Communication: Environmental Pollution, Oxidative Stress and Thioretinaco Ozonide: Effects of Glyphosate, Fluoride and Electromagnetic Fields on Mitochondrial Dysfunction in Carcinogenesis, Atherogenesis and Aging

Kilmer S. McCully

Pathology and Laboratory Medicine Service, Boston Veterans Affairs Medical Center, and Department of Pathology, Harvard Medical School, Boston, MA, USA

Abstract. Environmental pollutants, such as pesticides, herbicides, additives to food and water, and electromagnetic fields threaten public health by promotion of cancer, heart disease and chronic diseases of aging. Many of these pollutants cause adverse health outcomes by effects on mitochondrial function to produce oxidative stress through loss of the active site complex for oxidative phosphorylation, thioretinaco ozonide oxygen nicotinamide adenine dinucleotide phosphate, from opening of the mitochondrial permeability transition pore. Glyphosate, fluoride, and electromagnetic fields are examples of carcinogenic pollutants that promote loss and decomposition of the active site for oxidative phosphorylation, producing mitochondrial dysfunction and oxidative stress. Ionizing radiation has long been known to be carcinogenic, and non-ionizing electromagnetic fields from microwaves, radar, cell phones and cathode ray screens are carcinogenic and produce deleterious effects on capillaries, nerve cells, blood brain barrier, embryonic and germ cells, lenses and cardiac function. Adverse health effects of electromagnetic fields include cataracts, infertility, congenital malformations, cancer, lymphocytosis, leukemia, hearing loss, blindness, retinal hemorrhages, cardiac arrhythmias, dermatitis, hair loss, depression, memory loss, premature aging, heart attacks, and weaponized mind control. The hyperhomocysteinemia, suppressed immunity, and altered oxidative metabolism observed in atherosclerosis and dementia are attributed to deficiency of adenosyl methionine which results from increased polyamine biosynthesis by pathogenic microbes that are demonstrated in atherosclerotic plaques and cerebral plaques. Thus, environmental pollutants potentially promote diseases of aging, atherosclerosis, cancer, and premature aging by production of mitochondrial dysfunction.

Key words: adenosine triphosphate, adenosyl methionine, atrial fibrillation, autonomic nervous system, cardiac arrhythmia, carcinogenesis, cellular senescence, cycloastragenol, electromagnetic field, environmental pollution, fluoride, glyphosate, homocysteine, inflammation, melatonin, mitochondrial dysfunction, mitochondrial membrane potential, mitochondrial permeability transition pore, mycotoxin, oxidative phosphorylation, oxidative stress, ozone, telomere, thioretinaco ozonide.

Introduction

The modern technological revolution has introduced significant environmental pollution that threatens public health by promotion of cancer, heart disease, and chronic diseases of aging. Many of the technological pollutants, such as pesticides, herbicides, additives to food and water, and electromagnetic fields, produce adverse health outcomes by their effects on mitochondrial function to produce cellular oxidative stress.

Thioretinaco ozonide (TR_2CoO_3) is a complex of thioretinamide and cobalamin that is oxidized to the disulfonium derivative by ozone (O_3) [1]. Thioretinamide (TR) is the anti-carcinogenic, anti-neoplastic, and anti-atherogenic N-homocysteine thiolactonyl derivative of all-trans retinoic acid and homocysteine thiolactone. Thioretinaco ozonide

Address correspondence to Kilmer S. McCully MD, Pathology and Laboratory Medicine Service, Boston Veterans Affairs Healthcare System, 1400 Veterans of Foreign Wars Parkway, West Roxbury, MA 02132, and Department of Pathology, Harvard Medical School, Boston, MA 02114, USA; phone: 857 203 5990; fax: 857 203 5623; e mail: kilmer.mccully@va.gov

0091-7370/20/0300-408.

combines with oxygen (O_2), nicotinamide adenine dinucleotide (NAD^+), and inorganic phosphate (H_2PO_4-) to form the active site of oxidative phosphorylation for biosynthesis of adenosine triphosphate (ATP), $TR_2CoO_3O_2NAD^+H_2PO_4$- [2]. Loss of this active site for ATP biosynthesis from mitochondria produces mitochondrial dysfunction and oxidative stress [3].

Glyphosate, fluoride, and electromagnetic fields are examples of the vast array of technological pollutants, which cause adverse health effects by inducing mitochondrial dysfunction and oxidative stress through loss of the active site of oxidative phosphorylation from mitochondria [3]. Loss of the active site for ATP biosynthesis occurs by opening of the mitochondrial permeability transition pore (mPTP) and decomposition of the active site by electrophilic carcinogens, oncogenic viruses, microbes, and by reactive oxygen radicals produced by ionizing and non-ionizing radiation [4].

