

Index

A

ABC lipid transporters, 153
Acidic environment, 144
Adenosine A_{2A} receptor (A_{2A}R), 95, 97, 98
Adenosine receptor, 5
Aldo-keto reductase (AKR)
 AKR1C1, 35
 AKR1C2, 35, 36
 AKR1C3, 36
 AKR1C9, 36
 AKR1D1, 37
 HSDs, 34
All atoms (AA) simulation, 91
 α -Helical TMDs, 6
 α -Helices, 123, 128–130, 132, 134
 α Smooth surface, 91
Alzheimer's β -amyloid peptide, 17
Alzheimer's disease, 16, 90
Amphipathic helix, 13, 14, 49
Amphipathicity, 91
Amyloid proteins, 16, 17
Androgen receptor (AR), 31
Angiotensin II receptor type 1 (AT1R), 99
Aromatic residues, 48, 122, 123, 129, 130, 132, 134
Aster' proteins, 153
Atherosclerotic plaques, 90
ATP binding cassette (ABC) transporters, 17, 18

B

Bacillus megaterium, 39
Bacterial enzymes, 39
 β -Adrenergic receptor, 128, 129

β 2-Adrenergic receptor, 15, 16, 94–96
Beta-cryptogein, 49
 β Rough surface, 91
Binding site
 amyloid proteins, 17
 ATP, 17
 β 2 adrenergic receptor, 15
 cholesterol (*see* Cholesterol)
 GPCRs, 14
 rhodopsin, 14
 sterol, 13
Brain cholecystokinin receptor, 14
Bulk lipids, 98

C

Capsaicin receptor (TRPV1), 107
CARC motif, 110
 amino acids, 8
 biochemical rules, 8
 class I bitopic membrane proteins, 8, 9
 definition, 10
 γ -TM4 segment, 10
 (K/R)-X₁₋₅-(Y/F/W)-X₁₋₅-(L/V), 8
 membrane proteins, 9
 mirror topology, 10
 nicotinic acetylcholine receptor, 9, 10
 TMDs, 8, 10, 11
Ceramide, 91
Cerebellar degeneration, 143
CG MD simulations, 95, 98–100
Channel activity, 120
Channel modulation, 128, 129, 134
Chemokine type 2 receptor (CCR2), 99

