clin Lab Invest, 40,* 711-9. ↗

Ehlers, MR., Maeder, DL., Kirsch, RE. (1986). Rapid affinity chromatographic purification of human lung and kidney angiotensin-converting enzyme with the novel N-carboxyalkyl dipeptide inhibitor N-[1(S)-carboxy-5-aminopentyl]glycylglycine. *Biochim Biophys Acta, 883,* 361-72. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

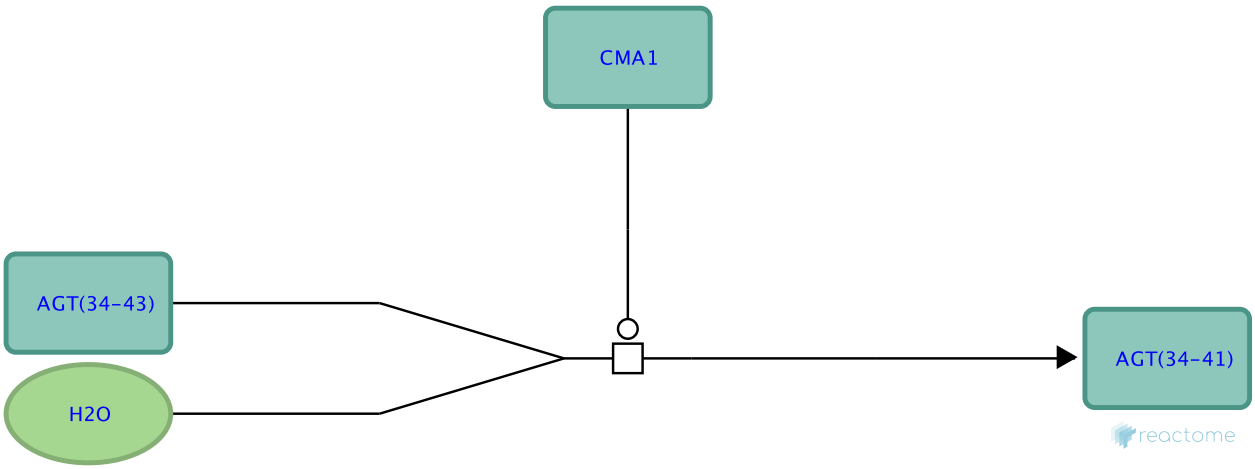
Chymase hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022383

Type: transition

Compartments: extracellular region



Chymase hydrolyzes angiotensin-(1-10) (angiotensin) to yield angiotensin-(1-8) (angiotensin II) at a higher rate than does angiotensin-converting enzyme (Reilly et al. 1982, Urata et al. 1990, Caughey et al. 2000, Richard et al. 2001).

Preceded by: Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10), Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10), Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Followed by: ACE2 hydrolyzes Angiotensin-(1-8) to Angiotensin-(1-7), ENPEP hydrolyzes Angiotensin-(1-8) to Angiotensin-(2-8)

Literature references

Urata, H., Kinoshita, A., Misono, KS., Bumpus, FM., Husain, A. (1990). Identification of a highly specific chymase as the major angiotensin II-forming enzyme in the human heart. *J Biol Chem, 265*, 22348-57. ↗

Richard, V., Hurel-Merle, S., Scalbert, E., Ferry, G., Lallemand, F., Bessou, JP. et al. (2001). Functional evidence for a role of vascular chymase in the production of angiotensin II in isolated human arteries. *Circulation, 104*, 750-2. ↗

Caughey, GH., Raymond, WW., Wolters, PJ. (2000). Angiotensin II generation by mast cell alpha- and beta-chymases. *Biochim Biophys Acta, 1480*, 245-57. ↗

Reilly, CF., Tewksbury, DA., Schechter, NM., Travis, J. (1982). Rapid conversion of angiotensin I to angiotensin II by neutrophil and mast cell proteinases. *J Biol Chem, 257*, 8619-22. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

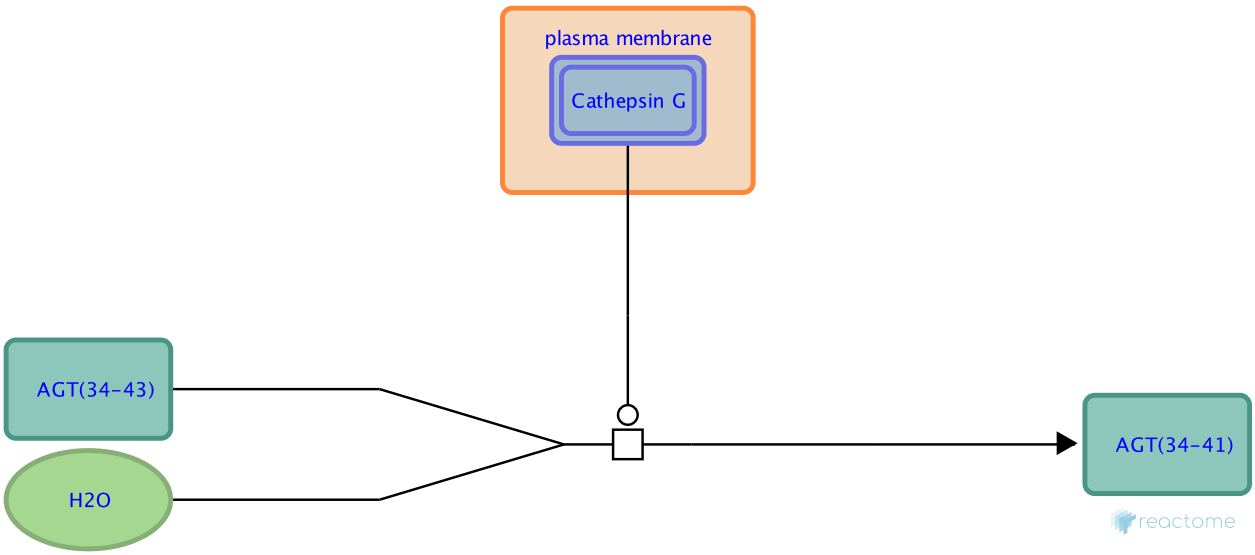
Cathepsin G hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022411

Type: transition

Compartments: extracellular region, plasma membrane



Cathepsin G hydrolyzes angiotensin-(1-10) (angiotensin I) to yield angiotensin-(1-8) (angiotensin II) (Reilly et al. 1982, Owen and Campbell 1998, Raymond et al. 2010). Cathepsin bound to the plasma membrane of neutrophils has a higher activity than does soluble cathepsin G (Owen and Campbell 1998).

