ChatGPT

Summary of studies about or referencing the pan-AMPK activator O304 (to 2025)

Background and relevance

O304 is a thiazol-3-one compound described as a **pan-AMPK** activator that enhances phosphorylation at threonine-172 on AMPK α1/α2 trimers. The compound has attracted interest because AMPK activation promotes glucose uptake, mitochondrial oxidative metabolism and cardiometabolic benefits without causing cardiac hypertrophy. Since its first report in 2018, O304 has been tested in multiple animal models and a small human proof-of-concept study. Subsequent reviews have positioned it as a potential **exercise mimetic** and therapeutic candidate for metabolic disease and aging.

Primary research on O304

JCI Insight 2018 – discovery and first human data

- **Model and design:** Steneberg et al. (2018) exposed diet-induced obese (DIO) mice and healthy human volunteers to O304. In mice, O304 increased AMPK phosphorylation, enhanced skeletal-muscle glucose uptake and cardiac glucose uptake, and reduced β-cell stress [1]. A double-blind phase IIa proof-of-concept in metformin-treated type 2 diabetes (T2D) patients showed reductions in fasting glucose and insulin resistance, improved calf microvascular perfusion and lower blood pressure [1]. Unlike some AMPK activators that cause cardiac hypertrophy, O304 increased stroke volume and cardiac output without inducing hypertrophy [1].

- **Key findings:** O304 improved glucose homeostasis, microvascular perfusion and cardiovascular function in DIO mice, and produced signals for reduced fasting glucose and improved insulin resistance in T2D patients [1]. These data launched O304 as a candidate metabolic therapy.

Scientific Reports 2021 – islet epigenomics

- **Model and design:** López-Pérez et al. investigated whether O304 protects pancreatic islets in high-fat diet mice. They compared islet gene expression and chromatin marks in control mice, high-fat diet mice and high-fat diet plus O304 mice. High-fat diet induced 1 621 differentially expressed genes relative to chow, whereas high-fat diet plus O304 showed only 657 changes, indicating strong protection [2]. O304 restored expression of key β-cell markers and partially reversed epigenetic changes [3].

- **Key findings:** The study showed that O304 largely prevented diet-induced gene-expression drift and histone-mark remodeling in islets. This gene-expression preservation was associated with improved glucose tolerance and insulin secretion [3]. The results support the idea that O304 relieves β-cell stress by normalizing systemic metabolism and epigenome.

Communications Biology 2021 – aging and exercise capacity

- **Model and design:** Ericsson et al. studied lean aged mice to test O304 as an **exercise mimetic**. Chronic O304 prevented and reversed age-associated hyperinsulinemia and insulin resistance, increased stroke volume and end-diastolic volume, lowered heart rate and improved treadmill endurance [4]. Dose-response analyses showed improvements in fasting insulin, HOMA-IR and stroke volume [5].

- **Key findings:** O304 enhanced metabolic flexibility and cardiac function in aged mice, and improved exercise capacity without overt adverse effects [4]. These data support the concept that O304 mimics some benefits of exercise and may improve quality of life in aging.

Frontiers in Pharmacology 2022 – kidney aging

- **Model and design:** Zhang et al. treated naturally aged mice and D-galactose–induced aging models with O304. O304 restored energy metabolism and promoted autophagy and mitochondrial homeostasis in aged kidneys [6]. Transcriptomic analyses showed induction of fatty-acid metabolism genes and down-regulation of DNA damage and collagen-organization pathways [6].

- **Key findings:** O304 reduced cellular senescence and fibrosis in aged kidneys, suggesting that AMPK activation may delay kidney aging [6].

Communications Biology 2023 – dual mechanism in severe diabetes

- **Model and design:** Norlin et al. used both db/db mice (insulin-resistant with residual insulin) and streptozotocin-treated mice (insulin-deficient). O304 stimulated insulin-independent glucose uptake and utilization in skeletal muscle and heart, acting as a mild mitochondrial uncoupler and increasing energy demand [7]. It also preserved β-cell function by reducing oxidative stress and supporting gene networks controlling insulin secretion [7].

- **Key findings:** O304 ameliorated hyperglycemia by **dually** promoting muscle glucose effectiveness and preserving β-cell function [7]. The results support O304's potential to address both insulin resistance and β-cell dysfunction.

Frontiers in Pharmacology 2024 – abdominal aortic aneurysm (AAA)

- **Model and design:** Chen et al. tested O304 in an angiotensin II–induced AAA mouse model. O304 activated AMPK signaling and suppressed the AMPK/mTOR/MMP pathway, prevented vascular smooth-muscle cell (VSMC) phenotypic switching, and significantly reduced aneurysm formation and blood pressure [8].

- **Key findings:** O304 lowered AAA incidence and size by inhibiting VSMC dedifferentiation and modulating mTOR and matrix-metalloproteinase pathways [8]. This study extends O304's therapeutic scope to vascular disease.

O304 clinical evidence

- The 2018 JCI Insight study included a **small phase IIa** trial in T2D patients on metformin. O304 lowered fasting plasma glucose and HOMA-IR, improved calf microvascular perfusion and reduced blood pressure without causing cardiac hypertrophy [1]. Larger, placebo-controlled trials have not yet been published, so human evidence remains limited.

