Vitamin C & Mitochondria Part 1 Redox in a 5G World

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The unrelenting increase in diseases in all major categories has led many to believe the exponential rise in artificial electromagnetic radiation (EMR) as the primary culprit. Although literature on this

topic abounds, there are unresolved issues regarding the non-thermal effect of EMR. It is now widely accepted that the root cause for almost all diseases is oxidative stress, and EMR is linked to the generation of diseases via the production of oxidative stress. Our bodies have evolved with a robust and complex redox system that has been able to counter oxidative stress successfully. Vitamin C (ascorbic acid, ascorbate) is at the heart of this remarkable redox system. However, the ability of ascorbic acid to facilitate this extensive redox system is now being critically challenged by our modern lifestyles. Oxidative stress generated by pervasive artificial and natural EMR, unhealthy lifestyles can result in the depletion of ascorbate. Inadequate substrates from dietary deficiencies may also inhibit the necessary regeneration of ascorbate. Absent ascorbate, our highly developed redox systems comes to a halt, taking with it as collateral damage the life-sustaining bioenergetic balance in mitochondria, ultimately resulting in disease in every form imaginable.

Introduction

Living species have the evolutionary pressure to become adapted to their environments. When the environmental conditions change, they may eventually become un-adapted, or even risk extinction. In general, when a structure or molecule becomes detrimental for a given species, accumulative changes evolve to allow the organism to become better adapted to the environment. When this change does not happen, the disadvantage negatively affects the reproductive index and the species eventually becomes extinct. The Earth

surface has been exposed to electromagnetic radiation (EMR) from the sun since its origin and the current oxygen concentration in the atmosphere has remained stable for the last billion years. Most organisms have successfully adapted to live under these EMR and oxygen conditions until several hundred years ago when increased spectrums of EMR from technology advancement began to drastically alter the living environment and the way living organisms respond to these changes.

Electromagnetic radiation (EMR) from manmade sources has been linked to the rise in diseases including the proliferation of cancer [1], neurodegenerative disorders [2], cardiovascular diseases [3] and even infertility [4, 5]. All EMR, natural or manmade, are electromagnetic vibrations consisting of electric and magnetic fields traveling through space at right angles to each other. Photons are the basic energy carriers in all EMR. EMR exert biologic effects through thermal, non-thermal, and photochemical reactions. Thermal reactions are dependent upon the absorption of heat and do not require the presence of light, whereas photochemical reactions involve the absorption of light and take place in the presence of light, independent of temperature. Photosynthesis in plants are prime examples of photochemical reactions.

It is widely believed that electromagnetic radiation in the form of radio waves is non-ionizing, and do not carry enough photon energy to separate electrons from atoms, breaking chemical bonds resulting in biochemical reactions or DNA damage. Photon energy from ultraviolet light (0.94-3.33 PHz) range from approximately 4 eV to 300 eV (electron volts), whereas the range of photon energies for visible light from infrared (0.3 THz - 0.43 Phz) to violet (0.94 PHz)

is 1.63 to 3.26 eV. Free electrons with energies from 1 eV to 20 eV can be generated from ionizing radiation. It has been shown that even when these electrons start to lose energies, free electrons carrying energies as low as 0.1 eV can attach themselves to DNA and cause single strand breaks, a process that normally would have required energies as high as 4.0 eV [6]. Which frequency in EMR can generate photon energy of 0.1 eV? 0.1 eV is equivalent to 24180 GHz or 24.18 THz, which is equivalent to 13.957 μm, or 13,957 nm, putting it in the range of the far infrared spectrum of light. Radio frequencies from navigational transmission, AM, FM radio broadcasts, television, cordless and mobile telephones, microwave ovens, satellite uplinks, microwave relays and radars all operate within the range of 3 kHz to 300 GHz only. To generate 0.001 eV, one needs at least 1 THz (terahertz) in intensity of frequency. As a result, the non-thermal effects of EMR has been a subject of intense scrutiny by science, as scientists and researchers try to understand how such low energy frequencies can be the cause of so many diseases including cancer.

The current understanding is the non-thermal effects from EMR are mediated by oxidative stress generated from oxygen radicals such as superoxide anion radical, singlet oxygen , hydroxyl radical, and perhydroxyl radical, collectively known as reactive oxygen species (ROS). All artificial electromagnetic radiation are polarized [11]. Ascorbic acid can depolarize EMR due to its birefringent qualities[12]. The ability to tunnel hydrogen and electrons gives ascorbic acid a distinct advantage in the attenuation of oxidative stress. As the perfect proton and electron donor, ascorbic acid plays a central role in the sophisticated, complex redox system designed by nature to counter and balance the destructive effects of oxygen. An imbalance between free radical generation

and sequestration leads to oxidative stress. Free radicals under certain conditions must be effectively quenched or the ensuing chain of reactions can cause mitochondrial dysfunction, cytotoxicity, DNA and mtDNA damage [7,8,9]. Disturbed redox status from free radical production can lead to inflammatory processes resulting in tissue damage. Excessive ROS from oxidative stress can attack cellular proteins, lipids and nucleic acids that lead to cellular dysfunctions in the form of reduced energy metabolism, altered cell signalling as well as cell cycle control, genetic mutations, decreased biological activity, immune activation and inflammation [13]. Abnormal immunity is believed to be related to oxidative imbalance. Diabetes is a prime example of organ-specific autoimmune disorders caused by oxidative stress induced inflammation [10] .

Part 1 of this article will explain how oxidative stress is created as a natural product of our existence, and the impressive redox system that has evolved using ascorbic acid as one of the primary facilitating agents to successfully counter oxidative stress. This section does not begin to offer a comprehensive coverage of how Vitamin C functions in our bodies, but it does attempt to offer an initial guide to understanding the importance of Vitamin C in supporting and maintaining the redox balance in our bodies. Part II of this article will show what is currently known about the mechanisms through which electromagnetic radiation generate excess reactive oxygen species (ROS) and other free radicals, depleting ascorbic acid and overwhelming the capacity to neutralize oxidative stress; and how ascorbic acid works with the plasma membrane redox system to maintain mitochondrial bioenergetics.

PART 1

Oxygen, Friend or Foe?

The introduction of free oxygen to earth's atmosphere approximately 2.45 billion years ago by photosynthetic organisms like the cyanobacteria (blue-green algae) initiated the Great Oxygenation Event. These photosynthetic organisms convert sunlight into energy and produce dioxygen (O2) as a 'waste' product. Many anaerobic species at the time were unable to adapt to the increased free oxygen in the atmosphere and suffered extinction as a result. [14] This rise in atmospheric O2 selectively pressured organisms to evolve using O2 as the basis of their metabolism. Oxygen-based metabolism turned out to be enormously advantageous from a metabolic standpoint because of a significant increase in energy production in the form of adenosine triphosphate ATP by the electron transport chain in mitochondria. However, oxidative metabolism demands a toll in the form of free radicals and reactive oxygen species being generated during imperfect electron transfers in the mitochondrial respiratory chain.

Free Radicals & Reactive Oxygen Species

A free radical is a molecule or atom that can exist independently with one or more unpaired electrons. Oxygen free radicals are derivatives of oxygen (O2) and they all contain an odd number of electrons in their outermost shells. Due to this peculiarity, these free radicals are highly unstable and reactive as they try to gain or lose an electron in their outermost shells to stabilize themselves. Free radicals can cause a tremendous amount of cellular damage because they are able to generate additional free radicals when they take electrons from other molecules, triggering exponentially increasing chain reactions known as free radical cascades. Here is an example of how a chain reaction might occur: an electron reacts with oxygen to form the superoxide anion radical ($O_2^{\cdot -}$). Inside cells, superoxide quickly turn into hydrogen peroxide. Hydrogen peroxide is a reactive oxygen species that has an even number of electrons in its outer shell and therefore is not a free radical. But H_2O_2 is lipophilic and can easily cross lipid-rich membranes, reacting with metals like iron and copper to generate highly toxic hydroxyl radicals. Hydroxyl radicals are able to interact with proteins, carbohydrates, nucleic acids, and lipids. Of all the oxygen species, the hydroxyl radical is the only one capable of attacking virtually all chemical bonds in biomolecules. The hydroxyl radical is regarded as the strongest oxidant of all oxygen species. Yet the chain reaction of the free radical cascade continues as hydroxyl radicals form the really toxic peroxyl radicals. Although slightly less reactive than hydroxyl radicals, peroxyl radicals have a longer half-life, and thus can travel further from their site of production to exert their damaging effects on cell membranes by means of lipid peroxidation. Peroxyl radicals are known to destroy polyunsaturated fatty acids (PUFA) in cell

membranes resulting in functional deterioration and death of cells. Just a few electrons leaked from the mitochondrial ETC can potentially have devastating cascading effects when they react with oxygen.