Preceded by: Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10), Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10), Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Followed by: ACE2 hydrolyzes Angiotensin-(1-8) to Angiotensin-(1-7), ENPEP hydrolyzes Angiotensin-(1-8) to Angiotensin-(2-8)

Literature references

Raymond, WW., Trivedi, NN., Makarova, A., Ray, M., Craik, CS., Caughey, GH. (2010). How immune peptidases change specificity: cathepsin G gained tryptic function but lost efficiency during primate evolution. *J Immunol, 185*, 5360-8. ↗

Reilly, CF., Tewksbury, DA., Schechter, NM., Travis, J. (1982). Rapid conversion of angiotensin I to angiotensin II by neutrophil and mast cell proteinases. *J Biol Chem, 257*, 8619-22. ↗

Owen, CA., Campbell, EJ. (1998). Angiotensin II generation at the cell surface of activated neutrophils: novel cathepsin G-mediated catalytic activity that is resistant to inhibition. *J Immunol, 160*, 1436-43. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

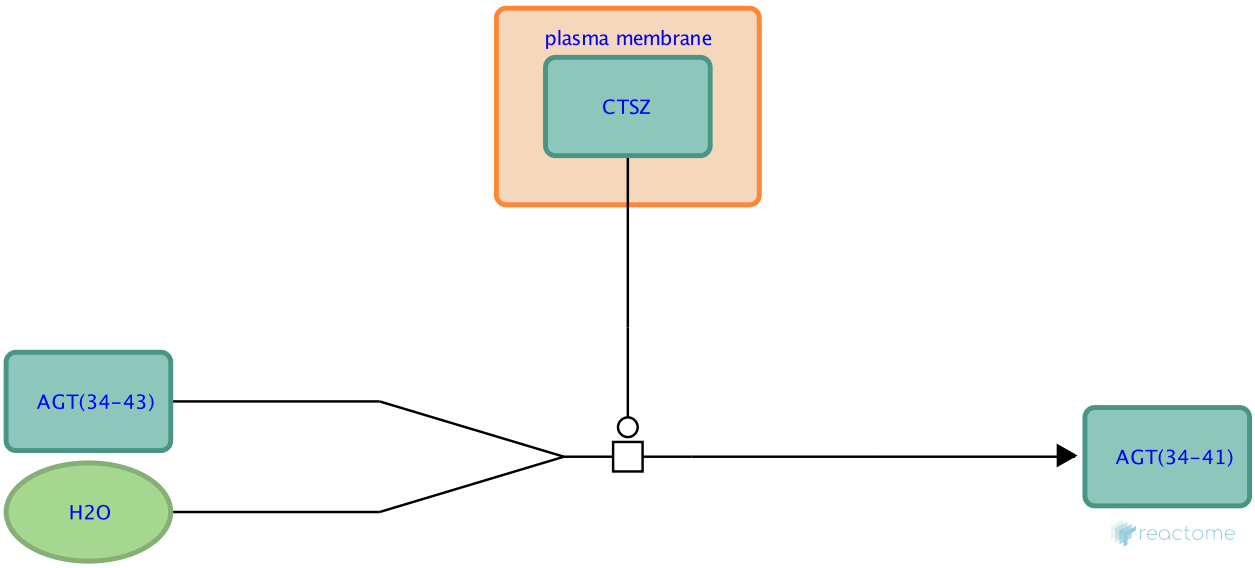
Cathepsin Z (Cathepsin X) hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022381

Type: transition

Compartments: extracellular region, plasma membrane



Cathepsin Z (cathepsin X) hydrolyzes angiotensin-(1-10) (angiotensin I) to yield angiotensin-(1-8) (angiotensin II) (Nagler et al. 2010).

Preceded by: Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10), Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10), Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Followed by: ACE2 hydrolyzes Angiotensin-(1-8) to Angiotensin-(1-7), ENPEP hydrolyzes Angiotensin-(1-8) to Angiotensin-(2-8)

Literature references

Nägler, DK., Kraus, S., Feierler, J., Mentele, R., Lottspeich, F., Jochum, M. et al. (2010). A cysteine-type carboxypeptidase, cathepsin X, generates peptide receptor agonists. *Int Immunopharmacol, 10*, 134-9. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

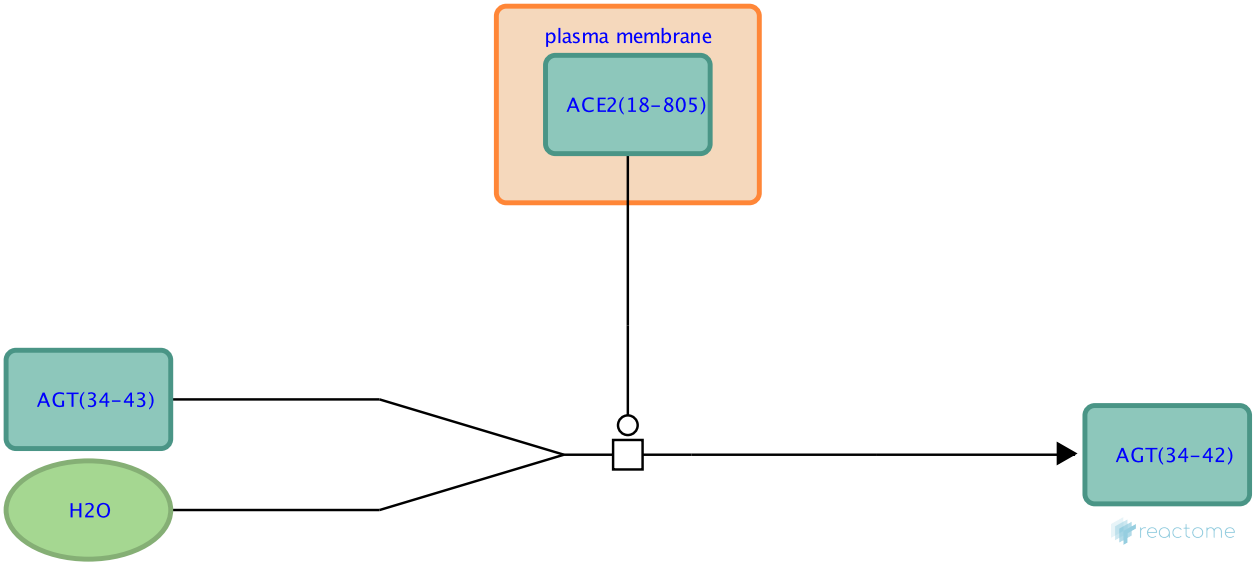
ACE2 hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-9) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022378

Type: transition

Compartments: extracellular region, plasma membrane



Angiotensin-converting enzyme 2 (ACE2) hydrolyzes angiotensin-(1-10) (angiotensin I) to yield angiotensin-(1-9) (Donoghue et al. 2000, Tipnis et al. 2000, Vickers et al. 2002, Rice t al. 2004). The activity of ACE2 on angiotensin I is weak (Rice et al. 2004), being 400-fold lower than the activity of ACE2 on angiotensin II (Vickers et al. 2002).

