Fatty acid binding proteins **FABP**

Concepts and terms.

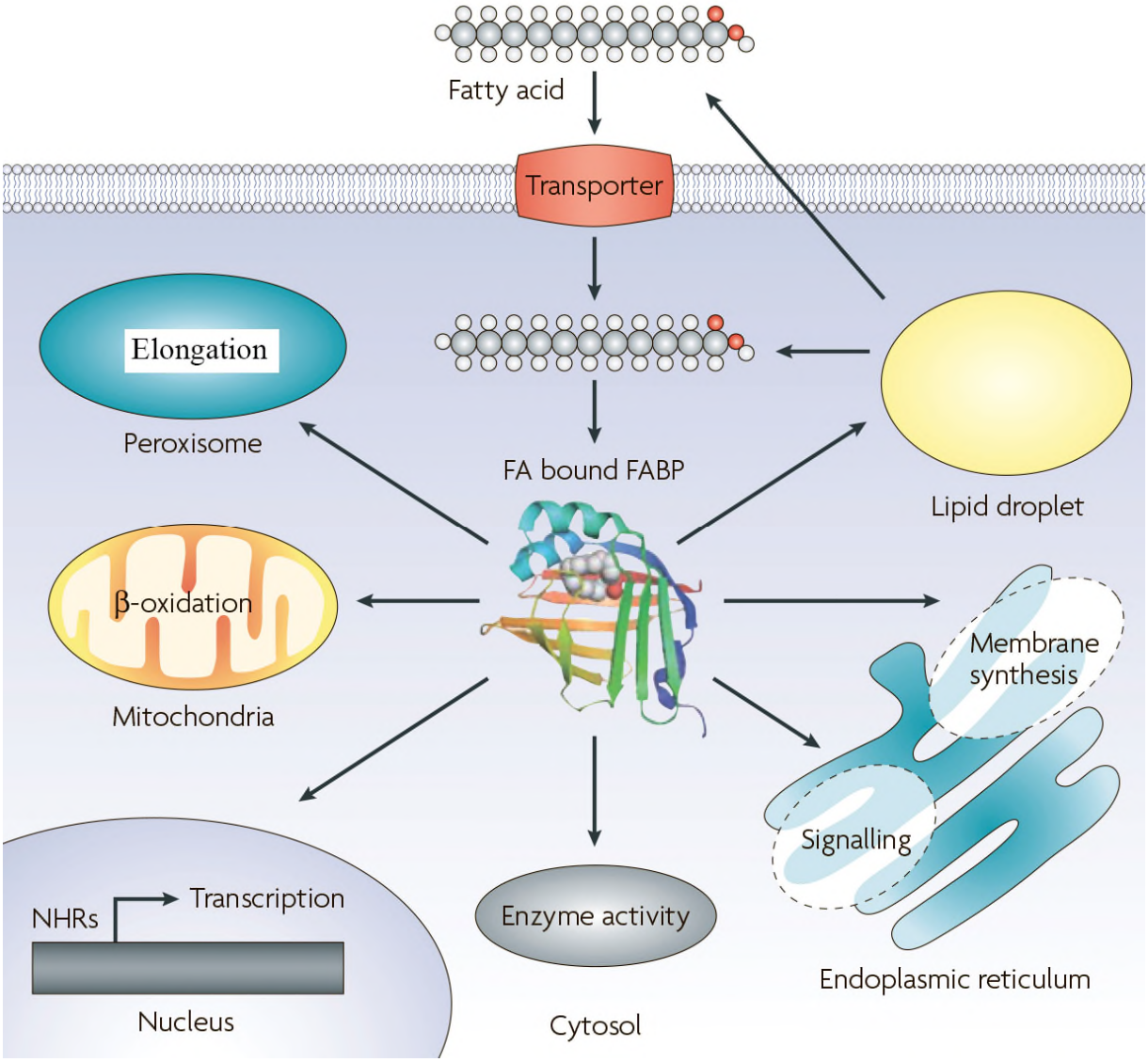
1. FABP fatty acids intracellular transport proteins.

2. Lipoproteins; **3**. Lipocalins; **4**. START and others .....water soluble proteins
transport phospholipids, sphingolipids, cholesterol, steroids, A, D, K and E vitamins.

