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A novel oral delta-5-desaturase inhibitor prevents atherosclerotic lesions, accompanied by changes in fatty acid composition and eicosanoid production in ApoE knockout mice - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether pharmacologically blocking delta-5-desaturase, an enzyme that converts DGLA (dihomo-gamma-linolenic acid) into arachidonic acid, could influence atherosclerosis in mice genetically predisposed to plaque formation. In ApoE knockout mice fed a Western diet, oral treatment with compound-326 for 15 weeks reduced lesion progression in the aorta, decreased arachidonic acid, and increased DGLA, without altering total cholesterol and plasma triglycerides.In section 5.3.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the research contributes to the narrative that the DGLA→arachidonic acid conversion represents a regulatable node that modifies the availability of lipid mediators involved in inflammation. Independent evidence confirms the biochemical pathway and the change in eicosanoids with good consistency; however, the outcomes regarding atherosclerosis are not uniform across experimental models. The conclusion is therefore mechanistically sound but not directly transferable to clinical prevention in humans.

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether the selective inhibition of delta-5-desaturase could slow down atherosclerosis, i.e., the accumulation of plaques in the arterial wall. The hypothesis was straightforward: by reducing the activity of the enzyme that converts DGLA into arachidonic acid, the availability of arachidonic acid to produce certain eicosanoids—local lipid molecules that can modulate inflammation, vascular function, and coagulation—would decrease.The relevance to section 5.3.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns precisely the DGLA arachidonicacid eicosanoidremodeling vascular lesion segment. The study does not directly evaluate hyperinsulinemia, the insulin–SREBP-1c–desaturase axis, or the conversion in humans. However, it can document, in a murine model, that the pharmacological blockade of the enzyme changes the ratio between substrate and product and is accompanied by fewer atherosclerotic lesions.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication, available in abstract form, describes an animal experiment conducted on ApoE knockout mice, which lack apolipoprotein E and are therefore susceptible to developing atherosclerosis when fed a high-fat Western diet. The animals received compound-326, a selective delta-5-desaturase inhibitor, orally at a dose of 3–10 mg/kg per day for 15 weeks.The outcomes evaluated included the progression of atherosclerotic lesions in the aorta, levels of arachidonic acid and DGLA in the liver and blood, eicosanoid production by blood cells, and plasma lipids. The abstract does not report the sample size of the groups, the sex and age of the animals, the quantitative composition of the diet, randomization procedures, any exclusion criteria, detailed analytical techniques, or complete statistical values. This information is not provided in the available material.

4. RESULTS

The main result was a significant reduction in the progression of aortic atherosclerotic lesions in mice treated with compound-326 compared to controls. In practical terms, the treated animals developed less visible disease in the aortic wall. The abstract does not report the numerical extent of the reduction, confidence intervals, or P-values.The drug significantly reduced arachidonic acid and significantly increased DGLA in the liver and blood. This direction of effect is consistent with the blocking of delta-5-desaturase: the DGLA substrate accumulates, while the arachidonic acid product decreases. In parallel, the production of eicosanoids derived from arachidonic acid decreased, while that of eicosanoids derived from DGLA increased in blood cells.Total cholesterol and plasma triglycerides were not modified by the treatment. This element is important because it indicates that, in this model, the smaller extent of the lesions was not accompanied by a measurable reduction in these two circulating lipids. However, it does not prove that the mechanism is exclusively inflammatory: other metabolic or vascular changes not described in the abstract could have contributed to the result.

5. INTERPRETATION

In simple terms, delta-5-desaturase acts as a transformation step: it converts one molecule, DGLA, into another, arachidonic acid. Reducing its activity therefore changes the materials available to produce different eicosanoids. The study analyzed shows that this metabolic shift occurred in mice and was accompanied by a slower progression of arterial plaques.The documented segment is directly: inhibition of delta-5-desaturase increase in DGLA and reduction of arachidonic acid decrease in eicosanoids derived from arachidonic acid and increase in those derived from DGLA fewer aortic lesions in the ApoE knockout model. The link with chronic inflammation is biologically plausible, as numerous eicosanoids influence immune cells and the vascular wall, but the abstract does not allow us to attribute the result to a single mediator nor to demonstrate an identical causal relationship in humans.The statement that arachidonic acid is merely a pro-inflammatory precursor would be overly simplistic. Arachidonic acid gives rise to mediators with different effects, sometimes pro-inflammatory and sometimes involved in the resolution or regulation of the biological response. For this reason, the final effect of inhibiting FADS1, the gene that encodes delta-5-desaturase, depends on the tissue, diet, cell type, and disease

