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Antibiotic-Like Actions of Vitamin D

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Abstract

Vitamin D is a secosteroid hormone that has expanding importance for a healthy lifestyle and disease prevention. A multitude of studies have highlighted that vitamin D acts not only in bone and calcium homeostasis but is critically important for human immunity. The discovery that the storage form of vitamin D (25-hydroxyvitamin D₃) can be locally converted to the active form (1,25-hydroxyvitamin D₃) in immune cells, epithelial cells and numerous other non-renal tissues highlights the importance of maintaining sufficient stores. When responding to a specific external stimulus, like bacterial invasion, intracrine synthesis of active vitamin D has the ability to regulate gene expression providing a specific response and directing cellular actions. These responses include the generation of antimicrobial peptides with production of these peptides dependent on vitamin D status. Vitamin D deficiency is associated with an increased rate of infection. This paper highlights the antibiotic like actions of vitamin D and importance of vitamin D sufficiency.

Introduction

Vitamin D can be obtained through diet in the form of D₂ (ergocalciferol, plant form) or D₃ (cholecalciferol, animal form) with D₃ more efficiently converted to the storage form 25-hydroxyvitamin D₃ or 25(OH)D. Unfortunately, diet provides very little of this necessary nutrient with approximately 80-90% of vitamin D₃ made endogenously

in the epidermis after exposure to the UVB rays in sunlight.¹ Due to West Virginia's location, from mid-October to mid-March negligible vitamin D is produced through cutaneous synthesis due to the decrease in atmosphere penetration of UVB rays. Whether cutaneously produced or injected, vitamin D₃ is bound to Vitamin D Binding Protein (VDBP) and circulated throughout the body.² Once vitamin D₃ reaches the liver, hydroxylation by CYP27A1 occurs to form 25(OH)D which is the major circulating form and best indicator of vitamin D status. Sufficiency is defined as > 30ng/ml.^{1,2,4} A second enzyme, CYP27B1, is found in over 30 cell types and acts to further metabolize 25(OH)D to form the locally produced intracrine 1,25(OH)₂D₃ which is the active form of vitamin D.^{1,3,4} Unlike the intracrine mechanism, the endocrine mechanism of vitamin D activation is in the proximal convoluted tubules of the kidneys where CYP27B1 is directly regulated by calcium and indirectly by PTH, linking vitamin D to a role in calcium homeostasis. Since its discovery, local production of active vitamin D has been shown to be important for optimal cellular functioning.

Vitamin D, Immunity and Toll-like Receptors

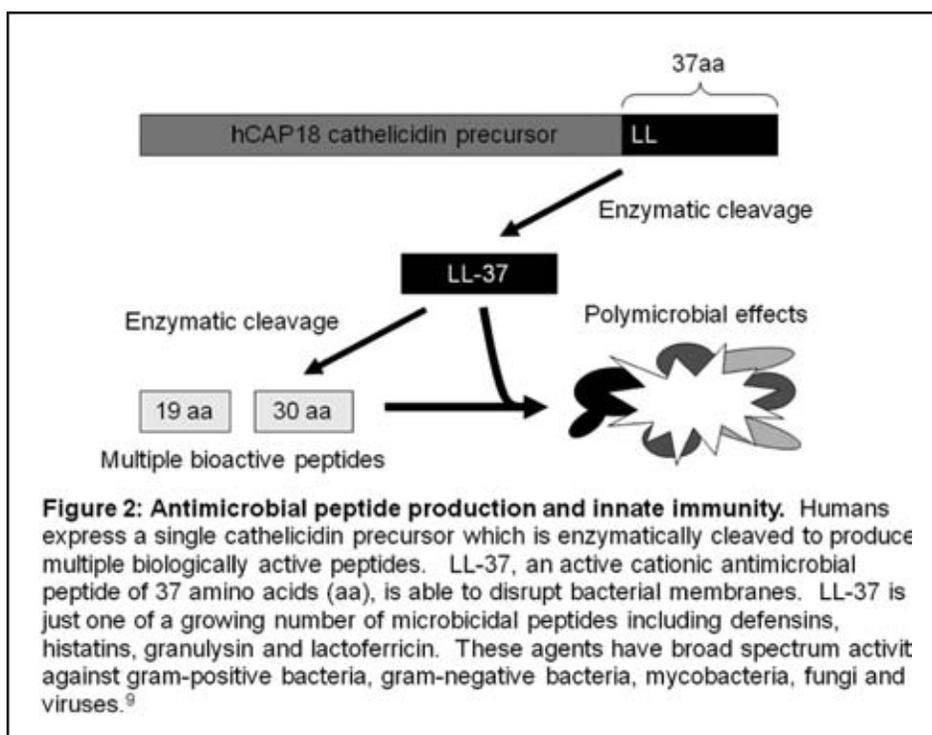
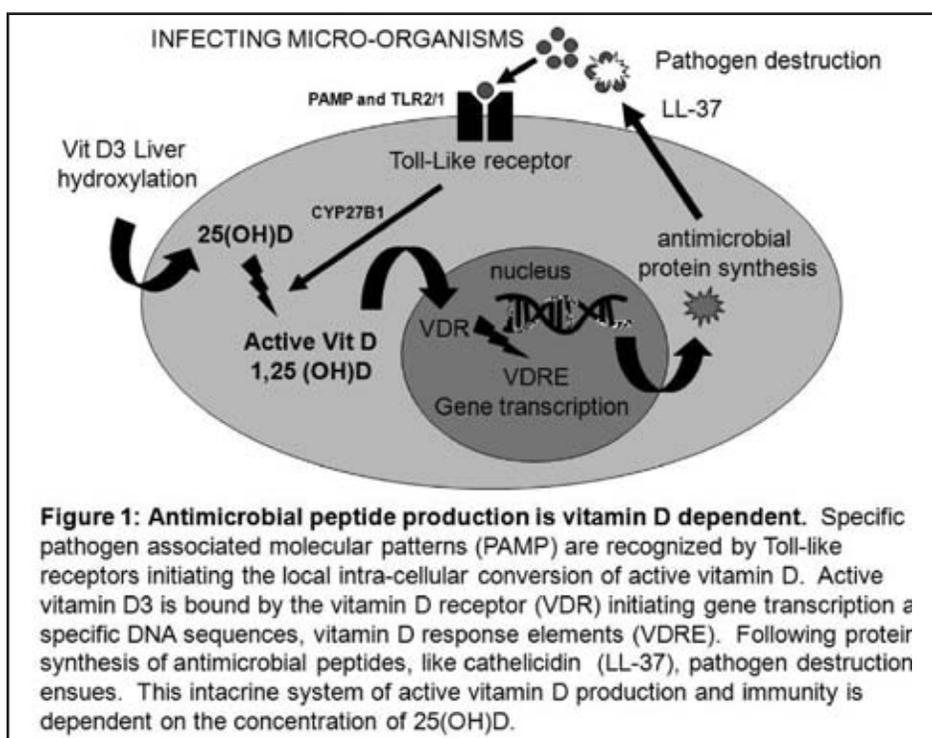
Active vitamin D has been shown to play a direct role in regulating transcription of approximately 3% of the human genome in over 30 different tissue types through vitamin D response elements (VDRE) on genes.^{2,5} Among its effects, vitamin D₃ has been found to be an immune regulator with the ability to stimulate antimicrobial defense in epithelial barriers.⁶ Of note,