Preceded by: Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10), Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10), Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Followed by: MME:Zn2+ hydrolyses AGT(34-42), ACE hydrolyzes Angiotensin-(1-9) to Angiotensin-(1-7)

Literature references

Donoghue, M., Hsieh, F., Baronas, E., Godbout, K., Gosselin, M., Stagliano, N. et al. (2000). A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res, 87*, E1-9. ↗

Tipnis, SR., Hooper, NM., Hyde, R., Karran, E., Christie, G., Turner, AJ. (2000). A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J Biol Chem, 275*, 33238-43. ↗

Vickers, C., Hales, P., Kaushik, V., Dick, L., Gavin, J., Tang, J. et al. (2002). Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. *J Biol Chem, 277*, 14838-43. ↗

Rice, GI., Thomas, DA., Grant, PJ., Turner, AJ., Hooper, NM. (2004). Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J, 383*, 45-51. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

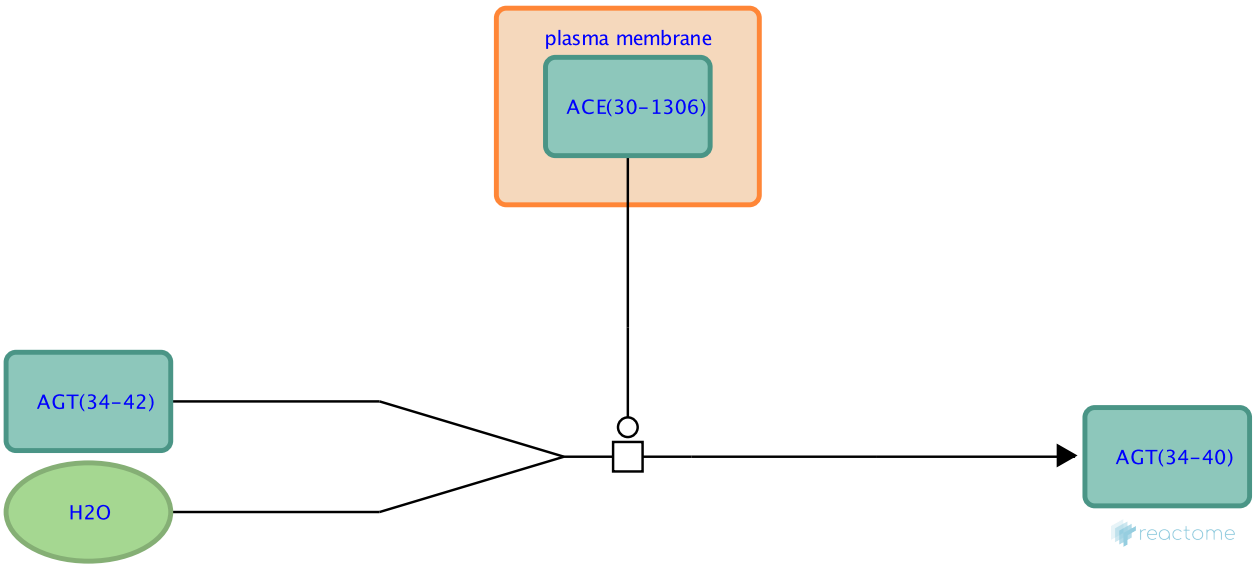
ACE hydrolyzes Angiotensin-(1-9) to Angiotensin-(1-7) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022398

Type: transition

Compartments: extracellular region, plasma membrane



Angiotensin-converting enzyme (ACE) hydrolyzes angiotensin-(1-9) to yield angiotensin-(1-7) (Rice et al. 2004).

Preceded by: ACE2 hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-9)

Literature references

Rice, GI., Thomas, DA., Grant, PJ., Turner, AJ., Hooper, NM. (2004). Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J, 383*, 45-51. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

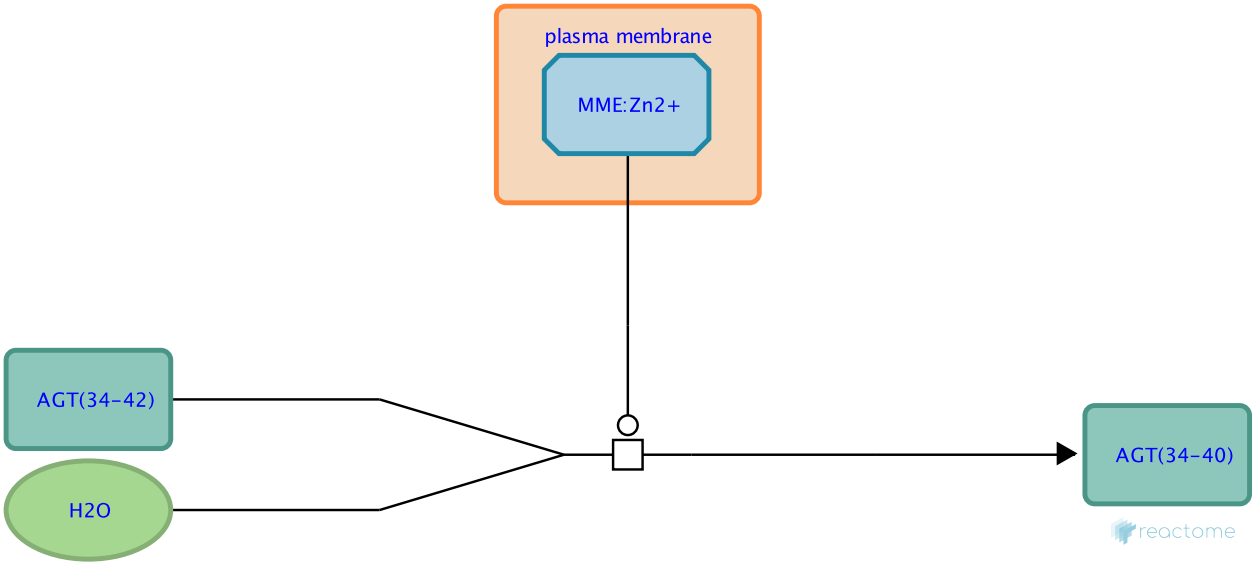
MME:Zn2+ hydrolyses AGT(34-42) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022368

Type: transition

Compartments: extracellular region, plasma membrane



Neprilysin (MME aka neutral endopeptidase NEP) hydrolyzes angiotensin-(1-9) (AGT(34-42)) to yield angiotensin-(1-7) (Rice et al. 2004). The hydrolysis of angiotensin-(1-9) catalyzed by neprilysin is more efficient than that catalyzed by angiotensin-converting enzyme (ACE) (Rice et al. 2004). MME is the major enzyme involved in the metabolic inactivation of a number of bioactive signaling peptides including the enkephalins, substance P, endothelin, bradykinin, atrial natriuretic factor, and the incretin hormone glucagon-like peptide 1. MME requires zinc as cofactor (Oefner et al. 2004, Oefner et al. 2007).

