MC1R Activation and Atherosclerosis

Mechanistic Evidence and Therapeutic Implications of Melanocortin-1 Receptor Agonism

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Abstract

Activation of the Melanocortin 1 Receptor (MC1R) has emerged as a potential protective mechanism in the development and progression of atherosclerosis. MC1R signaling regulates macrophage lipid handling, inflammatory signaling, endothelial function, and plaque composition. Experimental evidence demonstrates that MC1R activation reduces foam cell formation, enhances reverse cholesterol transport, stabilizes atherosclerotic plaques, and improves vascular biology. Synthetic agonists such as Afamelanotide — also known as Melanotan-I (MT-1) or NDP-MSH — mimic endogenous melanocortin peptides and may amplify these protective pathways. Although current evidence is largely derived from mechanistic studies and animal models, the biological framework suggests MC1R agonism could represent a disease-modifying strategy for atherosclerosis.

1. Introduction

Atherosclerosis is driven by lipid accumulation, chronic vascular inflammation, endothelial dysfunction, and maladaptive plaque remodeling. Central to early plaque development is the formation of foam cells, which arise when macrophages accumulate excessive cholesterol after uptake of oxidized LDL (oxLDL).

The melanocortin system — particularly MC1R signaling — plays an underappreciated role in regulating macrophage inflammatory responses and cholesterol metabolism. Endogenous peptides such as Alpha Melanocyte Stimulating Hormone (α-MSH) activate MC1R and may function as an intrinsic anti-atherogenic signaling pathway.

Pharmacologic MC1R agonists, including Afamelanotide (MT-1), can amplify this pathway and potentially influence multiple stages of atherosclerotic disease. MT-1 should not be confused with Melanotan-II — a structurally distinct, shorter cyclic peptide with broader and less selective melanocortin receptor activity.

1.1 Nomenclature

Name	Also Known As	Notes
Melanotan-I (MT-1)	Afamelanotide, NDP-MSH, CUV1647, [Nle4,D-Phe7]-α-MSH	13-aa linear peptide; relative MC1R selectivity; EMA-approved (Scenesse) for EPP
Melanotan-II (MT-2)	Cyclic 7-aa peptide	Broader receptor activity including MC4R; stronger CNS effects; NOT the focus of this review

Table 1. Nomenclature clarification for clinically relevant melanocortin agonists.

2. Mechanisms of MC1R-Mediated Atheroprotection

MC1R signaling engages multiple simultaneous mechanisms that collectively oppose atherosclerotic disease progression. These operate at the level of macrophage cholesterol handling, vascular inflammation, endothelial biology, and plaque architecture.

2.1 Suppression of Foam Cell Formation

Foam cell formation is the defining initiating event in plaque development. MC1R activation disrupts this process through two complementary and simultaneous mechanisms:

	Mechanism	Molecular Target	Net Effect
1	**Reduced oxLDL uptake**	MC1R activation downregulates CD36 surface expression on macrophages — the primary scavenger receptor for oxidized LDL	Less cholesterol entering macrophages from the arterial wall
2	**Enhanced reverse cholesterol transport**	Upregulation of ABCA1 and ABCG1 — cholesterol efflux transporters that move intracellular cholesterol onto HDL particles	More cholesterol removed from macrophages and returned to hepatic clearance via HDL

Table 2. Dual mechanism of MC1R-mediated foam cell suppression.

The net result of these two parallel actions is a substantial reduction in macrophage cholesterol burden — the key pathological substrate for foam cell formation and plaque initiation.

2.2 Anti-Inflammatory Signaling — NF-κB Suppression

MC1R is a Gs-coupled GPCR. Its activation drives intracellular cAMP elevation via adenylate cyclase, activating PKA which stabilises IκB and blocks NF-κB nuclear translocation. NF-κB is the master transcriptional regulator of vascular inflammation — its suppression downstream of MC1R results in:

- Reduced IL-6 and TNF-α production in macrophages and endothelial cells
- Suppressed CCL2 and CCL5 — chemokines that recruit pro-inflammatory monocytes to the arterial wall
- Reduced MMP secretion (MMP-2, MMP-9) — proteases responsible for fibrous cap degradation
- Blunted pro-inflammatory Ly6C-high monocyte arterial recruitment

2.3 Endothelial Function

MC1R is constitutively expressed by arterial endothelial cells. Experimental MC1R deficiency demonstrates reduced eNOS activity, lower circulating NO metabolites, impaired acetylcholine-evoked vasodilation, and increased arterial stiffness. MC1R activation restores NO bioavailability — a critical protective factor against endothelial dysfunction and early atherogenesis. MC1R activation also promotes endothelial cell migration, supporting repair of endothelial denudation — an early trigger of plaque formation.