Glyphosate. The herbicide glyphosate (n-phosphonomethylglycine) is carcinogenic in animal studies and in human exposure. Glyphosate produces mammary tumors in female rats, hepatic and dermal malignant tumors in male rats, and shortened lifespan of rats with hepatorenal syndrome induced by exposure to glyphosate [5]. Industrial human exposure to glyphosate increases the risk of multiple myeloma and leukemia in professional herbicide applicators [5,6]. Glyphosate suppresses the shikimate pathway in enteric bacteria, down-regulates half of genes encoding ATP synthase, and down-regulates cytochrome P450 oxidative enzymes [5].

Glyphosate may cause oxidative stress and inhibition of ATP biosynthesis by producing loss of the active site for oxidative phosphorylation, $TR_2CoO_3O_2NAD^+H_2PO_4$-, from mitochondria [3]. The electrophilic and nucleophilic zwitterion of glyphosate may interact with the nucleophilic O_3O_2 cluster and electrophilic disulfonium centers of thioretinaco ozonide, causing decomposition and loss of the active site of oxidative phosphorylation from the inner mitochondrial membrane. In addition, glyphosate may cause opening of the mitochondrial permeability transition pore, promoting loss of the active site of oxidative phosphorylation from mitochondria [4].

Fluoride. Fluoride anion stimulates oxygen consumption [7] and increases superoxide production in resting polymorphonuclear leukocytes [8]. Fluoride is a potent metabolic inhibitor of oxidative metabolism and ATP biosynthesis [9]. Fluoride disrupts the activity of many enzymes by interfering with normal hydrogen bonding, as shown by unexpectedly strong hydrogen bonds in amide-fluoride systems [10] and by analysis of the three-dimensional crystal structure of yeast cytochrome c peroxidase [11]. These findings support the view that fluoride inhibits enzyme function by altering the conformation of the polypeptide structure of proteins through its interaction with peptidyl amide groups [9].

The effect of fluoride on induction of oxidative stress is attributable to interaction of fluoride ions with the amide groups of thioretinaco ozonide [12], causing conformational change in the binding of thioretinamide groups to the cobalt atom of cobalamin. This effect of fluoride may inhibit binding of superoxide and other oxygen radicals to the active site of oxidative phosphorylation, resulting in inhibition of ATP biosynthesis and accumulation of oxygen radicals within cells, the hallmark of cellular oxidative stress. In addition, decomposition of the active site of oxidative phosphorylation by fluoride may promote its loss from mitochondria by opening of the mitochondrial permeability transition pore [3,4].

The extremely toxic gas, oxygen difluoride, OF_2, was investigated as a chemical weapon in World War I, but its effectiveness was limited by its decomposition in the presence of atmospheric water vapor. OF_2 is suspected of causing severe injuries and deaths in workers of the Manhattan Project in World War II because of its production from elemental fluorine and atmospheric oxygen in the synthesis of uranium hexafluoride [13]. The extreme toxicity of OF_2 is attributed to the similarity of its molecular structure to that of ozone, causing inhibition of oxidative phosphorylation by displacement of ozone from thioretinaco ozonide [12].

Electromagnetic fields. Ionizing radiation increases oxidative stress by increased production of reactive oxygen and reactive nitrogen species within cultured malignant and non-malignant cells,

associated with transient, reversible mitochondrial permeability transition (mPTP), and loss of membrane potential [14]. Ionizing radiation has long been known to be carcinogenic, and the loss of the active site for oxidative phosphorylation, $TR_2CoO_3O_2NAD^+H2PO_4$-, from opening of the mPTP explains the depletion of the active site from mitochondria during carcinogenesis [1].

Non-ionizing electromagnetic fields (EMF) from microwaves, radar, telecommunication technology, electrical transmission lines, cell phones, television and computer screens, have long been suspected of carcinogenic effects and other deleterious effects on capillaries, nerve cells, blood brain barrier, embryonic cells, germ cells, lenses, and cardiac function [15]. Because of the critical use of these technologies in guidance of ships, aircraft, and intercontinental missiles, much of the basic understanding of biological effects of EMF is classified because of national security concerns. Nevertheless, a substantial understanding of the non-thermal effects of EMF on biophysical characteristics of molecular, cellular, and tissue properties has been published [16]. Some of the important adverse biomedical effects attributable to EMF include cataracts, infertility, congenital malformations, cancer, lymphocytosis, leukemia, hearing loss, blindness, retinal hemorrhages, cardiac arrythmias, dermatitis, hair loss, depression, memory loss, premature aging, heart attacks, and weaponized mind control [15].

