Atorvastatin ADME

Huddart, R., Jassal, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

13/11/2022
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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 82

This document contains 1 pathway and 12 reactions (see Table of Contents)
Atorvastatin (ATV, brand name Lipitor), is a lipid-lowering drug of the statin class of medications. It inhibits the endogenous production of cholesterol in the liver, thereby lowering abnormally high cholesterol and lipid levels, and ultimately reducing the risk of cardiovascular disease. Statins inhibit the enzyme hydroxymethylglutaryl-coenzyme A reductase (HMGCR), which catalyzes the critical step in cholesterol biosynthesis of HMG-CoA conversion to mevalonic acid. Statins are the most commonly prescribed medication for treating abnormal lipid levels (Malhotra & Goa 2001). ATV and its hydroxy-metabolites collectively inhibit HMGCR to reduce circulating low-density lipoprotein cholesterol.

ATV is transported in the blood almost exclusively bound to plasma proteins (>98%) (Lennernas 2003), and is subject to pre-systemic clearance at the gastrointestinal tract and to first-pass hepatic clearance, which explains its low systemic bioavailability (~12%) (Garcia et al. 2003). Organic anion transporters OATP1B1, OATP1B3 and OATP2B1, encoded by SLCO1B1, SLCO1B3, and SLCO2B1, respectively are expressed on the sinusoidal membrane of hepatocytes and can facilitate the liver uptake of drugs such as ATV (Kalliokoski & Niemi 2009).

In hepatocytes (and to a lesser extent, the GI tract), ATV can be hydroxylated by cytochrome P450 3A4 (CYP3A4) to hydroxy-metabolites, or undergo lactonization via an unstable acyl glucuronide intermediate to ATV lactone (ATVL) mediated by UGT1A3 and 1A1. ATVL may also be hydroxylated by CYP3A4 to hydroxylactone-metabolites. The lactone metabolites are inactive against HMGCR, but can be hydrolyzed via paraoxonases (PONs) to their corresponding hydroxy acids, which are active against HMGCR. Elimination of ATV and its metabolites is principally biliary with apparently no significant enterohepatic recirculation. Half-life (t1/2) is approximately 14 h for atorvastatin and 20–30 h for its metabolites (Schachter 2005).

**Literature references**


https://reactome.org


**Editions**

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SLCO1B1,1B3,2B1-3 transport ATV from extracellular region to cytosol

**Location:** Atorvastatin ADME

**Stable identifier:** R-HSA-9757010

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

Solute carrier organic anion transporter family members OATP1B1, OATP1B3 and OATP2B1, encoded by the SLCO1B1 (Hsiang et al. 1999), SLCO1B3 (Schwarz et al. 2011) and SLCO2B183 (Knauer et al. 2013) genes, respectively, are expressed on the sinusoidal membrane of hepatocytes and can facilitate the liver uptake of atorvastatin (ATV) (review Kalliokoski & Niemi 2009). SLCO1B1 was shown to have the highest ATV uptake activity of the SLCO transporters (Vildhede et al. 2014). In a candidate-gene pharmacogenetic study, results suggested that SLCO1B1 was the best predictor for ATV pharmacokinetic variability and therefore ATV should be prescribed accordingly (Zubiaur et al. 2021).

**Followed by:** ABCB1,ABCC2 transport ATVs from cytosol to extracellular region, CYP3A4 monoxygenates ATV to 4-OH-ATV, CYP3A4 monoxygenates ATV to 2-OH-ATV, UGT1A3 lactonizes ATV to ATVL

**Literature references**


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https://reactome.org
CYP3A4 monooxygenates ATV to 2-OH-ATV

Location: Atorvastatin ADME

Stable identifier: R-HSA-9756169

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol

Atorvastatin (ATV) is hydroxylated to hydroxy-metabolites, predominantly by cytochrome P450 3A4 (CYP3A4) (Fujino et al. 2004, Park et al. 2008). Here, ATV hydroxylation to 2-hydroxyatorvastatin (2-OH-ATV, aka ortho-hydroxyatorvastatin) is described.

Preceded by: SLCO1B1,1B3,2B1-3 transport ATV from extracellular region to cytosol

Followed by: UGT1A3 lactonizes 2-OH-ATV to 2-OH-ATVL

Literature references


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https://reactome.org
CYP3A4 monooxygenates ATV to 4-OH-ATV

Location: Atorvastatin ADME

Stable identifier: R-HSA-9756162

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol

Atorvastatin (ATV) is hydroxylated to hydroxy-metabolites, predominantly by cytochrome P450 3A4 (CYP3A4) (Fujino et al. 2004, Park et al. 2008). Here, ATV hydroxylation to 4-hydroxyatorvastatin (4-OH-ATV, aka para-hydroxyatorvastatin) is described.

