Pregnenolone

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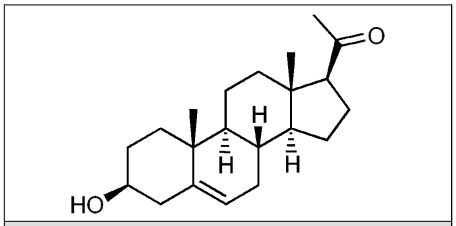


Systematic (IUPAC) name	
3β-hydroxypregn-5-en-20-one	
Identifiers	
CAS number	145-13-1 [1]
ATC code	None
PubChem	CID 8955 [2]
IUPHAR ligand	2376 [3]
DrugBank	EXPT02608 [4]
Chemical data	
Formula	$C_{21}H_{32}O_2$
Mol. mass	316.483 g/mol
Therapeutic considerations	
Pregnancy cat.	?
Legal status	?
✓ **(what is this?) (verify)** [5]	

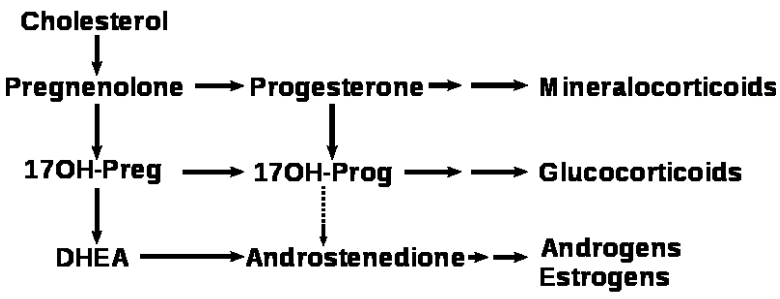
Pregnenolone is a steroid hormone involved in the steroidogenesis of progesterone, mineralocorticoids, glucocorticoids, androgens, and estrogens. As such it is a prohormone. Pregnenolone sulfate [6] is a $GABA_A$ antagonist and increases neurogenesis in the hippocampus.[7]

Chemistry

Like other steroids, pregnenolone consists of four interconnected cyclic hydrocarbons. It contains ketone and hydroxyl functional groups, two methyl branches, and a double bond at C5, in the B cyclic hydrocarbon ring. Like all steroid hormones, it is hydrophobic. Its esterified version, pregnenolone sulfate, is water-soluble.

Synthesis

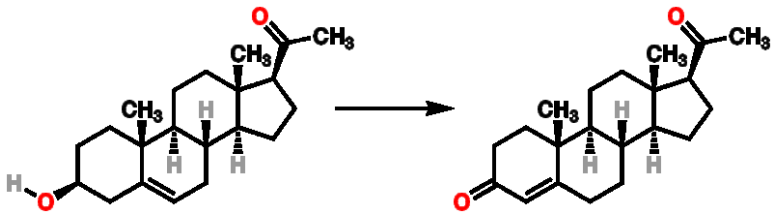
Pregnenolone is synthesized from cholesterol. This conversion involves hydroxylation at the side-chain at C20 and C22 positions, with cleavage of the side-chain. The enzyme performing this task is cytochrome P450scc, located in the mitochondria, and controlled by pituitary tropic hormones, such as ACTH, FSH, LH.



Production of Pregnenolone from Cholesterol and further metabolism

Prohormone

Pregnenolone undergoes further steroid metabolism in one of three ways.



Reaction: Pregnenolone-Progesterone

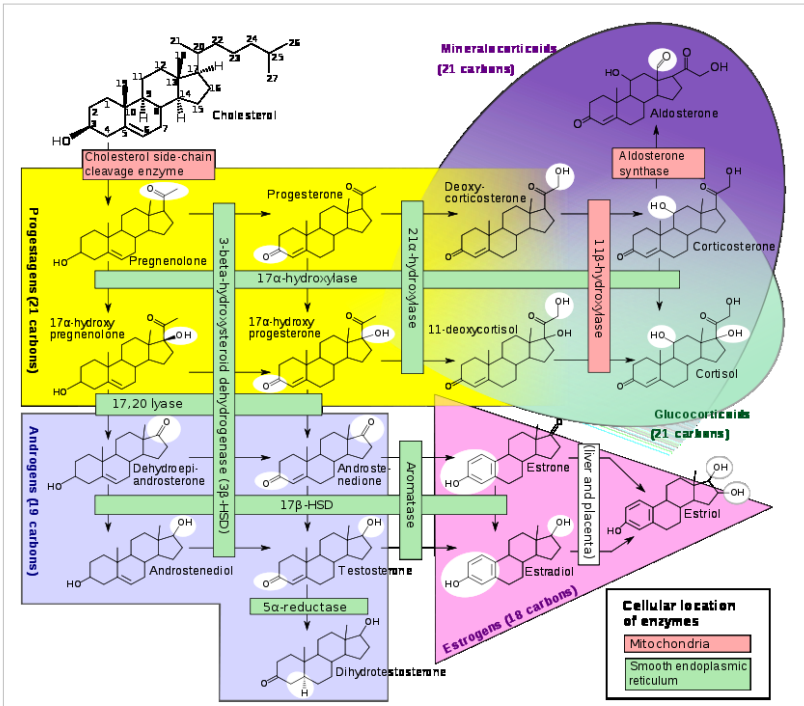
- Pregnenolone can be converted to progesterone. The critical enzyme step is two-fold using a 3-beta-hydroxysteroid dehydrogenase and a delta 4-5 isomerase. The latter transfers the double bond from C5 to C4 on the A ring. Progesterone is the entry into the delta-4-pathway, resulting in production of 17-hydroxy progesterone and androstenedione, precursor to testosterone and estrone. Aldosterone and corticosteroids are also derived from progesterone or its derivatives.
- Pregnenolone can be converted to 17-hydroxy-pregnenolone by the enzyme 17α-hydroxylase (CYP17A1). Using this pathway, termed delta-5 pathway, the next step is conversion to dehydroepiandrosterone (DHEA) using a desmolase. DHEA is the precursor of androstenedione.
- Pregnenolone can be converted to androsta-5,16-dien-3 beta-ol by 16-ene synthetase.