Recent studies on carcinogenesis in animals by the National Toxicology Program Carcinogenesis Study demonstrate an increase in malignant schwannomas of lung, malignant gliomas of brain, and cardiomyopathy from prolonged EMF exposure [17]. These findings support the view that EMF exposure is carcinogenic because of decomposition of thioretinaco ozonide and loss of the active site of oxidative phosphorylation from mitochondria [3]. Further support for the effect of EMF on cardiomyopathy is the observation of cardiac arrythmias induced in dogs by stimulation of the sympathetic and parasympathetic autonomic nervous system by externally administered low-level EMF [18]. The cardiac arrythmias induced by EMF exposure include bradycardia, atrial premature depolarizations, atrial tachycardia and atrial fibrillation.

In a study of several human cultured cancer cell lines, exposure to EMF is demonstrated to inhibit proliferation of breast, gastric, colon, and melanoma cells [19]. Exposure of the breast cancer and colon cancer cell lines to EMF demonstrated an increase in mitochondrial membrane potential, but ATP levels were unchanged. The effects of EMF are interpreted as an increase in respiratory activity of mitochondria, associated with down regulation of mitochondrial expression of phospho-extracellular regulated kinase, cytochrome c, and p53. Effects on fertility caused by inhibition of spermatogenesis and oogenesis by EMF are attributed to oxidative stress induced by decreased scavenging of reactive oxygen species (ROS) by mitochondria [20].

A possible example of EMF-induced effects on nerve, capillary, and cardiac function is the observation of pain, edema, erythema, dermatitis, and cardiac arrythmias caused by prolonged exposure of titanium prosthetic implants to EMF in modern automobiles equipped with radar, blue tooth, and wireless technology (DW Burke, personal communication). Presumably, electromagnetic fields from these sources produce electron currents on the surface of the titanium implants, causing mitochondrial dysfunction and oxidative stress by suppression of mitochondrial membrane potential and resulting in stimulation of nerves to cause pain and capillary damage to cause erythema, edema and dermatitis.

Mitochondrial dysfunction, atherosclerosis, aging and dementia. The homocysteine theory of arteriosclerosis was developed after the discovery of arteriosclerotic plaques in children with homocystinuria caused by enzymatic deficiencies of cystathionine synthase, methionine synthase, or methylenetetrahydrofolate reductase [21]. The hyperhomocysteinemia, suppressed immunity, and altered oxidative metabolism observed in atherosclerosis and dementia are attributed to deficiency of adenosyl methionine which results from increased polyamine biosynthesis by pathogenic microbes that are demonstrated in atherosclerotic plaques and cerebral plaques [22].Adenosyl methionine biosynthesis is dependent upon thioretinaco ozonide and ATP, and the deficiency of adenosyl methionine and impaired immune function in aging are attributed to depletion of thioretinaco ozonide from mitochondrial membranes.

Loss of the active site of oxidative phosphorylation, $TR_2CoO_3O_2NAD^+H_2PO_4^-$, from opening of the mitochondrial permeability transition pore (mPTP) is proposed to explain the origin of mitochondrial dysfunction in aging, atherosclerosis and carcinogenesis, thereby uniting the free radical and neuroendocrine theories of aging [23]. Cellular senescence is associated with shortening of telomeres and decreased activity of telomerase, and exposure of cultured endothelial cells to homocysteine causes cellular senescence, shortened telomeres and increased β-galactosidase, a marker of cellular senescence. Melatonin, a pineal neuro-hormone, and cycloastragenol, a telomerase activator, both prevent mitochondrial dysfunction by inhibition of mPTP opening [24]. The carcinogenic effects of EMF and mycotoxins are attributed to loss of thioretinaco ozonide from opening of the mPTP and decomposition of the active site of oxidative phosphorylation [23]. Thus, the environmental pollutants, glyphosate, fluoride, and electromagnetic fields all potentially promote diseases of aging, atherosclerosis, cancer, and premature aging by production of mitochondrial dysfunction.