antimicrobial actions of sunlight and vitamin D are not new concepts. In 1903, Dr. Niels Ryberg Finsen won the Nobel Prize for his work on the use of concentrated photo irradiation to cure lupus vulgaris, a cutaneous form of tuberculosis.⁷

Vitamin D's role in innate immunity begins with toll-like receptors (TLRs). Found on many white blood cells, the ability of these receptors to recognize certain pathogen associated molecular patterns (PAMPs) such as lipopolysaccharides and flagella allows the body to respond to pathogens regardless of prior exposure. In the case of invading organisms such as *M. tuberculosis*, the TLR1 and TLR2 receptors on macrophages and monocytes recognize the bacterium and form a heterodimer. In addition to stimulating phagocytosis, the heterodimer induces the expression of CYP27B1 and vitamin D receptor (VDR). The resulting increase in local 1,25(OH)₂D₃ and VDR expression creates an intracrine system that increases the oxidative burst potential of monocytes, recruits other immune cells to fight infection, and induces formation of natural antimicrobial peptides - most notably cathelicidins and human defensins.⁸

Vitamin D and Antimicrobial Peptide Production

Protection against assault from microbial pathogens involves a complex series of skin, mucosal surface and immune cell interactions that produce antimicrobial peptides and proteins in response to specific stimuli (see **Figure 1**, PAMP). In macrophages and monocytes, antimicrobial peptide production by the vitamin D intracrine system is best demonstrated by



the production of hCAP18, a cathelicidin antimicrobial peptide (CAMP) precursor that is cleaved to release LL37 (Figure 2).

LL37 has many protective mechanisms. A largely cationic

peptide, it can act as an antibiotic by disrupting the membranes of microbes through its interaction with their negatively charged capsular polysaccharides.¹⁰ It also protects against symptoms of infection by

neutralizing the fever-producing endotoxin of gram negative bacteria.⁸ By stimulating chemokine and cytokine production, LL37 can recruit other cells to participate in immune responses.¹⁰ Intracellularly, CAMP is able to stimulate autophagy which allows macrophages and monocytes to destroy intracellular organelles, proteins, or phagocytosed bacteria.¹¹ This is particularly important when one considers *M. tuberculosis* persists in macrophages by preventing autophagy.⁷

In addition to CAMP, 6 α -defensins and 4 β -defensins with anti-microbial properties are also induced by the 1,25(OH)D intracrine system.⁸ These peptides can act synergistically with cathelicidin to disrupt microbial membranes and stimulate autophagy.¹¹