Preceded by: ACE2 hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-9)

Literature references

Rice, GI., Thomas, DA., Grant, PJ., Turner, AJ., Hooper, NM. (2004). Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J, 383*, 45-51. ↗

Oefner, C., Roques, BP., Fournie-Zaluski, MC., Dale, GE. (2004). Structural analysis of neprilysin with various specific and potent inhibitors. *Acta Crystallogr D Biol Crystallogr, 60*, 392-6. ↗

Oefner, C., Pierau, S., Schulz, H., Dale, GE. (2007). Structural studies of a bifunctional inhibitor of neprilysin and DPP-IV. *Acta Crystallogr D Biol Crystallogr, 63*, 975-81. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

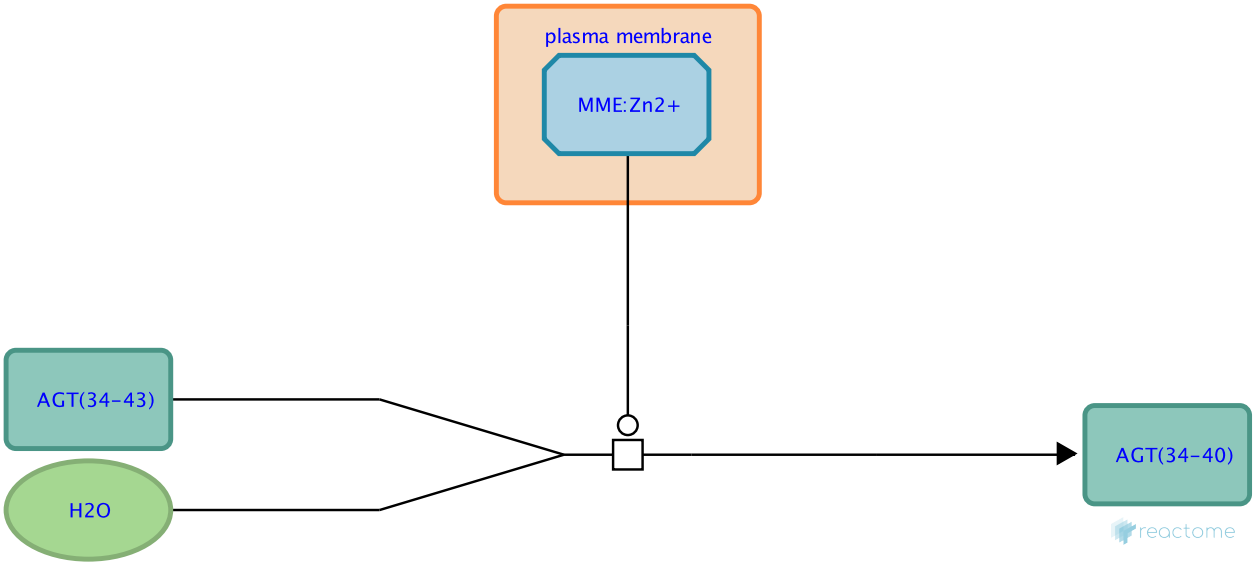
MME:Zn2+ hydrolyses AGT(34-43) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022396

Type: transition

Compartments: extracellular region, plasma membrane



Neprilysin (MME aka neutral endopeptidase NEP) hydrolyzes angiotensin-(1-10) (AGT(34-43), angiotensin I) directly to angiotensin-(1-7) (Rice et al. 2004). MME is the major enzyme involved in the metabolic inactivation of a number of bioactive signaling peptides including the enkephalins, substance P, endothelin, bradykinin, atrial natriuretic factor, and the incretin hormone glucagon-like peptide 1. MME requires zinc as cofactor (Oefner et al. 2004, Oefner et al. 2007).

Preceded by: Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10), Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10), Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Literature references

Rice, GI., Thomas, DA., Grant, PJ., Turner, AJ., Hooper, NM. (2004). Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J, 383*, 45-51. ↗

Oefner, C., Pierau, S., Schulz, H., Dale, GE. (2007). Structural studies of a bifunctional inhibitor of neprilysin and DPP-IV. *Acta Crystallogr D Biol Crystallogr, 63*, 975-81. ↗

Oefner, C., Roques, BP., Fournie-Zaluski, MC., Dale, GE. (2004). Structural analysis of neprilysin with various specific and potent inhibitors. *Acta Crystallogr D Biol Crystallogr, 60*, 392-6. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

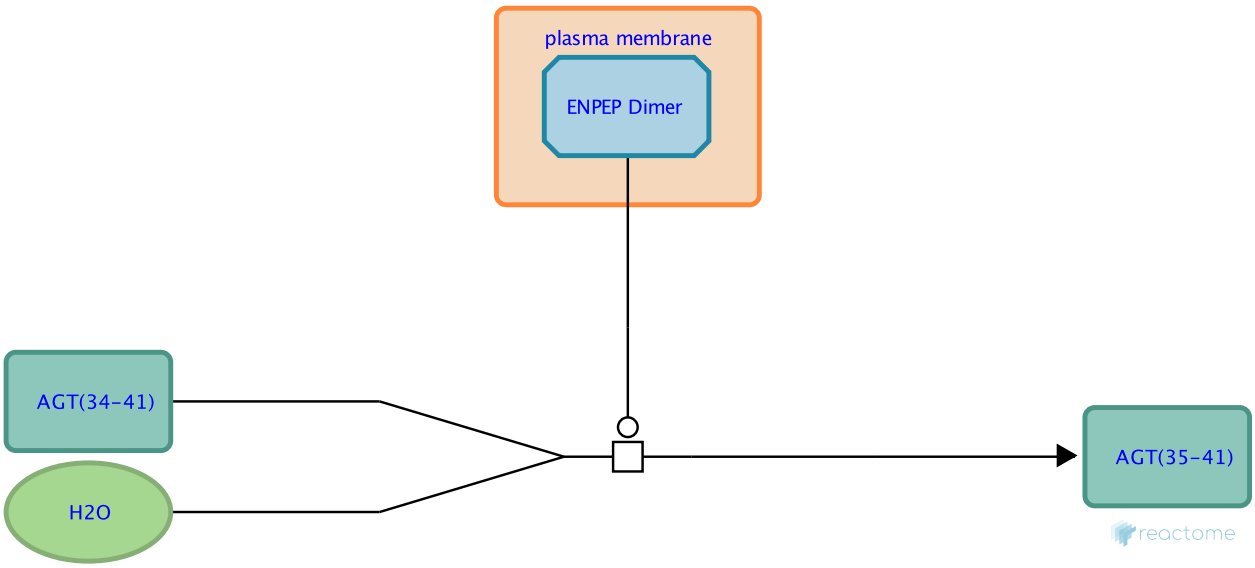
ENPEP hydrolyzes Angiotensin-(1-8) to Angiotensin-(2-8) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022399

Type: transition

Compartments: extracellular region, plasma membrane



Aminopeptidase A (APA, ENPEP) hydrolyzes the N-terminal amino acid of angiotensin-(1-8) (angiotensin II) to yield angiotensin-(2-8) (angiotensin III) (Goto et al. 2006). The catalysis is more specific and efficient in the presence of calcium ions (Goto et al. 2006).