FABP funkcijas šūnās © Nature Reviews Drug Discovery 2008 489-503..

Putative functions of FABP in the cell. Fatty-acid (FA) trafficking accompanied by the fatty acid-binding proteins (FABPs) in the cell . FABPs proposed to play a role as lipid chaperones in the transport of lipids to specific compartments in the cell: to lipid droplets for storage; to the endoplasmic reticulum for signalling, trafficking and membrane synthesis; to the mitochondria for β-oxidation; to the or peroxisome for elongation; to the enzymes to regulate their activity; to the nucleus for the control of lipid-mediated transcriptional programs via nuclear hormone receptors NHRs and other transcription factors that respond to lipids; and outside the cell membrane to signal in an autocrine or paracrine maner. So **lipid fluxes**, **metabolism** and **signalling**

Fabpl0	Liver	L-FABP
Fabp2	Intestinal	I-FABP
Fabp3	Heart	HFABP, MDGI
Fabp4	Adipocyte	AFABP, aP2
Fabp5	Epidermal	E-FABP, PA-FABP, mall
Fabp6	Real	ll-FABP, I-BABP, gastrotropin
Fabp7	Brain	B-FABP, MRG
Fabp8	Myelin	M-FABP, PMP2
Fabp9	Testis	T-FABP



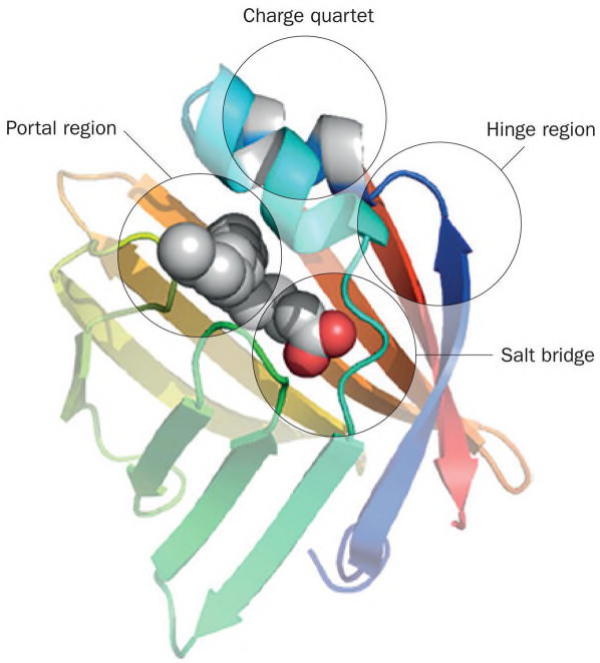
http://aris.gusc.lv/ChemFiles/FatAcLiverProt11/1/FABP4-5adiposEpiderm.pdf

FABP4 adipose FABP5 epidermal

J Med Chem. 2016;59(17):8094-8102; Nat Rev Endocrinol. 2015 Oct;11(10):592-605.**5HZ5.pdb**(1-133,0-132)

Fatty acid-binding proteins (FABPs) were originally described as intracellular proteins that can affect lipid fluxes, metabolism and signalling within cells. FABPs are critical mediators of metabolism and inflammatory processes, both locally and systemically, and therefore are potential therapeutic targets for immunometabolic diseases. In particular, genetic deficiency and small molecule-mediated inhibition of FABP4 (also known as aP2) and FABP5 can potently improve glucose homeostasis and reduce atherosclerosis in mouse models. Some FABPs are found outside the cells, and FABP4 undergoes regulated, vesicular secretion. The circulating form of FABP4 has crucial hormonal functions in systemic metabolism and involved for management of chronic metabolic diseases.

Fatty-acid-binding proteins (FABPs) are intracellular carriers for endocannabinoids, N-acylethanolamines, and related lipids. Administered FABP5 inhibitors produce analgesia of inflammatory pain in dorsal root ganglia and spinal cord. Fig. 1. Ribbon and domain structure of FABP4.