Vitamin D, Immunity and Epithelial Barriers

Similar to macrophages and monocytes, vitamin D is closely tied to the immunological function of epithelial barriers such as the respiratory epithelium, skin, and placenta.¹⁰ In addition to strengthening the connections between the epithelial cells, vitamin D can stimulate the formation of antimicrobial peptides similar to those seen in macrophages and monocytes.⁸ In the lungs, normal human bronchial epithelial cells can be induced by 1,25(OH)D to produce CAMP. This is especially significant when considering populations who frequently experience respiratory infections. Cystic fibrosis patients, for example, may benefit from vitamin D-induced CAMP production to help combat infection by *Pseudomonas aeruginosa*.¹⁰

Epithelial keratinocytes of damaged skin are also strong producers of CAMP. Factors released from injured cells promote the formation of CYP27B1, leading to a local increase in 1,25(OH)D. This rise in active vitamin D levels

increases the keratinocyte expression of TLR2 and TLR4 which prepares the epithelium to react to potential pathogens.¹² If TLR2 is activated, CAMP is produced by a mechanism similar to that of macrophages and monocytes and, LL37 stimulates keratinocyte migration and repair of damaged epithelium.¹⁰

Decidual and trophoblastic cells of the placenta constitutively express CYP27B1 to maintain a high level of 1,25(OH)D and therefore a high level of CAMP. This antibacterial environment could enhance the placenta's function as a barrier to preempt fetal infection from microbes such as *Listeria monocytogenes* and Group B *Streptococcus*.¹²

Vitamin D Stores and Seasonal Immunity

Vitamin D may also contribute to the seasonality of infections. Influenza epidemics for example, long noted to occur during the winter months, were historically attributed to increased transference from populations collecting indoors to avoid the cold.¹³ However, this hypothesis could not explain a 1977 study in which individuals given a live attenuated influenza vaccine in the winter were 8x more likely to display signs of infection

than when given the same vaccine in the summer.¹⁴ In years since, extensive work has detailed the global absence of influenza epidemics during months with the greatest sunlight intensity.¹⁵ This has helped implicate sunlight and corresponding vitamin D levels as a contributor of influenza's seasonality. As expected, vitamin D levels have been shown to be lowest during peak times of infection, and it is hypothesized that the decreased vitamin D levels lead to lower antimicrobial peptide and protein levels reducing one's ability to combat infection.¹⁶ Similarly, lower vitamin D levels could explain why individuals are more susceptible to live attenuated virus vaccines in the winter.

Like influenza, studies have also linked septicemia with UVB activated vitamin D. William Grant of the Sunlight, Nutrition and Health Research Center found that septicemia rates were highest in the winter and in the northeastern US, and were lowest in the summer and in the southwestern US – corresponding to the areas of low and high UVB levels respectively. Further supporting his conclusions, African Americans, who have decreased ability to activate vitamin D in the presence of UVB, were more likely than white Americans

to get septicemia.¹⁷ More recent studies have elaborated on this connection by finding a high prevalence of decreased vitamin D binding protein levels in addition to vitamin D deficiency in patients with sepsis.¹⁸ Randomized controlled clinical trials are currently in progress to establish the effect of vitamin D supplementation on ICU septic patients.

Several studies have investigated vitamin D supplementation's ability to prevent infection. One double blind trial of 208 women showed that no individuals reported an upper respiratory infection (URI)/influenza infection during the winter after receiving supplementation of 2,000 IU of vitamin D daily for a year; <5% reported URI/influenza during the winter after taking 800 IU, and >20% reported URI/Influenza during the winter when given the placebo.¹⁹ In a much more extensive study, a survey of 18,883 individuals 12 years and older showed that those with serum 25(OH)D levels of ≤ 10 ng/mL had 55% increased risk of having a recent URI compared to those with a serum 25(OH)D level of ≥ 30 ng/mL.²⁰ In addition to preventing influenza, vitamin D therapy has been shown to modulate disseminated intravascular coagulation and

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inflammatory cytokines in animal models of sepsis.¹⁸

Vitamin D Sufficiency

The most plentiful and stable metabolite of vitamin D is 25-hydroxyvitamin D and it is used as the primary indicator of vitamin D sufficiency (defined as 25(OH) D > 30ng/mL).^{21,22,23} Safety research by the Mayo Clinic supports an upper limit of up to 10,000 IU of vitamin D3 daily with the National Academy of Sciences recommending an upper intake level of 4,000 IU per day.²² Supplementation protocols for insufficiency are highlighted in reference 23.

Summary

Local production of active vitamin D is critical for human immunity. The apparent link between vitamin D stores and immunity comes from the ability of active vitamin D to induce several components of the innate immune system such as cathelicidin, defensins, and other genes that control oxidative burst potency. This link has been strengthened by discovering TLRs' role in locally increasing active vitamin D levels to create an intracrine system. It is becoming apparent that vitamin D sufficiency is important in many facets of optimal human health and immunity including the impact of seasonal changes on communicable diseases.

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