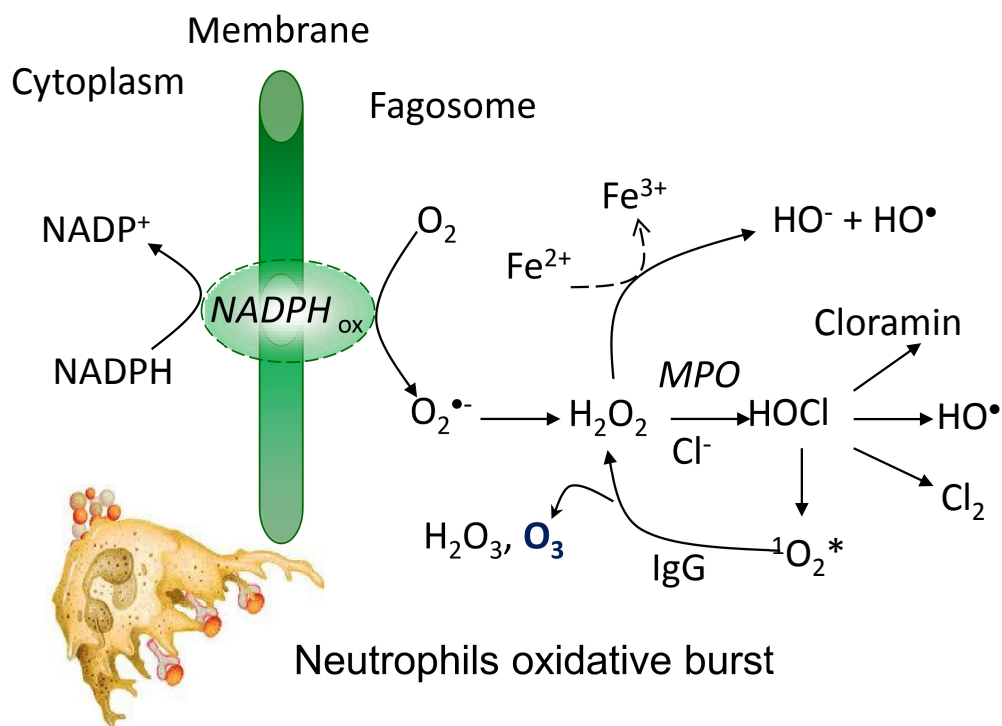


Antibody-catalyzed ozone generation by human neutrophils
2003. O₃ is present in human physiology !!!!!



Neutrophils oxidative burst

Authors demonstrate the physiological presence of an ozone-similar mediator during inflammation, indicating ozone as a new bio-molecule with striking effects which must be considered and studied following new strategies with newly constructed randomized-standardized clinical studies.

Bernard M. Babior *et al.* PNAS March 18, **2003** 100(6): 3031–3034

OZONE THERAPY (O₃_x)