The structure of FABP4 is depicted as a ribbon with bound oleic acid in space-filling spheres (carboxylate oxygen atoms in red). Also shown are four domains of FABP4: portal region for ligand entry and exit; charge quartet used for protein–protein interactions Asp17, Asp18, Lys21, Arg30; the salt bridge where the fatty acid carboxylate forms ion pairs with basic residues within the cavity Arg106, Arg126, Tyr128; the hinge where the helix-turn-helix region rotates to enable access of ligands to the cavity Glu14, Asn15, Phe16. Amino acid numbering system start on N-trminus finish on C-terminus:

Lipolytic enzyme hormone-sensitive lipase (HSL). FABP4 interact with HSL via a domain contained on the helix-turn-helix motif defined by Asp17, Asp18, Lys21 and Arg30.[84] Asp17–Arg30 and Asp18–Lys21 in FABP4 form two ion pairs that interact with similarly charged residues on HSL (for example, Asp18 of FABP4 interacts with Lys196 of HSL) to form a complex on the lipid droplet surface.[85] This interaction facilitates fatty acid transfer and is consistent with the model by which FABP4 facilitates lipolysis-hydrolysis of ester bonds.

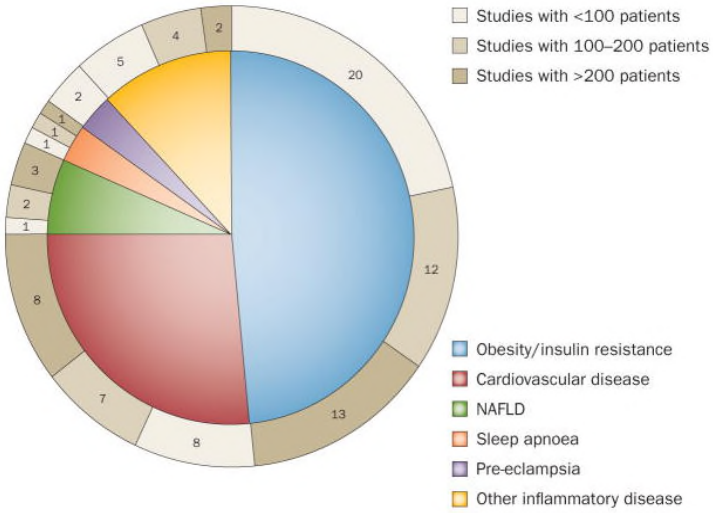
Lipids functioning as structural building blocks or fuel sources, and as intracellular and extracellular signalling molecules.

Lipids modify the action or location of proteins, such as kinases or ion channels, signal via proteins such as cell surface G-protein coupled receptors and serve as ligands for transcription factors.[1–3]

Fatty acids regulate hormone action, for example by inhibiting the insulin-stimulated phosphoinositide 3-kinase pathway[4,5] and activating inflammatory molecules such as inhibitor of nuclear factor κB kinase subunit β (IKK-β)[6] and c-jun N-terminal kinase (JNK),[7,8] or engage pattern recognition receptors which can contribute to metabolic regulation and disease.[9]

Fatty acid binding proteins (FABPs). are small molecular weight intracellular protein of ~12 kDa ability to noncovalently bind to long chain fatty acids.[12] It’s are in the liver, myocardium, adipose tissue and kidney.[12,13] It’s are crucial mediators of metabolic activities.[14]

Functional diversity of FABPs is generated via lipid interactions with these chaperone proteins to support systemic homeostatic networks of immunometabolism by facilitating signalling within and between cells and communication between organs.



Therapeutically targeting this class of proteins in metabolic and immunometabolic diseases.[14]

Fig. 3. The association of circulating levels of FABP4 with different human diseases. A summary of studies in humans showing the association of different immunometabolic diseases with circulating levels of FABP4 organized by number of patients. Numbers in the outer circle represent the number of studies in each category. Abbreviations: NAFLD, nonalcoholic fatty-liver disease.

