A HYPOTHESIS ON BIOLOGICAL PROTECTION FROM SPACE RADIATION THROUGH THE USE OF THERAPEUTIC GASES

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Propose a method of biologically protecting from space radiation that would enable safe human presence in space for long durations.

1. **IDENTIFY THE CHALLENGE OF SPACE RADIATION**

2. **RADIATION CHEMISTRY OF WATER & RADIATION BIOLOGY**
   a. radiolysis process
      - illustrate radiation’s role in generating reactive species (radicals)
   b. similarities between radiolysis & radiation biology
      - show the role of radicals in causing damage
      - show the process for radiation induced damage

3. **HYPOTHESIS**
   - identify methods for protection
   - purpose desirable biochemical attributes for applying methods
   - examine implementation/application for space exploration

4. **SUMMARY**
Radiation & The Space Environment Summary

- **COMPOSITION:** highly charged, high energy (HZE) nuclei

- **NATURE:** HZE creates the following character traits:
  - highly ionizing
  - penetrating
  - generates secondary radiation from interactions
  - typically low intensity

- **IMPLICATIONS:** nature & character causes:
  - difficulty shielding
  - biological damage harder to repair
  - uncertainty of biological risk from low intensities & unpredictability of true exposure

- **CONCLUSION:** need to understand & reduce risk
Radiation Chemistry & Biology Overview

- **RADIOLYSIS**: dissociation of water by radiation
  - appears to have a fundamental role in how radiation causes biological damage
  - process outcome depends on net result of competing reactions & can be altered

- **RADIATION DAMAGE**: results from a chain of events
  - initiated by ionization
  - propagated by chemical reactions
  - cause molecular & biological transformations
  - ultimately manifest into medical diseases

- **HYPOTHESIS**: applying medical gases may increase natural resistance to radiation
  - possess chemical properties for effective radical scavenging & bond repair
  - capacity to induce biological processes which enhance & support natural resistance & repair mechanisms
Radiolysis: Dissociation of Water by Radiant Energy

**Energy Deposition**

- **Mechanisms**
  - Ionization
  - Excitation

- **Yields**
  - Ions \( (H_2O^+, \text{sub-excitation electrons (e^-)} \)
  - Excited molecules \( (H_2O^*) \)

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**Free Radical Formation**

**Mechanisms**

1. **Ionization**
   - \( H_2O^+ + H_2O \rightarrow H_3O^+ + OH \)
   - Charge neutralization \( H_3O^+ + e^- \rightarrow 2H + OH \)

2. **Decomposition**
   - \( H_2O^* \rightarrow H + OH \) \( (10^{-14} \text{ sec}) \)
   - Ionization \( H_2O^* \rightarrow H_2O^+ + e^- \)

3. **Thermalization**
   - \( e^- \rightarrow e^-_{aq} \) \( (10^{-12} \text{ sec}) \)

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**Chemical Reactions**

- **Radical-radical rx.**
  - Like—like: water decomposition
  - “Forward reaction”
  - Transformation into different molecular decomposition products \( (H_2O_2, O_2, H_2, \text{etc.}) \)
  - Removes chemically active radicals
  - Alters electrochemical nature of water
  - Potential for (1) corrosion (2) pressure rise

- **Radical—molecular decomposition product**
  - “Backward reaction”
  - Water reformation
  - Reduces potential (1) corrosion (2) pressure rise.

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**Within reaction radius?**

- Yes
- No

**Forward Rx**
- Decomposition

**Backward Rx**
- Reformation

**Radicals diffuse into bulk of water**
Is Radiolysis Related to Radiation Induced Damage?

**Cellular Composition**

- 80%—water
- 5%—DNA
- 10-20%—RNA
- remainder—protein


**Effect of Radiolysis Products on DNA**

**IONS:** little or no effect
- “Ions will probably have little effect as the DNA contains numerous ionizable positions at the phosphate group.”

**EXCITED MOLECULES:** may caused localized breaks
- “Excited hydrolysis products may transfer the excitation energy to the DNA, leading to a localized break in the sugar-phosphate chain.”

**MOLECULAR DECOMPOSITION PRODUCTS:** highly reactive
- “Free radicals like OH and oxidizing products like \( H_2O_2 \) are highly reactive and can add to unsaturated bonds which upsetting the sensitive hydrogen-π-bonding and may break the bonding between two helices.”