Preceded by: ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Cathepsin G hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Cathepsin Z (Cathepsin X) hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Chymase hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Secreted ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8)

Followed by: ANPEP hydrolyzes Angiotensin-(2-8) to Angiotensin-(3-8)

Literature references

Goto, Y., Hattori, A., Ishii, Y., Mizutani, S., Tsujimoto, M. (2006). Enzymatic properties of human aminopeptidase A. Regulation of its enzymatic activity by calcium and angiotensin IV. *J Biol Chem, 281*, 23503-13. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

ANPEP hydrolyzes Angiotensin-(2-8) to Angiotensin-(3-8) ↗

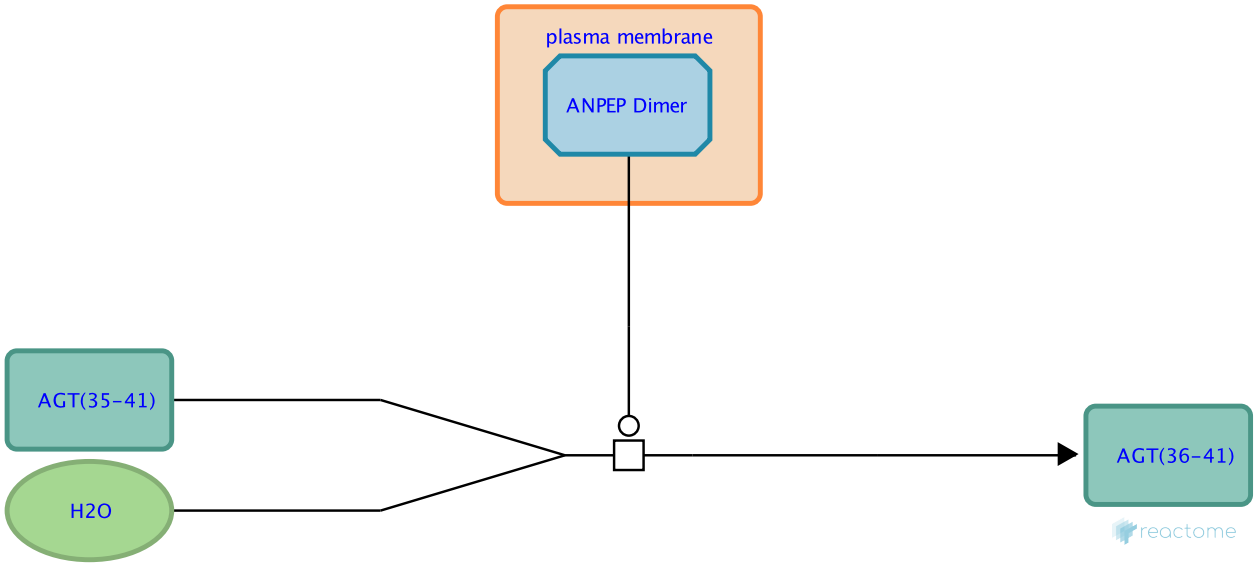
Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022393

Type: transition

Compartments: extracellular region, plasma membrane

Inferred from: ANPEP hydrolyzes Angiotensin III to Angiotensin IV (Oryctolagus cuniculus)



Aminopeptidase N (APN, ANPEP, aminopeptidase M, alanyl aminopeptidase) hydrolyzes angiotensin-(2-8) (angiotensin III) to yield angiotensin-(3-8) (angiotensin IV) (see the positive control reactions in Diaz-Perales et al. 2005). Aminopeptidase O (AOPEP) also hydrolyzes angiotensin-(2-8) to angiotensin-(3-8) in vitro (Diaz-Perales et al. 2005) but AOPEP is located in the nucleolus in vivo (Axton et al. 2008) and angiotensin-(2-8) has not been observed in the nucleus.

Preceded by: ENPEP hydrolyzes Angiotensin-(1-8) to Angiotensin-(2-8)

Literature references

Díaz-Perales, A., Quesada, V., Sánchez, LM., Ugalde, AP., Suárez, MF., Fueyo, A. et al. (2005). Identification of human aminopeptidase O, a novel metalloprotease with structural similarity to aminopeptidase B and leukotriene A4 hydrolase. *J Biol Chem, 280*, 14310-7. ↗

Axton, R., Wallis, JA., Taylor, H., Hanks, M., Forrester, LM. (2008). Aminopeptidase O contains a functional nucleolar localization signal and is implicated in vascular biology. *J Cell Biochem, 103*, 1171-82. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

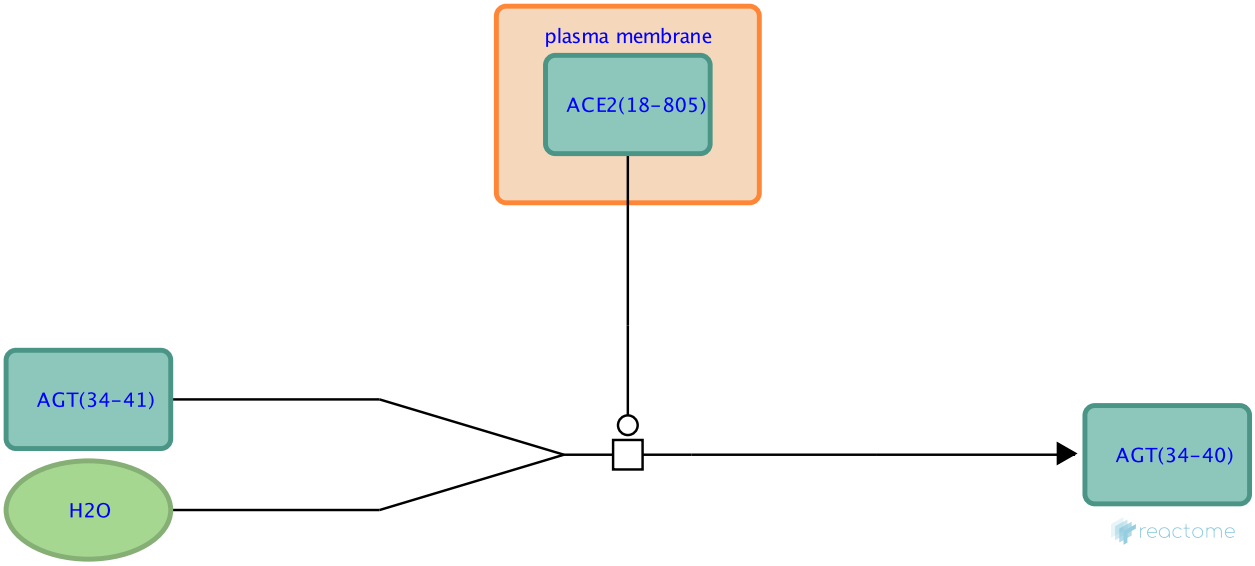
ACE2 hydrolyzes Angiotensin-(1-8) to Angiotensin-(1-7) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2022379

Type: transition

Compartments: extracellular region, plasma membrane



Angiotensin-converting enzyme 2 (ACE2) hydrolyzes angiotensin-(1-8) (angiotensin II) to yield angiotensin-(1-7) (Vickers et al. 2002, Rice et al. 2004). The activity of ACE2 on angiotensin-(1-8) is 400-fold higher than on angiotensin-(1-10) (Vickers et al. 2002).