References

1. McCully KS. Chemical pathology of homocysteine. II. Carcinogenesis and homocysteine thiolactone metabolism. Ann Clin Lab Sci 1994;24:27-59.
2. McCully KS. The active site of oxidative phosphorylation and the origin of hyperhomocysteinemia in aging and dementia. Ann Clin Lab Sci 2015;45:222-225.
3. McCully KS. Loss of the thioretinaco ozonide oxygen adenosine triphosphate complex from mitochondria produces mitochondrial dysfunction and carcinogenesis. Ann Clin Lab Sci 2018;48:386-393.
4. McCully KS. Chemical pathology of homocysteine. VII. Cholesterol, thioretinaco ozonide, mitochondrial dysfunction, and prevention of mortality. Ann Clin Lab Sci 2019;49:55-68.
5. Samsel A, Seneff S. Glyphosate's suppression of cytochrome P450 enzymes and amino acid biosynthesis by the gut microbiome: pathways to modern diseases. Entropy 2013;15:1416-1463.
6. Andreotti G, Freeman LEB. Glyphosate use and cancer incidence in the Agricultural Health Study. J Natl Cancer Inst 2018;110:djx233.
7. Sbarra AJ, Karnovsky ML. The biochemical basis of phagocytosis. I. Metabolic changes during the ingestion of particles by polymorphonuclear leukocytes. J Biol Chem 1959;234:1355-1362.
8. Gabler WL, Leong PA. Flouride inhibition of polymorphonuclear leukocytes. J Dent Res 1979;58:1933-1939.
9. Yiamouyiannis J. Flouride: the Aging Factor. Health Action Press, Delaware, Ohio, 1993; pp 26-33, 94-99.
10. Emsley J, Jones DJ, Miller JM, Overill RE, Waddilove RA. An unexpectedly strong hydrogen bond: Ab initio calculations and spectroscopic studies of amide-flouride systems. J Am Chem Soc 1981;103:24-28.
11. Edwards SL, Poulos TL, Kraut J. The crystal structure of fluoride-inhibited cytochrome c peroxidase. J Biol Chem 1984;259:12984-12988.
12. McCully KS. Chemical pathology of homocysteine. IV. Excitotoxicity, oxidative stress, endothelial dysfunction, and inflammation. Ann Clin Lab Sci 2009;39:219-232.
13. Bryson C. The Flouride Deception. Seven Stories Press, New York, 2004; pp 287-288.
14. Leach JK, Van Tuyle G, Lin PS, Schmidt-Ullrich R, Mikkelsen RB. Ionizing radiation-induced, mitochondria-dependent generation of reactive oxygen/nitrogen. Cancer Res 2001;61:3894-3901.
15. Brodeur P. The Zapping of America. Microwaves, Their Deadly Risk, and the Cover-Up. WW Norton & Company, New York, 1977.
16. Illinger KH. Biological Effects of Nonionizing Radiation. American Chemical Society, Washington DC, 1981.
17. Wyde M, Cesta M, Blystone C, Elmore S, Foster P, Hooth M, Kissling G, Malarkey D, Sills R, Stout M, Walker N, Witt K, Wolfe M, Bucher A. Report of the partial findings from the National Toxicology Program Carcinogenesis studies of cell phone radiofrequency radiation in Hsd: Sprague Dawley SD rats (whole body exposure). Cold Spring Harbor Laboratory bioRχiv 2018 doi: https://doi.org/10.1101;055699.
18. Scherling BJ, Yamanashi WS, Hou Y, Jacobson JI, Jackman WM, Lazzara R. Magnetism and cardiac arrhythmias. Cardiol Rev 2004;12:85-96.
19. Destefanis M, Viano M, Leo C, Gervino G, Ponzetto A, Silvagno F. Extremely low frequency electromagnetic fields affect proliferation and mitochondrial activity of human cancer cell lines. Int J Radiat Biol 2015;91:964-972.
20. Santini SJ, Cordone V, Falone S, Mijit M, Tatone C, Amicarelli F, Di Emedio G. Role of mitochondria in the oxidative stress induced by electromagnetic fields: focus on reproductive systems. Oxid Med Cell Longev 2018;ID 5076271:1-18.
21. McCully KS. Homocysteine metabolism, atherosclerosis, and diseases of aging. Compr Physiol 2016;6:471-505.
22. McCully KS. Hyperhomocysteinemia, suppressed immunity, and altered oxidative metabolism caused by pathogenic microbes in atherosclerosis and dementia. Front Aging Neurosci 2017;9:324.
23. McCully KS. Chemical pathology of homocysteine. VI. Aging, cellular senescence, and mitochondrial dysfunction. Ann Clin Lab Sci 2018;48:677-687.
24. McCully KS. Melatonin, hyperhomocysteinemia, thioretinaco ozonide, adenosylmethionine and mitochondrial dysfunction in aging and dementia. Ann Clin Lab Sci 2018;48:126-131.