Even though eleven distinct sites in the mitochondrial electron transport chain have been identified to leak electrons that produce superoxide (O2-) and/or hydrogen peroxide (H2O2), with Complex I, II and Complex III showing the highest level of leakage [15], mitochondria are not the only source of free radicals and reactive oxygen species generated in our bodies.

Singlet Oxygen & Photosensitizers

When molecular oxygen is excited electronically, singlet oxygen, a form that can be highly toxic to cells is created. In the body, singlet oxygen can be generated from photochemical reactions in the presence of light, or in dark reactions during inflammatory responses when superoxide react with peroxynitrite, a free radical created from nitric oxide, to produce singlet oxygen [16]. Molecular oxygen in the neutral triplet spin state is inert and do not form chemical bonds. But when O2 is energetically excited, or when it accepts an electron through enzymatic reactions, the highly reactive singlet oxygen is formed.

The photochemical reactions of oxygen with light in the UV-B to infrared frequencies usually require the participation of photosensitizers. When photosensitizers absorb light and become electronically excited, they transfer the absorbed energies to surrounding molecules such as oxygen, generating free

radicals in two types of reactions. Type I reactions generate superoxide radicals and Type II reactions produce singlet oxygen [17]. There are a large number of endogenous and exogenous compounds that can be photoactivated in the UV and visible regions of the electromagnetic spectrum. The ability of an endogenous or exogenous photosensitizer to produce singlet oxygen and/or other free radicals can be measured by its quantum yield. The higher the quantum yield, the more free radicals are generated by the photosensitizer.

Titanium dioxide, the ubiquitous colorant of choice in most food, drug and cosmetic applications, is highly photosensitive. Electrons in titanium dioxide are easily excited by photons in the UV-B to UV-A range, leading to the formation of free radicals like superoxide or even hydroxyl radicals [53]. Many pharmaceutical drugs are also exogenous photosensitizers. All the fluoroquinolones are powerful photochemical carcinogens [18]. Fluoroquinolones like Ciprofloxacin have a quantum yield of $\Phi\Delta$ 0.09 which is slightly higher than lipofuscin, an intracellular age pigment [19]. Liposfuscin, with a quantum yield of only $\Phi\Delta$ 0.08 has been shown to mediate blue light-induced damage via ROS in retinal pigment epithelium cells. When excited by blue light in the visible spectrum, lipofuscin has been found to generate singlet oxygen with a peak at 440 nm [20], or even the highly reactive hydroxyl radical leading to mtDNA damage and decreased cell viability [21]. Singlet oxygen has been shown to be the cause for age-related mtDNA lesions in human cells through the generation of common deletion, the 4,977 base pair deletion [22]. Yet our bodies are full of endogenous photosensitizers, some with extremely high quantum yields capable of generating harmful free radicals. Some of these photosensitizers include a form of vitamin A known as 11-cis

retinal (ΦΔ 0.55), riboflavin (ΦΔ0.54-0.49), FMN (ΦΔ 0.51), and provitamin D2 ergosterol (ΦΔ 0.85) [19]. Why do our bodies need chromophores (photosensitizer) with high quantum yields like 11-cis retinal?

Melanopsin & Retinals: What's the Story?

Retinal, or vitamin A, is the chemical basis of vision in animals. Retinal is highly photosensitive because it facilitates the conversion of light into metabolic energy, as observed in some microorganisms. Melanopsin is a retinal photopigment that displays peak spectral sensitivity at ~480 nm. This photopigment plays an important non-image-forming role in the setting of circadian rhythms, sleep and other functions. Optimal functioning of melanopsin depends on the conversion (isomerization) of 11-cis-retinal into all-trans-retinal in the presence of blue light. 11-cis-retinal, with its high quantum yield, is nature's preferred light sensing chromophore [23]. Many believe unbound vitamin A from blue light exposure is dangerous because all-trans-retinal is a chemically reactive aldehyde, capable of forming toxic conjugates with proteins and lipids, leading to degeneration of the retina via the production of singlet oxygen and other reactive oxygen species [24] . However, melanopsin is bistable, meaning it is fully capable of regenerating all-trans-retinal back into 11-cis-retinal, providing there is a presence of light in the ORANGE spectrum [25]. In addition, nature has provided humans with an extensive defensive network to counter free radical damage created by endogenous photosensitizers within reason. All-trans-retinal becomes cytotoxic only when the eye is exposed to excessive artificial blue light. Aside from 11-cis-retinal, melanin is probably the most powerful photoreactive biomolecule in humans, yet it is also the most

perplexing.

Is Melanin Photoprotective or Phototoxic?

Melanin is accepted as a photoprotective pigment found throughout nature. In humans it exists predominantly in the form of eumelanin. Melanin is responsible for photoprotection in the human skin and eyes. All melanins absorb UV-B, UV-A and visible light. Melanin has also been shown to exhibit a dose dependent antioxidant ability to scavenge free radicals generated during in vitro hypoxanthine-oxidase enzymatic reactions that do not involve UV radiation [26]. Yet melanin has been substantially implicated in the development of dangerous melanoma cancers in the skin and eyes. Studies have demonstrated the generation of both Type I (superoxide generation) and Type II (singlet oxygen generation) photochemical reactions by melanin that led to the formation of pre-mutagenic DNA lesions. When stimulated with UV radiation (355 nm) as well as visible light (532 nm), both eumelanin and pheomelanin produced singlet oxygen with similar yields, with pheomelanin showing a higher production efficiency. Pheomelanin is a more effective photosensitizer than melanin, and is found mostly in people with red hair and fair skins [27].

This paradoxical effect of melanin probably lies in its unique ability to conduct electricity. Science now understands melanin to be an electronic-ionic hybrid conductor capable of bioelectronic proton-to-electron transduction, and not the amorphous organic semiconductor it was once thought to be. However, electrical conductivity in melanin depends on photoionization and spin properties of free radicals. The comproportionation equilibrium that affects

melanin's ability to dope electrons and protons also determines the proportions of the hydroxyquinone, semiquinone, and quinone free radicals in melanin [28, 29]. The quinone/semiquinone/hydroquinone triad is known to generate superoxide and hydrogen peroxide [30]. When iozined by photons, melanin can generate three melanin radicals per molecule of oxygen consumed [31]. The ionization threshold for both eumelanin and pheomelanin is at 282 nm, with pheomelanin exhibiting a second ionization threshold between 303 and 350 nm. This lower ionization requirement observed in pheomelanin probably is the cause for the frequent occurrence of UV-induced skin cancers in red-haired individuals [32]. Yet there exists an inverse relationship between skin pigmentation and the incidence of sun-induced skin cancers [33]. Many reasons have been cited but very few mention the intriguing relationship between thioredoxin reductase and melanin.

Melanin & Thioredoxin Reductase, the Ascorbate Connection?

In 1987 scientists discovered thioredoxin reductase, a membrane-associated enzyme that can quench free radicals before they can penetrate the plasma membranes of keratinocytes and melanocytes. The researchers tested healthy human subjects with different skin types with varying levels of pigmentation. They found a tight correlation between thioredoxin reductase activity and the level of melanin pigmentation in the skin. The darkest type VI skin according to the Fitzpatrick classification had a five-fold increase in enzyme activity over type I skin. In addition, skin areas with vitiligo showed a consistent decrease in thioredoxin reductase activity compared to unaffected areas in the same subject [34]. Seven years later, these researchers confirmed that thioredoxin reductase

expression was indeed increased when melanin biosynthesis was induced by radiation in guinea pigs, leading to the conclusion that melanin and thioredoxin reductase could be the body's response mechanism to oxidative stress. Even though the expression of thioredoxin reductase increased, the levels and activities of other endogenous antioxidant enzymes like superoxide dismutase, catalase, and glutathione reductase actually decreased [35] . Now isn't that interesting! How does thioredoxin reductase on cell membranes provide oxidative damage protection without the help of these important antioxidants?

