AOP ID and Title:

SNAPSHOT

Created at: 2019-01-04 08:59

AOP 124: HMG-CoA reductase inhibition leading to decreased fertility

Short Title: HMGCR inhibition to male fertility

Authors

Kellie Fay

Status

Author status	OECD status	OECD project	SAAOP status
Under development: Not open for comment. Do not cite		1.29	Under Development

Abstract

During sexual differentiation and gonadal development in utero or in ovo, androgenic tissues develop, in part, under the control of testosterone (Viger et al. 2005). Reduction of circulating testosterone during this crucial time of development can result in malformed reproductive tracts in males. Exposure to drugs (e.g., statins) or other compounds may cause male reproductive tract abnormalities by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme in the production of cholesteron, the precursor of testosterone.

Summary of the AOP

Events

Molecular Initiating Events (MIE), Key Events (KE), Adverse Outcomes (AO)

Sequence	Type	Event ID	Title	Short name
1	MIE	804	Inhibition, HMG-CoA reductase (https://aopwiki.org/events/804)	Inhibition, HMG-CoA reductase
2	KE	805	Decreased, mevalonate (https://aopwiki.org/events/805)	Decreased, mevalonate
3	KE	807	Decreased, cholesterol (https://aopwiki.org/events/807)	Decreased, cholesterol
4	KE	808	Decreased, Testosterone (https://aopwiki.org/events/808)	Decreased, Testosterone
5	KE	809	malformed, Male reproductive tract (https://aopwiki.org/events/809)	malformed, Male reproductive tract
6	AO	330	Decrease, Fertility (https://aopwiki.org/events/330)	Decrease, Fertility

Key Event Relationships

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
Inhibition, HMG-CoA reductase (https://aopwiki.org/relationships/804)	adjacent	Decreased, mevalonate	High	

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
Decreased, mevalonate (https://aopwiki.org/relationships/805)	adjacent	Decreased, cholesterol		
malformed, Male reproductive tract (https://aopwiki.org/relationships/808)	adjacent	Decrease, Fertility		
Decreased, cholesterol (https://aopwiki.org/relationships/806)	non-adjacent	Decreased, Testosterone		
Decreased, Testosterone (https://aopwiki.org/relationships/807)	non-adjacent	malformed, Male reproductive tract		

Overall Assessment of the AOP

This AOP was developed primarily from one study of exposure of rats in utero to simvastatin (as well as a phthalate ester; Beverley et al., 2015) and biological plausibility. It currently should be considered putative and untested.

Domain of Applicability

Life Stage Applicability

Life Stage	Evidence
Fetal	Low

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Rattus rattus	Rattus rattus		NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10117)

Sex Applicability

Sex	Evidence
Male	

References

Beverly, B. E. J., et al. (2014). "Simvastatin and Dipentyl Phthalate Lower Ex Vivo Testicular Testosterone Production and Exhibit Additive Effects on Testicular Testosterone and Gene Expression Via Distinct Mechanistic Pathways in the Fetal Rat." Toxicological Sciences.

Appendix 1

List of MIEs in this AOP

Event: 804: Inhibition, HMG-CoA reductase (https://aopwiki.org/events/804)

Short Name: Inhibition, HMG-CoA reductase

Key Event Component

Process	Object	Action
hydroxymethylglutaryl-CoA reductase activity	3-hydroxy-3-methylglutaryl-coenzyme A reductase	decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:124 - HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	MolecularInitiatingEvent

Biological Context

Level of Biological Organization
Cellular

How it is Measured or Detected

The activity of HMG-CoA reductase inhibition may be measured by a commercially available kit which measures a decrease in absorbance at 340 nm, which represents the oxidation of NADPH by the catalytic subunit of HMGR in the presence of the substrate HMG-CoA. Sterol Regulatory element-binding factor 1 (SREBF) is the transcription factor controlling downstream regulation of HMG-CoA reductase. The ToxCast assay ATG_SREBF1_CIS_up is one method of measuring transcriptional control of HMG-CoA reductase.

List of Key Events in the AOP

Event: 805: Decreased, mevalonate (https://aopwiki.org/events/805)

Short Name: Decreased, mevalonate

Key Event Component

Process	Object	Action
	mevalonate	decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:124 - HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Event: 807: Decreased, cholesterol (https://aopwiki.org/events/807)

Short Name: Decreased, cholesterol

Key Event Component

Process	Object	Action
	cholesterol	decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:124 - HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Event: 808: Decreased, Testosterone (https://aopwiki.org/events/808)

Short Name: Decreased, Testosterone

Key Event Component

Process	Object	Action
	testosterone	decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:124 - HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	KeyEvent

Biological Context

Level of Biological Organization
Individual

Event: 809: malformed, Male reproductive tract (https://aopwiki.org/events/809)

Short Name: malformed, Male reproductive tract

Key Event Component

Process	Object	Action
	male reproductive system	morphological change

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:124 - HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	KeyEvent

Biological Context

Level of Biological Organization
Individual

Organ term

Organ term
male reproductive system

List of Adverse Outcomes in this AOP

Event: 330: Decrease, Fertility (https://aopwiki.org/events/330)

Short Name: Decrease, Fertility

Key Event Component

Process	Object	Action

Process	Object	Action
	fertility	decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:124 - HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	AdverseOutcome

Biological Context

Level of Biological Organization
Individual

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
mice	Mus sp.	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10095)
human	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)

Appendix 2

List of Key Event Relationships in the AOP

List of Adjacent Key Event Relationships

Relationship: 804: Inhibition, HMG-CoA reductase leads to Decreased, mevalonate (https://aopwiki.org/relationships/804)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	**adjacent**	**High**	

Relationship: 805: Decreased, mevalonate leads to Decreased, cholesterol (https://aopwiki.org/relationships/805)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	**adjacent**		

Relationship: 808: malformed, Male reproductive tract leads to Decrease, Fertility (https://aopwiki.org/relationships/808)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	**adjacent**		

List of Non Adjacent Key Event Relationships

Relationship: 806: Decreased, cholesterol leads to Decreased, Testosterone (https://aopwiki.org/relationships/806)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	**non-adjacent**		

Relationship: 807: Decreased, Testosterone leads to malformed, Male reproductive tract (https://aopwiki.org/relationships/807)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
HMG-CoA reductase inhibition leading to decreased fertility (https://aopwiki.org/aops/124)	**non-adjacent**		