http://aris.gusc.lv/ChemFiles/FatAcLiverProt11/1/FABP7-5brainEpiderm.pdf

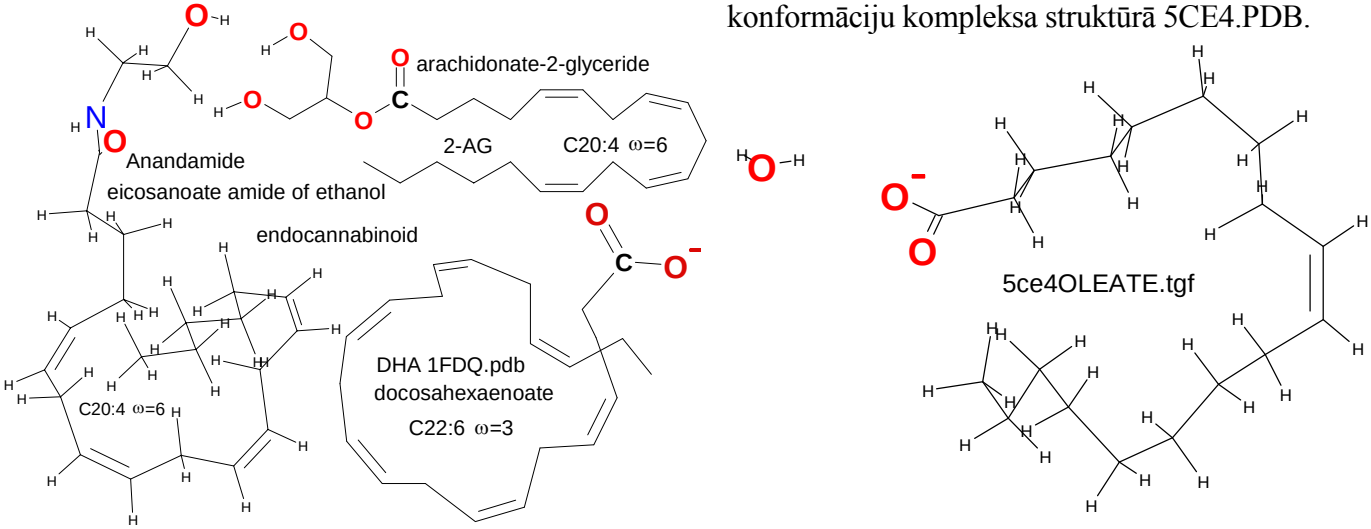
The Antinociceptive Agent replace Anandamide in FABP5 and FABP7 at Two Different Sites

Biochemistry. 2017;56(27):3454-3462.5URA (1-132,1-132); Subst Abuse. 2017; 11: 1-9.

Human FABP5 and FABP7 are intracellular14-15 kDa lipid-binding proteīns as well as endocannabinoid transporters anandamide (AEA) and 2-arachidonoylglycerol (2-AG), arachidonic acid derivatives that function as fatty acid signalling, cell growth, regulation, differentiation, neurotransmitters and mediate a diverse set of physiological and psychological processes. Antinociceptive Agent inhibits the activities of FABP5 and FABP7 and produces antinociceptive and anti-inflammatory effects. Only Agent was present in the crystal structures. The substrate entry portal region binding at the canonical ligand-binding pocket in the crystal structures.

Intracellular fatty acids-binding proteins (FABPs) transport the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG), arachidonic acid derivatives that function as neurotransmitters and mediate a diverse set of physiological and psychological processes. The endocannabinoids bind to FABPs, the crystal structures of FABP5 in complex with AEA, 2-AG as well as a common hydrogen bond to the Tyr131 residue. FABP5–endocannabinoid interactions may be useful for future efforts in the development of small-molecule inhibitors to raise endocannabinoid levels. Cannabinoid receptors produce their physiological and psychological effects processes controlled by the central and peripheral nervous systems.

Expression of brain fatty acid binding protein (B-FABP) is spatially and temporally correlated with neuronal differentiation during brain development. Human B-FABP clearly exhibits high affinity for the poly-unsaturated n-3 fatty acids α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid and for mono-unsaturated n-9 oleic acid (Kd from 28 - 53 nM) over poly-unsaturated n-6 fatty acids, linoleic acid and arachidonic acid (Kd from 115 - 206 nM). B-FABP has low binding affinity for saturated long chain fatty acids. Human B-FABP in complex with oleic acid shows that the oleic acid hydrocarbon tail assumes an "U-shaped" konformāciju kompleksa struktūrā 5CE4.PDB.



1FDQ.pdb DHA docosahexaenoic acid C22:6 ω=3 hydrocarbon tail adopts a helical conformation.