Ascorbic Acid & the Dynamic PMRS, Plasma Membrane Redox System

Thioredoxin Reductases are part of an extensive, dynamic and influential network of plasma membrane enzymes that regulate redox balance in the cellular environment. These enzymes were not formally classified until the early 2000's because they were primarily NADH or NADPH oxidases that had been known under various other names based upon their physiological electron acceptors. Most of these plasma membrane redox enzymes that have been identified so far use ascorbic acid almost ***EXCLUSIVELY*** as their electron acceptor and donor, due to the unique characteristics of ascorbic acid [36]. In addition to proton and electron tunneling, ascorbic acid has a reduction potential of +282 mV, allowing it to easily donate and accept electrons while being relatively stable [37].

Redox Balance in Mitochondria

Redox stands for Reduction-Oxidation. Redox potential, or reduction potential measures the tendency of a chemical species to gain or lose electrons. Thus a redox reaction will involve the transfer of electrons between two chemical species. Redox potential is measured in volts (V) or millivolts (mV). A high positive number means the species has a greater tendency to gain electrons (or be reduced). Whereas a lower number or negative number means the species will lose electrons (or be oxidized) easily. For example, the redox pair of NAD+/NADH where NAD+ is the oxidized form of NADH, has a reduction potential of -320 mV. NAD+/NADH will be oxidized or give up its electron to any species with a more positive number, but it will be reduced or gain an electron from a species with a more negative number. Free radicals like hydroxyl and peroxyl radicals are lethal because they have extremely high reduction potentials between +1000 to +2300 mV. These free radicals will grab electrons or oxidize any species with a lower redox potential [103]. The state of health in an organism depends on the continued balancing processes between reduction and oxidation.

Mitochondria have evolved to generate energy while balancing reduction and oxidation. Stressed mitochondria produce more ROS that will eventually lead to mitochondrial dysfunction and diseases. It is now recognized that mitochondrial dysfunction under oxidative stress could be the cause for aging; acute or chronic diseases including metabolic disorders such as obesity, diabetes; cancer; neurodegeneration; and cardiovascular disease. Maintaining a balanced redox environment could be the key to health and survival, as any extreme in either direction causes redox imbalance. An excess of reduction capacity will result in slower electron flow through the mitochondrial electron transport chain leading

to increased generation of superoxide free radicals; whereas excess oxidation that is not properly scavenged by reducing equivalents will result in an overflow of uncontrolled ROS that eventually overwhelms the delicate energetic balance in the cellular environment [38].

The Major Redox Players: Pyridine Nucleotide Pools NAD/NADH, NADP/NADPH

Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) are the pyridine nucleotide pools that balance the forces of reduction and oxidation in mitochondria. The NAD/NADH pool regulate energy-producing catabolic processes that involve the generation of ROS, while the NADP/NADPH pool provides both antioxidant defences as well as free radical generation under certain conditions [39]. Both NAD and NADP are electron carriers. NAD+ and NADP+ in their oxidized forms will accept hydride ions to produce their reduced forms of NADH and NADPH. Since the primary role of the NADP pool is to provide electrons in anabolic pathways, this pool is often maintained in a highly reduced state, with the NADPH/NADP+ ratio kept quite high. In contrast, the NAD pool as electron acceptors in catabolic pathways require them to be maintained in an oxidized state. Therefore, the NADH/NAD+ ratio must be kept low in order for glycolysis to proceed properly to supply all the requisite mitochondrial substrates.

NADH is generated in the citric acid (aka TCA tricarboxylic acid, or Krebs) cycle, as well as during glycolysis. NADH functions as an electron carrier in the

electron transport chain (ETC) in mitochondria, and its presence is critical for optimal ATP production. When NADH is oxidized in Complex I by NADH dehydrogenase, electrons are passed along the ETC to oxygen, the final electron acceptor, forming water (H2O); while at the same time, the energy released from the oxidation of NADH creates a proton gradient that facilitates the translocation of H+ protons across the mitochondrial inner membrane from the matrix to the intermembrane space. The resultant higher membrane potential creates a proton motive force that drives the ATP synthase to produce ATP. An inadequate level of NADH will collapse the inner membrane potential, while an excess of NADH will produce superoxide from electron leaks when the electron transport chain is unable to utilize all the electrons to reduce oxygen to water. Cells depend on their mitochondria to maintain redox balance, using NADH and NADPH as effective reducing equivalents to balance oxidation [40]. What happens when mitochondria in a cell becomes dysfunctional?

Mitochondria & The Plasma Membrane Redox System (PMRS)

The importance of an extensive, dynamic redox system in plasma membranes of living organisms has not been fully explored by science until more recently, where critical biological functions of transmembrane proteins like thioredoxin reductases, cytochrome B561, CYB5R, DCYTB and VDAC are being discovered. The existence of the plasma membrane redox system (PMRS) being expressed in every living cell including bacteria, cyanobacteria, yeasts, algae, plants and animals is well established. PMRS activity is ubiquitous in living organisms because it is nature’s secret weapon in the maintenance of redox balance. PMRS activity modulates the ratios of NAD+/NADH in the cytosol of

cells. When mitochondria becomes dysfunctional, the PMRS activities are increased as a response to maintain NAD+/NADH ratio to promote cell survival. Cells deficient in mitochondria have been found to survive through electron and proton transport processes supported by the PMRS, coupled to an enhanced glycolytic metabolism [41].

Mitochondria with deficient mtDNA will have impaired ATP production that lowers the oxidation of NADH into NAD+. Without ATP generated in mitochondria, a cell will have to rely on other processes like glycolysis to generate energy. Yet glycolysis cannot proceed without adequate NAD+ formed during oxidative phosphorylation (OXPHOS). How do cells manage to survive without the presence of a functional respiratory chain to supply NAD+ in its oxidized form of NADH? Oxidation of NADH and the maintenance of intracellular NADH/NAD+ homeostasis is the primary function of PMRS. Plasma membrane redox systems rely upon ascorbate and NADH as electron acceptors and donors to control redox balance, at the same time neutralizing oxidative stress.

Ascorbic Acid & Its Stable Free Radical, Semidehydroascorbate

Vitamin C (ascorbic acid) exists predominantly in the ionic form of ascorbate at physiological pH. Ascorbate is a potent free radical scavenger in plasma and cells due to its ability to reduce damaging reactive oxygen species while being relatively stable. When ascorbate donates one electron to reduce ROS, it forms the stable ascorbyl free radical known as semidehydroascorbate (SDA) or monodehydroascorbate (MDHA). All the important plasma membrane redox

proteins depend on the effective recycling of the redox pair ascorbate and semidehydroascorbate to maintain redox balance, using NAD(P)H as primary electron donors [42]. Ascorbate and semidehydroascorbate are the predominant forms found in plasma of humans and animals, with with DHA detected at ***ZERO*** levels [43]. Living organisms prefer the one-electron oxidation redox pair because DHA, dehydroascorbate, the two-electron oxidation product of ascorbate is highly unstable, with a half-life of only 6 minutes. Unless DHA can be reduced by glutathione (GSH), NADPH or even NADH, DHA often rapidly undergoes an irreversible ring opening to form 2,3-L-diketogulonate and L-erythrulose which will further degrade into metabolites that include oxalate and L-threonate [44]. It is due to this reason that ascorbic acid is often thought to deplete glutathione (GSH). In vivo and in vitro studies reveal that ascorbic acid actually may enhance and increase GSH levels.

Ascorbic Acid, NADPH/NADH & Glutathione: the G6PD Connection?

A 1993 study on human subjects found that supplementing with merely 500 mg of vitamin C increased glutathione levels in red blood cells by 50% [45]. In a 2001 study, researchers found that when erythrocytes (red blood cells) from human subjects were exposed to DHA (in vitro), GSH, NADPH and NADH were depleted in a dose-dependent manner. These researchers noticed that when glucose was added to the medium containing erythrocytes and DHA, there was no change in GSH and NADH levels, but the level of NADPH was decreased [46]. Yet in an old study performed in 1978, researchers found the oxidation of NAD(P)H was completely reversed upon the addition of glucose in hamster fibroblast cells exposed to DHA [47].

Have you ever wondered why ascorbic acid is the highest in fruits, and fruits have the highest levels of sugars found in nature? The metabolism of sugar involves glycolysis which nets 2 NADH molecules from the oxidation of 2 NAD+ molecules. Inhibition of glycolysis has been shown to lower intracellular NADH/NAD+ ratio by more than two-fold. Glucose probably has the lowest energy cost required in the production of NADH. NADH is also the preferred reducing agent for the ascorbyl free radical. Therefore, the addition of glucose to cell mediums is likely to generate enough NADH to prevent further oxidation of the ascorbyl free radical into DHA, rescuing the depletion of GSH. But the question remains, why is NADPH decreased in one study and not the other, even though both studies added glucose to the cell medium that were exposed to DHA?