Neurosteroid

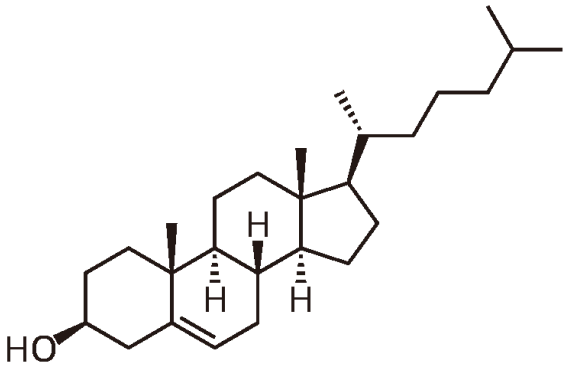
Pregnenolone and its sulfate, like dehydroepiandrosterone and its sulfate and progesterone, belong to the group of neurosteroids that are found in high concentrations in certain areas in the brain, and are synthesized there. Neurosteroids affect synaptic functioning, are neuroprotective, and enhance myelinization. Pregnenolone and its sulfate ester are under investigation for their potential to improve cognitive and memory functioning.[8]

Pregnenolone sulfate was shown to activate the Transient Receptor Potential M3 ion channel in hepatocytes and pancreatic islets causing calcium entry and subsequent insulin release.[9]

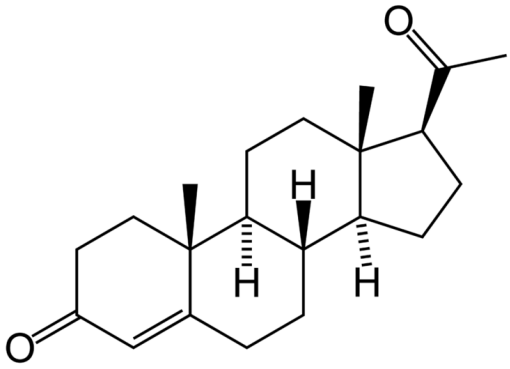
Additional images



Steroidogenesis, showing pregnenolone near top left.



Cholesterol



Progesterone

References

[1] http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?term=145-13-1&rn=1

[2] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=8955

[3] http://www.iuphar-db.org/DATABASE/LigandDisplayForward?ligandId=2376

[4] http://www.drugbank.ca/cgi-bin/show_drug.cgi?CARD=EXPT02608

[5] http://en.wikipedia.org/w/index.php?&diff=cur&oldid=367224932

[6] http://www.ncbi.nlm.nih.gov/pubmed/10350561

[7] Mayo, W; Lemaire, V; Malaterre, J; Rodriguez, Jj; Cayre, M; Stewart, Mg; Kharouby, M; Rougon, G; Le, Moal, M; Piazza, Pv; Abrous, Dn (January 2005). "Pregnenolone Sulfate Enhances Neurogenesis and Psa-Ncam in Young and Aged Hippocampus" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=15585350). *Neurobiology of Aging* **26** (1): 103–14. doi:10.1016/j.neurobiolaging.2004.03.013. PMID 15585350. PMC 15585350.

[8] Vallée M, Mayo W, Le Moal M (2001). "Role of pregnenolone, dehydroepiandrosterone and their sulfate esters on learning and memory in cognitive aging.". *Brain Res Brain Res Rev* **37** (1-3): 301–12. doi:10.1016/S0165-0173(01)00135-7. PMID 11744095.

[9] Wagner TF, Loch S, Lambert S, *et al.* (November 2008). "Transient receptor potential M3 channels are ionotropic steroid receptors in pancreatic beta cells". *Nature cell biology* **10** (12): 1421. doi:10.1038/ncb1801. PMID 18978782.

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