



Review

Vitamin-induced intracellular electrons are the mechanism for their well-known beneficial effects: A review

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ABSTRACT

A new conception of the action mechanisms of vitamins and some other compounds without a vitamin status is briefly presented. It is based on results obtained through pulse radiolysis, molecular radiation biological investigations, and in vitro studies. The data clearly show that antioxidant vitamins (C, E, β -carotene) and B vitamins and related compounds possess the capability to emit “solvated electrons” in aqueous solutions or polar media. In consequence, the well-known vitamin effects are attributed to the action of the emitted solvated electrons and the resulting vitamin free radicals rather than the vitamin molecules per se, as generally accepted.

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Introduction

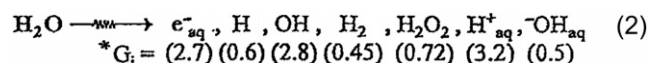
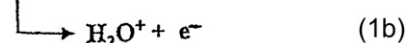
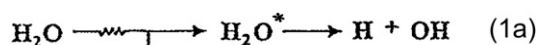
Vitamins are closely related to coenzymes under physiologic conditions and act primarily as biological catalysts in the organism. In contrast to plants and primitive organisms, which at least partly can synthesize essential compounds, including vitamins, the human physiology depends on a sufficient supply through nutrients. Any deficiency in vitamin levels can lead to characteristic health disorders [1–4].

The human metabolism permanently produces reducing (“solvated electrons” [e_{aq}^-], H, R^\bullet , etc.) and oxidizing (OH, $O_2^{\bullet-}$, ROO^\bullet , etc.) free radicals through certain enzymes, such as cytochrome P450 reductase or oxidase [5,6]. The reactions of such free radicals with biological molecules are very fast and frequently superimpose each other. However, they can be studied individually and precisely by time-resolving techniques, such as pulse radiolysis, laser flash photolysis, and others [7–10]. These free radicals are similarly produced by exposure to ionizing radiation. These processes may be exploited to simulate the physiologic processes in vitro. This allows a characterization and better understanding of the reaction mechanisms of biomolecules such as vitamins and the identification of the basic molecular processes after radiation exposure. In the present review, the latter is briefly outlined and the reaction mechanisms of vitamins are discussed in detail.

Water radiolysis

Biological tissues on average contain 50% to 70% water, depending on age. The absorption of ionizing radiation (γ -ray, electrons, etc.) in water or diluted aqueous solutions results in the formation of reducing and oxidizing free radicals, which are similar to those physiologically generated within the mammalian metabolism. Therefore, the mechanisms of the interaction of specific free radicals with individual biomolecules, such as vitamins, can be simulated and studied in vitro under precisely defined conditions by exposure to γ -rays or in some instances to ultraviolet (UV) radiation.

By the exposure of diluted aqueous vitamin solutions to ionizing radiation, the water molecules undergo radiolysis (equations 1a and 1b). The resulting primary radiolytic products and their yields (G value = number of molecules per 100 eV of absorbed energy = 1.6×10^{-17} J) are shown in equation 2.



* G_i = (2.7) (0.6) (2.8) (0.45) (0.72) (3.2) (0.5)

* G_i = Initial G-value

The excited water molecule (H_2O^*) dissociates into H and OH radicals (equation 1a). However, H_2O^* can also transfer energy to

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adjacent organic molecules. Alternatively, water molecules can be ionized, resulting in a water cation (H_2O^+) and an electron (e^-). By mutual effect with solvent molecules, the electron becomes thermalized (e_{th}^- ; $E < 10$ eV) and subsequently e_{aq}^- within about 0.3×10^{-12} s at room temperature. The e_{aq}^- represents the basic form of an H atom, which is the acid form of the primary reducing species [9–12].

The G values of acting free radicals essentially depend on the competing reactions with the dissolved compounds, e.g., gas molecules in the aqueous solution. The e_{aq}^- scavenged by one molecule can be transferred to another molecule having a higher electron affinity.

The energy and electron transfer processes are very fast reactions and play an essential role in initial molecular processes in radiation biology [12].

Photophysical processes

By monochromatic UV light ($\lambda = 254$ nm, $E = 4.85$ eV/hv), the vitamin molecules in solution are excited into the singlet state and can undergo various photophysical processes. These include, among others, the emission of e_{aq}^- and fluorescence. Figure 1 presents a modified Jablonski diagram of the possible photophysical processes initiated by electronically excited molecules [11,12].

The emission of e_{aq}^- and fluorescence originate from the lowest vibration level of the first singlet state. Therefore, their quantum yields, $Q(e_{\text{aq}}^-)$ and $Q(F)$, are in strong relation. The individual quantum yields of these processes depend on the molecular structure of the specific compound, the kind of substituent (e.g., $-\text{OH}$, $-\text{O}_2^{\bullet-}$, $-\text{PO}_3\text{H}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, etc.), the excitation energy, the pH of the aqueous solution, and temperature. By increasing the energy input (excitation to S_2 state), the $Q(e_{\text{aq}}^-)$ is increased as a consequence of the e_{aq}^- emission from each vibration level of the S_2 state [11,12].