Is G6PD Over-rated in the Maintenance of NADPH?

The fact that the addition of glucose to erythrocytes did not prevent the decrease of NADPH inevitably leads to the consideration of whether glucose-6-phosphate dehydrogenase (G6PD) is the culprit. The enzymatic activity of G6PD in the pentose phosphate pathway generates NADPH, the important electron donor that reduces oxidized glutathione (GSSG) back to glutathione. Glutathione (GSH) and catalase are both dependent upon NADPH in the reduction of H2O2 to water [48]. In addition, reduced glutathione defends against oxidative damage in hemoglobin by maintaining hemoglobin in the soluble form. G6PD is constitutively expressed in all organisms and cell types. Deficiency in G6PD is one of the most prevalent disease-causing mutations worldwide. However, G6PD deficiency is only associated with moderate health

risks without significant effect on longevity. It is now believed that G6PD mutations reached their prevalence due to the protection conferred against severe malaria complications [49] .

G6PD deficiency is a common genetic variant in humans, and often is the cause of hemolytic anemia. Although G6PD is the rate-limiting step in NADPH production, it is important to point out the fact that the G6PD enzyme is located only in the cytosol where it will ***NOT*** be available to mitochondria to reduce all the superoxide/H2O2 produced inside mitochondria. This can only mean that there are other sources for NADPH aside from G6PD. In fact, it is now known that the production of NADPH in the pentose phosphate pathway by G6PD is rather insignificant when compared to the other pathways that have been uncovered. Until 2001, G6PD was believed to be the major source of NADPH production until the discovery of the widely expressed isocitrate dehydrogenase (IDH). IDH has three isoforms found in mitochondria and the cytosol of most cells, including that of human erythrocytes [50, 51]. Isocitrate dehydrogenase (IDH) has been found to be more active in NADPH production than G6PD. In rat liver, NADPH produced by IDH exceeded that of G6PD by 16 to 18-fold. Similarly, in pancreatic islets, the mitochondrial pyruvate-malate shuttle between the cytosol and mitochondrial matrix has been found to generate more NADPH than G6PD in the cytosolic pentose phosphate pathway [52]. Of all these major alternate NADPH production pathways in mitochondria, none is more important and influential than NNT.

NNT Generates NADPH from NADH

Nicotinamide nucleotide transhydrogenase (NNT) was first discovered in bacterial extracts in 1951. This gene is widely expressed in all major human tissues, with overexpression found in the heart. Located in the inner mitochondrial membrane, the NNT gene encodes an enzyme which produces high concentrations of NADPH using energy generated from the mitochondrial proton gradient in a manner that is similar to how the ATP synthase uses the energy from the translocation of protons into the mitochondrial matrix to generate ATP. It is believed that ***half*** of the mitochondrial NADPH in the brain is produced by the inner membrane NNT, while inhibition of this enzyme can cause significant oxidative stress [54]. However, NNT generates NADPH only when it is in the forward motion. When there is inadequate supply of NADH which inevitably results in the collapse of the mitochondrial membrane potential, the NNT will operate in a reverse mode where NADPH is ***OXIDIZED*** to generate NADH in order to rescue the collapsing membrane potential [55]. In fact, NNT has been found to operate in reverse mode, oxidizing NADPH into NADH in pancreatic b-cells at low glucose concentration [56]

It is now very clear why with the addition of glucose and DHA to the cell culture mediums, the erythrocytes were able to maintain GSH and NADH levels yet sustaining a decrease in NADPH; while the fibroblast cells did not lose any NADPH. Fibroblast cells contain mitochondria, whereas erythrocytes do not. Mitochondria NNT was able to completely regenerate all oxidized NADPH from NADH. The addition of glucose ensured the adequate supply of NADH to both cell cultures, allowing DHA to be reduced back into ascorbate without further degradation, while ascorbate eliminated oxidative stress,

rescuing GSH in both erythrocytes and NADPH in fibroblasts. It is important to remember that DHA is almost never found in plasma. Erythrocytes may not have mitochondria, but they have a robust plasma redox system that effectively and continuously recycle ascorbate and its one-electron oxidation free radical semidehydroascorbate, using NADH as the electron donor. Thioredoxin reductase are redox enzymes in the PMRS that rely on ascorbate and NAD(P)H to neutralize ROS. It is no wonder that when the body increases melanin production as a defense against oxidative stress, concomitant increase in thioredoxin activity was found to be accompanied by a decrease in activity of other endogenous antioxidant enzymes like superoxide dismutase, catalase, and glutathione reductase [35]. Why is ascorbate preferred over other electron donors and acceptors?

Ascorbate: the Universal Proton-Electron Currency Supplier

What makes an ideal free radical scavenger? With what we have learned so far about oxygen, an ideal free radical scavenger would be able to react rapidly with free radicals but poorly with molecular oxygen. There are many endogenous and exogenous antioxidants that are one-electron donors. However, these donors may also reduce molecular oxygen to superoxide. In fact, at physiological pH, a lot of the free radicals found in biological systems are uncharged. Strictly speaking, the reduction of these free radicals is a hydrogen atom transfer process. As a general rule, hydrogen atom transfer is the energetically favored mechanism in free radical reduction. In addition to being an electron donor, ascorbate has been found to act as a hydrogen atom donor in

enzyme mediated reactions [57]. Most biological reactions occur at neutral or slightly acidic pH, rendering outer-sphere electron transfers rather inefficient. The unique attributes of ascorbate where it can combine fast proton-electron transfers with high reactivity in enzymes that are designed to use it, yet remain relatively stable and unreactive until activated by those enzymes renders ascorbate to be the most efficient and effective reductant found in living systems [58]. How the various plasma membrane redox enzymes make use of ascorbate and its free radical semidehydroascorbate can easily demonstrate why electromagnetic radiation can exert such damaging effects over living organisms.

Many of the plasma membrane redox enzymes were previously known as AFR (Ascorbyl Free Radical) reductases or the NADH:AFR reductases. Recent discoveries of their important biological functions led to the identification of the genes that code these important enzymes such as cytochrome b561 (cyt b561), cytochrome b5 reductase (CYB5R or b5R), duodenal cytochrome b (DCYTB), thioredoxin reductase (TR), and the voltage-dependent anion channel (VDAC). Let us take a look at some of the major, critical functions assumed by these PMRS enzymes, and why ascorbic acid is indispensable as their proton-electron currency supplier.

Even though the first Cytochrome b561 (Cyt-b561) was discovered in 1971, it was only recognized as a class of distinct di-heme membrane proteins involved in ascorbate regeneration within the past decade or so. Ubiquitously present in plants and animals, the Cyt-b561 gene has broad expression in 27 human tissues analysed to date, with the highest expression found in adrenal and prostate,

followed by thyroid, stomach, lung, duodenum and brain [58]. Does the two heme molecules in Cyt-b561 mean it is involved in iron metabolism involving ascorbate? Absolutely. Cyt-b561 proteins are the only membrane-associated ferrireductases that have been identified so far [60]. This discovery also resolved the long-time debate on whether ascorbate inhibits or enhances iron absorption in vivo.

Ascorbate, Metals and the Fenton Reaction

The thermodynamically low reduction potential of the ascorbate/AFR redox pair (+282 mV) places ascorbate in a most advantageous position where all oxidizing free radicals with greater reduction potentials (more positive value), such as the HO• [hydroxyl radical] , RO• [alkoxyl radical], LOO• [lipid peroxyl radical] , GS• [glutathione radical] , urate, and even the Vitamin E tocopheroxyl radical (TO•) can be regenerated (reduced) by ascorbate. Being an effective reducing agent, ascorbate is able to reduce catalytic metals such as ferric iron (Fe3+) and cupric ion (Cu2+) to ferrous iron (Fe2+) and copper I (Cu1+). However, one of the most contentious prooxidant effects of ascorbic acid is probably the Fenton Reaction, where ascorbate reacts with free iron to produce superoxide and hydrogen peroxide (H2O2) that leads to the formation of the reactive cytotoxic hydroxyl radical. Yet in vivo studies have never shown the prooxidant reactions of ascorbic acid with catalytic metals like iron in a conclusive manner [61]. What is the explanation for this conundrum?

