Title: Inorganic nitrate reservoir in skeletal muscle: a "glycogen-like" role to control metabolic-vascular coupling

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Inorganic nitrate is the stable end product of nitric oxide (NO) metabolism but also a precursor of NO synthesis via the nitrate-nitrite-NO pathway (1,2). Specifically, inorganic nitrate is converted first into nitrite in the mouth via the reducing capacity of commensal bacteria and, subsequently, the ingested nitrite is reduced into NO in the stomach and in distal microvascular beds (2,3). This elegant synthetic pathway appears to compensate for the downregulation of the NO enzymatic pathway in conditions associated with low oxygen tension (i.e., tissue hypoxia) to maintain the production of NO (2,3).
Until recently, blood was considered the most important reservoir of inorganic nitrate (2); this was confuted in 2015 by the discovery of higher nitrate concentrations in skeletal muscle in rats and subsequently confirmed in humans (4,5). Experimental studies in rats have showed that stores are mobilised in rats fed a nitrate-deprived diet but there is an over-compensatory accretion of dietary nitrate in skeletal muscle during a high-nitrate refeeding period (6). Similarly, nitrate stores are mobilised during exercise in both rats (7) and humans (8) with a parallel decrease in nitrite concentrations which seems to indicate an increased production of NO triggered by a higher metabolic demand.
While glycogen in skeletal muscle releases glucose units to support skeletal muscle energetic demands in a post-absorptive state, these findings, although preliminary, seems to point to a "glycogen-like" physiological role of nitrate reservoir in muscle with release of NO to enhance perfusion-metabolism coupling in skeletal muscle. Studies are urgently needed to define the physiological roles of the inorganic nitrate stores in skeletal muscle and open potential opportunities to test its validity 1) as a potential biomarker of skeletal muscle health and 2) as a the therapeutic target for the prevention and treatment of metabolic and musculoskeletal disorders.

Key References

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