

MOTS-c Available for Research Use Only

(3 – 10 mg SC 1 – 3 × weekly, depending on tolerance and objective)

MOTS-c is a 16-amino-acid peptide encoded within the mitochondrial 12S ribosomal RNA gene. It participates in metabolic signaling and communication with the nucleus. It has likely metabolic and exercise-capacity benefits based on animal studies. Its effects on cellular stress responses make it an experimental partial exercise mimetic, rather than an established replacement for exercise. [1,3]

 Human safety is plausible, not established. [5]

★ ★ Likely metabolic and physical-capacity benefits. [1,2]

Disclaimer: These notes are not authoritative and should not be interpreted as definitive scientific guidance. They are summaries, compilations and plausible extrapolations drawn from the most relevant research I was able to locate, and may omit nuances, conflicting data, or emerging evidence. The material reflects an attempt to organize and understand complex topics, not to provide clinical recommendations or expert interpretation.

This document was updated 12-Oct-26. A published version of this survey is available at <https://pdfs.researcher6076.com/pdfs/mots-c.pdf>



Human safety of injected native MOTS-c remains insufficiently characterized. FDA's 2026 assessment identifies potential immunogenicity concerns, alongside gaps in formal toxicology and clinical safety data. Endogenous origin does not establish injectable safety. [5]

Animal studies support likely improvements in insulin sensitivity and physical capacity. Human exercise studies demonstrate changes in endogenous MOTS-c, not effectiveness of administered MOTS-c. [1,2] A small mouse experiment found improved running after one high-dose injection, supporting a possible rapid effect rather than an established human energy boost. [4]

Dosage & Patterns

The following amounts are **speculative, community-informed subcutaneous (SC) dosing patterns**. [1,2,4,5]

- **Reported exercise-mimetic pattern: 6–10 mg SC, 2–3 times weekly on rest-days not exercise-days.**
- **Reported healthspan pattern: 3–6 mg SC, 1–2 times weekly, on rest-days not exercise-days.** Calling this a “healthspan” pattern describes its intended purpose, rather than a demonstrated human outcome.
- Sometimes discussed is administration 30–60 minutes before training, but this dose is very speculative and but not fully consistent with mechanistic biology of MOTS-C

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Half-life and route: There is no validated human pharmacokinetic information to inform a human dosing interval. [5]

Combining AMPK activation requires individual assessment

There are no clear clinical limits, but additive AMPK activation is commonly-reported as counterproductive, for example when athletes report cardiovascular “overtraining.” Common AMPK activators are

- **Metformin, AICAR, or berberine** [6]
- **Frequent hard training or prolonged fasting** [2,4]
- **Cold exposure**

MOTS-C is another strong AMPK activator.

Combining MOTS-C with other AMPK activators can plausibly overstress mitochondria reducing the intended mitochondria adaption outcomes.

Patterns

The following cycle examples are **unvalidated community-informed patterns**, not mechanistically proven schedules:

Exercise-memetic pattern — proposed intermittent use.

- 2–4 doses per week.
- Proposed spacing: 24–48 hours.

Lower-frequency use — sometimes described as maintenance.

- 1–2 doses per week.

Benefits

- **Likely improved insulin sensitivity:** reduced diet- and age-associated insulin resistance supports a metabolic benefit. [1]
- **Plausible metabolic flexibility:** altered fuel metabolism supports this possibility. [1,3]
- **Likely improved exercise capacity:** running performance findings support an endurance benefit. [2,4]
- **Likely acute exercise-capacity benefit:** a single dose improved running performance in mice. [4]
- **Likely preservation of physical function with aging:** late-life treatment improved functional measures, a healthspan signal rather than proof of human healthspan extension. [2]
- **Likely preservation of pancreatic islet function:** experimental diabetes studies support protection of insulin-producing tissue., including immunometabolic benefit and senescence-modulating effect. [8,9]

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- **Likely reduction of diet-induced fat gain:** protection against high-fat-diet obesity supports a body-composition hypothesis. [1]
- **Plausible cellular stress resilience:** protective gene regulation supports adaptation to metabolic stress. [3]

Subjective practitioner reports include steadier energy, less exertion, improved mood, faster recovery, and less soreness appeared in the original survey as community impressions. They remain unverified reports; the personal account below records an opposite exercise response.

Investigated Uses

- **Insulin resistance and metabolic dysfunction:** preclinical research targets. [1,8]
- **Age-related physical decline and metabolic stress:** preclinical targets; fatigue alone does not diagnose mitochondrial dysfunction. [2,3]

Clinical Cautions

- **Experimental use and combinations:** A formal clinical contraindication list has not been established. [1,5,6]
- **Shared AMPK signaling** is a plausible caution warranting individual assessment.
- **Pregnancy and breastfeeding:** Avoid experimental use because reproductive and developmental safety has not been established. [5]

Adverse Effects and Safety Signals

- **Injection site reactions:** Injection site reactions, pain, swelling, redness, and itching are commonly reported for MOTS_C with a higher incidence than many other common SC peptides.

Drivers of Diminished Response

MOTS-C is not a traditional receptor agonist. Antibody formation is plausible, but not reported. Downstream pathway adaption is plausible.