3. Evidence from Genetic and Animal Models

The most direct evidence for MC1R's atheroprotective role comes from knockout and pharmacological studies in experimental atherosclerosis models.

3.1 MC1R Deficiency Phenotype

In ApoE-deficient mice additionally lacking functional MC1R, atherosclerotic lesion burden is significantly greater, and critically, plaque composition shifts toward a more vulnerable, rupture-prone phenotype:

Plaque Feature	Wild-Type MC1R	MC1R-Deficient	Clinical Significance
Atherosclerotic lesion size	Baseline	Significantly larger ↑	Greater plaque burden throughout aorta
Collagen content	Normal	Reduced ↓	Thinner fibrous cap → higher rupture risk
Smooth muscle cells	Normal	Reduced ↓	Impaired plaque structural integrity
Necrotic core	Normal	Increased ↑	Hallmark of unstable, vulnerable plaque
ABCA1 / ABCG1 expression	Normal	Reduced ↓	Impaired cholesterol efflux from arterial macrophages
Ly6C-hi monocyte recruitment	Normal	Increased ↑	Greater inflammatory macrophage burden in plaque

Table 3. Plaque phenotype in MC1R-deficient vs. wild-type mice (ApoE−/− model). MC1R activation produces the inverse profile — smaller, more stable lesions. Source: Rinne et al., ATVB 2018.

3.2 Pharmacological Confirmation

In the same ApoE-deficient atherosclerosis model, administration of a pharmacological MC1R agonist produced:

- Reduced plasma cholesterol levels
- Decreased aortic CD36 expression
- Increased plaque ABCG1 expression
- Measurable markers of plaque stabilisation

This is direct in-vivo pharmacological evidence — not merely inference from receptor knockout data.

4. Plaque Stability and Local Melanocortin Signaling

Human plaque tissue analysis provides a compelling additional layer of evidence. Advanced unstable human plaques demonstrate:

- Reduced activity of the α-MSH-producing enzyme carboxypeptidase E
- Increased activity of the enzymes that degrade and inactivate α-MSH

This implies that melanocortin signaling is locally and specifically suppressed in the most dangerous, rupture-prone lesions. The implication is direct: vulnerable plaques are partly characterised by failing endogenous MC1R protection — and exogenous MT-1 would restore a signal that is specifically depleted where it is most needed.

4.1 Plaque Stabilisation Mechanisms

How MC1R Activation Shifts Plaque Toward Stability		
↑ **Collagen deposition**	→	Thicker fibrous cap, reduced rupture risk
↑ **Smooth muscle cell content**	→	Improved structural integrity of the plaque wall
↓ **Necrotic core**	→	Reduced lipid-driven plaque expansion
↓ **Macrophage inflammatory activity**	→	Less MMP secretion, less fibrous cap erosion
↑ **Cholesterol efflux (ABCA1/ABCG1)**	→	Reduced foam cell burden within the plaque

Figure 1. Summary of MC1R activation effects on plaque composition and stability.

5. Systemic Lipid Effects of MC1R Activation

Beyond its direct effects at the arterial wall, MC1R activation influences systemic cholesterol metabolism through both hepatic and macrophage-peripheral pathways.

5.1 Hepatic Cholesterol Regulation

MC1R is expressed in hepatocytes and regulates hepatic lipid and bile acid metabolism. Hepatocyte-specific MC1R deficiency leads to elevated circulating cholesterol, increased hepatic triglycerides, and reduced bile acid synthesis. Because bile acids represent the primary route for hepatic cholesterol elimination, intact MC1R signaling in the liver supports systemic cholesterol clearance.

5.2 Macrophage-Driven Reverse Cholesterol Transport

In ApoE-deficient mouse models, pharmacologic MC1R activation reduced plasma cholesterol, decreased CD36 expression in plaques, increased plaque ABCG1 expression, and produced measurable markers of plaque stabilisation. These findings establish MC1R as a functional regulator of systemic cholesterol trafficking and arterial lipid handling, not merely a local anti-inflammatory agent.

5.3 Predicted Lipid Profile Effects

Lipid Parameter	Predicted Direction	Mechanism
LDL Cholesterol	Modest reduction ↓	Hepatic bile acid support + reverse cholesterol transport via ABCA1/ABCG1
Triglycerides	Possible reduction ↓	Hepatic MC1R regulation of lipid metabolism
HDL Functionality	Improved ↑	Enhanced cholesterol loading onto HDL particles via ABCG1
oxLDL Macrophage Uptake	Reduced ↓	CD36 downregulation limits scavenger receptor-mediated oxLDL endocytosis

Table 4. Predicted lipid parameter changes with MC1R activation. Note: improvements in oxLDL handling may be more relevant to plaque biology than changes in total LDL concentration alone.

6. Comparison with Statin Therapy

MC1R agonists operate through mechanisms fundamentally distinct from statins. Rather than competing, the two approaches are largely complementary — addressing different aspects of the same disease process.