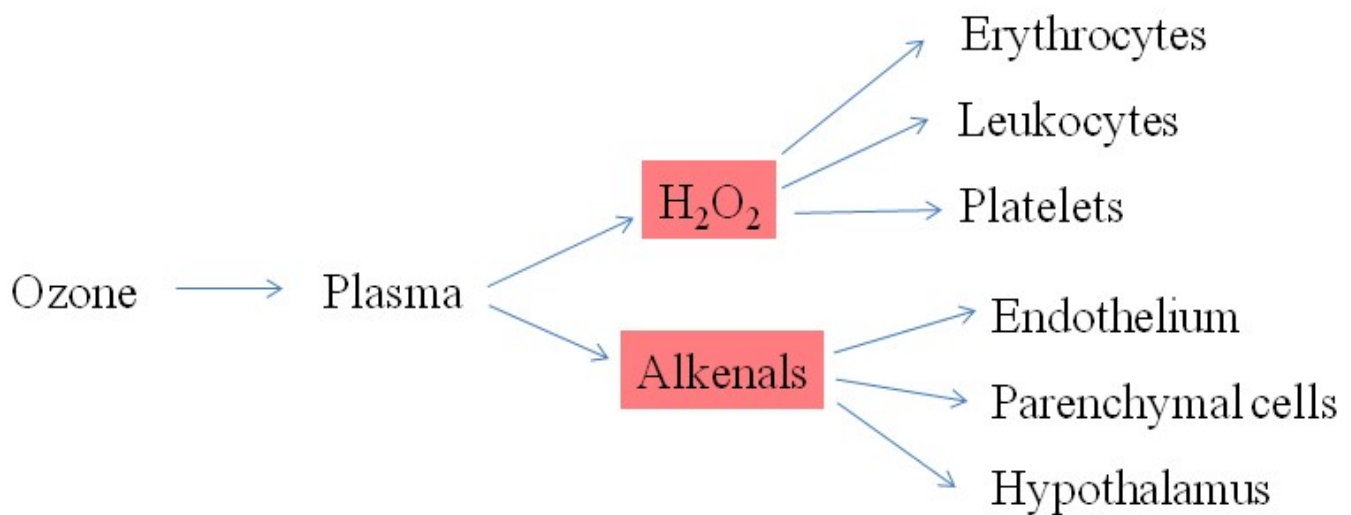
- ❖ Ozone has no receptors, its pharmacological mechanism of action is indirect, through its mediators.
- ⦿ The response dependent of the activation of nuclear transduction mechanisms signals (Nrf2: Nuclear factor (erythroid-derived 2)-like 2) and protein synthesis, e.g. SOD (superoxide dismutase), CAT (catalase), HO1 (heme oxygenase 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}

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

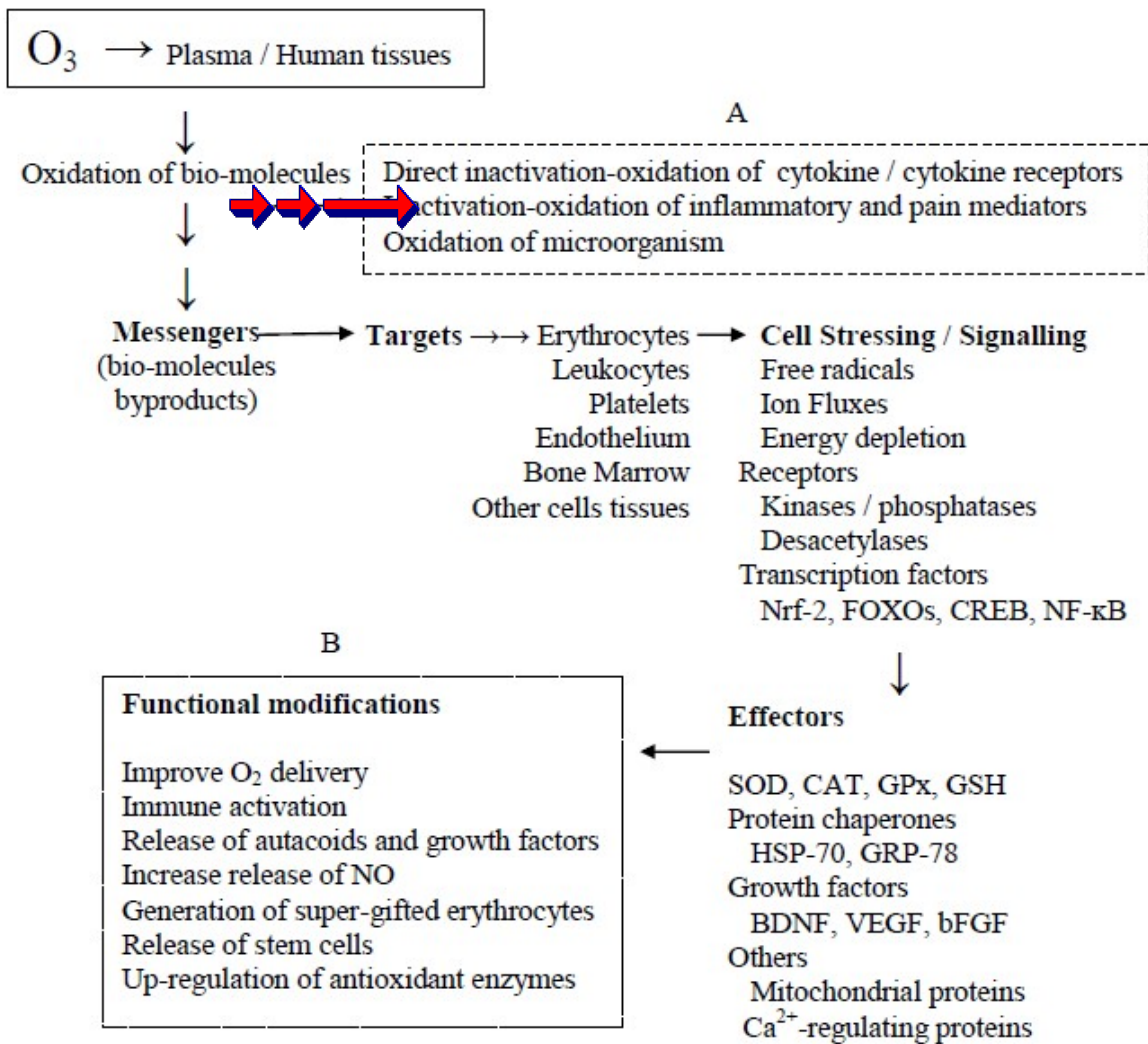
2. Viebahn-Hänsler, R., Fernández, O.S.L. & Fahmy, Z. Ozone in Medicine: The Low- Dose Ozone Concept. Guidelines and Treatment Strategies. *Ozone Science & Engineering* 34, 408-424 (2012).

