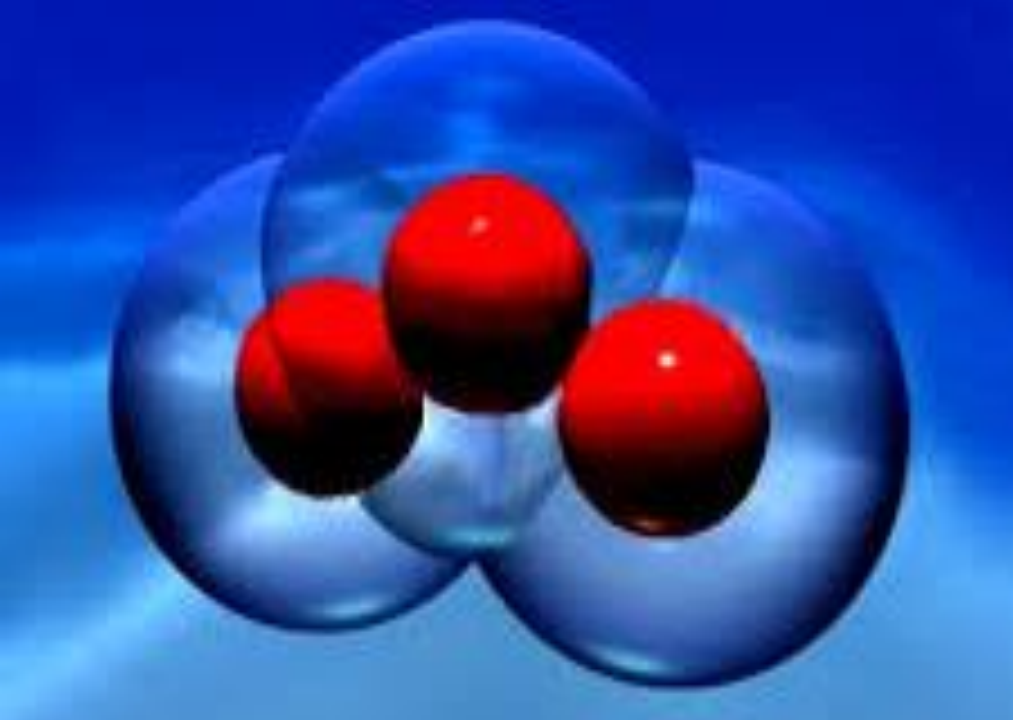


Ozone Therapy

Welcome to the Ozonosphere!



How Does Ozone Work?

Ozone has no receptors; its pharmacological mechanism of action is indirect, through its mediators.

The response dependent of the activation of nuclear transduction mechanisms signals (Nrf2: Nuclear factor (erythroid-derived 2)-like 2) and protein synthesis, e.g. SOD (superoxide dismutase), CAT (catalase), HO1 (hemeoxygenase 1), etc.)

Ozone therapeutic indications are based on the knowledge that low physiological dose of ozone may play important roles within the cell.^{1,2,3,4} Ozone does NOT work through free radical mechanisms

While ozone itself lasts only microseconds in blood, the reaction of ozone and blood lipids leads to the production of more stable but still highly reactive oxygen species (such as peroxides), which would react similarly, and perhaps mimic the pro-oxidant mechanism of immune system defense

It does work through the generation of many species of lipid peroxides

Biological Responses of Ozone Therapy

- Improves blood circulation and oxygen delivery.
- Enhances general metabolism by improving oxygen delivery.
- Upregulates cellular antioxidant enzymes
- Activates the immune system and enhances the release of growth factors.
- Stimulates the neuroendocrine system.
- Activates neuroprotective systems.

Mild/Moderate Oxidative Stress



Biological responses induced via the activation of Nrf2/ARE with mild/moderate oxidative stress

- Increasing the levels of direct antioxidants, such as GSH.
- Stimulating GSH regeneration via glutathione and thioredoxin reductase.
- Increasing the levels of enzymes that detoxify oxidants (i.e., catalase, SOD, GPx, GSTr, NADH-quinone, oxidoreductase, (NQO1),HO-1, HSP70, etc).
- Increasing the levels of phase II enzymes.
- Inhibiting cytokine-mediated inflammation
- Reducing iron overload, and subsequent oxidative stress induced via elevated ferritin.
- Protection from apoptosis induced via oxidative stress.
- Increasing DNA repair activity.

HOW OZONE ACTS (III)

| Effector Molecules | Cell Targets | Biological Effects | Therapeutic Results |
|---|----------------------------|---|---|
| LATE PHASE Lipid signals (LOPs): Hydroperoxides, lipoperoxides, malonyldialdehyde, 4-hydroxynonenal | Hepatocytes | Improved Metabolism | Slight increase of fibrinogen and prothrombin |
| | Reticuloendothelial System | | Virucidal increase |
| | Erythroblasts | Upregulation of heme-oxygenase I (HSP-32) | Improved Transport and delivery of CO2 |
| | Other cells | Upregulation of Antioxidant enzymes | Adaption to COS |
| | Bone Marrow | | |

1. Viviana, C. & Gabriele, T. Exposure to low ozone concentrations induces cytoskeletal reorganization, mitochondrial activity and nuclear transcription in epithelial human cells. in *EuropeanaCooperation of Medical Ozone Societies Congress* (Zurich, 2014).

2. Viebahn-Hänsler, R., Fernández, O.S.L. & Fahmy, Z. Ozone in Medicine: The Low-Dose Ozone Concept. Guidelines and Treatment Strategies. *Ozone Science & Engineering***34**, 408-424 (2012).

3. Bocci, V. Is it true that ozone is always toxic? The end of a dogma. *ToxicolApplPharmacol***216**, 493-504 (2006).

4. Gregorio Martínez-Sánchez "Ozone as U-ShapedDose RespponesMoleculesHormentines" Dose Response (Prepress) FormerlyNonlinearlyin Biology, Toxicology, and Medicine. Copyright © 2010 Universityof Massachusetts. ISSN: 1559-3258 DOI: 10.2203/doseresponse 10-001.