The crossover effect, dictated by the amount of ascorbic acid used during in vitro experiments, is the key to this puzzle.

In the presence of oxygen and ascorbate, catalytic metals will initiate radical chain oxidations, leading to the formation of superoxide, H2O2 and hydroxyl free radicals. If the amount of ascorbate used in the experiment is not enough to terminate these chain reactions, more oxidative damage will occur as a result. That is why in experiments where a high level of ascorbate was used, the chain length of these radical generating processes were short and relatively few oxidative damage would be observed [62]. A similar crossover effect in ascorbate can also be observed inside the body, not from increased concentration, but rather from a continuous regeneration of the ascorbyl free radical back into ascorbate by the various plasma membrane redox enzymes. These enzymes mostly depend on NAD(P)H as electron donors for these regeneration processes, which may also involve other endogenous antioxidants like vitamin E and Coenzyme Q, depending on the type of reactions required for the quenching of free radicals. In order for ascorbate to effectively stop oxidative chain reactions, it must be a powerful free radical quencher.

Ascorbate: the Powerful Free Radical Scavenger

It is believed that during the transition from aquatic to terrestrial mode of life 350 million years ago, evolution presented terrestrial organisms with ascorbic acid to counter increased oxygen toxicity in the atmosphere. As a result, the adaptive increase in the concentration of superoxide dismutase (SOD) in amphibians was only slightly higher than the levels found in fish, even though the amount of oxygen on land is 30-fold higher than in oceans. The average concentration of ascorbic acid in rat tissues however, is 1000 times that of

superoxide dismutase [63]. In addition to superoxide, singlet oxygen is probably one of the most common and powerful free radicals derived from oxygen.

Singlet oxygen is formed when the atoms in the triplet ground state are excited by photon energy from photosensitizers like porphyrin, 11-cis retinal, lipofuscin. EMR from UV-B, UV-A and blue light are known for their ability to generate singlet oxygen [19, 65]. Ascorbic acid has been demonstrated to COMPLETELY quench all singlet oxygen generated in solution at room temperature [68].

Ascorbate Quenches Singlet Oxygen/Fenton Reaction-Induced UPE in Skin

Ultraweak photon emissions (UPE) from our skin is a reliable indicator in the formation of reactive oxygen species such as singlet oxygen and/or hydroxyl radicals generated from Fenton reactions. When sodium ascorbate was added to skin biopsy prior to application of Fenton's reagent that induces the toxic Fenton reaction, it was discovered that ultraweak photon emission was significantly suppressed due to the effective quenching of singlet oxygen and other cytotoxic free radicals [69]

It is now very clear why an increase in melanin pigmentation in skin is accompanied by an increase in thioredoxin reductase, an NAD(P)H-dependent PMRS enzyme involved in the regeneration of ascorbate and its ascorbyl free radical. Although melanin can generate superoxide and hydrogen peroxide

which leads to the formation of singlet oxygen and/or hydroxyl radical, with adequate ascorbate regenerated by thioredoxin reductase, nature has provided the ultimate protection for our skin [36].

The Cytochrome b561 family and Your Health

The understanding of the importance of the CYB561 family of PMRS proteins began to emerge as new proteins and their functions are being identified. Cytochrome b561 (Cyt-b561) is adapted specifically to react with ascorbate and its one-electron oxidation ascorbyl free radical, semidehydroascorbate using distinct, rapid proton-electron transfers [71]. Localized in cell membranes and mitochondria inner membranes, these di-heme Cyt-b561 proteins is responsible for electron transfers involving metals, moving protons back and forth during electron transfer. This process of concerted proton-electron transfer is fundamental to movement of electrons in metal redox actions. Ascorbic acid and its free radical is the preferred redox agent because of its ability to transfer both protons and electrons. This the reason why Cyt-b561 only reacts with ascorbate and semidehydroascorbate [72].

Ascorbic Acid & Neurodegeneration

Physiological functions supported by the CYB561 family proteins include stress defense, cell wall modifications, iron metabolism, tumor suppression, and various neurological processes. The decreased expression of a CYB561 homologue has been shown to result in reduced memory retention in the Drosophila mutant [73]. Needless to say, Cyt-b561 dysfunction would be

closely related to neurodegenerative diseases such Parkinson's, Alzheimer's and Huntington's diseases, all of which display abnormal accumulations of iron as defining characteristic. Dysfunction of cytochrome b-561 could subject individuals to abnormal accumulation of Fe(III) and/or generation of cytotoxic free radicals from the rapid cycling between Fe(III) and Fe(II) [74] .

In Parkinson's Disease, the loss of dopamine is correlated to elevated ferric iron, Fe (III), and decreased neuroprotective antioxidants like glutathione. Increased ROS can lead to Fenton reactions that substantially increase Fe (III) levels in the brain. Cyt-b561 proteins are involved in ascorbate regeneration and the reduction of Fe(III) to Fe(II). This is a most important aspect because a CYB561-core domain is associated with the dopamine b-monooxygenase redox domains (DOMON), coupling Cyt-b561 activity to dopamine β-hydroxylase activity. Any decrease in the enzyme's activity leads to increased concentration of Fe(III) and decreased dopamine. An increase in Fe(III) at expense of Fe(II) inevitably result in reduced dopamine synthesis because tyrosine hydroxylase requires Fe(II) as cofactor for activity, and becomes inactive upon addition of Fe(III) [74]. Is it becoming clear now why red blood cells prefer to accumulate only ascorbate and semidehydroascorbate, but not dehydroascorbate (DHA), the two-electron oxidation free radical?

Iron, Copper Absorption: the Role of Dyctb & Ascorbate

Hemoglobin is the main component found in erythrocytes (red blood cells). Hemoglobin are the major oxygen carriers in blood, with one molecule of hemoglobin binding up to four molecules of oxygen. The active site within

hemoglobin is the heme group, which consists of a charged iron Fe(II) ion surrounded by porphyrins. Porphyrins are highly photosensitive, reacting to a wide spectrum of visible light from UV to infrared that can often result in the production of reactive singlet oxygen [64]. How does nature safeguard erythrocytes in this perfect storm for the creation of singlet oxygen?

Erythrocytes have been found to demonstrate high cytochrome b561 enzyme activity on their plasma membranes. Cyt-b561 proteins mediate intramolecular electron-transfer reactions across plasma membranes, using ascorbate exclusively as proton-electron donors, and sometimes regenerating them with NADH [66]. All Cyt-b561 proteins discovered so far are ascorbate-dependent, using ascorbate on the cytoplasmic side as an electron donor to reduce substrates on the non-cytoplasmic side. Any ROS will be quickly quenched by circulating ascorbate, and the ascorbyl free radical will be regenerated by Cyt-b561 enzymes on the plasma membranes [78].

In 2006, the duodenal cytochrome b561 (DCytb) isoform was discovered in human erythrocytes. DCytb, as a member of the cytochrome b561 family belonging to the extensive NAD(P)H-dependent plasma membrane redox system (PMRS), is actively involved in the reduction of extracellular semidehydroascorbate (ascorbyl free radical) using intracellular ascorbate as electron donor in erythrocytes [66, 67]. Like Cyt-b561, DCytb is also a di-heme transmembrane protein that relies on intracellular ascorbate as electron donor to reduce extracellular ferric iron. DCytb is currently accepted to play a critical role in the absorption of nonheme iron in the gut prior to uptake by ferrous-iron transporters. [78].

In addition to the rapid reduction of iron prior to cellular uptake, ascorbate also facilitates copper reduction by DCtyb. Thus the optimal absorption and utilization of iron and copper by DCytb is dependent on the availability of ascorbate and related proton-electron recycling processes [70]. Inadequate ascorbate in Dyctb can lead to decreased copper absorption. Excess Fe(III) has been shown to inhibit uptake of copper from ceruloplasmin due to the involvement of Dyctb in the absorption process. Excess Fe(III) overwhelms the reduction capacity of Dyctb, leading to reduced absorption of copper [75, 76, 77] .

Anemia, HFE Hereditary Hemochromatosis, and Methemoglobin

It is obvious that the Cyt-b561 family of PMRS enzymes exert great influence over an extensive area of biological functions. The real question is, since the Cytb-561 enzyme relies exclusively on ascorbate, what do you think will happen if the body is deficient in ascorbic acid? The expression and activity of Dcytb have been found to be closely correlated with chronic anemia and hypoxia [78]. Emerging evidence also indicates that genetic variants in the DCytb gene could be the cause for the iron overload disorder, HFE hereditary hemochromatosis [70].