- Chinese hamster ovary cells (CHO cells), 113
- Chiral isomer, 16
- Chirality, 91
- Cholestatrienol, 14
- Cholesterol
- atherosclerotic plaques, 90
 - biological role, 90
 - CLR-protein interactions, 70
 - conformational states, receptor, 98
 - crystal structures, 71, 76, 77
 - epicholesterol, 4
 - esterification, 143
 - esters, 140
 - GPCR structures
 - A2a adenosine receptor structures, 79, 80
 - β 2 adrenergic and serotonin receptors, 77
 - flexibility, 76
 - PDB ID: 4E1Y, 70, 77
 - 7TM, 77
 - structural features, 79
 - TM, 77
 - homeostasis, 4
 - human health, 90
 - hydroxyl group and hydrocarbon region, 4
 - Kir channels (*see* Inwardly rectifying potassium (Kir) channels)
 - lipid molecule, 90
 - mammalian physiology, 68
 - membrane constituents, 90
 - in membrane fusion, 18–20
 - membrane proteins, 79, 82
 - mol fraction, 5
 - NMR study, 5
 - PDB, 70, 71
 - physical properties, 4, 140
 - stereochemical isomers, 4
 - structure, 140, 141
 - 3D structure, 91
 - three-letter code CLR, 69
 - transporters, NPC1 and NPC2, 153
 - TRPV1 (*see* TRPV1)
- Cholesterol binding
- beta-cryptogein, 49
 - molecular characteristics (*see* Transmembrane vs. soluble protein domains)
 - multiple transmembrane helices, 49
 - soluble protein domains, 50
 - structures of proteins complexes, 50, 52
 - transmembrane protein crystal structures complex, 49
 - transmembrane protein domains, 51
- Cholesterol consensus motif (CCM), 48, 95, 109, 129
- Cholesterol-enriched phases, 5
- Cholesterol homeostasis, 29, 48
- Cholesterol iso-octyl tail, 145
- Cholesterol-protein interactions, 81, 82
- Cholesterol recognition interaction amino acid consensus (CRAC), 90
- Cholesterol-recognition motifs
- α -helical TMDs, 6
 - amphipathic helix, 13, 14
 - binding to GPCRs, 14–16
 - CARC motif, 8–11
 - cholesterol trafficking, 17–18
 - CRAC motif, 6–8
 - human phospholipid scramblase 1, 6
 - ion channels, 16–17
 - and membrane proteins, 5
 - protein domains, 5
 - SSD (*see* Sterol-sensing domains (SSD))
- Cholesterol sulfate, 141
- Cholesterol trafficking, 17–18
- CH-Pi stacking interactions, 7
- ChUP proteins, 18
- Coarse-grained (CG) simulation, 91
- Complex disorder, 90
- Cortisol regulation, 38
- CRAC motif, 6, 8, 48, 109, 110, 129
- aliphatic cycle, 7
 - aromatic structure, tyrosine stacking, 6
 - and cholesterol, 8
 - CH-Pi stacking interactions, 7
 - definition, 6
 - head-to-head/tail-to-tail geometry, 6
 - maximal size, 7
 - mirror topology, 10
 - molecular docking studies, 8
 - N-terminal branched residue, 6
 - TMD, 7, 8
 - vectorial nature, 7
- Creutzfeldt-Jakob diseases, 16
- Cryo-electron microscopy, 13
- Crystal structure
- B-factors, 77
 - CLR, 71
 - distance matrix, 71
 - flexibility, 77
 - hydrophobic tail, 76
 - RMSD, 71, 75
 - VDW, 77
- C-terminal luminal domain (CTD), 142, 152
- CYP109E1, 39
- CYP154C5, 39
- CYP51, 30, 38

Cytochrome P450 11A1 (CYP11A1), 28
Cytochrome P450 46A1 (CYP46A1), 29
Cytochrome P450 enzymes, 28

D

7-Dehydrocholesterol reductase, 11
Demyelination, 143
De-novo biosynthesis, 140
Deoxycortisone, 34
Detergent-resistant membranes (DRMs), 108
Distance matrix, 71, 76, 79, 81
DNA-binding domain (DBD), 31
Dorsal root ganglia (DRG), 106, 108, 109
Drug interactions, GPCRs, 92, 93

E

Ebola virus, 11, 19
11 β -HSD type1, 38
11 β -hydroxysteroid dehydrogenase (11 β -HSD), 38
Enantiomorphs, 5
Endogenous lipid mediators, 107
Endo-lysosomal system, 140
Endoplasmic reticulum (ER) proteins, 153
Ent-cholesterol, 4, 5, 16, 19, 94
Epicholesterol, 4, 16, 94, 110
Epithelial sodium channels (eNaC), 120
Estrogen receptor (ER), 31
Eukaryotic cells, 92
Extracellular signal-related kinase (ERK), 94

F

F11 cells, 108
5 α -dihydrotestosterone (5 α -DHT), 35
5 β -dihydroprogesterone, 37
Flotillin, 108