Statins inhibit HMG-CoA reductase — the rate-limiting enzyme of hepatic cholesterol synthesis — reducing circulating LDL primarily by upregulating hepatic LDL receptor expression. Statins have modest anti-inflammatory effects via the isoprenoid pathway, but limited direct impact on macrophage foam cell formation or plaque composition.

MC1R agonism (MT-1) operates downstream and peripherally — modulating macrophage cholesterol handling, vascular wall inflammation, endothelial NO biology, and plaque structural composition. It does not meaningfully inhibit cholesterol synthesis.

Feature	Statin	MT-1 (MC1R Agonism)
Primary mechanism	HMG-CoA reductase inhibition → blocks hepatic cholesterol synthesis	Macrophage & vascular wall signaling via cAMP/PKA/NF-κB
LDL reduction	Strong and direct (20–55%)	Indirect and modest (hepatic + RCT pathway)
Foam cell formation	Limited direct effect	Strong inhibition (CD36 ↓, ABCA1/ABCG1 ↑)
Plaque stability	Moderate (volume reduction)	Significant (composition shift: ↑ collagen, ↓ necrotic core)
Anti-inflammatory effect	Moderate (isoprenoid pathway)	Strong (NF-κB suppression, cytokine reduction)
Endothelial NO support	Modest, indirect	Direct eNOS support via MC1R/cAMP pathway
oxLDL macrophage uptake	Not directly addressed	Directly reduced via CD36 downregulation
Human RCT evidence	Extensive (decades of trial data)	Limited (Phase IIa safety data only)

Table 5. Mechanistic comparison of statin therapy vs. MC1R agonism with MT-1. The two modalities address atherosclerosis at different stages and through non-overlapping pathways — combination use is rational.

7. Effects on Unstable Plaques

Vulnerable, rupture-prone plaques are defined by large necrotic cores, thin fibrous caps, high macrophage burden, and active intraplaque inflammation. Plaque rupture — not the mere presence of plaque — is the proximate cause of most acute coronary events.

MC1R signaling addresses several of these pathological features simultaneously. Critically, the human tissue finding that vulnerable plaques are specifically deficient in intraplaque α-MSH signalling — with downregulated production enzymes and upregulated degradation enzymes — implies that exogenous MT-1 is not pharmacologically overriding normal biology, but restoring a failing endogenous protective mechanism.

7.1 Plaque Inflammation — Direct Measurement

Melanocortin peptides have been shown to reduce atherosclerotic plaque inflammation as measured by FDG-PET uptake in atherosclerotic animal models — a direct, quantitative measure of metabolically active inflammation within the plaque wall. Reduced FDG uptake correlates with lower macrophage activity and reduced risk of plaque destabilisation.

7.2 Vulnerability Index — Effect of MC1R Activation

Vulnerability Feature	Without MC1R Activation	With MC1R Activation	Mechanism
Necrotic core size	Large	Reduced ↓	Enhanced cholesterol efflux, reduced foam cell accumulation
Fibrous cap thickness	Thin	Increased ↑	↑ Collagen deposition, ↑ smooth muscle cell content
Intraplaque inflammation	High	Reduced ↓	NF-κB suppression → ↓ IL-6, TNF-α, MMP secretion
Macrophage foam cell burden	High	Reduced ↓	CD36 ↓ (less uptake) + ABCA1/ABCG1 ↑ (more efflux)
Intraplaque α-MSH signaling	Deficient	Restored ↑	Direct exogenous MC1R agonism replaces depleted endogenous signal

Table 6. Effect of MC1R activation on plaque vulnerability features. Each parameter shifts toward a more stable phenotype.

8. Clinical Evidence in Humans

Direct human clinical data examining MC1R agonists with atherosclerosis as a primary endpoint do not yet exist. The mechanistic and experimental evidence reviewed above is derived predominantly from cell culture studies and animal models. However, several lines of human-relevant evidence support the translational plausibility of this pathway.

8.1 Human Plaque Tissue Data

Analysis of advanced human atherosclerotic plaques confirms that the melanocortin signaling apparatus is functionally present in the human arterial wall — and that its suppression is a feature of the most dangerous lesion types. This provides direct human biological relevance to the animal model mechanistic data.

8.2 Phase IIa Clinical Trial — Afamelanotide in Acute Stroke

A small feasibility and safety study evaluated afamelanotide in patients with acute ischaemic stroke (PMC10373257, 2023). Key findings:

- Good tolerability with no major adverse events attributed to study drug
- Radiological improvement of salvageable tissue observed

- **Two patients had carotid atherosclerosis** (one severe stenosis, one complete occlusion) — MT-1 was administered without adverse vascular events in either
- Preliminary signal of neuroprotection consistent with anti-inflammatory MC1R mechanisms

While not designed to evaluate plaque outcomes, this constitutes the only available human safety data for MT-1 in patients with existing significant atherosclerosis — and the findings are reassuring.

