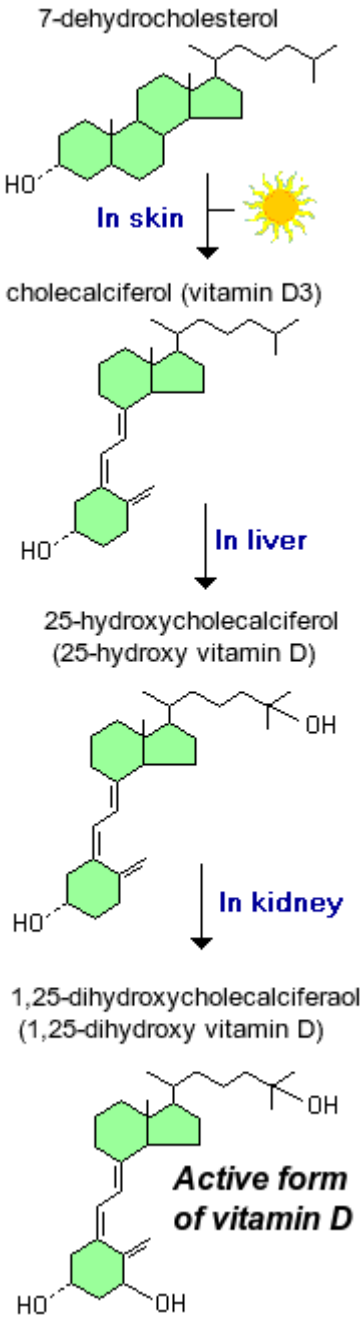
Vitamin D (Calcitriol)

Bioactive vitamin D or calcitriol is a steroid hormone that has long been known for its important role in regulating body levels of calcium and phosphorus, and in mineralization of bone. More recently, it has become clear that receptors for vitamin D are present in a wide variety of cells, and that this hormone has biologic effects which extend far beyond control of mineral metabolism.

Structure and Synthesis



The term vitamin D is, unfortunately, an imprecise term referring to one or more members of a group of steroid molecules. Vitamin D_3, also known as **cholecalciferol** is generated in the skin of animals when light energy is absorbed by a precursor molecule 7-dehydrocholesterol. Vitamin D is thus not a true vitamin, because individuals with adequate exposure to sunlight do not require dietary supplementation. There are also dietary sources of vitamin D, including egg yolk, fish oil and a number of plants. The plant form of vitamin D is called vitamin D_2 or ergosterol. However, natural diets typically do not contain adequate quantities of vitamin D, and exposure to sunlight or consumption of foodstuffs purposefully supplemented with vitamin D are necessary to prevent deficiencies.

Vitamin D, as either D_3 or D_2, does not have significant biological activity. Rather, it must be metabolized within the body to the hormonally-active form known as 1,25-dihydroxycholecalciferol. This transformation occurs in two steps, as depicted in the diagram to the right:

1. **Within the liver**, cholecalciferal is hydroxylated to *25-hydroxycholecalciferol* by the enzyme 25-hydroxylase.
2. **Within the kidney**, 25-hydroxycholecalciferol serves as a substrate for 1-alpha-hydroxylase, yielding *1,25-dihydroxycholecalciferol*, the biologically active form.

Each of the forms of vitamin D is hydrophobic, and is transported in blood bound to carrier proteins. The major carrier is called, appropriately, vitamin D-binding protein. The halflife of 25-hydroxycholecalciferol is several weeks, while that of 1,25-dihydroxycholecalciferol is only a few hours.

Control of Vitamin D Synthesis

Hepatic synthesis of 25-hydroxycholecalciferol is only loosely regulated, and blood levels of this molecule largely reflect the amount of amount of vitamin D produced in the skin or ingested. In contrast, the activity of 1-alpha-hydroxylase in the kidney is tightly regulated and serves as the major control point in production of the active hormone. The major inducer of 1-alpha-hydroxylase is parathyroid hormone; it is also induced by low blood levels of phosphate.

Interesting species differences exist in the ability to synthesize vitamin D through the sunlight-mediated pathway described above. The skin of humans, horses, pigs, rats, cattle and sheep contain adequate quantities of 7-dehydrocholesterol which can effectively be converted to cholecalciferol. In contrast, the skin of dogs and cats constains significantly lower quantities of 7-dehydrocholesterol than other species, and its photochemical conversion to cholecalciferol is quite inefficient; dogs and cats thus appear to rely on dietary intake of vitamin D more than do other animals.