model.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial independent confirmation concerns the central biochemical pathway. In mice with complete genetic inactivation of Fads1, Fan and colleagues observed an increase in DGLA and a reduction of arachidonic acid in tissues; furthermore, series 1 prostaglandins derived from DGLA increased, while series 2 prostaglandins derived from arachidonic acid decreased [1]. This directly confirms that the loss of delta-5-desaturase remodels the DGLA/arachidonic acid ratio and the production of lipid mediators. The limitation is significant: total genetic elimination of the enzyme is more drastic than partial pharmacological inhibition and produced major alterations in growth and survival in the mice.A second independent study evaluated Fads1 knockout mice on an ApoE knockout background, fed a Western diet. In this model, mice lacking Fads1 presented 40% less atherosclerotic plaque in the aorta compared to controls and, consistent with reduced enzymatic activity, a strong increase in DGLA and a decrease in arachidonic acid in hepatic and cerebral phospholipids [2]. This result directly confirms the direction observed in the analyzed study, but it also derives from animals and permanent genetic manipulation. Furthermore, the study detected systemic metabolic changes, including a reduction in circulating lipids, which makes it more difficult to isolate the contribution of vascular inflammation.The chain is also supported by data in humans, but at a different level. In thirty participants, Hester and colleagues studied a genetic variant in the FADS cluster associated with arachidonic acid synthesis. The genotype was associated with both the ratio between arachidonic acid and its precursors and the production of leukotriene B4 and 5-HETE in stimulated blood, two eicosanoids produced through the lipoxygenase pathway [3]. This does not prove that a genetic variant is equivalent to a drug, nor does it measure atherosclerosis, but it confirms in humans that variations in the FADS pathway can be reflected in the availability of arachidonic acid and certain eicosanoid mediators.

7. CONFLICTING EVIDENCE

There are experimental results that directly contradict the idea that reduced FADS1 activity is always protective for blood vessels. Gromovsky and colleagues selectively reduced Fads1 in the tissues of hyperlipidemic mice and observed, under specific dietary conditions, an increase in liver inflammation and atherosclerosis [4]. The authors also detected a decrease in pro-resolving lipid mediators derived from arachidonic acid, EPA, and DHA.This result does not deny that blocking delta-5-desaturase reduces arachidonic acid and increases its precursors. However, it shows that reducing the availability of long-chain fatty acids can also deprive mediators that are useful for the resolution of inflammation of their substrates. The differences may depend on the site of genetic silencing, the degree of inhibition, the diet, and the fact that FADS1 also participates in the metabolism of omega-3 fatty acids. Consequently, the reduction in plaques observed in the analyzed study cannot be considered a universal effect of FADS1 inhibition.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the results of the study under review from independent publications that confirm or qualify the narrative in the book's paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal, pharmacological intervention	ApoE knockout mice on a Western diet	Compound-326 reduced AA, increased DGLA, modified eicosanoids, and limited aortic lesions without altering total cholesterol and plasma triglycerides.	direct confirmation	moderate
[1]	Animal, genetic knockout	Fads1 knockout mice	The absence of Fads1 increased DGLA, reduced AA, increased series 1 prostaglandins, and reduced series 2 prostaglandins.	direct confirmation	moderate
[2]	Animal, genetic knockout	Fads1 knockout mice on an ApoE knockout background on a Western diet	Loss of Fads1 reduced AA, increased DGLA, and was associated with 40% less aortic plaque.	direct confirmation	moderate
[3]	Mechanistic observational in humans	30 adults genotyped for rs174537	The variant in the FADS cluster was associated with fatty acid ratios and the production of leukotriene B4 and 5-HETE in stimulated blood.	biologically consistent evidence	low
[4]	Animal, tissue silencing	Hyperlipidemic mice with selective Fads1 reduction	Reduction of Fads1 increased atherosclerosis and liver inflammation in specific dietary contexts.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the claim that delta-5-desaturase is a regulatable point in the conversion from DGLA to arachidonic acid and that its pharmacological blockade modifies the eicosanoid profile in ApoE knockout mice. The concomitant reduction in aortic lesions is consistent with the book's narrative and is supported by another mouse model.The most prudent conclusion is that the DGLA arachidonic acid metabolic pathway is well-supported at a mechanistic level and is relevant to lipid mediators of inflammation. However, it has not been proven that reducing FADS1 is universally protective against atherosclerosis or that it represents a preventive treatment in humans. The opposing effects observed in some models require broader experimental and clinical validation.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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