Preceded by: SLCO1B1,1B3,2B1-3 transport ATV from extracellular region to cytosol

Followed by: UGT1A3 lactonizes 4-OH-ATV to 4-OH-ATVL

Literature references


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**UGT1A3 lactonizes ATV to ATVL**

**Location:** Atorvastatin ADME

**Stable identifier:** R-HSA-9756156

**Type:** uncertain

**Compartments:** endoplasmic reticulum membrane, cytosol

The acid form of atorvastatin (ATV) can be converted to its lactone form (ATVL) primarily by UDP-glucuronosyltransferase 1A3 (UGT1A3), with small contributions from UGT1A1 and 2B7 (Prueksaritanont et al. 2002, Schirris et al. 2015). The lactonization process involves the formation of an unstable acyl glucuronide intermediate (not described here). Increased generation of ATVL due to polymorphisms in UGT1A1, 1A3, and 2B7 may be contributing factors in statin-induced myopathies (Riedmaier et al. 2010). In vitro, the lactone forms of ATV show a higher potency to induce myotoxicity in human skeletal cells than their acid counterparts (Skottheim et al. 2008, Cho et al. 2012). Carriers of less strongly expressed alleles of UGT enzymes may have decreased exposure to the suspected muscle-toxic metabolite atorvastatin lactone (Stormo et al. 2013).

**Preceded by:** SLC01B1,1B3,2B1-3 transport ATV from extracellular region to cytosol

**Followed by:** CYP3A4 monooxygenates ATVL to 2-OH-ATVL, ABCB1,ABCC2 transport ATVs from cytosol to extracellular region, PON1,3 hydrolyse ATVL to ATV, CYP3A4 monooxygenates ATVL to 4-OH-ATVL

**Literature references**


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The acid form of 2-hydroxyatorvastatin (2-OH-ATV) can be converted to its lactone form (2-OH-ATVL) primarily by UDP-glucuronosyltransferase 1A3 (UGT1A3), with small contributions from UGT1A1 and 2B7 (Prueksaritanont et al. 2002, Schirris et al. 2015). The lactonization process involves the formation of an unstable acyl glucuronide intermediate (not described here). Increased generation of ATVL due to polymorphisms in UGT1A1, 1A3, and 2B7 may be contributing factors in statin-induced myopathies (Riedmaier et al. 2010). In vitro, the lactone forms of ATV show a higher potency to induce myotoxicity in human skeletal cells than their acid counterparts (Skottheim et al. 2008, Cho et al. 2012). Carriers of less strongly expressed alleles of UGT enzymes may have decreased exposure to the suspected muscle-toxic metabolite atorvastatin lactone (Stormo et al. 2013).

**Preceded by:** CYP3A4 monoxygenates ATV to 2-OH-ATV

**Followed by:** PON1,3 hydrolyse 2-OH-ATVL to 2-OH-ATV, ABCB1,ABCC2 transport ATVs from cytosol to extracellular region

**Literature references**


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**UGT1A3 lactonizes 4-OH-ATV to 4-OH-ATVL**

**Location:** Atorvastatin ADME

**Stable identifier:** R-HSA-9756183

**Type:** uncertain

**Compartments:** endoplasmic reticulum membrane, cytosol

The acid form of 4-hydroxyatorvastatin (4-OH-ATV) can be converted to its lactone form (4-OH-ATVL) primarily by UDP-glucuronosyltransferase 1A3 (UGT1A3), with small contributions from UGT1A1 and 2B7 (Prueksaritanont et al. 2002, Schirris et al. 2015). The lactonization process involves the formation of an unstable acyl glucuronide intermediate (not described here). Increased generation of ATVL due to polymorphisms in UGT1A1, 1A3, and 2B7 may be contributing factors in statin-induced myopathies (Riedmaier et al. 2010). In vitro, the lactone forms of ATV show a higher potency to induce myotoxicity in human skeletal cells than their acid counterparts (Skottheim et al. 2008, Cho et al. 2012). Carriers of less strongly expressed alleles of UGT enzymes may have decreased exposure to the suspected muscle-toxic metabolite atorvastatin lactone (Stormo et al. 2013).

**Preceded by:** CYP3A4 monoxygenates ATV to 4-OH-ATV

**Followed by:** ABCB1,ABCC2 transport ATVs from cytosol to extracellular region, PON1,3 hydrolyse 4-OH-ATVL to 4-OH-ATV

### Literature references


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CYP3A4 monooxygenates ATVL to 2-OH-ATVL

Location: Atorvastatin ADME

Stable identifier: R-HSA-9756138

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol

Atorvastatin lactone (ATVL) is hydroxylated to hydroxy-metabolites, predominantly by cytochrome P450 3A4 (CYP3A4) (Park et al. 2008). Statin lactones are metabolized to a much higher extent than their acid forms by CYP enzymes, suggesting that metabolism of the lactone is the relevant pathway for atorvastatin elimination (Jacobsen et al. 2000, Fujino et al. 2004, Filppula et al. 2021). Described here is the formation of 2-hydroxyatorvastatin lactone (2-OH-ATVL).

