

Commentary on the Phototoxicity and Absorption of Vitamin B₂ and Its Degradation Product, Lumichrome

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Abstract

In this commentary, we present two views related to the study of riboflavin (vitamin B₂): (i) future research into the photo toxicity of riboflavin and its photo-degradation product, lumichrome, should consider effects under visible light and ultraviolet (UV) light in skin because the photochemistry of these reactions differ; and (ii) future research should consider the possibility that excess lumichrome, which is metabolized from riboflavin by intestinal bacteria and is much less water-soluble than riboflavin, could be more readily absorbed and lead to symptoms that resemble those of fat-soluble vitamins.

Keywords: Vitamin B₂; Riboflavin; Lumichrome

Introduction

Vitamin B₂ (riboflavin, Figure 1) is a water-soluble vitamin that has been the subject of active research. Kino et al. have studied riboflavin derivatives, the reaction of DNA oxidation by riboflavin derivatives as photosensitizers, and DNA-photo-oxidative products *in vitro* [1-19]. Here, we present two views in regards to further research related to riboflavin and its derivative, lumichrome (Figure 1).

On the Phototoxicity of Riboflavin and Lumichrome

Riboflavin has a flavin ring and functions as a photosensitizer. Specifically, the flavin ring is photo-excited by ultraviolet light A (UVA) at 365 nm or blue light at 440 nm. By the photo-excited flavin ring, 2,5-diamino-4H-imidazol-4-one (imidazolone) is generated from guanine because guanine is the nucleotide base most susceptible to oxidation in DNA (Figure 1) [1-6,20]. 2,2,4-Triamino-5(2H)-oxazolone (oxazolone) is formed via hydrolysis of imidazolone (Figure 1) [20]. Imidazolone or oxazolone may be able to cause a G→C transversion by forming a base pair with guanine [1,2,7-13,21]. It has been suggested that riboflavin can be phototoxic in skin tissue [22-27], and our studies support this suggestion. Further investigations are necessary to clarify the photo toxicity of riboflavin.

In addition, it has been shown that riboflavin is degraded by light [22,26-29], and lumichrome is formed by degradation of riboflavin by UVA at 365 nm or blue light at 440 nm under near physiologically neutral conditions [4]. This degradation has not occurred under physiological conditions in the absence of light.

Because lumichrome absorbs light only weakly at 440 nm, lumichrome is not able to act as a photosensitizer under blue light at 440 nm [4]. Therefore, photo irradiation of skin tissue at 440 nm may continue to oxidize guanine as long as riboflavin remains in skin tissue. On the other hand, photo irradiation of skin tissue at 365 nm would allow guanine oxidation to continue even after complete conversion of riboflavin to lumichrome. This difference between the effects of UVA and visible light on riboflavin photo-metabolism in skin tissue should be considered in the future.

On the Absorption of Riboflavin and Lumichrome

The symptoms of riboflavin deficiency are generally known; and excess riboflavin intake is generally considered nontoxic [29,30],

although it has been reported that excess can cause diarrhea and polyuria [31].

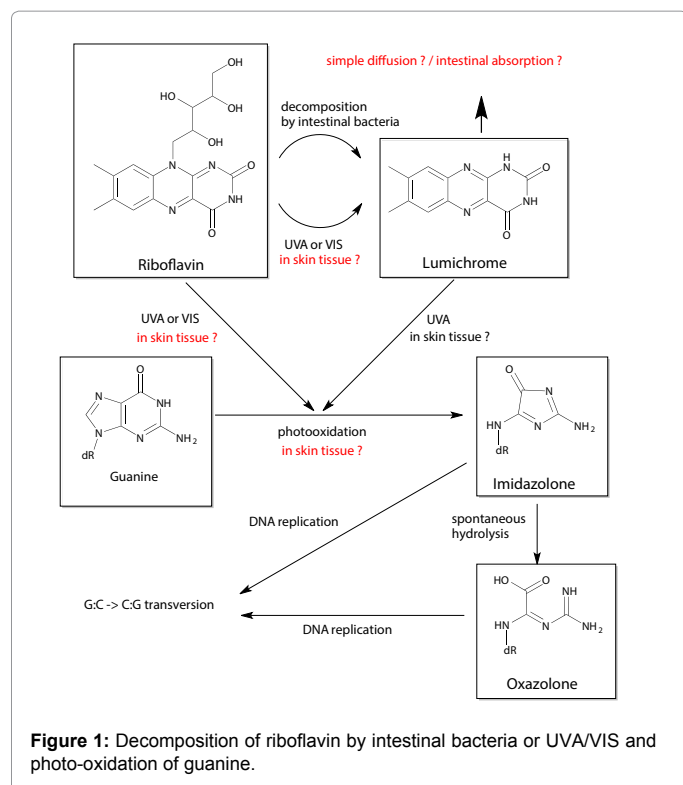
The solubility of riboflavin in water at room temperature is 180-890 μM, although it varies depending on crystalline structure [32]. In general, fat-soluble vitamins are absorbed into cells by simple diffusion across the cell membrane and water-soluble vitamins are absorbed by specific transporters. Riboflavin transporter (RFVT) 1, RFVT2, and RFVT3 were identified as Na⁺-independent transporters of riboflavin, and they participate in the absorption of riboflavin from the intestinal tract [22,33-36]. The upper limit for the intestinal absorption of riboflavin in adults is 66.4 μmol [22,23]. Therefore, riboflavin absorption cannot exceed the upper limit of intestinal absorption even when taken in excess, and then it is generally accepted that excess riboflavin intake is not toxic in human. However, it is unknown whether excess lumichrome intake is toxic. In fact, it has been reported that riboflavin is converted to lumichrome by riboflavin hydrolase in *Pseudomonas riboflavina* in soils [37-41]. A species of *Nocardia* also converts riboflavin to lumichrome [42,43]. Moreover, intestinal bacteria in human and rat convert riboflavin to lumichrome [44-50]. Hence, it is possible that intestinal bacteria generate lumichrome by metabolizing riboflavin [29]. In addition, it has been suggested that lumichrome can be formed from riboflavin in biological tissue [51]. Compared with riboflavin, lumichrome lacks four hydroxyl groups (Figure 1). Thus the water solubility of lumichrome, approximately 35 μM according to the calculation [52], is much lower than that of riboflavin. Accordingly, lumichrome is more fat-soluble than riboflavin, thus it is possible that lumichrome is absorbed by simple diffusion in a manner similar to fat-soluble vitamins. Future studies should consider whether lumichrome is able to be absorbed by simple diffusion.

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Conclusion

We have presented here two views regarding riboflavin metabolism. Firstly, the difference between visible light and UVA in skin tissue should be considered because the oxidation capacities of riboflavin and lumichrome differ under different wavelengths. Next, the effects of excess lumichrome uptake should be pursued, since it is generated from riboflavin by intestinal bacteria. In addition, since lumichrome is more fat-soluble than riboflavin, its transfer by simple diffusion needs to be considered.

Lumichrome has been detected in cow and human milk [53,54]. This fact suggests that lumichrome is derived from photo-degradation in skin tissue and/or the intestinal absorption. Biologically, lumichrome acts as a metabolic antagonist of riboflavin, and the inhibitory effect of lumichrome is greater than that of lumiflavin [55]. Therefore, these possibilities should be considered in future studies.

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