The Nitrate–Nitrite–Nitric Oxide Pathway

How the body turns an ingested nitrogen compound into a useful signalling molecule

Jamison Johnson · June 2026

A short discussion document for technical and general readers. Not medical or dietary advice.

The idea in one paragraph

We do not get our nitrogen from the air — atmospheric N_2 is chemically inert and passes through us untouched — we get it from food, mainly protein. But there is a real and well-studied route by which a simple ingested nitrogen compound is converted, inside the body, into a active signalling molecule: nitric oxide (NO). Eat nitrate (abundant in leafy greens and beetroot), and a chain of steps turns part of it into NO, which relaxes blood vessels, lowers blood pressure, and makes muscles use oxygen more efficiently. This is the rigorous version of "ingesting a nitrogen compound for benefit," and it is an active research field — with some genuinely unresolved tensions worth understanding before drawing conclusions.

How the pathway works

The body makes NO two ways. The classical route builds it from the amino acid L-arginine using nitric oxide synthase (NOS) enzymes. The second, more recently appreciated route runs in reverse, recycling the inorganic anions nitrate (NO_3^-) and nitrite (NO_2^-) — once dismissed as inert waste — back into NO [1].

The dietary version is the entero-salivary circulation. Nitrate from vegetables is absorbed, and roughly a quarter of it is concentrated by the salivary glands and secreted into the mouth. Humans cannot efficiently reduce nitrate themselves; commensal bacteria on the tongue do it, converting nitrate to nitrite. Swallowed nitrite is then further reduced to NO in the acidic stomach and in tissues — partly via deoxygenated haemoglobin acting as a nitrite reductase [1,4]. Critically, this reduction is favoured by low oxygen and low pH, exactly the conditions where the classical NOS route falters, so it behaves like a physiological backup system [1].

In plain terms: vegetables supply the raw material, mouth bacteria do a step our own cells can't, and the body finishes the job where NO is most needed.

What the evidence shows

- **Blood pressure.** Dietary nitrate produces modest reductions in systolic blood pressure in human studies [3], consistent with the pathway's vasodilatory role [2].
- **Exercise efficiency.** Nitrate-rich beetroot juice reduces the oxygen cost of submaximal exercise by roughly 3–5% and can improve high-intensity tolerance [6]; the effect is real but less consistent in elite endurance athletes [7].
- **Cellular efficiency.** Dietary inorganic nitrate has been reported to improve mitochondrial efficiency in humans [5].

- **Gastrointestinal and other roles.** NO generated from salivary nitrite supports gastric mucosal blood flow and has antimicrobial activity in the stomach [1].

Most of this evidence rests on short-term studies and surrogate endpoints — blood pressure, performance, biomarkers — rather than long-term hard outcomes such as cardiovascular events. That is the honest ceiling on current claims.

The paradoxes — where the research gets interesting

1. The mouthwash paradox. Because a bacterial step is essential, killing the bacteria breaks the pathway. Antiseptic (chlorhexidine) mouthwash used twice daily for a week raises systolic blood pressure in healthy people, and stopping it re-enriches nitrate-reducing bacteria on the tongue [9]; in treated hypertensives, three days of antibacterial mouthwash raised systolic pressure by about 2.3 mmHg [10], a finding supported by later meta-analysis [11]. A routine "good hygiene" product has an unintended systemic cost. It is also why researchers use chlorhexidine deliberately as a tool to switch the pathway off.

2. The villain-or-hero paradox. The very same anions are cast both as carcinogens and as protectants. Processed meat is an IARC Group 1 carcinogen for colorectal cancer [13], and ingested nitrate/nitrite "under conditions that result in endogenous nitrosation" is rated probably carcinogenic, Group 2A [12] — yet nitrate-rich vegetables are consistently tied to better cardiovascular health. The leading reconciliation is chemistry of the food matrix: vegetables deliver nitrate alongside vitamin C and polyphenols that steer nitrite toward NO and block formation of carcinogenic N-nitrosamines, whereas cured meat plus high-heat cooking and amine precursors favours nitrosamine formation [14]. This source-dependent hypothesis is plausible and partly evidenced, but not yet settled — it is being tested directly in controlled human trials [15].