**The Role of Radiolysis:** dominating effect for large doses & dose rates
- “The matrix effect considers the particle-water interaction in which ions, radicals and excited atoms are produced. This is the dominating effect at large radiation doses and dose rates...Free radicals and oxidizing products interact directly with cell DNA, causing the DNA-strands to break. One can state that at such high does the cell is simply poisoned by decomposition products and the whole organ may be destroyed.”


**DNA Damage by Radiation**
Effect of Linear Energy Transfer (LET) on Radiolysis


\[ RBE = \frac{D_x}{D} \]

**BIOLOGICAL ANALOGUE:**

RELATIVE BIOLOGICAL EFFECTIVENESS (RBE)

Higher LET Radiation Could Have A More Biological Effect Because It Produces More Water Decomposition Products
Effect of Dose Rate on Radiolysis

(+) dose rate
➢ (+) frequency of energy deposition
➢ (+) number of particle tracks
➢ (+) overlapping of particle tracks
➢ (+) probability of radical-radical reaction

(+) dose rate → water decomposition

100 Gy in 100 sec

\[ [\text{H}_2\text{O}_2] = 2.25 \times 10^{-7} \text{ mol/dm}^3 \]

Fig. 1. Radiolytic products in air-free pure water. Dose rate: 1 Gy per second. Doses up to 1000 Gy.

100 Gy in 1 μs

\[ [\text{H}_2\text{O}_2] = 9 \times 10^{-6} \text{ mol/dm}^3 \]

Fig. 2. Formation of radiolytic products in air-free pure water following a 100 Gy electron pulse delivered in 1 × 10^{-6} seconds.


Higher dose rates could be more lethal because higher dose rates produce more water decomposition products.
Effect of Impurities on Radiolysis

- **SUSPENDED PARTICLES**: little or no effect
  - “...in general, the presence of suspended or colloidal impurities does not result in increased decomposition rates or equilibrium concentrations of decomposition products.”

- **DISSOLVED IONIC IMPURITIES**: promotes water reformation or decomposition depending on type
  - “...in general, the presence of ionic impurities results in increased decomposition rates and equilibrium concentrations of decomposition products, some impurities producing slight increase and other producing very large increases.”
  - “At low temperatures, some ionic impurities such as KBr, KI, and CuSO4 may produce partial pressures of 1,500 psi under radiation conditions that produce only a partial pressure of less than 10 psi for relatively pure water. At high temperature, i.e., above 400°F, exploratory work has shown that certain impurities strongly catalyze the backward reaction. Such impurities are copper, rhodium, palladium, platinum, silver, and iodine; and tin, iron, and titanium to a lesser extent.”

- **BIOLOGICAL ANALOG**: chemical modifiers
  - “A number of radiosensitizing chemicals and drugs are known. Some sensitize hypoxic cells, but have little or no effect on normally aerated cells. Other agents known as radioprotectors reduce biological effectiveness....which scavenge free radicals.”
Effect of Dissolved Gas Impurities on Radiolysis

Dissolved gases can alter the chemical reaction scheme to affect the balance between water decomposition vs. reformation.

**Fig. 1.** Radiolytic products in air-free pure water. Dose rate: 1 Gy per second. Part A: Doses up to 100 Gy. Part B: Doses up to 1000 Gy.

**Fig. 4.** Oxygen depletion and build-up of hydrogen and hydrogen peroxide in air-saturated water. Dose rate: 1 Gy per second.

**Fig. 5.** Depletion of oxygen by irradiation in the presence of surplus hydrogen. Dose rate: 1 Gy per second.

Biological analogue for the effect of dissolved gases

\[ O_2 \text{ radiosensitizing effect could be a result of water decomposition} \]
\[ N_2 \text{ desensitizing effect could be from hypoxia which reduces } O_2 \text{ concentrations & thus water decomposition} \]

Radiosensitivity effect of \( O_2 \)

Effect of dissolved oxygen


Radical Scavenging in Nuclear Reactors

**IONIC IMPURITIES**

\[
\begin{align*}
\text{OH} + \text{Br}^- & \rightarrow \text{Br} + \text{OH}^- \\
\text{H} + \text{Br} & \rightarrow \text{Br}^- + \text{H}^+ \\
\text{OH} + \text{Cu}^+ & \rightarrow \text{Cu}^{++} + \text{OH}^- \\
\text{H} + \text{Cu}^{++} & \rightarrow \text{Cu}^+ + \text{H}^+
\end{align*}
\]

