Calcitriol

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Calcitriol (INN), also called **1,25-dihydroxycholecalciferol** or **1,25-dihydroxyvitamin D_3**, is the hormonally active metabolite of vitamin Dwith three hydroxyl groups (abbreviated **1,25-$(OH)_2D_3$**or simply **1,25$(OH)_2$D**).[6] It was first identified by Michael F. Holick in work published in 1971.[7] Calcitriol increases the level of calcium (Ca^{2+}) in the blood by increasing the uptake of calcium from the gut into the blood, increasing reabsorption of calcium by the kidneys, and possibly increasing the release of calcium into the blood from bone.[8]

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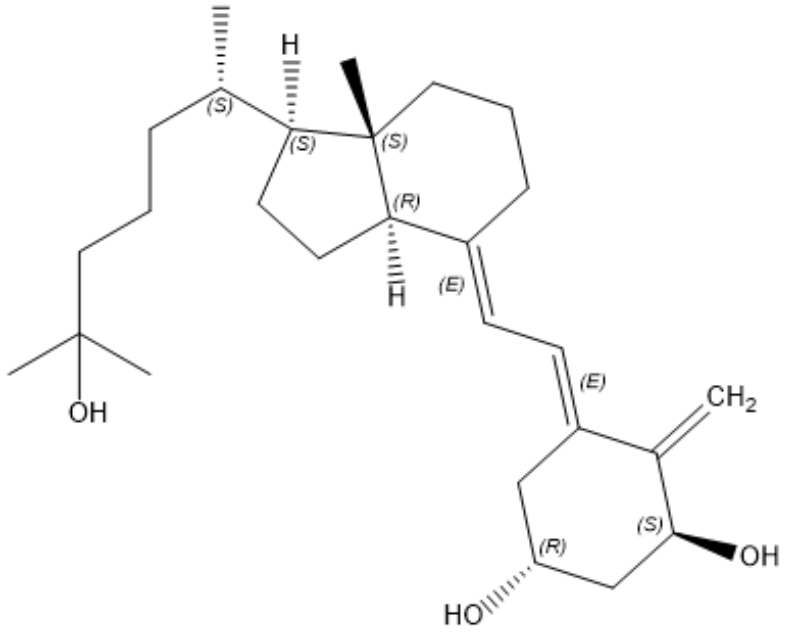
Nomenclature [edit]

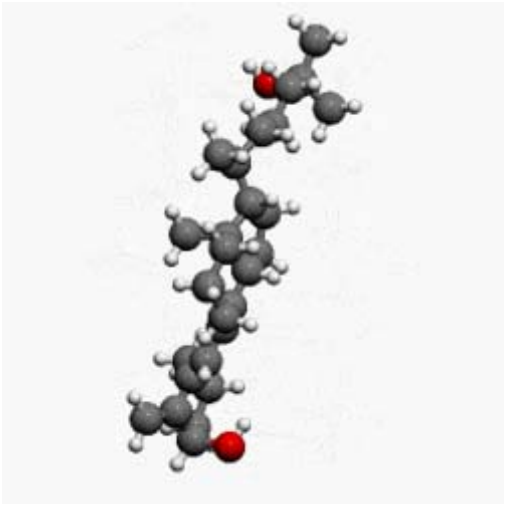
Calcitriol usually refers specifically to 1,25-dihydroxycholecalciferol.
Because cholecalciferolalready has one hydroxyl group, only two are further specified in the nomenclature.

Pharmaceutical trade names [edit]

Calcitriol is marketed under various trade names including Rocaltrol (Roche), Calcijex (Abbott), Decostriol (Mibe, Jesalis), Biowoz

Calcitriol





Clinical data

Pronunciation	US: /ˌkælsɪˈtraɪ.ɒl/;[1][2][3][4][5] UK: /kælˈsɪtri.ɒl/
Trade names	Rocaltrol, Calcijex, Decostriol
MedlinePlus	a682335
Pregnancy category	AU: B3 US: C (Risk not ruled out)
Routes of administration	Oral, IV, topical
ATC code	A11CC04 (WHO) D05AX03 (WHO)

Legal status

Legal status	AU: S4 (Prescription only) CA: ℞-only

(Solmarc) and Vectical (Galderma), Rolsical (Sun Pharma).