Preceded by: UGT1A3 lactonizes ATV to ATVL

Followed by: PON1,3 hydrolyse 2-OH-ATVL to 2-OH-ATV

Literature references


Sewing, KF., Soldner, A., Christians, U., Jacobsen, W., Kirchner, G., Benet, LZ. et al. (2000). Lactonization is the critical first step in the disposition of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor atorvastatin. Drug Metab Dispos, 28, 1369-78.

Editions

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CYP3A4 monooxygenates ATVL to 4-OH-ATVL

Location: Atorvastatin ADME

Stable identifier: R-HSA-9756180

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol

Atorvastatin lactone (ATVL) is hydroxylated to hydroxy-metabolites, predominantly by cytochrome P450 3A4 (CYP3A4) (Park et al. 2008). Statin lactones are metabolized to a much higher extent than their acid forms by CYP enzymes, suggesting that metabolism of the lactone is the relevant pathway for atorvastatin elimination (Jacobsen et al. 2000, Fujino et al. 2004, Filppula et al. 2021). Described here is the formation of 4-hydroxyatorvastatin lactone (4-OH-ATVL).

Preceded by: UGT1A3 lactonizes ATV to ATVL

Followed by: PON1,3 hydrolyse 4-OH-ATVL to 4-OH-ATV

Literature references


Sewing, KF., Soldner, A., Christians, U., Jacobsen, W., Kirchner, G., Benet, LZ. et al. (2000). Lactonization is the critical first step in the disposition of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor atorvastatin. Drug Metab Dispos, 28, 1369-78.

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2021-10-12 Authored, Edited Jassal, B.
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Serum paraoxonase/arylesterase 1 and Serum paraoxonase/lactonase 3 (PON1 and PON3 respectively) were identified as the major enzymes involved in the hydrolysis of atorvastatin-lactone (ATVL) to atorvastatin (ATV) in human liver (Riedmaier et al. 2011). They are predominantly associated with the ER membrane (Gonzalvo et al. 1998, Riedmaier et al. 2011). It is very likely that these two enzymes also convert the corresponding hydroxyl-metabolites.

Preceded by: UGT1A3 lactonizes ATV to ATVL

Literature references


PON1,3 hydrolyse 2-OH-ATVL to 2-OH-ATV

Location: Atorvastatin ADME

Stable identifier: R-HSA-9756136

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol

Inferred from: PON1,3 hydrolyse ATVL to ATV (Homo sapiens)

Serum paraoxonase/arylesterase 1 and Serum paraoxonase/lactonase 3 (PON1 and PON3 respectively) were identified as the major enzymes involved in the hydrolysis of atorvastatin-lactone (ATVL) to atorvastatin (ATV) in human liver (Riedmaier et al. 2011). They are predominantly associated with the ER membrane (Gonzalvo et al. 1998, Riedmaier et al. 2011). It is very likely that these two enzymes also convert the corresponding 2-hydroxyl-metabolite.

Preceded by: CYP3A4 monooxygenates ATVL to 2-OH-ATVL, UGT1A3 lactonizes 2-OH-ATV to 2-OH-ATVL

Literature references


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**Preceded by:** UGT1A3 lactonizes 4-OH-ATV to 4-OH-ATVL, CYP3A4 monooxygenates ATVL to 4-OH-ATVL

**Literature references**


ATP-binding cassette sub-family C member 2 (ABCC2, aka MRP2) (Ellis et al. 2013) and ATP-dependent translocase ABCB1 (ABCB1, aka P-glycoprotein 1) (Hochman et al. 2004) mediate the efflux of atorvastatin (ATV) and its lactone intermediates into bile.

**Preceded by:** UGT1A3 lactonizes ATV to ATVL, SLCO1B1,1B3,2B1-3 transport ATV from extracellular region to cytosol, UGT1A3 lactonizes 4-OH-ATV to 4-OH-ATVL, UGT1A3 lactonizes 2-OH-ATV to 2-OH-ATVL

**Literature references**


Atorvastatin ADME

- SLC01B1,1B3,2B1-3 transport ATV from extracellular region to cytosol
- CYP3A4 monooxygenates ATV to 2-OH-ATV
- CYP3A4 monooxygenates ATV to 4-OH-ATV
- UGT1A3 lactonizes ATV to ATVL
- UGT1A3 lactonizes 2-OH-ATV to 2-OH-ATVL
- UGT1A3 lactonizes 4-OH-ATV to 4-OH-ATVL
- CYP3A4 monooxygenates ATVL to 2-OH-ATVL
- CYP3A4 monooxygenates ATVL to 4-OH-ATVL
- PON1,3 hydrolyse ATVL to ATV
- PON1,3 hydrolyse 2-OH-ATVL to 2-OH-ATV
- PON1,3 hydrolyse 4-OH-ATVL to 4-OH-ATV
- ABCB1,ABCC2 transport ATVs from cytosol to extracellular region