Human heart FABP3 http://aris.gusc.lv/ChemFiles/FatAcLiverProt11/1/FABP3humanHeart.pdf

IUCrJ. 2016 Jan 16;3(Pt 2):115-26.5CE4; Angew Chem Int Ed Engl. 2015;54(5):1508-11. 4TJZ,4TKB,4TICH,4TKJ,3WVM

Bioorg Med Chem Lett. 2016;26(20):5092-5097.Fabp3 Human heart 5HZ9 4WBK,3WBG(1-133)3WBG,2HMB,5CE4

Synchrotron Radiat. 2013 Nov 1; 20(Pt 6): 923–928. 3WBG(1-133.1-133)

Angew Chem Int Ed Engl. 2015;54(5):1508-11. 4TJZ,4TKB,4TICH,4TKJ,3WVM 1HMR,1HMS,1HMT,5CE4(1-132.1-133)

Long-chain fatty acids (FAs) with low water solubility require fatty-acid-binding proteins (FABPs) to transport them from cytoplasm to the mitochondria for energy production. Evaluating the affinity of FAs, sub-Angstrom X-ray crystallography to accurately determine their 3D structure, and energy calculations of the coexisting water molecules using the computer program WaterMap. The heart FABP (FABP3) preferentially incorporates a U-shaped FA of C10–C18 using a lipid-compatible water cluster, and excludes longer FAs using a chain-length-limiting water cluster. Proteins recognize diverse lipids with different chain lengths.

To date, more than 40 subtypes of FABPs have been identified,4 most of which share a highly conserved three-dimensional structure.3 FABP3, one LCFA molecule in a U-shape is accommodated in the binding cavity together with about 13 ordered water molecules.5 FABPs 4, 5, 7, and 8 in the binding sites of nonspecific lipid transporters universally expressed from bacteria to humans,6 the FAs are c10 – C18 (Figure S1). The U-shape conformation of bound FA is critical for the incorporation of FAs with different chain lengths into the binding site of FABP3 and the other FABPs, and raise an intriguing question as to how the proteins do this by using a rigid β-clam architecture and ordered water molecules in the pocket.

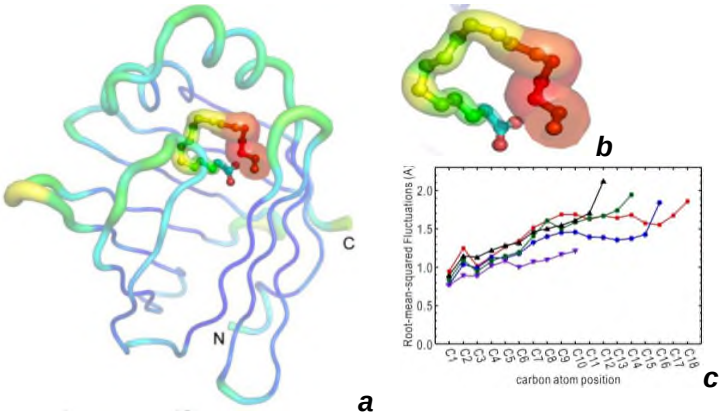
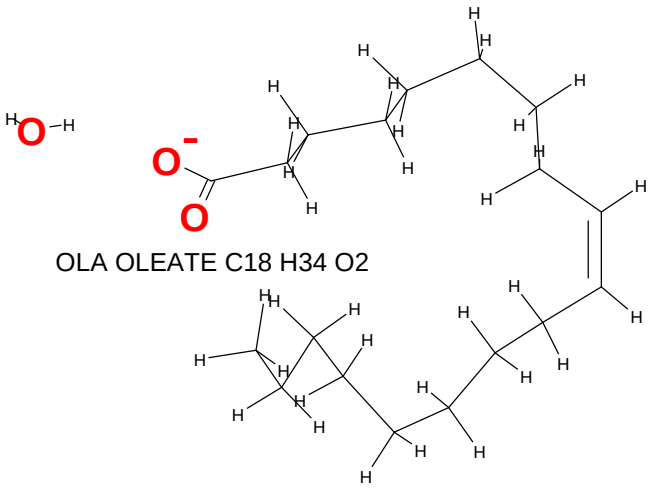


Figure S2. **Thermal fluctuation of FABP3-F complex.** (**a**) and (**b**) Fluctuations in the FABP3 C18:0 co-crystal structure obtained at room temperature shown with temperature factor (small in thinner and blue, and larger in thicker and red). Fluctuations of five SFAs bound to FABP3 in solution state deduced from 20 ns of MD simulati (C10:0 in violet, C12:0 in black, C14:0 in green, C16:0 in blue, and C18:0 in red). (**e**) Amino acid sequence of FABP3; Blue highlight: residues in contact with the FA; yellow: residues in contact w water in the pocket; pink: residues of hydrogen-bonded to the carboxylate of the FA.