3. The individual-variability paradox. Because the first reduction step is microbial, the response depends on a person's oral microbiome and habits (diet, tongue cleaning, mouthwash use). The same nitrate dose does not produce the same NO in everyone [9]. Any clean intervention has to account for this.

Open questions worth pursuing

- Whether nitrate's health effect truly depends on source (vegetable vs. water vs. cured meat), and how strongly the co-ingested antioxidant matrix governs the NO-versus-nitrosamine split [14,15].
- Whether the surrogate benefits (blood pressure, exercise economy) translate into reduced long-term cardiovascular events.
- How to individualise dosing around a person's oral microbiome, and whether protecting the nitrate-reducing bacteria is itself a useful target.
- Optimal dose and timing (current performance work points to roughly 6–12 mmol nitrate, with little added benefit beyond, taken in advance) [7].

Bottom line

The instinct that there is untapped value in getting a nitrogen-bearing molecule into the body by routes other than eating protein is sound — and the worked-out version already exists. You do not breathe nitrogen; you ingest nitrate and let your own biology, with help from resident bacteria, convert it into a signalling gas. The benefits are established at the level of blood pressure, exercise efficiency, and physiology; the long-term outcomes and the source-dependent safety question remain genuinely open. That open space — not the inert gas — is where the real work is.

References

1. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate–nitrite–nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov. 2008;7(2):156–167. doi:10.1038/nrd2466
2. Lundberg JO, Carlström M, Larsen FJ, Weitzberg E. Roles of dietary inorganic nitrate in cardiovascular health and disease. Cardiovasc Res. 2011;89(3):525–532.
3. Larsen FJ, Ekblom B, Sahlin K, Lundberg JO, Weitzberg E. Effects of dietary nitrate on blood pressure in healthy volunteers. N Engl J Med. 2006;355(26):2792–2793.
4. Cosby K, Partovi KS, Crawford JH, et al. Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. Nat Med. 2003;9(12):1498–1505.
5. Larsen FJ, Schiffer TA, Borniquel S, et al. Dietary inorganic nitrate improves mitochondrial efficiency in humans. Cell Metab. 2011;13(2):149–159.
6. Bailey SJ, Winyard P, Vanhatalo A, et al. Dietary nitrate supplementation reduces the O_2 cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans. J Appl Physiol. 2009;107(4):1144–1155.
7. Jones AM, Thompson C, Wylie LJ, Vanhatalo A. Dietary nitrate and physical performance. Annu Rev Nutr. 2018;38:303–328.
8. Kapil V, Haydar SMA, Pearl V, Lundberg JO, Weitzberg E, Ahluwalia A. Physiological role for nitrate-reducing oral bacteria in blood pressure control. Free Radic Biol Med. 2013;55:93–100.
9. Tribble GD, et al. Frequency of tongue cleaning impacts the human tongue microbiome and the enterosalivary circulation of nitrate (chlorhexidine raised systolic blood pressure). 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6406172/
10. Bondonno CP, et al. Antibacterial mouthwash blunts oral nitrate reduction and increases blood pressure in treated hypertensive men and women. Am J Hypertens. 2015. https://pubmed.ncbi.nlm.nih.gov/25359409/
11. Toonen E, et al. The effect of chlorhexidine mouthwash on blood pressure: a systematic review and meta-analysis. Int J Dent Hyg. 2026. https://onlinelibrary.wiley.com/doi/10.1111/idh.70035
12. IARC Monographs, Vol. 94: Ingested nitrate and nitrite under conditions that result in endogenous nitrosation — probably carcinogenic to humans (Group 2A). https://www.ncbi.nlm.nih.gov/books/NBK326552/
13. IARC (2015): processed meat classified as carcinogenic to humans (Group 1), based on colorectal cancer evidence.
14. Editorial: Dietary nitrate — friend or foe? (source-dependent NO-versus-N-nitrosamine hypothesis). Front Nutr. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11629538/

15. INFORMER trial: N-nitrosamine formation after nitrate intake by source (meat, vegetable, water). ClinicalTrials.gov NCT05075720.

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