**HYDROGEN WATER CHEMISTRY (HWC)**

\[
\begin{align*}
2\text{H}_2 + \text{OH} & \rightarrow \text{H}_2\text{O} + \text{H} \\
\text{H} + \text{H}_2\text{O}_2 & \rightarrow \text{H}_2\text{O} + \text{OH} \\
2\text{H}_2 + \text{O}_2 & \rightarrow 2\text{H}_2\text{O}
\end{align*}
\]

**BIOLOGICAL ANALOG: RADIONUCLIDE PROTECTORS**

- Cysteine
- Cysteamine (MEA)
- 2-Aminoethylisothiouronium·HBr·HBr (AET)
- 2-Mercaptoethylguanidine·HBr (MEG)

**REDUCTION OF CORROSION POTENTIAL IN A MECHANICAL SYSTEM**

Could \( \text{H}_2 \) be a highly effective radioprotector with less poisonous byproducts permitting administration of higher dosage?

Competing Processes in Nuclear Systems


Decomposition \((B(n,\alpha))\) High LET

Reformation \((\gamma, e^-)\) Low LET


RADICAL SCAVENGERS CAN ENHANCE THE SCAVENGING CAPACITY OF THE SYSTEM CHANGING THE CRITICAL POINT WHERE THE DECOMPOSITION PROCESS DOMINATES

Biological Analogue of Competing Processes

\[ \text{INCIDENCE (PER 100,000 PER YEAR)} \]

- \( \text{DOSE (Gy)} \)
  - 0
  - 5

\[ \text{NORMAL INCIDENCE} \]

IT APPEARS THAT THERE ARE BIOLOGICALLY THERE ARE ALSO COMPETING PROCESS BETWEEN REPAIR vs. DAMAGE

- damage
- insensitivity
- repair


Multiple mechanisms but the details are unknown

“The cell is protected by different DNA repair mechanism which try to restore the damage. We don’t know the details, except when the repair goes wrong (e.g. a replacement of a lost nucleotide by a ‘wrong” base pair, etc.).”


More effective in vivo

“The repair system is believed to be more effective in a living organism, where the cells are in continuous exchange with the surrounding cells and body fluids, than in the tissue samples often studied in the laboratory...”


Related to scavenging so can be supported/enhanced similar to the “competing reactions” scenario

“The cell contains natural radical scavengers. As long as they are in excess of the radiolysis products, the DNA may be protected. When the products exceed the amount of scavengers, radiation damage and cancer induction may occur. In principle, there could thus be a threshold dose for radiation damage, at which the free radicals formed exceed the capacity of scavenging. The scavenging capacity may differ from individual to individual depending on his/her physical condition.”


“Also, chemical protectors can be introduced into the system which will compete successfully for the OH and H radicals formed. This will reduce the indirect effect”

Protection Through Enhancement of Scavenging Capacity

- Nuclear Engineering
- Biochemical
- Health

**Damage Processes**
- Oxidant Stress Sources
- Production of Reactive Species

**Repair/Non-Damage Processes**
- Non-hazard cell replication
- Cell death
- Cell repair

**Hydrogen Water Chemistry**
- Radical Scavenging
- Antioxidants

**Therapeutic Gas**

Addresses Indirect But What About Direct Effects?
Relative Contribution of Direct & Indirect Damage Mechanisms

1. indirect ionization may dominate for DNA damage
   - "... an excess of water in dilute solutions of DNA, however, the indirect effect predominates and double chain breaks are produced...."

2. direct ionization has negligible contribution for dilute solutions with small molecules
   - "Normally, in dilute solutions of small molecules, the radiation dose that will cause a considerable proportion of the solute to react with free radicals will only suffice to ionize directly a negligible proportion of the solute molecules. Thus, the direct action of the radiation on the solute molecules is small."

3. direct ionization contribution increases when mobility is inhibited (e.g solid, frozen solution, etc.) or large molecules in solution
   - "However, the fraction of the total reactions which are related to the direct effect can be increased in several ways. If material is irradiated dry, the water molecules have been removed so that there will be only direct interactions with the molecules of the material. If a solution is frozen, the mobility of the radicals which are produced in the water molecules is decreased. This will decrease the possibility of indirect action and result in a greater proportion of the interactions being of the direct type."