For energy production in the skeletal and heart muscle,1 the efficient cytosolic delivery of fuel such as long-chain fatty acids (LCFAs) is crucial. Mitochondrial metabolism prefers fatty acids (FAs) of a certain range of chain length. Thus, specific transporter and carrier proteins of the “fuel” FAs have been created as exemplified by the fatty-acid-binding proteins (FABPs).2, 3 FAs with flexible alkyl chains that do not exhibit a defined structure or noticeable electrostatic interactions. The human heart-type FABP (FABP3) identifies FAs not by exact matching but by broad recognition of fundamental structural similarities among numerous FAs.

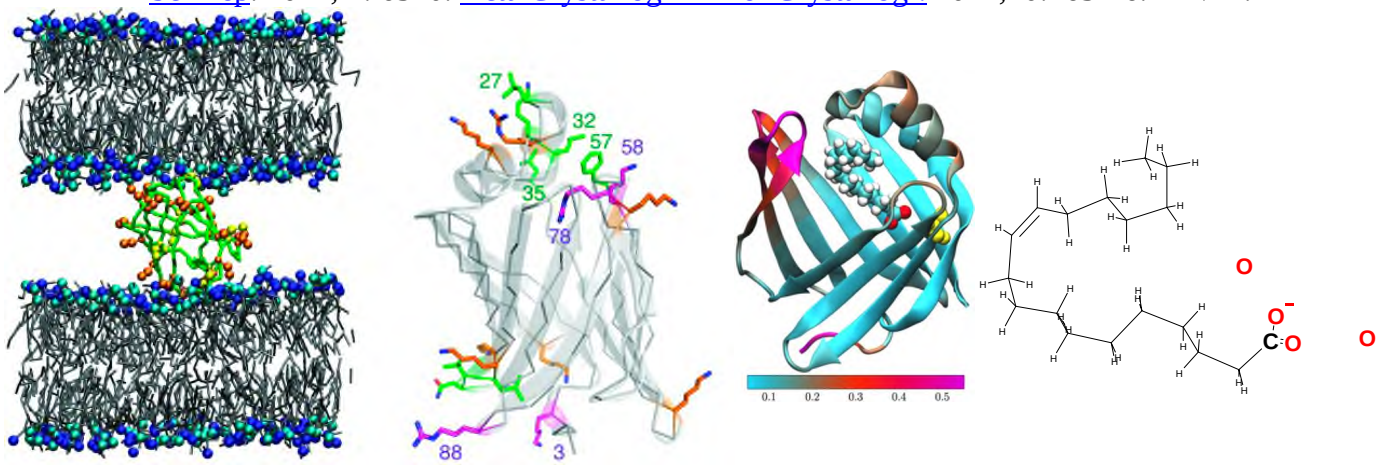
5CE4(1-132.1-133) FABP3 Human heart

http://aris.gusc.lv/ChemFiles/FatAcLiverProt11/1/FABP8myp2PMP2.pdf

Cilvēka mielīna P2 FABP8 molekula

P2 pie fosfolipīdu membrānas saistās ar pozitīvi lādētām un hidrofobām grupām vienlaicīgi ar izvietotu taukskābi muciņas struktūras iekšpusē

Sci Rep. 2017; 7: 6510. Acta Crystallogr D Biol Crystallogr. 2014;70:165-76. 4BVM.PDB