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

4. Gregorio Martínez-Sánchez "Ozone as U-Shaped Dose Responses Molecules Hormentines" Dose Response (Prepress) Formerly Nonlinearly in Biology, Toxicology, and Medicine. Copyright © 2010 University of Massachusetts. ISSN: 1559-3258 DOI: 10.2203/dose response 10-001.



A scheme showing the reaction of ozone with plasma. The generated hydrogen peroxide triggers biochemical pathways in blood cells, while alkenals, after the infusion of ozonated blood into the donor, act on a variety of cells.



HORMESIS

- Hormesis is a reproducible and generalizable biological phenomenon and is a fundamental component of many, if not most, dose-response relationships.
- Low levels/doses of numerous stressors (e.g., exercise, intermittent fasting, hypoxia, heat, cold, radiation, electricity, toxins, chemicals/drugs) are known to stimulate a wide range of preconditioning/adaptive responses that may profoundly affect the success of medical interventions for a vast spectrum of disorders.
- Stressors that trigger adaptive responses also offer ways to enhance healthy aging, improve human performance, and prevent damage in tissues exposed afterward to injurious levels of stressors, including severe psychological stress.

HORMENTINE BEHAVIOUR

- ◉ Therefore, it is of interest that small amounts of ROS and Lipid Hidroperoxides can elicit the up-regulation of antioxidant enzymes on the basis of the phenomenon described under the term of *hormesis* (Calabrese 2008).
- ◉ On the basis of this phenomenon that says: the exposure of an organism to a low level of an agent, harmful at high levels, induces an adaptive and beneficial response (Stark 2008),
- ◉ At the same time, it has been postulated that Lipid Hidroperoxides (LH), by acting as long-distance messengers, can transmit to all organs the information of an acute oxidative stress (Bocci 2002) awakens many metabolic pathway that were silent.