   - "The dose required to produce a chemical change in a given proportion of the molecules of a substance, by direct action, is inversely proportional to the molecular weight of the substance assuming that the ionic yield is constant. (the larger molecules are more likely to be in the path of the radiation)...."

   - "The direct effect is not very important in consideration of simple chemical systems, but is of importance in macromolecular and biological systems because of the presence of many large molecules."

What is Radiation Damage?

**Biologically Important Molecules**
- Proteins
- Enzymes
- Nucleic Acids
- Lipids
- Carbohydrates

**Chemical Changes from Radiation**
Appears to predominately involve loss of H atom
- "when aqueous organic solution is irradiated, the usual "indirect" reaction on the organic molecule is the removal of either a H atom or an entire radical group (such as the –CH₃ “methyl” group) from the molecule"
- "saturated hydrocarbons probably undergo a hydrogen extraction & are converted into alcohols in a two step process"
- "acetic acid most frequently loses a hydrogen atom…"
- "energy which is absorbed any place in the molecule can be transmitted down the molecular chain to the weakest bond... They hydrogen bonds are among the weakest in the molecule and thus, are the first to be broken by radiation."


**DNA Changes from Radiation**
"Cross linking process is thought to be primarily a direct effect of the radiation, while double-chain breaks are largely indirect."


1. **Loss of H Atom in Lipid Leading to Resonant Structure**

Perhaps H atom donation could prevent DNA mutation & facilitate repair from direct ionization
Progression of Radiation Induced Damage

1. **Biological Damage Results from a Chain of Events That Begins with Chemical Changes Leading to Biological Changes.**

2. **Protection Might Be Provided by Interrupting the Damage Process Early in the Chain of Events**

**Chemical Changes**
- ionization breaks bonds
- loss of H atom or radical group (\(-\mathrm{CH}_3\))
- creates chemically reactive organic radicals

**Molecular Transformation**
- reactions enable cross linking, peroxidation, etc.
- alter molecular structure

**Macro Molecular Changes**
- new properties as a result of structural changes
  - biochemical functionality altered

**Cellular Changes**
- increased membrane permeability
- chromosome aberrations
- chemical change in DNA molecule

**Tissue & Organ System Changes**
- decreased concentration of all cellular elements
- ulcers & erosion potentiating infection
- necrosis
- hemorrhaging
- etc.
“A number of radiosensitizing chemicals and drugs are known. Some sensitize hypoxic cells, but have little or no effect on normally aerated cells. Other agents known as radioprotectors reduce biological effectiveness...which scavenge free radicals. Still other chemicals modifiers have little effect on cell killing but substantially enhance some multistep processes, such as oncogenic cell transformation. For carcinogenesis or transformation, such biological promoters can dwarf the effects of physical factors such as LET and dose rate, on dose-response relationships”


**CHEMICAL PROTECTION**

1. Increase Radical Scavenging Capacity

2. Inhibit Radical Production (e.g. reduce oxygen concentrations via tissue hypoxia)
   - decrease blood flow through vasoconstrictor
   - lower blood pressure through vasodilator
   - impair oxygen transport (e.g. CO)

3. Repair Biological Radicals
   - H atom donation

**BIOLOGICAL PROTECTION**

1. Increase Time for Natural Repair Mechanism
   - delay cell in radiation resistant phase of cell cycle through interference with mitosis
   - anti-apoptosis (prior to mitosis of mutation)

2. Management of Biological Response to Insult
   - anti-inflammatory
   - alter metabolic rates
   - destroy mutation (trigger apoptosis)
Evolution of Radiation Damage & Purposed Protection Strategies

**INHIBITION OF DIRECT IONIZATION**
- natural cell insensitivity (target type, cell type, cell cycle stage)
- natural repair mechanism
- increase time for natural repair mechanism

**INHIBITION OF INDIRECT IONIZATION**
- natural DNA repair mechanisms
- antioxidant radical scavenging
- decrease radical generation

**CORRECTION OF MUTATIONS**
- apoptosis (cell death) / non-harmful replication
- recombinant DNA technology
- triggering of apoptosis of mutated cells
- H donation from H₂ scavenger

**MANAGEMENT OF BIOLOGICAL RESPONSE**
- Anti-inflammatory
- Immune System Stimulation / Regulation
- natural radical scavenging
- apoptosis (cell death) / non-harmful replication

