

Comment re: Nitrite Activates Estrogen Receptor- α

In Response:

Our study reports that nitrite (10^{-7} – 10^{-5} mol/L) activates estrogen receptor- α in MCF-7 breast cancer cells (1). Nitrate (10^{-6} mol/L) also activates estrogen receptor- α in the absence, but not in the presence, of an oxidoreductase inhibitor. Although several enzymes reduce nitrate to nitrite, the enzyme(s) in MCF-7 cells has not been identified. Consequently, the flavoprotein inhibitor, diphenyleneiodonium, was used to block the reduction of nitrate. As many culture media have added nitrate (0.05–100 mg/L), the experiments were conducted in improved minimum essential medium (IMEM) containing 5% charcoal-treated calf serum (CCS). IMEM has no added nitrite/nitrate. To address the question of serum nitrite/nitrate, some experiments were repeated in IMEM without serum or containing 1% CCS and similar results were obtained (data not reported).

Although the primary source of circulating nitrites/nitrates is the oxidation of nitric oxide, exogenous exposures contribute to plasma concentrations (2, 3). Occupational exposures occur in the manufacture of explosives, paper, and glass and in the manufacture/use of fertilizers. Diet also influences plasma concentrations (4). Nitrate is low in water (0–18 mg/L) but has increased over the last few decades (4) due to the use of fertilizers, contamination from dumps, oxidation of ammonia from human/animal waste, and treatment of drinking water with chloramines. High amounts of the anions are present in cured and processed meats (nitrites and nitrates; 2.7–945 and 0.2–6.4 mg/kg, respectively) and in some fruits and vegetables (nitrate; 200–2,500 mg/kg) as a result of greenhouse cultivation (5). The total estimated daily dietary exposure to nitrites/nitrates ranges from 1.2 to 3 mg and 39 to 268 mg, respectively (4). Tobacco contains nitrates (0.05–13 mg/g) and smokers have a 2-fold to 3.7-fold higher serum concentration. Medications also contribute to exposure. Although alcohol does not contain significant amounts, alcohol consumption increases serum nitrite/nitrate. Serum concentrations may not reflect tissue concentrations. Some tissues have higher, whereas others have lower, concentrations of nitrite (0.45–22.5 μ mol/L) and the amount of soluble anion varies (25–78%) suggesting that a significant fraction of nitrite may not be biologically available.

In animal models, increasing serum nitrite to the upper physiologic range alters signaling pathways, inhibits cytotoxicity after ischemia-reperfusion injury, and increases vasodilation. In humans, increasing serum concentrations has similar beneficial effects on the cardiovascular system. However, environmental exposure to nitrite/nitrate is associated with non-Hodgkins lymphoma, astrocytoma, liver, stomach, pancreatic, and bladder cancers. Breast cancer is associated with farming, tobacco smoke, and alcohol, and patients with breast cancer have elevated serum (246–363 μ mol/L) and breast tissue (745 nmol/g) nitrite/nitrate levels. A clear link between environmental exposure to the anions and cancer remains to be established.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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