Methemoglobin is a form of hemoglobin in which the iron of the heme group is oxidized from the ferrous (Fe2+) to the ferric (Fe3+) state. The ferric hemes of methemoglobin are unable to bind oxygen; and as a result, tissue hypoxia occurs when the concentration of this form of hemoglobin is elevated. Another member of the di-heme Cyt-b561 family, Cytochrome b5 reductase (CYB5R,

b5R, or CB5R) is intimately related with methemoglobin. The major function of the soluble form of CYB5R in erythrocytes is to reduce methemoglobin back to hemoglobin. Deficiency of the enzyme is now believed to be the cause of hereditary methemoglobinemia [78]. The interesting part about b5R is that even though this NADH-dependent enzyme uses ascorbate as electron donor, b5R also uses coenzyme Q (CoQ) for the reduction of the ascorbate free radical at the cell surface. Cytochrome b5 reductase maintains CoQ and ascorbate in their reduced state to support redox reactions. CoQ together with CYB5R, NADH and ascorbate can prevent lipid peroxidation in liposomes and plasma membranes [79]. The question to ask is, with both CoQ and NADH as reducing agents, why does CYB5R require ascorbate?

CYB5R, Cancer & Demethylation: the Ascorbate Connection

Cytochrome b5 reductases (CYB5R) are believed to have important functions in the extension of lifespan and confer protection against metabolic disorders. In addition to the regeneration of ascorbate, CYB5R regulates lipid metabolism, cholesterol synthesis, elongation and desaturation of fatty acids, and monooxygenation of cytochrome p450. Overexpression of CYB5R in neuronal cells resulted in improvement of mitochondrial function with increased ATP production without generation of additional ROS; and resistance to oxidative damage by H2O2. Whereas overexpression of CYB5R in mice showed inhibition of chronic pro-inflammatory pathways, modest lifespan extension and reduced liver carcinogenesis in addition to improved mitochondria function and decreased oxidative damage [80,81]. Why would increased expression of CYB5R reduce carcinogenesis? CYB5R may be a functional tumor suppressor

gene frequently inactivated by hypermethylation of its promoter in various types of cancers [82].

In humans, CYB5R is encoded by four genes CYB5R1, CYB5R2, CYB5R3 and CYB5R4. The isoform CYB5R3 has ubiquitous cytoplasmic expression and its membrane-bound form is present in mitochondria, nucleus, endoplasmic reticulum and plasma membrane [83]. Since the CYB5R3 gene is a tumor suppressor gene, it is not surprising that CYB5R3 is expressed in ALL cancer cell types [84]. Yet hypermethylation of its promoter will inactivate this protein.

Aberrant DNA methylation is a hallmark of cancer. Hypermethylation of tumour suppressor genes is one of the common aberrations in DNA methylation in cancer cells [85]. However, DNA methylation is reversible, and it is believed that cancer growth can be blocked when tumor-suppressor genes are activated by demethylation [86]. Ascorbic acid has been shown to promote DNA demethylation through enhanced expression of 5-hmC. DNA demethylation depends on the proper functioning of the Ascorbate/Fe (II)/alpha-ketoglutarate-dependent TET (ten-eleven translocation) enzymes. TET is responsible for the conversion of 5-methylcytosine (5-mC) into 5-hydroxymethylcytosine (5-hmC). Reduced ascorbate levels in human cancers such as leukemia, melanoma, colorectal adenoma, and gastric cancers, all exhibited reduced levels of 5-hmC; whereas the restoration of 5-hmC levels was able to decrease malignancies [87].

This is probably one of the major reasons why CYB5R regenerates ascorbate by using CoQ. Another reason, and probably an even more important reason, is the relationship between Vitamin E and ascorbate that is underappreciated by most.

Vitamin E, CoQ & Ascorbate: The Redox Dream Team

Humans and animals do not produce Vitamin E; therefore it is an essential vitamin synthesized by photosynthetic plants, algae, and cyanobacteria. Vitamin E (tocopherol) is considered to be a most powerful antioxidant because unlike ascorbic acid which is lipophobic, vitamin E is able to interact readily with polyunsaturated acyl groups and quickly quench lipid peroxyl radicals and other cytotoxic reactive oxygen species (ROS). Its role in the protection of fatty acids from lipid peroxidation is uncontested [88]. One of the reasons why Vitamin E is such a powerful antioxidant against lipid peroxidation is its ability to tunnel hydrogen with ubiquinol, the reduced form of CoQ. Together with ubiquinol, Vitamin E is able to break radical chain reactions in lipid radicals generated by heat, light, metals, or other radicals. Unless the chain reaction is stopped, these lipid radicals will continue to react with oxygen to form peroxyl, hydroxyl, and even lipid peroxide radicals. However, the quenching of lipid radicals by vitamin E turns it into the dangerous tocopherolxyl radical which must be reduced because the tocopheroxyl radical will react with lipid molecules and enhance the free radical chain reactions [89]. Even though ubiquinol can effectively reduce the vitamin E radical, once oxidized, ubiquinone must be regenerated by other redox mechanisms. What happens if there isn't enough reduced ubiquinone to regenerate the vitamin E radical?

Ascorbate, Vitamin E & CYB5R: The Melanopsin-Retinal Connection

CYB5R is not only a tumor suppressor, it has been shown to COMPLETELY suppress both blue light-induced peroxidation and retinal degeneration in

mature Drosophila melanogaster with overexpressed CYB5R. CYB5R activities can quench lipid peroxidation, protecting cells from oxidative damage. Photoreceptors like melanopsin are especially at risk from lipid peroxidation because they have photosensory membranes that are rich in polyunsaturated fatty acids. Any ROS-induced free radical chain reaction that is allowed to propagate across cell membranes will compromise membrane organization and cellular integrity [90]. There is a deep reason why ascorbic acid concentration is higher by 3-fold in the retina than in the retinal pigment epithelial cytosol [91]. Melanopsin is found in intrinsically photosensitive retinal ganglion cells (ipRGCs), these are neurons that are located in the retina. When melanopsin is unable to regenerate all-trans-retinal back into 11-cis-retinal due to excessive blue light exposure without the requisite orange spectrum, all-trans-retinal may react with surrounding proteins and lipids to generate singlet oxygen and other cytotoxic reactive oxygen species. The presence of functional CYB5R may be able to break the toxic chain reactions. As a result of quenching free radicals, the oxidation of vitamin E must also be reduced. Why is ascorbic acid preferable over other reductants in reducing the vitamin E free radical?

Ascorbate has been found to reduce the tocopheroxyl radical at extremely efficient rates without engaging molecular oxygen, thus bypassing the generation of oxygen free radicals like superoxide. Similar to vitamin E, ascorbate is also capable of hydrogen tunneling [92] and will readily reduce the tocopheroxyl radical by single hydrogen atom transfer [57]. Muscular dystrophy is a result of failure to repair damaged myocytes. In animal models severe vitamin E deficiency has been seen to result in lethal myopathy due to the failure to respond to plasma membrane disruption injuries. The addition of

ascorbate to vitamin E has been found to promote plasma membrane repair activities by vitamin E. By regenerating vitamin E, ascorbate enhanced vitamin E-dependent cell repair in myocytes [93].

The ability of ascorbate to translocate protons also has a deep impact in the protection of mitochondrial bioenergetics in the context of oxidative stress induced by electromagnetic radiation. Part 2 of this article will explain in detail how EMR creates oxidative stress that ultimately leads to cancer and diseases including but not limited to coronary heart disease, hypertension, metabolic syndrome, diabetes, kidney dysfunction, pulmonary insufficiency, atherosclerosis, rheumatoid arthritis, inflammatory autoimmune diseases, neurodegenerative diseases such as Alzheimer's and Parkinson's and age-related macular degeneration.

Ascorbate truly is nature's best gift to living organisms to counter oxidative stress as a result of just being alive. What has been presented to you today is but a mere token of its inestimable capacity. Before I leave you to ponder over how much science has YET to discover about all the important functions of ascorbate in our bodies, it is important to understand how dietary choices can affect ascorbate utilization.

Diet, Redox & Ascorbate

Even though photon exposure from natural and artificial sources can regulate and modify our biological functions, lifespan extension is really about the balance between environmental photon input and redox bioenergetics. Redox

bioenergetics absolutely depend on substrate availability. The foods you eat will determine the type of substrates available to sustain redox balance, ultimately affecting all metabolic pathways.