G

GIRK channels, 120
Glucocorticoids, 38
Glucocorticoid steroid hormones, 33
Glucocorticoid receptor (GR), 31
Glycolipid GM3, 98
GPCR-membrane environment, 92, 93
G-protein coupled receptors (GPCRs), 71–75, 77, 79, 84
A_{2A}R, 94, 95, 97, 98
 β 2 adrenergic receptor, 15, 16, 94–96
binding sites, 90

biophysical effects, 14
CCM, 15
cholestatrienol, 14
and cholesterol, 14
cholesterol/cholesterol hemisuccinate, 93
cholesterol-depletion, M β CD, 94
cholesterol-receptor interactions, 15
classification, 92
CRAC/CARC algorithms, 15
drug interactions, 92, 93
ent-cholesterol, 94
entropy, 93
enzyme catalyzes, 14
epi-cholesterol, 94
ERK and c-Fos, 94
function, 14
hydrogen bonds, 93
in meso technology, 15
in silico studies, 98
lipid bilayers, 93
and membrane constituents, 90
monoacylglycerol matrix, 15
multiple binding sites, 93
oligomerization, 98–100
receptors (*see* GPCR receptors)
serotonin 5-HT(1A) receptor, 14
serotonin_{1A} receptor, 94–96
stabilization, 94, 95
structural studies, 15
TM helix V, 95
TM surfaces, 92
XFELs, 95, 97
X-ray diffraction data, 94

H

Handoff model, 148
HE1, 143
HEK293 cells, 109
Heterotetrameric Kir3 channels, 120
Hill coefficient, 110
Holo vs. apo NPC2 structures, 145
Homomers, 120
Human phospholipid scramblase 1, 6
Hydrophobic aliphatic residues, 48
Hydrophobic handoff^{*} transfer model, 151
Hydrophobic pocket, 16
Hydrophobic residues, 130
25-Hydroxycholesterol, 141
Hydroxysteroid dehydrogenases (HSDs), 34
3-Hydroxy-3-methylglutaryl coenzyme A-reductase (HMG-CoAR), 11

I

- In meso* technology, 15
- Inverted CRAC (CARC) motif, 48
- Inwardly rectifying potassium (Kir) channels
 - BK channels function, 121
 - cholesterol enrichment, 120, 122
 - classification, 121
 - crystallographic structures, 121
 - inverse relationship, 120
 - ion channels, 121
 - Kir2.1 (*see* Kir2.1)
 - Kir3.2 (*see* Kir3.2)
 - Kir3.4 (*see* Kir3.4*)
 - KirBac1.1 channel, 121
 - lipid bilayers, 121
 - membrane properties, 121
- Ion channels, 16–17
 - blocker, 112
 - features, 112
 - Kir2.1, 130, 132–134
 - Kir3.2, 130, 132–134
 - Kir3.4*, 130, 132–134
 - membranes of cells, 105
 - multimeric proteins, 106
 - nicotinic acetylcholine receptor, 121
 - parameters, 112
 - polymodal, 106
 - sterol, 109
 - transmembrane proteins, 113
 - TRPV, 121
 - TRPV1 (*see* TRPV1)
 - voltage-gated, 106

K

- 3-Ketosteroid Δ 1-dehydrogenase, 39
- Kir2.1
 - characteristics, 128–131
 - computational analysis, 125
 - hydrophobic residues, 122
 - ion channels, 130, 132–134
 - mutations, 122
 - principal binding region, 123, 124
 - transmembrane domain, 122, 123
 - transmembrane residues, 123–125
- Kir3.2
 - characteristics, 128–131
 - computational-experimental approach, 125
 - homotetramers, 125
 - ion channels, 130, 132–134
 - predictions, computational analysis, 125
 - principal/transient sites, 127
 - residues, 125, 127
 - transmembrane domain, 125, 126
 - unbiased computational studies, 125

Kir3.4*

- characteristics, 128–131
- homomeric, 128
- ion channels, 130, 132–134
- non-annular hydrophobic principal region, 128
- PI(4,5)P₂, 128
- principal binding region, 128
- residues, 128
- transient cholesterol binding site, 128
- transmembrane domain, 127, 128
- KirBac1.1 channel, 121
- Kir channels, *see* Inwardly rectifying potassium (Kir) channels