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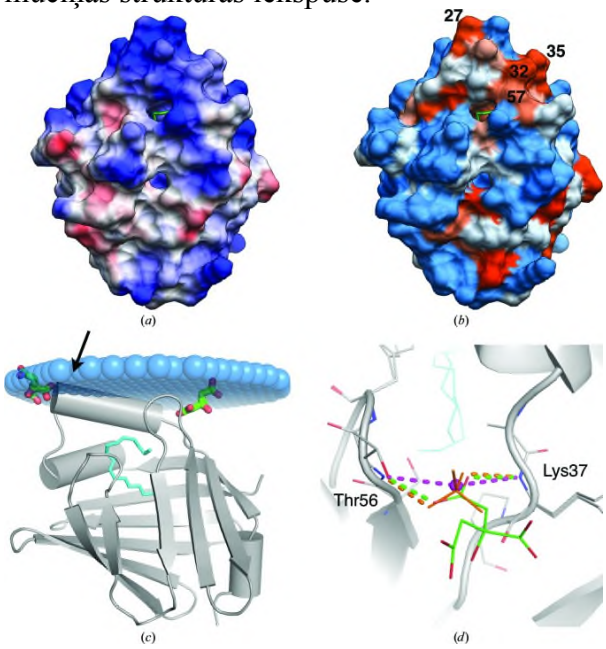
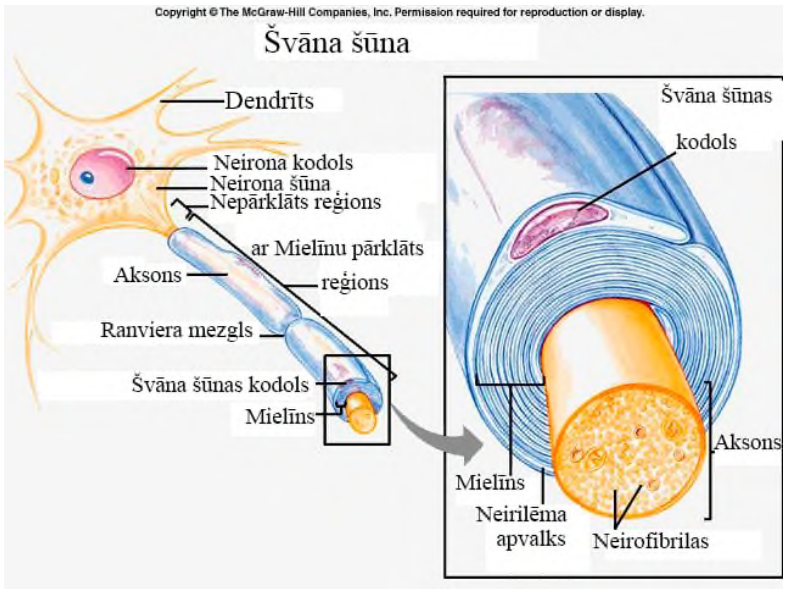
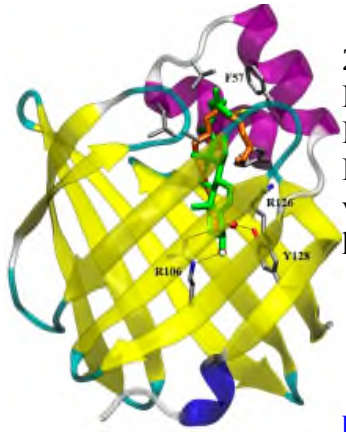




(a) P2 virsma krāsota atbilstoši elektrostatiskajam potenciālam

(b) virsma krāsota atbilstoši Kites–Dūlitla skalai, kurā oranža ir hidrofoba grupa un zila ir polarā grupa. Olbaltumviela P2 (a) un (b) ar portālo reģionu virsotnē. (c) piesaistās membrānai ar Lys37 pozitīvo lādiņu mielīna šūnā



PLoS One. 2010; 5(4): e10300.

2WUT.pdb **Holesterola liganda saistīšana P2.**

Holesterola (zaļā krāsa) labvēlīgākā saistošā kompleksa struktūra P2 molekulā. Palmitāta pozīcija (oranžā krāsā) paradīta kristālā salīdzināšanai. Polārās grupas diviem ligandiem ir elementu krāsā CPK. Saistoša mijiedarbība veidojas ar Arg106, Arg126, un Tyr128 parādītas ar melnām līnijām. Hidrofobās kontaktu grupas arī tiekparādtas P2 molekulā.

FABP10 Liver FABP2 intestinal Enterocytes

http://aris.gusc.lv/ChemFiles/FatAcLiverProt11/1/FABP10-2LiverIntest.pdf

FABP6,2 Fatty Acid Binding Protein 6,2 Gastrotropin ileal bile IBABP-L

http://aris.gusc.lv/ChemFiles/FatAcLiverProt11/1/FABP6cholatGastroTropin.pdf