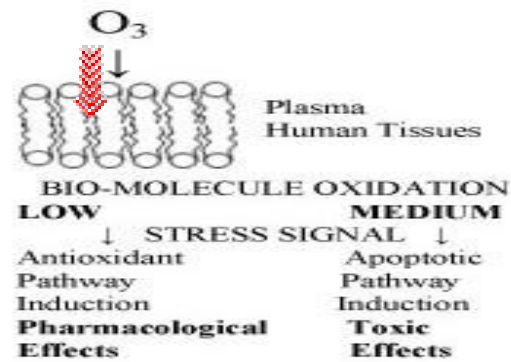
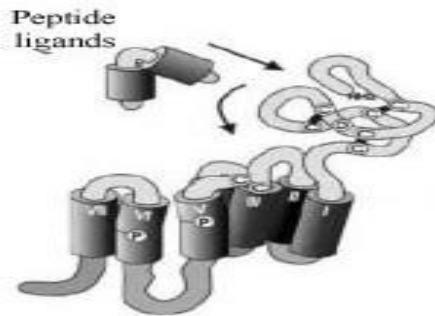
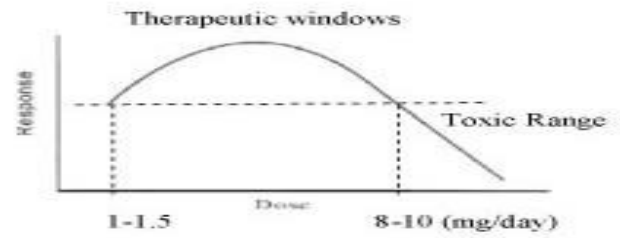
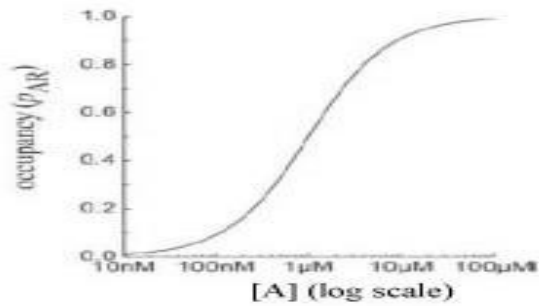
HORMENTINE BEHAVIOUR

- ◉ Typical sigmoid shape observed in pharmacology respond to a defined mechanism of interaction drug/receptor.
- ◉ However, when the action mechanisms is more complex, the dose effect behavior became more complex.
- ◉ Ozone acting as a pro-drug, realizes this shock and generates a number of messengers able to reach all cells in the organism.

Receptor depended drug (A)



Ozone



Dose-Response (Prepress)