In addition to G6PD deficiency, iron and copper absorption, many are concerned with the increase of oxalates as a result of ascorbic acid intake. Oxalates are formed as metabolites in the degradation of ascorbate, when the two-electron oxidation ascorbate free radical, dehydroascorbate (DHA) undergoes irreversible ring opening to form 2,3-L-diketogulonate [44].

Oxalate, Ascorbate & the GRHPR Gene: the NAD(P)H connection

The GRHPR gene is widely expressed in human tissues and codes for an enzyme that converts glyoxylate into glycolate. Mutations in the GRHPR gene has been found to be the cause for primary hyperoxaluria type 2, where the body overproduces oxalate. Excess oxalate can lead to kidney and/or bladder stones. Absent or impaired enzyme activity by GRHPR leading to the buildup of glyoxylate is the main reason for increased oxalates [94]. It is most interesting that the GRHPR gene in human liver has been found to be co-expressed with the sodium-dependent Vitamin C transporter 1 (SVCT1). This co-expression increases uptake of ascorbate together with the GRHPR enzyme. Why would our body want to increase ascorbate if it results in oxalates? The key is actually not oxalate, but its precursor, glyoxylate.

Peroxisomes, which are responsible for the catabolism of very long chain fatty acids, branched chain fatty acids, D-amino acids, and polyamines, and the

reduction of hydrogen peroxide, depend on glyoxylate for optimal functioning. Dysfunction in peroxisomal alanine:glyoxylate aminotransferase is known to cause primary hyperoxaluria type 1. The presence of ascorbate is critical because peroxisomes depend on ascorbate to scavenge excess radicals in their matrix. In addition, ascorbate also acts as a cofactor in αlpha-oxidation reactions in peroxisomes [95]. So, the oxalate issue is now not as obvious as one would want to believe. However, the real issue that determines the proper functioning of GRHPR is actually the NADH/NADPH ratio.

The GRHPR reductase that is responsible for the conversion of glyoxylate into glycolate is NADPH/NADH dependent. GRHPR can use either NADH or NADPH as electron donors but it prefers to use NADPH. Needless to say, without adequate NADPH or NADH, GRHPR will not function properly [96]. If your body is low on NADPH due to diet choices or high oxidative stress, then GRHPR will have to resort to NADH. NADH can also be limited by a low carbohydrate diet. Under this scenario, increased ascorbate intake would most probably result in high oxalate formation, as there will not be enough NADH to regenerate oxidized ascorbate, and the two-electron oxidation DHA free radical will further degrade into oxalate because GRHPR enzymes as well as peroxisomes are unable to function optimally due to limited substrate availability. It is no accident that nature coupled ascorbic acid with high sugar containing fruits!

Fatty Acid Oxidation & Cold Thermogenesis: The Ascorbate Connection

When selecting a diet that will complement ascorbic acid, it is important to remember that Niacin is a component of two coenzymes: Nicotinamide adenine dinucleotide (NAD) where NAD+ is the oxidized form, and NADH is the reduced form; and nicotinamide adenine dinucleotide phosphate (NADP) where NADP+ is the oxidized form, and NADPH is the reduced form. In general, a diet low in carbohydrates will yield more NAD+ than NADH. Low NADH will also lead to low NADPH as the Nicotinamide nucleotide transhydrogenase (NNT) will operate in reverse to generate NADH from NADPH.

When one is on a diet or lifestyle that involves a high degree of fatty acid metabolism, the presence of adequate ascorbate is important. In fact, excess fat accumulation could be due to ascorbate deficiency. Supplementation of ascorbic acid has been found to enhance ketogenesis and decreases in cholesterol concentration as well as triglycerides accumulation in guinea pigs. L-carnitine plays an important function in the transport of long-chain fatty acids into mitochondria where beta-oxidation will take place. Ascorbate is a requisite co-factor in the synthesis of L-carnitine [97]. A treadmill experiment conducted on 78 sedentary non-smoking individuals showed that individuals with marginal ascorbate levels burned 25% less fat per kg body weight than those replete with ascorbate. When those ascorbate depleted individuals were replete with ascorbate, their fat energy expenditure during exercise increased by 4-fold. Interestingly, fatty acid oxidation during exercise was inversely correlated to fatigue [98].

It is believed that cold stress can activate brown adipose tissue (BAT), transforming energy from food into heat, improving health and lipid profiles.

However, the heat generation in BAT is often accompanied with high rate of oxygen consumption [99]. Brown adipose tissues of animals placed under cold stress have been shown to double the accumulation of ascorbate [100]. Increased ascorbate concentration in BAT was found to offer significant protection against oxidative stress and lipid peroxidation induced by increased oxygen utilization [101].

Cold exposure may confer healthful benefits in some, but incur increased stress in others with deficient thyroid functions. During cold exposure, the body responds by increasing heat production and heat conservation. Effective thermogenesis is achieved by thyroid hormones and BAT activity. However, cold exposure increases the production of reactive oxygen species due to the increased oxidative metabolism induced by increased thyroid hormone activity. Thyroid activity in rats after four weeks of cold exposure was found to be significantly increased as compared to control group. However, the supplementation with ascorbic acid normalized thyroid hormone activity. The rats supplemented with ascorbate showed reduction in serum T3, T4 and TSH levels. Even though these thyroid hormone levels were lower than the group without ascorbate supplementation they were still slightly higher than the control group not exposed to cold stress [102].

Diet, lifestyle and electromagnetic radiation exposure are all important factors affecting our redox balance. Although the threat of electromagnetic radiation is very real, nature has provided us with more than adequate resources to successfully challenge the dominance of EMR. With a better understanding of how ascorbate functions, and the judicious incorporation of ascorbate into our

lives, the future of the our species cannot be brighter. I sincerely hope you have enjoyed this article. Do let me know if you have comments or questions. Part 2 will be released in the near future. Stay tuned and thank you for reading.

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David Alan Tyner 2y

Thank you Doris, for an excellent article.

I now better understand your response to my comments on fb, regarding inherent damages of multiply polarized and arrayed (MIMO) beams of mmwave energy, as well as similar for 4G LTE and minitowers.

We agree ascorbate is a fabulously effective solution and the answer why folks aren't even sicker from rapidly accelerating 5G deployments. We need more medical support to disseminate this crucial and critical information. As a prescription to mitigate and ameliorate nnEMF (non-ionizing non-native) harms.

What I don't understand is your dismissal of actual harms, to those humans already too low in ascorbate availability, from decades of poor diet and/or various types of inflammatory diseases (or other epigenetic issues). They're the canaries in the coal mine getting EHS, and suffering egregiously as even worse tech explosions propagate from insidious, ubiquitous, and unrelenting militarization of 5G tech.

I'm sure they'll benefit from higher Vitamin C supplementing — yet it's not really officially a supplement, when our bodies cannot produce it? Correct ?

Like Reply | 1 Like

Doris Loh 1y

David Alan Tyner No apologies required. Together we learn, together we grow, and together we triumph. Blessings.

Like Reply | 1 Like

David Alan Tyner 1y

Doris Loh
My apologies, my lack of understanding — was my lack of understanding

Like Reply

Chris van Offeren 2y

Where is part 2?