The Vitamin D Receptor and Mechanism of Action

The active form of vitamin D binds to intracellular receptors that then function as transcription factors to modulate gene expression. Like the receptors for other steroid hormones and thyroid hormones, the vitamin D receptor has hormone-binding and DNA-binding domains. The vitamin D receptor forms a complex with another intracellular receptor, the retinoid-X receptor, and that heterodimer is what binds to DNA. In most cases studied, the effect is to activate transcription, but situations are also known in which vitamin D suppresses transcription.

The vitamin D receptor binds several forms of cholecalciferol. Its affinity for 1,25-dihydroxycholecalciferol is roughly 1000 times that for 25-hydroxycholecalciferol, which explains their relative biological potencies.

Physiological Effects of Vitamin D

Vitamin D is well known as a hormone involved in mineral metabolism and bone growth. Its most dramatic effect is to facilitate intestinal absorption of calcium, although it also stimulates absorption of phosphate and magnesium ions. In the absence of vitamin D, dietary calcium is not absorbed at all efficiently. Vitamin D stimulates the expression of a number of proteins involved in transporting calcium from the lumen of the intestine, across the epithelial cells and into blood. The best-studied of these calcium transporters is *calbindin*, an intracellular protein that ferries calcium across the intestinal epithelial cell.

Numerous effects of vitamin D on bone have been demonstrated. As a transcriptional regulator of bone matrix proteins, it induces the expression of osteocalcin and suppresses synthesis of type I collagen. In cell cultures, vitamin D stimulates differentiation of osteoclasts. However, studies of humans and animals with vitamin D deficiency or mutations in the vitamin D receptor suggest that these effects are perhaps not of major physiologic importance, and that the crutial effect of vitamin D on bone is to provide the proper balance of calcium and phosphorus to support mineralization.

It turns out that vitamin D receptors are present in most if not all cells in the body. Additionally, experiments using cultured cells have demonstrated that vitamin D has potent effects on the growth and differentiation of many types of cells. These findings suggest that vitamin D has physiologic effects much broader that a role in mineral homeostasis and bone function. As one example, many immune cells not only express vitamin D receptors, but are capable of synthesizing active vitamin D, and deficiency in vitamin D has been associated with increased incidence of autoimmune disease and susceptibility to disease.

Disease States

Vitamin D deficiency: The classical manifestations of vitamin D deficiency is rickets, which is seen in children and results in bony deformaties including bowed long bones. Deficiency in adults leads to the disease osteomalacia. Both rickets and osteomalacia reflect impaired mineralization of newly synthesized bone matrix, and usually result from a combination of inadequate exposure to sunlight and decreased dietary intake of vitamin D.

Vitamin D deficiency or insufficiency occurs in several other situations, which you might predict based on the synthetic pathway described above:

Genetic defects in the vitamin D receptor: a number of different mutations have been identified in humans that lead to hereditary vitamin D resistance.

Severe liver or kidney disease: this can interfere with generation of the biologically-active form of vitamin D.

Insufficient exposure to sunlight: Elderly people that stay inside and have poor diets often have at least subclinical deficiency. Ironically, it appears that hypovitaminosis D is very common in some of the most sunny countries in the world - the cause of this problem is the cultural dictate that women be heavily veiled when outside in public.

Sunscreens, especially those with SPF ratings greater than 8, effectively block synthesis of vitamin D in the skin. However, people that use such sunscreens religiously live in industrial countries where many foods are supplemented with vitamin D, and vitamin D deficiency is thereby averted by dietary intake.

Vitamin D toxicity: Excessive exposure to sunlight does not lead to overproduction of vitamin D. Vitamin D toxicity is inevitably the result of *overdosing* on vitamin D supplements. Certainly, vitamin D supplements are a valuable treatment for individuals with deficiencies. However, ingestion of excessive (milligram) quantities of vitamin D over periods of weeks of months can be severely toxic to humans and animals due primarily to hypercalcemia. In fact,

baits containing large quantities of vitamin D are used very effectively as rodenticides.

Vitamin D supplementation to prevent cancer and cardiovascular disease: There has been considerable interest in the potential for vitamin D supplements to suppress development of cancer or prevent cardiovascular disease. Most of this enthusiasm is based on studies with laboratory animals, but human trials have failed to support beneficial effects vitamin D supplementation in preventing such diseases.

References

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Advanced and Supplemental Topics

- Endocrine Control of Calcium Homeostasis

Updated January 2019. Send comments to Richard.Bowen@colostate.edu

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