Derivative compound: ATX-304 (formerly O304)

A 2025 JCI Insight paper described **ATX-304**, a dual AMPK and mitochondrial activator identified as **formerly O304**. The authors reported that ATX-304 improved glucose homeostasis and cardiovascular function in T2D patients on metformin and diet-induced obese mice, increased insulin sensitivity, reduced insulin resistance and improved cardiac function [9]. ATX-304 increases AMPK activity by suppressing dephosphorylation at threonine 172 and increases cellular respiration via mild mitochondrial uncoupling [9]. In mouse models of choline-deficient high-fat diet–induced liver disease (MASLD), ATX-304 reduced body fat, cholesterol and liver steatosis and ameliorated fibrosis, suggesting metabolic switching benefits [10].

Additional primary references to O304 in other research

Stem-cell transplantation study

A 2025 study on adipose stromal vascular-fraction cell transplantation for type 1 diabetes cited O304 as an example of an AMPK activator that enhances skeletal-muscle glucose uptake and alleviates glycogen accumulation in skeletal muscle and heart even without insulin [11]. The mention demonstrates O304's recognition in metabolic research outside of AMPK-specific contexts but does not provide new experimental data on O304.

How reviews and mechanistic articles discuss O304

Pan-AMPK activator class (Molecular Cell 2021)

The review **AMPK: restoring metabolic homeostasis over space and time** described a class of pan-AMPK activators—including compounds 991, PF-739, MK-8722 and O304—that enhance skeletal-muscle glucose uptake and lower blood glucose in preclinical models [12]. The authors noted that potent activators like MK-8722 can cause cardiac glycogen accumulation, whereas O304 has shown metabolic benefits without hypertrophy, highlighting the need for careful drug design [12].

Systematic review on exercise mimetics (Nutrients 2025)

A 2025 systematic review of exercise mimetics summarized that O304 reduces fasting plasma glucose and insulin resistance, improves microvascular perfusion and blood pressure, and enhances exercise capacity and cardiac function in aging mice [13]. The review's table of compounds lists O304 as a pan-AMPK activator affecting systemic tissues and the cardiac system, noting that it prevents insulin resistance and improves cardiac function [14].

Small-molecule AMPK modulators (J Med Chem 2025)

A medicinal chemistry review described O304 as a **thiazol-3-one** AMPK activator that suppresses dephosphorylation of AMPK at threonine-172. The mechanism of action and binding site remain unknown, and O304 appears to increase AMPK phosphorylation only in cells with intrinsic AMPK activity [15]. The review urged further investigation into the compound's pharmacology and safety [15].

MAPK and AMPK signaling interplay (J Hematol Oncol 2020)

An overview of MAPK and AMPK crosstalk noted that O304 is undergoing clinical trials for diseases outside of cancer and highlighted the need for AMPK-specific activators [16]. The review underscores O304's recognition as a clinical candidate but does not provide new data.

Adaptation to exercise (Annu Rev Physiol 2022)

This review contrasted different AMPK activators: MK-8722 improves glucose homeostasis but causes cardiac hypertrophy, whereas O304 increases cardiac glucose uptake, reduces cardiac glycogen and improves cardiac function **without hypertrophy** [17]. The article suggested that O304 could be a safer therapeutic to mimic exercise benefits [17].

AMPK and diseases (Biology 2022)

A review on AMPK-targeting molecules described O304 as a potential ADP mimetic that protects AMPK from dephosphorylation, increases glucose uptake and pAMPK levels in skeletal muscle, and reduces hyperglycemia, hyperinsulinemia and insulin resistance [18]. In a summarizing table, the review highlighted that O304 mimics ADP, lowers hyperglycemia and hyperinsulinemia without causing cardiac hypertrophy and functions as an exercise mimic [19].

Other review mentions

The FEBS Journal 2025 article on activating AMPK to improve phenotypes due to mtDNA depletion cited the 2021 islet study but provided no further discussion on O304 [20]. **Fine-tuning AMPK in physiology and disease using point-mutant mouse models** (Disease Models & Mechanisms 2024) did not reference O304 despite being an AMPK-centric review. These omissions highlight that O304, while notable, is not universally discussed in general AMPK literature.

Take-home messages

- **Preclinical versatility:** O304 shows consistent metabolic benefits across models of obesity, aging, severe diabetes, kidney aging and vascular disease, improving glucose uptake, insulin resistance, β-cell health and organ function [1] [7]. Its broad impact stems from pan-AMPK activation, mitochondrial uncoupling and modulation of gene expression and autophagy.

- **Clinical promise with limited data:** Human evidence consists of a small metformin-background T2D trial showing improved glycemia, microvascular perfusion and blood pressure [1]. More robust trials are needed to assess efficacy and safety.

- **Safety profile:** Unlike some AMPK activators that cause cardiac glycogen accumulation, O304 improved cardiac function without hypertrophy [1]. Reviews emphasize this safety advantage [17].

- **Emerging derivative:** ATX-304, a dual AMPK and mitochondrial activator formerly known as O304, extends metabolic benefits to non-alcoholic fatty-liver disease and reinforces AMPK activation as a therapeutic strategy [10].

- **Continued research:** O304 is widely cited as an exercise mimetic and ADP mimetic, and further studies are needed to elucidate its binding site, optimize dosing and confirm long-term effects. [15] [18].

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[4] [5] AMPK activator O304 improves metabolic and cardiac function, and exercise capacity in aged mice - PMC
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[6] AMPK Activator O304 Protects Against Kidney Aging Through Promoting Energy Metabolism and Autophagy - PMC
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