**TREATMENT OF MANIFESTATIONS**
- radiotherapy
- surgery
- medical treatments

**RADIATION CHEMISTRY**
- energy deposition ≤10⁻¹⁵ sec
- free radical formation 10⁻¹⁵ – 10⁻¹² sec
- chemical reactions 10⁻¹² – 10⁻⁶ sec

**RADIATION BIOLOGY**
- biochemical changes ≤1 sec
- cell division affected minutes

**MOLECULAR BIOLOGY & BIOCHEMISTRY**
- gastrointestinal & central nervous systems changes days
- lung fibrosis weeks
- cataracts, cancer, & genetic effects in offspring years

**RADIATION INTERACTIONS**
- RADIOLYSIS
- THERAPEUTIC GASES (H₂, CO, H₂S, & NO) POSSESS MANY OF THESE BIOCHEMICAL PROPERTIES

**MECHANISMS**
- natural repair mechanisms
- antioxidant radical scavenging
- decrease radical generation
- H donation from H₂ scavenger
ADMINISTRATION & APPLICATION IN SPACE
Drinking, Injection, or Inhalation

**GENERATION BY CHEMICAL REACTION**

[Image: Magnesium Stick Insert]

Mg + 2H₂O → Mg(OH)₂ + H₂

**DISSOLUTION IN SOLUTION**

**DRINKING WATER**


**SALINE INJECTION**


**H₂, H₂S, CO & NO ADDITIONS TO ATMOSPHERE (SPACECRAFT/STATION/SUIT)**

[Image: Diagram of Flammability Triangle]

Summary

1. High charge & energy (HZE) nature of space radiation makes it difficult to shield and particularly damaging to DNA.

2. Biological damage develops from a series of events that start with chemical modifications initiated by ionization (direct & indirect) and which lead to molecular transformations that manifest into biological diseases.

3. Hypothesized a biochemical approach to interrupt the damage process by interfering with chemical reactions and managing biological responses.

4. Hypothesized that medical gases can support & enhance natural repair & protection as: radical scavengers, tissue pre-conditioners, and signaling molecules to manage biological response.

5. Administration of a medical gas therapy in space applications appears feasible & reasonable.

6. Qualification & optimization of a medical gas therapy for human application remains to be addressed.
QUESTIONS?

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Radiation Chemistry & Biology Summary

• **RADIATION CHEMISTRY OF WATER**: radiolysis has a fundamental role in radiation induced damage
  – radiation generates deleterious radicals similar to biochemically damaging reactive oxygen species (ROS)
  – factors leading to higher radical production also lead to more biological lethality
  – radical production is the net result of competing chemical processes in which the outcome can be altered

• **BIOLOGY OF RADIATION DAMAGE**: loss of atom/molecule by bond breakage from ionization
  – chain of chemical events initiated by direct & indirect ionization
  – natural biological resistance from radical scavengers (damage avoided when in excess of radicals)
  – natural repair occurs from uncertain mechanism (more effective in-vivo)
  – biological factors relate to chemical aspects that affect radical production (e.g. tissue hypoxia, metabolic rate, circulation & transport, etc.)

• **HYPOTHESIS**: biochemically enhance & support natural resistance & repair mechanisms
  – chemical protection by reducing radical generation (e.g. biological induction of tissue hypoxia)
  – chemical protection by increasing scavenger capacity & efficacy using H₂ gas as an antioxidant
  – potentially enhance natural repair by H atom donation
  – enhance natural repair by providing more time for repair mechanism action
  – biologically manage response to damage (e.g. anti-inflammatory, etc.)
GENERAL CONSIDERATIONS FOR SPACE EXPLORATION SYSTEMS: minimize weight, size, & power consumption

ADMINISTRATION BY DRINKING WATER:
- loss of medical gas from solution?
- loss of medical gas from host?
- if gas generated by reaction, consumption of byproducts?

ADMINISTRATION BY INHALATION:
- gas mixture flammability limits?
- gas interactions?
- \( O_2 \) concentrations / partial pressure (asphyxiation)?

ADMINISTRATION BY INJECTION:
- loss of gas from solution?

QUALIFICATION OF MEDICAL GAS THERAPY:
- optimum therapy or custom therapy development (mixture for preconditioning & post exposure treatment)?
- understanding mechanics? (penetration, distribution, detoxification)
- effectiveness? (dose reduction factor, DRF = LD50:LD30)