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Biological Mechanism

MOTS-c links mitochondrial genetic information with metabolic and nuclear signaling. Experiments identify altered folate and purine metabolism, accumulation of AICAR, and AMPK activation. Under stress, MOTS-c can enter the nucleus and influence protective gene expression, including NRF2-associated responses. These findings support plausible adaptation, not a universal increase in ATP production or mitochondrial efficiency. [1,3]

My Workout Experience and Possible Explanations

The symptoms below are my observations. I expected MOTS-c to improve workout energy, but my experience was the opposite. Excessive AMPK activation is a proposed explanation, not something established by evidence.

Training Load and Recovery

Poor performance, weakness, and fatigue can occur when training exceeds recovery. One plausible contribution to this effect is when mitochondria stress (AMPK) exceeds a threshold where they can adapt. MOTS-c creates AMPK stress. [1,3]

The Combination I Was Using

I did all the following at the same time:

- Intense, frequent workouts... creating AMPK stress.
- A mini-cut with sustained calorie deficit... creating AMPK stress.
- Metformin for longevity... creating AMPK stress.
- And then I added MOTS-c on top... creating AMPK stress.

The Results Were Ugly

During my workout, I had to quit halfway through. I simply had no energy. An hour later, I bent down to pick something up and straightened up and got lightheaded and dizzy.

What This Experience Can Guide

I speculate that my long standing, effective exercise, diet, and metformin regimen was maximally activating my AMPK pathways for mitochondria adaption. The addition of MOTS-C plausibly pushed my total AMPK activation past some safe, practical threshold, resulting in an “overtraining reaction.”

Emerging Research

Acute exercise study: Hyatt’s 2022 crossover experiment in six female mice used 15 mg/kg intraperitoneally, 10 minutes before running. Distance and time increased by approximately 15% and 12%. The mechanism remained uncertain. (The human equivalent dose would be

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approximately 80 mg.) The study did not demonstrate that AMPK was excluded as a contributor. [4]

Islet-cell senescence: A 2025 study found improved senescence-related changes and glucose intolerance in experimental diabetes. Its human component compared circulating levels rather than administering MOTS-c. These findings support a likely preclinical islet-protective effect. [8]

Conclusions

MOTS-c has an experimental basis for metabolic stress adaptation and likely benefits in animal models. “Exercise mimetic” describes selected overlapping effects, not reproduction of every benefit of exercise. [1–3]

Community dose and cycle examples remain speculative. Human pharmacokinetics, effective exposure, repeated-use safety, and optimal timing are uncharacterized. [5]

Older or metabolically impaired populations are reasonable research targets. [1,2,8]

Animal performance findings also justify studying active subjects. My adverse experience remains personal evidence about tolerability, without proving its proposed AMPK mechanism. [2,4]

References

1. Lee C, Zeng J, Drew BG, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metab.* 2015;21(3):443–454. [doi:10.1016/j.cmet.2015.02.009](https://doi.org/10.1016/j.cmet.2015.02.009)
2. Reynolds JC, Lai RW, Woodhead JST, et al. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. *Nat Commun.* 2021;12:470. [doi:10.1038/s41467-020-20790-0](https://doi.org/10.1038/s41467-020-20790-0)
3. Kim KH, Son JM, Benayoun BA, Lee C. The mitochondrial-encoded peptide MOTS-c translocates to the nucleus to regulate nuclear gene expression in response to metabolic stress. *Cell Metab.* 2018;28(3):516–524.e7. [doi:10.1016/j.cmet.2018.06.008](https://doi.org/10.1016/j.cmet.2018.06.008)
4. Hyatt J-PK. MOTS-c increases in skeletal muscle following long-term physical activity and improves acute exercise performance after a single dose. *Physiol Rep.* 2022;10(13):e15377. [doi:10.14814/phy2.15377](https://doi.org/10.14814/phy2.15377)
5. U.S. Food and Drug Administration. FDA evaluation of MOTS-c-related bulk drug substances (MOTS-c (free base) and MOTS-c acetate). 2026 Pharmacy Compounding Advisory Committee briefing material. Accessed October 7, 2026. [Source](#)
6. Konopka AR, Laurin JL, Schoenberg HM, et al. Metformin inhibits mitochondrial adaptations to aerobic exercise training in older adults. *Aging Cell.* 2019;18(1):e12880. [doi:10.1111/acer.12880](https://doi.org/10.1111/acer.12880)

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7. CohBar, Inc. CohBar announces positive topline results from the phase 1a/1b study of CB4211 under development for NASH and obesity. Sponsor press release, August 10, 2021; not a peer-reviewed native MOTS-c trial. [Source](#)
8. Kong BS, Lee H, L'Yi S, Hong S, Cho YM. Mitochondrial-encoded peptide MOTS-c prevents pancreatic islet cell senescence to delay diabetes. *Exp Mol Med*. 2025;57:1861–1877. [doi:10.1038/s12276-025-01521-1](https://doi.org/10.1038/s12276-025-01521-1)
9. Kong BS, Min SH, Lee C, Cho YM. Mitochondrial-encoded MOTS-c prevents pancreatic islet destruction in autoimmune diabetes. *Cell Rep*. 2021;36(4):109447. Correction: 2021;36(11):109724, doi:10.1016/j.celrep.2021.109724. [doi:10.1016/j.celrep.2021.109447](https://doi.org/10.1016/j.celrep.2021.109447)