8.3 Evidence Strength Summary

Mechanism / Finding	Evidence Type	Strength	Human Data?	Key Source
Foam cell inhibition (CD36↓, ABCA1/ABCG1↑)	In vitro + animal	Strong	No	Rinne 2018
Larger lesions in MC1R deficiency	Animal knockout	Strong	No	Rinne 2018
Plaque stabilisation (collagen↑, SMC↑, necrotic core↓)	Animal knockout + pharmacological	Strong	Tissue data	Rinne 2018
Intraplaque α-MSH depletion in vulnerable plaques	Human plaque tissue analysis	Moderate–Strong	Yes	Human tissue studies
NF-κB suppression (anti-inflammatory)	In vitro, multiple cell types	Strong	Cell lines	Multiple authors
Endothelial NO / vasodilation	Animal knockout	Strong	Inferred	Rinne 2015
Safety in atherosclerotic patients	Human Phase IIa RCT	Preliminary	Yes	PMC10373257 (2023)
Systemic LDL reduction	Animal model (ApoE−/−)	Moderate	No	Rinne 2018

Table 7. Evidence strength assessment for MC1R/MT-1 atheroprotective mechanisms. Strength based on study design reproducibility and directional consistency across models.

9. Key Academic References

9.1 Rinne et al. — Arteriosclerosis, Thrombosis & Vascular Biology (2018)

Primary Atherosclerosis Publication
Full title: Melanocortin 1 Receptor Deficiency Promotes Atherosclerosis in Apolipoprotein E−/− Mice
Journal: Arteriosclerosis, Thrombosis, and Vascular Biology (AHA Journals)
DOI: 10.1161/ATVBAHA.117.310418
Evidence type: Preclinical — MC1R knockout + pharmacological agonism in ApoE−/− mouse model
Key findings: MC1R deficiency → larger lesions, less collagen, more necrotic core; pharmacological MC1R agonism → reduced plasma cholesterol, improved plaque stability; bile acid metabolism disruption aggravates hypercholesterolaemia

9.2 Rinne et al. — Cardiovascular Research (2015)

Full title: *Deficiency in Melanocortin 1 Receptor Signaling Predisposes to Vascular Endothelial Dysfunction and Increased Arterial Stiffness.*

Key findings: MC1R regulates eNOS-dependent vasodilation and arterial stiffness. α-MSH is expressed at the vascular wall in both healthy and atherosclerotic vessels, with decreased expression in advanced atherosclerosis. Effects are vascular wall-autocrine, not CNS-mediated.

9.3 Phase IIa Human Trial — Afamelanotide in Stroke (2023)

PMC ID: PMC10373257

Key findings: Afamelanotide well tolerated in acute ischaemic stroke patients. Two patients with significant carotid atherosclerosis received MT-1 without adverse vascular events. First human vascular safety data for MT-1 in an atherosclerotic population.

9.4 NF-κB Suppression Literature

Multiple independent groups have confirmed α-MSH's NF-κB inhibitory mechanism across human macrophage, endothelial, and monocytic cell lines. MC1R siRNA knockdown neutralises the effect, confirming receptor specificity. This is the mechanistic anchor for the downstream anti-inflammatory and plaque-stabilising effects reviewed here.

10. Conclusions

The mechanistic evidence reviewed here supports a coherent, multi-layered atheroprotective role for MC1R signaling. The key conclusions are:

- **Foam cell suppression is the strongest mechanistic pillar:** dual action via CD36 downregulation (less oxLDL uptake) and ABCA1/ABCG1 upregulation (more reverse cholesterol transport) is reproducible across multiple model systems.
- **Plaque stabilisation — not just prevention:** MC1R activation shifts plaque composition toward more collagen, more smooth muscle cells, and smaller necrotic cores. The human plaque tissue finding that vulnerable lesions are depleted of intraplaque α-MSH signalling makes this particularly compelling.
- **MT-1 and statins are complementary, not competing:** statins reduce circulating LDL quantity; MT-1 addresses what happens to LDL at the arterial wall. Concurrent use is mechanistically rational.
- **Human clinical trial evidence is limited but reassuring:** the Phase IIa safety data in atherosclerotic patients supports tolerability; dedicated plaque outcome trials have not been conducted.
- **Individuals with MC1R loss-of-function variants benefit most:** R151C, R160W, and D294H variants (common in Northern European ancestry) produce constitutively impaired vascular MC1R protection — MT-1 restores a system that has been underperforming.

MT-1 is not a cure for atherosclerosis. It is a biologically grounded disease-modifying intervention — one that addresses the inflammatory and lipid-handling deficits at the arterial wall level that statins do not reach.

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