Preceded by: ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Cathepsin G hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Cathepsin Z (Cathepsin X) hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Chymase hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8), Secreted ACE hydrolyzes Angiotensin-(1-10) to Angiotensin-(1-8)

Literature references

Vickers, C., Hales, P., Kaushik, V., Dick, L., Gavin, J., Tang, J. et al. (2002). Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. *J Biol Chem, 277*, 14838-43. ↗

Rice, GI., Thomas, DA., Grant, PJ., Turner, AJ., Hooper, NM. (2004). Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J, 383*, 45-51. ↗

Editions

2011-11-19	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

Mast Cell Carboxypeptidase hydrolyzes Angiotensin-(1-10) to Yield Angiotensin-(1-9)

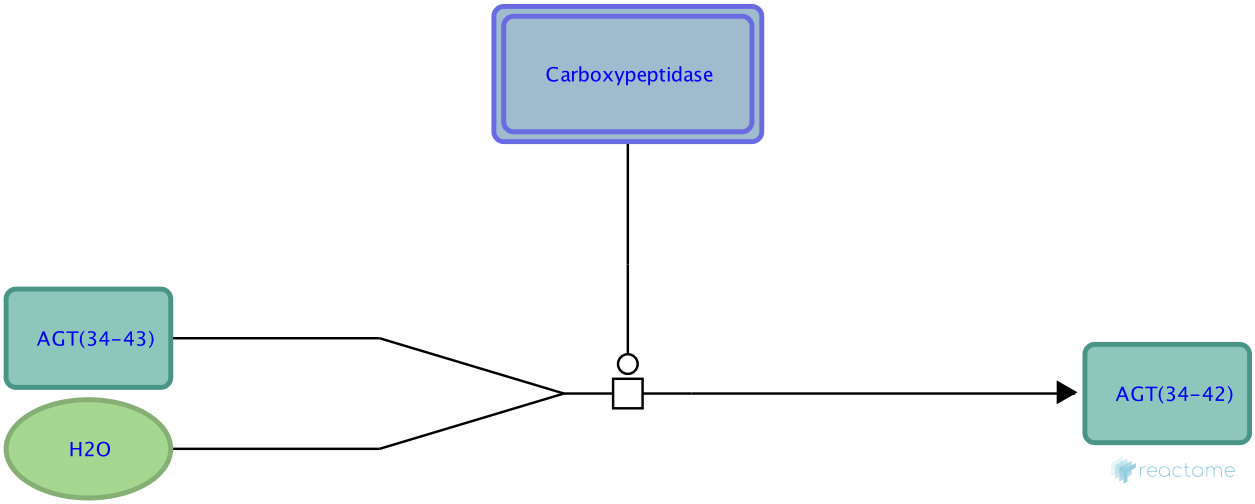
↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-2028294

Type: transition

Compartments: extracellular region



Mast cell carboxypeptidase (CPA3) hydrolyzes a single amino acid residue from the C-terminus of angiotensin-(1-10) (angiotensin I) to yield angiotensin-(1-9).

Preceded by: Renin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10), Renin hydrolyzes Angiotensinogen to Angiotensin-(1-10), Prorenin:Prorenin Receptor hydrolyzes Angiotensinogen to Angiotensin-(1-10)

Literature references

Goldstein, SM., Kaempfer, CE., Kealey, JT., Wintroub, BU. (1989). Human mast cell carboxypeptidase. Purification and characterization. *J Clin Invest, 83*, 1630-6. ↗

Goldstein, SM., Kaempfer, CE., Proud, D., Schwartz, LB., Irani, AM., Wintroub, BU. (1987). Detection and partial characterization of a human mast cell carboxypeptidase. *J Immunol, 139*, 2724-9. ↗

Editions

2011-12-23	Authored, Edited	May, B.
2012-08-06	Reviewed	Joseph, J.

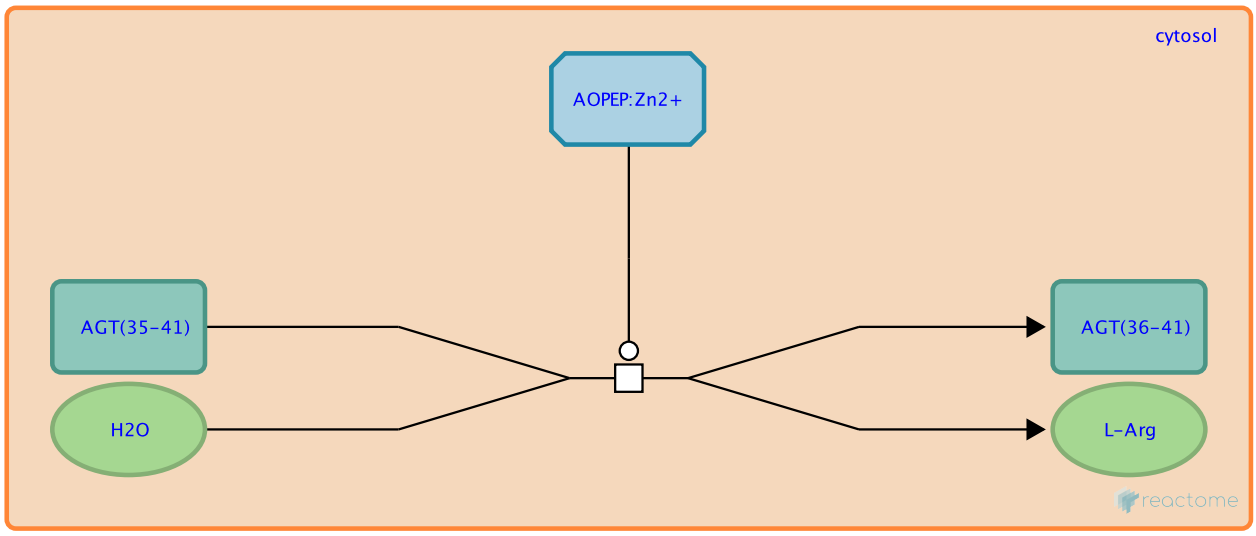
AOPEP:Zn2+ hydrolyses AGT(35-41) to AGT(36-41) ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-8851929

Type: transition

Compartments: cytosol



Aminopeptidase O (AOPEP, AP-O) is a member of the M1 family of zinc metallopeptidases or gluzincins. AOPEP contains a large catalytic gluzincin domain which has the archetypal metalloprotease zinc-binding site ending in a family-specific Glu residue (HEXXHX[18]E) typical to this family. AOPEP is able to catalyse the hydrolsis of an arginine residue (L-Arg) from angiotensin III (AGT(35-41)) to form angiotensin IV (AGT(36-41)), a bioactive peptide of the renin-angiotensin pathway. AOPEP does not contain a recognisable signal sequence or type II transmembrane domain, indicating that it likely belongs to the cytoplasmic subfamily of gluzincins (Diaz-Perales et al. 2005). AOPEP mRNA transcripts are predominantly detected in the pancreas, placenta, liver, testis, and heart. Expression of the AOPEP in heart and testis could suggest involvement in the regulation of cardiac and male reproductive physiology (Diaz-Perales et al. 2005).

Literature references

Díaz-Perales, A., Quesada, V., Sánchez, LM., Ugalde, AP., Suárez, MF., Fueyo, A. et al. (2005). Identification of human aminopeptidase O, a novel metalloprotease with structural similarity to aminopeptidase B and leukotriene A4 hydrolase. *J Biol Chem, 280*, 14310-7. ↗

Editions

2016-01-12	Authored, Edited	Jassal, B.
2016-04-05	Reviewed	D'Eustachio, P.