L

- Leucines, 54
- Ligand binding domain (LBD), 31–34
- Ligand-binding pocket, 32
- Ligand-gated receptors, 108
- Lipid bilayers, 91–93, 100, 114, 121
- Lipid rafts, 91, 92, 108
- Lipid recognition motifs
 - binding affinity, 5
 - cholesterol (*see* Cholesterol)
 - headgroup structure, 4
 - membrane, 4, 5
 - qualitative binding behavior, 4
 - water-soluble molecule, 4
- Lipophilic ligands, 107
- Liquid-liquid immiscibility, 5
- Low density lipoproteins (LDLs), 140
- Lysosomal cholesterol transport, 151
- Lysosomes, 140, 144–147, 152, 155

M

- Mammalian physiology, 68
- MELADL, 12
- Membrane cholesterol depletion, TRPV1, 108–109
- Membrane components, 4
- Membrane fusion
 - biological systems, 18
 - cholesterol, 18, 19
 - N-acetyl-LWYIK-amide, 19, 20
 - SNARE proteins, 18, 19
 - types, 18
 - viral fusion proteins, 19
- Membrane proteins
 - bitopic, 8
 - CARC domain, 8
 - and cholesterol (*see* Cholesterol)

- cholesterol-recognition motifs
 - (*see* Cholesterol-recognition motifs)
- CLR, 79
- CLR-protein distances, 82
- CLR-protein interactions, 82
- CRAC domain, 8
- crystal structures, 10
- distance matrix, 79
- Dmin plot, 79, 80, 82
- integral, 6
- membrane-embedded regions, 20
- paradigmatic superfamilies, 20
- SCAP, 11
- SVD, 82
- TMDs, 8
- transporters, 17
- types, 10
- X-ray structures, 15
- Methyl- β -cyclodextrin (M β CD), 94, 108
- Middle luminal domain (MLD), 142, 147–152
- Mineralocorticoid hormone aldosterone, 28
- Mineralocorticoid receptor (MR), 31
- Mineralocorticoids, 34
- Mirror topology, 10
- Molecular dynamics (MD) simulation, 91
- Molecular Operating Environment (MOE), 61, 62
- Monoacylglycerol matrix, 15
- Multi-scale simulations, 99
- Mycobacterium tuberculosis*, 38

- N**
- N-acetyl-LWYIK-amide, 19, 20
- Neurological disease, 17, 20
- Nicotinic acetylcholine receptor (nAChR), 9, 10, 129
- Niemann–Pick C1 (NPC1), 31
- Niemann–Pick C2 (NPC2), 31
- Niemann–Pick disease type C (NPC), 61
 - biochemical insights, 143
 - cell types, 143
 - clinical and pathological evaluation, 140
 - LDL-mediated processes, 143
 - NPC1 (*see* NPC1)
 - NPC2 (*see* NPC2)
- N-methyl-D-glucamine (NMDG), 113
- Nocardia farcinica*, 39
- Non-annular transmembrane sites, 130
- Non-stereospecific mechanism, 16
- Noxious signals, 106
- NPC1
 - cholesterol transporters, 153
 - gene sequencing, 145
 - mutagenesis, 145
 - NTD, 142, 145–147
 - SSD, 142, 145–147
 - structures, 140, 142, 144, 145
 - transport mechanism model, 147–153
- NPC2
 - acidic environment, 144
 - β sheets, 143
 - β -strands, 145
 - cartoon representation, 142, 143
 - cholesterol transporters, 143, 153
 - complementary molecular modeling, 144
 - deficient cells, 143
 - hydrophobic pockets, 143
 - membrane interactions, 144
 - membrane vesicles, 144
 - molecular basis, 144
 - plasticity, 144
 - porcine model, 143
 - structures, 140, 142–145
 - sulfate moiety, 144
 - surface regions, 144
 - transport mechanism model, 147–153
- N-terminal domain (NTD)
 - binding site, 145
 - cholesterol-bound, 147
 - crystal structures, 149
 - and CTD, 152
 - in vitro* work, 146
 - and MLD, 149, 152
 - NPC1, 145–149
 - NPC2, 147, 148
 - PDB ID 3JD8, 142
- Nuclear receptors
 - AR, 33
 - AR LBD, 33
 - ER, 32
 - ER LBD, 32
 - GR, 33
 - GR LBD, 33
 - LBD, 31, 32
 - ligand-activated transcription factors, 31
 - ligand-binding pocket, 32
 - MR, 34
 - MR LBD, 34
 - PR, 32
 - PXR, 34
 - ROR, 34