Like Reply | 1 Like

Karin Burke Dip. Couns. B. Psy. Sc. MACA. 2y

https://watermark.silverchair.com/2611.pdf?token=AQEC-AHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAApEwgg-KNBgkqhkiG9w0BBwagggJ-MIICegIBADCCAnMGCSqGSIb3DQEHATAe-BglghkgBZQMEAS4wEQQMvjD7tZRphrHu9pyNAgEQgIICRAczphuflL-CF_Z_Uij53rKouDxRwaoCZFk20AaOV2bc909HS0YvYEYlHRGMGtwxJt-tY3Y-Thcrq6CXV4DC3f_wJUmojMO2e-U1iQZblNUiB9RCndWFbXM1qo-raI88oaAiGus8fUYNAZsvE2PbuIjqb6eH3PRCaqGTGSAvrY2lYLXcnm-RyNMRRv2sMAnKwbCO_EaEh4mGSPqOWasjqHitusNXcdxfR8eobJBbm-Fg7cCPEhgidEdqikxIZilJOK0_MjZ-rCCH0a241JQuqGobKTOlDtOqEN-ZJ_PvAwJjSU7SfbhvEtvTK3j8NIKCvMy9UNe7sMYbVY-Za9lq0-5Q-Tza-8pkrk0WDAF_nh6exTiNyirWKOx2MHsvWisXLZjpxeuJDeSz95OVmLR-Lo1l_gXoyEh7uF1CNHG0HL2vdxgm0JoqzrOU6C1E6cdeTK-Le_CQMw-FUI9xBc9mgHK6UgrGUh2crCniodD9L_GSHTj-4VKGXeNiFeKmAT-p4s524CBAxD-rGMFk4ASphEwiSupXANucWZkf-pKbhhquFx-qcaTLcXN-GrST1Xg3rjlNW5ilEQTJf6z_M_WGSh3eY7MpbynDv2JhRLGmVaJiD-itjzp8hZ2eU14ntLmvOtyPAR-xVrR1BauXwFp-Fn3vdzmJlmPBJfnhiRe-YN1XM7D41XSz9gedgjpTECKhDaegaS7Td6W-IwyxqqiLdFYWyqfPA-p48sl_XaVxj5E3CE25rkayMymiMvPdjLJ9KR0_evgglXMnxu_-FmMV4

Like Reply

Karin Burke Dip. Couns. B. Psy. Sc. MACA. 2y

There is also an amazing connection between vitamin C and Selenium https://www.sciencedirect.com/science/article/abs/pii/S0753332218311636 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3723386/ https://akjournals.com/view/journals/1886/9/3/article-p73.xml

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Like Reply

LinkedIn User 3y

In my practice, I see a lot of patients with severe vitamin C deficiency. This makes perfect sense.

Like Reply

Doris Loh 3y

Alexander Zubkov, that is also why many readers report a truly diverse range of health improvements upon supplementing with Vitamin C. It is such a simple and natural solution for most people. Our high technology environment actually depletes vitamin C at an incredibly fast pace, and supplementation becomes a necessity in modern life. Please read the prequel to this article to understand how Vitamin C can counter the effects of electromagnetic radiation. Thank you for reading!
https://www.linkedin.com/pulse/electromagnetic-radiation-quantum-decoherence-vitamin-doris-loh/

Like Reply | 1 Like

Giovanni d'Errico ⁜ 3y

Thanks for sharing this majestic work.

The subject of your research has been treated in a formal way (before being carefully erased from the pages of history of medicine) by prof. George Lakhovsky in the books "la matière", and "le secret de la vie" (available in English with title "the secret of life"). His comprehensive theory about cellular oscillation (la théorie de l'oscillation cellulaire) includes many of the findings you reported, and grounds everything in physics.

Like Reply | 5 Likes

> **Giovanni d'Errico** ⁜ 3y
>
> Doris Loh Prokaryotes & light. Tooth cavities come to mind: sooner or later doctors will realize that they're result of bacterial emissions of micro-radiation that causes the decay of the hard tissue. Also "Healing is voltage" (old lecture) by prof. Jerry Tennant comes to mind. Anyways, I'll continue reading.
> At least 200 ;) Cheers!
>
> Like Reply | 2 Likes
>
> > **Doris Loh** 3y
> >
> > Giovanni d"Errico, I read your LinkedIn profile and I am very impressed by the depth and expanse of your skills and knowledge. The reason why I said we are interconnected is I am about to work on a book on longevity. The work of Lakhovsky cannot come at a more synchronistic manner. Have you read the prequel to the REDOX paper? I think you will enjoy it just as much. https://www.linkedin.com/pulse/electromagnetic-radiation-quantum-decoherence-vitamin-doris-loh/
> > Salute to living beyond 120!
> >
> > Like Reply

Karin Burke Dip. Couns. B. Psy. Sc. MACA. 4y

Brilliant Article.. I have long been a fan of Vitamin C.. like the recent research on how Vitamin C: a new auxiliary treatment of epilepsy?. https://www.ncbi.nlm.nih.gov/pubmed/24948051

Like Reply | 1 Like

Doris Loh 3y

Karin Burke, you will find that Vitamin C, because it is a redox balancer, is involved in almost every biological process imaginable. That is why it is able to affect conditions like epilepsy. I will be writing a post soon on epilepsy and vitamin C on my facebook homepage where you can find more research on Vitamin C. https://www.facebook.com/doris.loh.23 Thank you for reading!

Like Reply | 1 Like

Thierry Sanchez 4y

newbie here, but what about ascorbic acid downsides? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6097542/
What type do you people use? would Liposomal C be a better way to take it? lots of tutorials on how to make at home, but haven't tried...

Like Reply | 2 Likes

Doris Loh 4y

You are most welcome. Feel free to ask more questions. Together we learn, together we grow, and together we shall triumph!

Like Reply | 1 Like

Thierry Sanchez 4y

Thanks for your time!

Like Reply | 1 Like

Jette Bilberg Lauritsen 4y

Grateful for being able to replenish my body with redox molecules every day.

Like Reply | 1 Like

Doris Loh 4y

Colleen Hartford, I believe Jette Bilberg Lauritsen was referring to ascorbic acid when she used the term 'redox molecules', as I described ascorbic acid as an important redox balancing element in this article.

Like Reply

LinkedIn User 4y

What redox molecules?

Like Reply

David Alan Tyner 4y

People ought to be informed that there is a solution to this quandary: "Oxidative stress generated by pervasive artificial and natural EMR, unhealthy lifestyles can result in the depletion of ascorbate. Inadequate substrates from dietary deficiencies may also inhibit the necessary regeneration of ascorbate. Absent ascorbate, our highly developed redox systems comes to a halt, taking with it as collateral damage the life-sustaining bioenergetic balance in mitochondria, ultimately resulting in disease in every form imaginable."

Accidentally, Intercal discovered a side effect of a unique drying process making pH neutral ascorbate, now sold as Ester-C, which created a fat soluble form of Vitamin C. The key ingredient was threonate a metabolite that solves the age old problem of pissing away any reserves (being innately water soluble), because Vit-C cannot be stored.

I have no stake in the businesses involved, and know of this because my colleague's dad worked there.

There's plenty of evidence to back up only using this double metabolic pipeline of crucial nutrients into every cell, particularly those who lose fingers and toes from diabetes (lack of circulation and lack of Vit C where needed most).

https://www.esterc.com/

Like Reply | 1 Like

Ulrich GENISSON 4y

Magnificent ! an article incredibly rich!

Like Reply | 1 Like

Doris Loh 4y

Ulrich Genisson, thank you for that! The more I learn about ascorbic acid, the more I realize we don't know as much as we think we do. This piece really starts to highlight how much we can achieve by incorporating ascorbic acid into our diet. I look forward to your thoughts and comments. Blessings.

Like Reply | 2 Likes

NANCY Peden D.D. 4y

Doris, on my phone and doing first scan. This reads very well. For this moment I was especially caught by the issue of hypermethylation as I am COMT++ and my methylation can swing radically if I eat too many Methyls and easily hypermethylate. It is one reason we MTHFR must watch our homocysteine. Too low=hypermethylation.
I will just leave that as what I have learned dealing COMT++. Interestingly I recently heard of psychiatrist who tests .homocysteine as these swimgs in methylation can cause panic attacks. Interesting as we an anxiety ridden society.
From the folks I work I suspect COMT++ is more common than I was taught.
I want to get where I can read better soon and I suspect this all will challenge many. Aside from EMR I am concerned bioengineering proposed by Harvard and billgates to block the sun intending to deal not climate change but global warming. That this is even being taken seriously concerns me deeply and certainly impacts all you are saying here.
I love your dream team as guidance and now am very curious as to dietary guidance as high meat is recommended by some and high fruit by others.
 Very lucid paper. Much to consider and intuitively it feels very useful. Oh you did sneak in that darn bifringement that I still do not understand. Confused about quantum biochem and the observer effect. will get there eventually.
I hope this raises the interest it deserves.

Like Reply | 2 Likes

Doris Loh 4y

Nancy, thank you so much for taking the time to share your thoughts. Methylation can have huge impact, even for those without severe MTHFR variants. Science is just beginning to understand Vitamin C's role in epigenetics. The recent discovery that it can influence demethylation will have long-lasting impact on our understanding as to why vitamin C keeps cancer under control. To be honest, I hardly covered half of what should be included in Part 1. I think vitamin C will be my lifelong project. The Birefringence concept has been difficult for many, not just you. So I decided I'll approach vitamin C from a different angle. And look where it landed me. Blessings.

Like Reply | 2 Likes

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