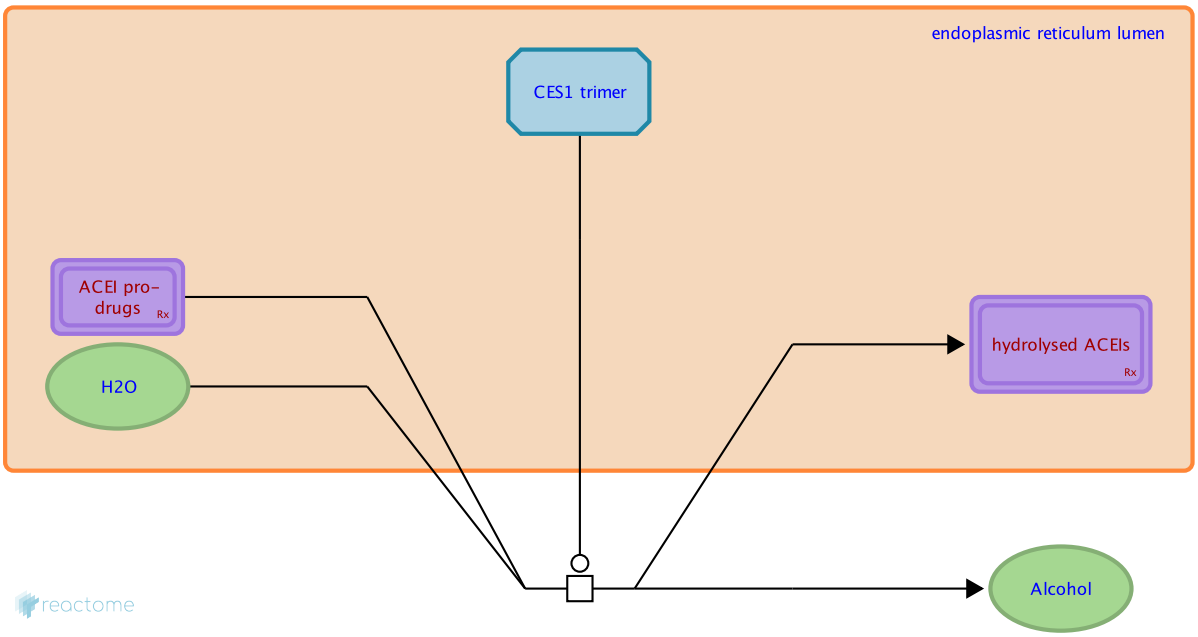
CES1trimer hydrolyses ACEI pro-drugs to ACEIs ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-9619024

Type: transition

Compartments: extracellular region



Mammalian carboxylesterases (CES) are a well conserved family that catalyse the hydrolysis of a vast array of endogenous and exogenous substrates including environmental toxins and drugs. CES-mediated hydrolysis plays an important role in the disposition of a number of widely prescribed therapeutic agents from a diverse range of drug classes including angiotensin-converting enzyme inhibitors (ACEIs). In humans, two carboxylesterases, CES1 and CES2, are important enzymes in drug metabolism (Brzezinski et al. 1994, Pindel et al. 1997). Both are expressed in liver but levels of CE1 are much higher than CE2. Most ACEI prodrugs (except captopril and lisinopril) are administered as esterified prodrugs which are probably susceptible to hydrolysis by CES1 trimer (Thomsen et al. 2014). The resultant active drugs (suffix 'prilat') can inhibit the conversion of angiotensin I to angiotensin II, thereby contributing to the antihypertensive effect of these drugs. Some CES1 genetic variants (eg. G143E) may impair ACEI activation, and consequently affect therapeutic outcomes of ACEI prodrugs (Wang et al. 2016).

Followed by: ACEIs translocate from ER lumen to extracellular region

Literature references

Brzezinski, MR., Abraham, TL., Stone, CL., Dean, RA., Bosron, WF. (1994). Purification and characterization of a human liver cocaine carboxylesterase that catalyzes the production of benzoylecgonine and the formation of cocaethylene from alcohol and cocaine. *Biochem. Pharmacol., 48*, 1747-55. ↗

Pindel, EV., Kedishvili, NY., Abraham, TL., Brzezinski, MR., Zhang, J., Dean, RA. et al. (1997). Purification and cloning of a broad substrate specificity human liver carboxylesterase that catalyzes the hydrolysis of cocaine and heroin. *J. Biol. Chem., 272*, 14769-75. ↗

Thomsen, R., Rasmussen, HB., Linnet, K. (2014). In vitro drug metabolism by human carboxylesterase 1: focus on angiotensin-converting enzyme inhibitors. *Drug Metab. Dispos., 42*, 126-33. ↗

Editions

2018-09-14	Authored, Edited	Jassal, B.
2018-09-14	Reviewed	Toomey, JR.

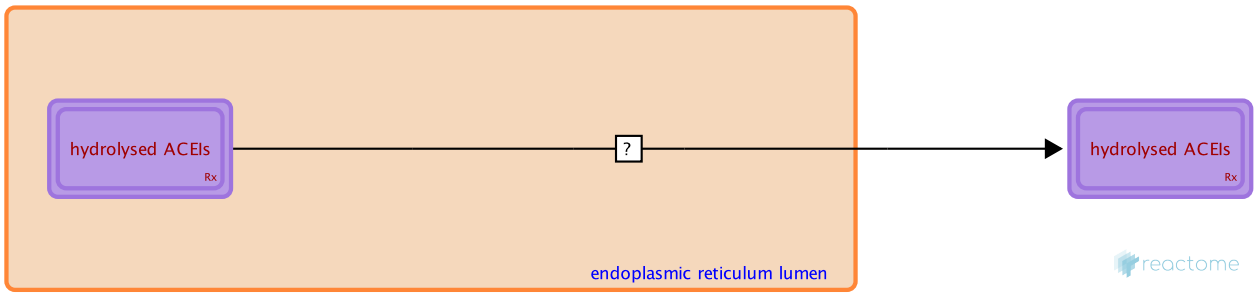
ACEIs translocate from ER lumen to extracellular region ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-9619034

Type: uncertain

Compartments: endoplasmic reticulum lumen, extracellular region



To exert their biological effects on extracellular angiotensin, angiotensin-converting enzyme inhibitors (ACEIs) translocate to the extracellular region by an unknown mechanism (Johnston et al. 1986).

Preceded by: CES1trimer hydrolyses ACEI pro-drugs to ACEIs

Followed by: ACEIs bind ACE

Literature references

Johnston, CI., Jackson, B., Cubela, R., Larmour, I., Arnolda, L. (1986). Evaluation of angiotensin converting enzyme (ACE) in the pharmacokinetics and pharmacodynamics of ACE inhibitors. *J. Cardiovasc. Pharmacol., 8*, S9-14. ↗

Editions

2018-09-14	Authored, Edited	Jassal, B.
2018-09-14	Reviewed	Toomey, JR.