- O**
- Oligomerization, GPCRs, 98–100
- Oligomerization process, 17
- Open probability (Po) of TRPV1, 110

Oxidative stress, 143
 Oxysterol-binding proteins, 30
 Oxytocin receptor, 14

P

Parkinson diseases, 16
 Patch clamp technique, 110
 Patched1 homolog 1 (PTCH1)
 receptor, 153
 Peripheral-type benzodiazepine receptor, 129
 P450eryF, 38
 Phosphatidylcholine (PC), 98
 Phosphatidylethanolamine (PE), 98
 Phosphatidylinositol 4,5-bisphosphate
 (PIP2), 98
 Phosphatidylserine (PS), 98
 Photoaffinity labeling studies, 12
 Photolabeling, 12
 Plasma membrane, 140
 Polar amino acid, 110
 Polymodal ion channels, 106
 Pore dilation, 112
 Pregnane X receptor (PXR), 34
 Pregnenolone, 28
 Progesterone receptor (PR), 31
 Protein Data Bank (PDB), 27, 50, 52, 62,
 68–77, 81, 83
 Protein-protein complex, 149
 Protein-steroid complex
 AKR (*see* Aldo-keto reductases (AKR))
 bacterial enzymes, 38, 39
 cytochrome P450 enzymes
 cholesterol homeostasis, 29
 CYP11A1, 28, 29
 CYP46A1, 29
 CYP51, 30
 hemoproteins, 28
 mineralocorticoid hormone
 aldosterone, 28
 pregnenolone, 28
 Hedgehog signaling, 31
 intracellular cholesterol trafficking, 30
 nuclear steroid receptors
 (*see* Nuclear receptors)
 oxysterol regulation, 30
 SDRs, 37, 38
 Protein structure, 31
 PyMol, 53

Q

Qualitative binding behavior, 4

R

Research Collaboratory for Structural
 Bioinformatics (RCSB), 50
 Research Collaboratory for Structural
 Bioinformatics Protein Data Bank
 (RCSB PDB), 129
 Retinoic acid-related orphan nuclear receptors
 (ROR), 34
Rhodococcus erythropolis, 39
Rhodococcus jostii, 39
 Root mean square deviation (RMSD), 71, 75, 76

S

Saccharomyces cerevisiae, 30
Saccharopolyspora erythraea, 38
 Scarce antagonists, 107
 Serotonin 5-HT(1A) receptor, 14
 Serotonin_{1A} receptor, 94–96
 17 β -hydroxysteroid dehydrogenase
 (17 β -HSD), 37
 Seven transmembrane helix (7TM), 71
 Short-chain dehydrogenases/reductases
 (SDRs), 37
 Singular value decomposition (SVD), 70,
 82, 83
 Sliding model, 148
 Smoothened (SMO), 153
SMPD1 gene, 140
 SNARE proteins, 18, 19
 Sphingomyelinase deficiency, 140
 Sporadic disorder, 90
 StAR-related lipid transport (START)-domain
 proteins, 153
 Steroid metabolism, 27, 37, 40
 Steroid monooxygenase, 39
 Steroidogenic acute regulatory domain
 (StARD), 153
 Steroid trafficking, 28, 30, 40
 Sterol, 4, 91
 Sterol-binding pocket, 146
 Sterol regulatory element-binding protein-
 cleavage activating protein (SCAP),
 11, 12, 49
 Sterol-sensing domains (SSD), 49, 142,
 145–147
 cholesterol transport, 11
 7-dehydrocholesterol reductase, 11
 functional properties, 12
 HMG-CoAR, 11
 vs. loop 1, 12
 MELADL, 12
 metabolism and storage, 11