Mechanism of e_{aq}^- generation by UV excitation

The generation of e_{aq}^- from a biological molecule can occur as a consequence of energy input originating from various reactions. These reactions are rather complex and frequently involve interactions with parallel, superimposed reactions or energy-transfer processes [12]. A simplified example of such a process, induced by UV light, is the e_{aq}^- emission from electronically excited aniline into the singlet state, where one e^- of the outer level is triggered into a higher energy level. Subsequently, the strong dipole character of the water molecules results in the reorientation of their positive poles toward the e^- . The energy

input from the UV radiation and the solvation energy of e^- and H^+ are high and may overcome the ionization potential of aniline and water in the gaseous phase. As a consequence, e_{aq}^- is emitted (Fig. 2).

Recent investigations have found that essentially all vitamins in polar media containing water can emit electrons when excited into a singlet state. Moreover, the vitamins can react with the e_{aq}^- and/or can transfer them to other biological molecules, thus acting not only as electron donors but also as “electron mediators” [12]. One example is the role of nicotinamide in redox reactions of the coenzyme couple nicotinamide adenine dinucleotide (NAD^+) \leftrightarrow reduced nicotinamide adenine dinucleotide (NADH) [12]. In conclusion, the emission of e_{aq}^- and the electron transfer processes play an important role in the organism [13,14].

This review does not discuss the various aspects and roles of vitamins in nutrition and medicine, which have been reviewed elsewhere (e.g., [1–4]). However, the isomeric nature of vitamins and its consequences, which are related to their ability to eject e_{aq}^- , need to be mentioned. The isomers of a given compound have the same molecular composition but a different chemical structure and spatial arrangement, resulting in different physical and chemical characteristics. This is well established for various organic molecules, including enzymes and vitamins [15]. The isomeric structure of vitamins also affects their ability to emit e_{aq}^- , because e_{aq}^- is dependent on the specific molecular structure, as mentioned earlier [11,12]. The knowledge of the e_{aq}^- ejection process offers a deeper insight into the reaction mechanisms of vitamins. Hence, the present review focuses on reaction mechanisms based on details of electron emission and the resulting transients and their biological consequences. The electron transfer from vitamins to other biological systems causing a synergistic effect with certain anticancer compounds used in oncologic therapies is reviewed.

Antioxidant vitamins

The vitamins C, E, and β -carotene are efficient antioxidants [1–4]. They may act as cellular radiation protectors [16], but may also enhance the cytostatic efficiency of mitomycin C (MMC) in cell cultures by electron transfer [17]. Moreover, they react with e_{aq}^- (Table 1).

Vitamin C (VitC; ascorbic acid) transients, resulting from the emission of e_{aq}^- in air-free aqueous media [12] and from an interaction with OH, H, or e_{aq}^- have been intensively studied by pulse radiolysis [12,18–24]. The ascorbate free radical (AH^\bullet), as the main intermediate, has a characteristic absorption spectrum with maxima at 300 nm ($\epsilon = 2200$ L \cdot mol $^{-1}$ \cdot cm $^{-1}$) and 360 nm (3400 L \cdot mol $^{-1}$ \cdot cm $^{-1}$). The AH^\bullet radical decays by disproportionation ($k = 1.7 \times 10^7$ L \cdot mol $^{-1}$ \cdot s $^{-1}$), resulting into dehydroascorbic acid (DHA) [17,24]. Some of its biological actions are discussed later.

Vitamin E (VitE; α -tocopherol) reactions also have been investigated by pulse radiolysis and laser flash photolysis. The obtained spectroscopic characteristics and reaction kinetics of the resulting transients strongly depend on the applied organic solvents or on the aqueous micelle media [9,25,26]. Using dimethyl sulfoxide (DMSO) as a solvent, VitE emits electrons by converting to $\text{VitE}^{\bullet+}$ (radical cation). These species have an absorption spectrum with a main maximum at 425 nm ($\epsilon = 2250$ L \cdot mol $^{-1}$ \cdot cm $^{-1}$) and disappear ($k = 4.7 \times 10^8$ L \cdot mol $^{-1}$ \cdot s $^{-1}$) [20,27]. VitE also reacts with e_{aq}^- , forming a radical anion ($\text{VitE}^{\bullet-}$), whereby the rate constant is solvent dependent (Table 1).

The β -carotene (β -car) dissolved in aqueous alcoholic solutions reacts with e_{aq}^- very fast (Table 1), resulting in

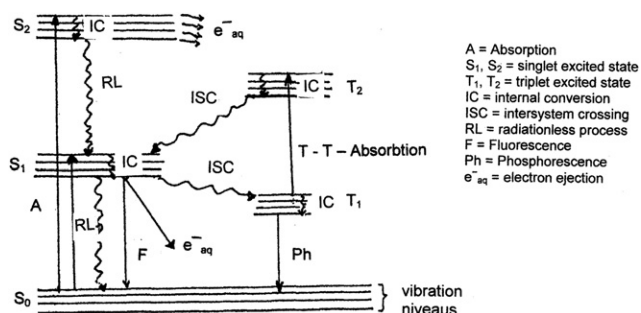


Fig. 1. Modified Jablonski diagram of the photophysical processes of excited organic molecules.

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