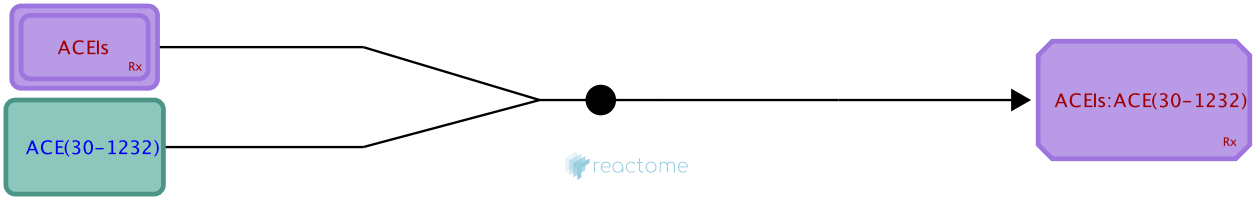
ACEIs bind ACE ↗

Location: Metabolism of Angiotensinogen to Angiotensins

Stable identifier: R-HSA-9614933

Type: binding

Compartments: extracellular region



Angiotensin-converting enzyme (ACE) is a central component of the renin–angiotensin-aldosterone system (RAAS), controlling blood pressure by regulating the fluid volume in the body. It converts the hormone angiotensin I (ATI) to the active vasoconstrictor angiotensin II (ATII). Therefore, ACE indirectly increases blood pressure by causing blood vessels to constrict. ACE inhibitors (ACEIs) block the conversion of ATI to ATII, thereby lowering arteriolar resistance and increasing venous capacity. The first ACEI, captopril, was developed from a peptide found in pit viper venom, used by the indiginous Brazilian tribes as an arrowhead poison (Patlak 2004). ACEIs decrease the production of ATII, which prevents aldosterone release from the adrenal cortex. This allows the kidney to excrete sodium ions along with obligate water, and retain potassium ions. This has the effect of decreasing blood volume, leading to decreased blood pressure (Kono et al. 1979, 1982). ACEIs are widely used as pharmaceutical drugs primarily for the treatment of hypertension (elevated blood pressure) and congestive heart failure (Abrams et al. 1984, Johnston et al. 1984, 1986).

ACEIs can be divided into three groups based on their molecular structure; sulfhydryl-containing agents (captopril, zofenopril), dicarboxylate-containing agents (includes enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, cilizapril and spirapril) and the phosphonate-containing agent fosinopril. Captopril (Capoten), was the first ACE inhibitor developed in 1975 and gaining FDA approval in 1981 (Smith & Vane 2003). Unlike the majority of ACE inhibitors, captopril is not administered as a prodrug (the only other being lisinopril). It is used in the treatment of hypertension and some types of congestive heart failure (Hollenberg 1984, Turini et al. 1983). It is also used to improve survivability after myocardial infarction and to preserve kidney function in diabetic nephropathy. Zofenopril is administered as a prodrug and is metabolized in the liver to the active form zofenoprilat (Jiang et al. 2011, Tian et al. 2015). It is used in the treatment of hypertension and ischemic heart disorders (Nilsson 2007, Ambrosioni 2007).

Enalapril is a prodrug that is metabolized by the liver into the active form enalaprilat (Shioya et al. 1992). It is used to treat hypertension, diabetic nephropathy, and heart failure (Davies et al. 1984, Gomez et al. 1985). Ramipril is an ACE inhibitor (Bunning 1984) which is administered as a prodrug and metabolized by the liver to its active form ramiprilat (Vasmant & Bender 1989). It is used to treat mild to moderate hypertension and congestive heart failure (Frampton & Peters 1995). Quinapril is a second-generation ACE inhibitor, administered as a pro-drug which is converted to its active metabolite, quinaprilat in the liver (Cetnarowski-Cropp 1991). It inhibits plasma ACE activity in studies with healthy volunteers (Sedman & Posvar 1989). Quinapril is used in the treatment of patients with hypertension and congestive heart failure (Plosker & Sorkin 1994). Efficacy is comparable to other ACE inhibitors but with a lower incidence of adverse events or withdrawals than captopril or enalapril (Frank et al. 1990).

Perindopril is an ester prodrug that is metabolized in the liver to its active form perindoprilat. It is used

to treat hypertension, heart failure and stable coronary artery disease (Chalmers & MacMahon 2003). Lisinopril was the third ACE inhibitor (after captopril and enalapril) to be approved for clinical use in the treatment of hypertension (Pool et al. 1987) and congestive heart failure (Giles 1989). Chemically, it is the lysine analogue of enalapril. Unlike other ACE inhibitors, it is not a prodrug and is excreted unchanged in the urine (Armayor & Lopez 1988, Noble & Murray 1988). Benazepril is administered as an ester prodrug and metabolized by the liver to its active form benazeprilat (Sioufi et al. 1988). It is used primarily in the treatment of hypertension, congestive heart failure, and heart attacks (Gengo & Brady 1991, Balfour & Goa 1991). Imidapril is an ACE inhibitor (Robinson et al. 2007), administered as a prodrug which is metabolized in the liver to the active form, imidaprilat (Hoogkamer et al. 1997). It is used in the treatment of mild to moderate essential hypertension (Palma-Gamiz et al. 2007) as well as preventing the onset of heart failure in patients after a myocardial infarction (Dolezal 2006).

Trandolapril is a prodrug that is metabolized in the liver to its active form trandolaprilat (Conen & Brunner 1993). Is an ACE inhibitor used to treat hypertension and congestive heart failure (Ducky & Brunner 1992, Diaz & Ducharme 2008). Cilazapril is a prodrug converted to the active drug cilazaprilat in the liver (Deget & Brogden 1991). It is used for the treatment of hypertension and congestive heart failure (Waterfall 1989, Szucs 1991). Cilazapril is branded as Dynorm, Inhibace and Vascace in various countries but is not available in the US. Spirapril is a prodrug metabolized to the active metabolite spiraprilat (Bellissant et al. 1997). It is used in the treatment of mild to moderate hypertension, administered once daily due to its long duration of action but with a narrow dose range ((Hayduk & Kraul 1999). Fosinopril is the only member of a phosphinic acid derivative which undergoes rapid hydrolysis mainly in the gastrointestinal mucosa and liver to the active form fosinoprilat (Cur et al. 2007). It is used for the treatment of hypertension and some types of chronic heart failure (Murdoch & McTavish 1992, Davis et al. 1997).

Preceded by: ACEIs translocate from ER lumen to extracellular region

Literature references

Kono, T., Ikeda, F., Oseko, F., Imura, H., Endo, J. (1979). Effects of angiotensin I-converting enzyme inhibitor, SQ 14225, in nomal men. *Endocrinol. Jpn., 26*, 411-8. ↗

Kono, T., Oseko, F., Ikeda, F., Nakano, R., Taniguchi, A., Imura, H. et al. (1982). Effects of a new angiotensin-converting enzyme inhibitor, MK 421, in normal men and patients. *Endocrinol. Jpn., 29*, 615-22. ↗

Editions

2018-07-30	Authored, Edited	Jassal, B.
2018-09-14	Reviewed	Toomey, JR.

Table of Contents