Formerly Nonlinearity in Biology, Toxicology, and Medicine

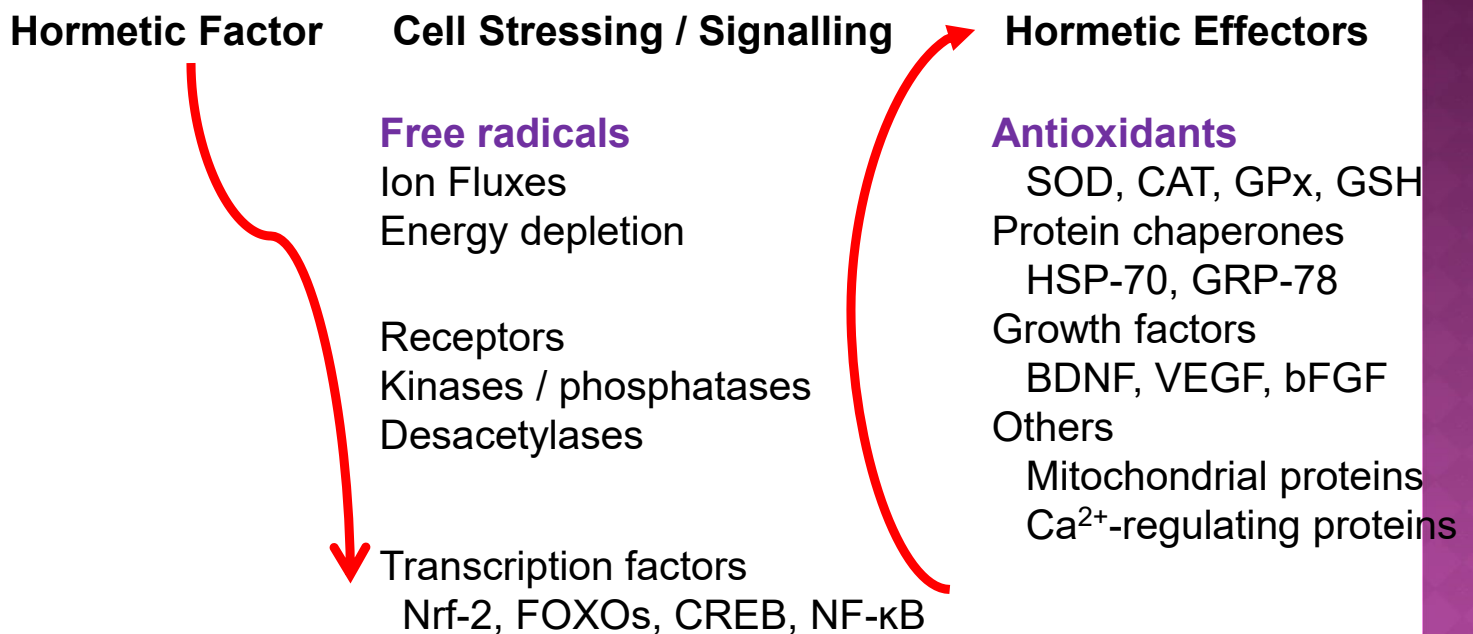
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ISSN: 1559-3258 DOI: 10.2203/dose-response.10-001.Martinez- Sanchez

HORMENTINE BEHAVIOUR

- ◉ If the disease has gone too far, cells become anergic and are unable to respond to the treatment.
- ◉ Indeed, it was observed that after intensive chemotherapy and pre-terminal cancer patients do not improve with ozone therapy.
- ◉ The ozone treatment is now envisaged as a transitory and miniaturized oxidative stress resulting in a sort of therapeutic “shock” for the ailing organism which will lead to a renewed synthesis of Heat Shock Protein (HSP) and antioxidant enzymes.
- ◉ That is also the reason why you should always start using low ozone concentrations just above the threshold level to better achieve the ozone tolerance and in-line with the concept “start low, goes slow”. (Bocci)

THE CELLULAR AND MOLECULAR INFORMATION FLOW AND MEDIATES HORMESIS IN ORGANISMS AND CELLS



Modified from: M.P. Mattson. *Ageing Research Reviews* 7(2008)1–7

HORMESIS

- ⦿ **The acceptance of the concept of hormesis has been accelerated in recent years (Cook and Calabrese 2006).**
- ⦿ Hormesis has been observed in the fields of:
 1. medicine (Celik et al. 2005, Calabrese and Blain 2009)
 2. molecular biology (Randic and Estrada 2005),
 3. pharmacology (Chiueh et al. 2005, Zhang et al. 2009),
 4. nutrition (Lindsay 2005),
 5. aging and geriatrics (Rattan et al. 2009),
 6. agriculture (Calabrese and Blain 2009),
 7. microbiology (Brugmann and Firmani 2005)
 8. immunology (Dietert 2005), toxicology (Shanker 2008)
 9. exercise physiology (Radak et al. 2008),
 10. and carcinogenesis (Cox 2009)
 11. It has also been observed in relation to disparate outcomes from the isolated single cellular process to the more holistic (e.g., growth, longevity, disease, death)