Function [edit]

Calcitriol increases blood calcium levels ([Ca^{2+}]) by:

- Promoting absorption of dietary calcium from the gastrointestinal tract.
- Increasing renal tubular reabsorption of calcium, thus reducing the loss of calcium in the urine.
- Stimulating release of calcium from bone. For this it acts on the specific type of bone cells referred to as osteoblasts, causing them to release RANKL, which in turn activates osteoclasts.[9]

Calcitriol acts in concert with parathyroid hormone(PTH) in all three of these roles. For instance, PTH also indirectly stimulates osteoclasts. However, the main effect of PTH is to increase the rate at which the kidneys excrete inorganic phosphate (P_i), the counterion of Ca^{2+}. The resulting decrease in serum phosphate causes hydroxyapatite ($Ca_5(PO_4)_3OH$) to dissolve out of bone thus increasing serum calcium. PTH also stimulates the production of calcitriol (see below).[8]

	UK: POM (Prescription only)
	US: ℞-only
Pharmacokinetic data	
Protein binding	99.9%
Metabolism	Renal
Biological half-life	5–8 hours (adults), 27 hours (children)
Excretion	Faeces (50%), urine (16%)
Identifiers	
IUPAC name	[show]
CAS Number	32222-06-3 ✓
PubChem CID	5280453
IUPHAR/BPS	2779
DrugBank	DB00136 ✓
ChemSpider	4444108 ✓
UNII	FXC9231JVH
ChEBI	CHEBI:17823 ✓
ChEMBL	CHEMBL846 ✓
ECHA InfoCard	100.046.315
Chemical and physical data	
Formula	$C_{27}H_{44}O_3$
Molar mass	416.64 g/mol
3D model (Jmol)	Interactive image
SMILES	[show]
InChI	[show]
	(verify)

Many of the effects of calcitriol are mediated by its interaction with the calcitriol receptor, also called the vitamin D receptor or VDR. For instance, the unbound inactive form of the calcitriol receptor in intestinal epithelial cells resides in the cytoplasm. When calcitriol binds to the receptor, the ligand-receptor complex translocates to the cell nucleus, where it acts as a transcription factor promoting the expression of a gene encoding a calcium binding protein. The levels of the calcium binding protein increase enabling the cells to actively transport more calcium (Ca^{2+}) from the intestine across the intestinal mucosa into the blood.[8]

The maintenance of electroneutrality requires that the transport of Ca^{2+} ions catalyzed by the intestinal epithelial cells be accompanied by counterions, primarily inorganic phosphate. Thus calcitriol also stimulates the intestinal absorption of phosphate.[8]

The observation that calcitriol stimulates the release of calcium from bone seems contradictory, given that sufficient levels of serum calcitriol generally prevent overall loss of calcium from bone. It is believed that the increased levels of serum calcium resulting from calcitriol-stimulated intestinal uptake causes bone to take up more calcium than it loses by hormonal stimulation of osteoclasts.[8] Only when there are conditions, such as dietary calcium deficiency or defects in intestinal transport, which result in a reduction of serum calcium does an overall loss of calcium from bone occur.

Calcitriol also inhibits the release of calcitonin,[*citation needed*] a hormone which reduces blood calcium primarily by inhibiting calcium release from bone.[8] (The effect of calcitonin on renal excretion is disputed.)[10]

Biosynthesis and its regulation [edit]

Calcitriol is produced in the cells of the proximal tubuleof the nephron in the kidneys by the action of 25-hydroxyvitamin D_3 1-alpha-hydroxylase, a mitochondrial oxygenase and an enzyme which catalyzes the hydroxylation of 25-hydroxycholecalciferol (calcifediol). The activity of the enzyme is stimulated by PTH. The reaction is an important control point in Ca^{2+} homeostasis.[8]

The production of calcitriol is also increased by prolactin, a hormone which stimulates lactogenesis (the formation of milk in mammary glands), a process which requires large amounts of calcium. It is decreased by high levels of serum phosphate and by an increase in the production of the hormone FGF-23 by osteocyte cells in bone.[*citation needed*]

Metabolism [edit]

Calcitriol becomes calcitroic acid through the action of 24-hydroxylase. Calcitroic acid is excreted in the urine.[*citation needed*]

Medical use [edit]

Calcitriol is prescribed for:[11]

- Treatment of hypocalcaemia – hypoparathyroidism, osteomalacia (adults), rickets (infants, children), renal osteodystrophy, chronic kidney disease
- Treatment of osteoporosis
- Prevention of corticosteroid-induced osteoporosis

Calcitriol is also sometimes used topically in the treatment of psoriasis, however the evidence to support its efficacy is not well established.[12] The vitamin D analogue calcipotriol is more commonly used for psoriasis. Research on the noncalcemic actions of calcitriol and other VDR-ligand analogs and their possible therapeutic applications has been reviewed.[13]

Calcitriol is also administered orally for the treatment of psoriasis[14] and psoriatic arthritis.[15]

Adverse effects [edit]

The main adverse drug reaction associated with calcitriol therapy is hypercalcemia – early symptoms include: nausea, vomiting, constipation, anorexia, apathy, headache, thirst, pruritus, sweating, and/or polyuria. Compared to other vitamin D compounds in clinical use (cholecalciferol, ergocalciferol), calcitriol has a higher risk of inducing hypercalcemia. However, such episodes may be shorter and easier to treat due to its relatively short half-life.[11]

Interactive pathway map [edit]

Click on genes, proteins and metabolites below to link to respective articles. [§ 1]