- NPC1, 11
 NPC1, 12, 13
 photoaffinity labeling studies, 12
 photolabeling, 12
 SCAP, 11, 12
 YIYF, 13
 Storch laboratory, 144
Streptomyces hydrogenans, 39
 Stretch-activated cation channels (SACs), 120
 Sulfonylurea receptor (SUR) subunits, 120
- T**
- Tetrahydrogestrinone (THG), 33
 Thermosensitive channel, 113
 Thermo-TRP channels, 106
 3 β -hydroxyl group, 91
 3D structure, cholesterol, 91
 Three-letter code CLR, 69
 Transient receptor potential (TRP) channels, 16
 endogenous compounds, 107
 mammals, 106
 thermo-TRP channels, 106
 transmembrane domains, 106
 voltage-gated ion channels, 106
 Transient receptor potential (TRP) non-selective cation channels
 classification, 106
 Transient receptor potential canonical channel (TRPC1), 120
 Transmembrane (TM), 70, 77, 92
 Transmembrane domains (TMDs)
 α -helical, 6
 CARC motif, 8, 10, 11
 CRAC motif, 7, 8
 Transmembrane vs. soluble protein domains
 amino acid residue, 54, 58, 59
 aromatic residues, 58
 asparagine and aspartate, 60
 C17-C20-C22-C23 dihedral angle, 61, 62
 cholesterol molecule (C1-C6), 60
 cholesterol molecule vs. closest protein residue, 54
 complementary ways, 58
 database structures, 53
 hydrophobic aliphatic residues, 54
 hydrophobic and aromatic residues, 60
 hydrophobic aromatic residues
 phenylalanine, 58
 hydrophobic environment, 52, 54, 58
 hydrophobic vs. hydrophilic chemical moieties, 63
 MOE, 61
 NPC1, 61
 NPC2, 61
 positively charged residues, 58, 60
 proximal residues, 52
 residues, 52, 53
 ring system, 61
 side-chain/backbone functional groups, 60
 types, residues, 54
 Transport mechanism model
 from NPC2 to NPC1
 cholesterol molecule, 149
 crystal structure, 152
 CTD, 152
 energy barrier, 149
 handoff model, 148
 hydrophobic handoff' transfer model, 151
 lysosomal cholesterol transport, 151
 MLD, 142, 147–149, 151, 152
 NTD, 147–153
 protein-protein complex, 149
 reaction pathway, 149
 sliding model, 148
 SSD, 149, 151
 structures, 147
 transfer mutants, 147
 Triton X-100 detergent, 108
 TRPM2, 132–134
 TRPV1
 capsaicin receptor, 107
 CARC motif, 110
 CCM, 109
 cholesterol depletion/enrichment, 112–113
 CRAC motif, 109, 110
 direct and specific interactions, 109
 DRG neurons, 109
 epicholesterol, 110
 Hill coefficient, 110
 human TRPV1 channel, 111, 112
 ion channel topology, 106
 ion-permeability, 114
 M β CD, 109
 membrane cholesterol depletion, 108–109
 molecular docking simulation, 111, 112
 noise analysis experiments, 110
 open probability (Po), 110
 patch clamp technique, 110
 plasma membrane/modifications, 109
 temperature responses, 113–114
 three-dimensional structure, 107
 and TRPV4, 109
 TRPV3, 113, 114
 TRPV4, 109

20 α -hydroxyprogesterone, 35
2D structure, cholesterol, 91
Type II diabetes, 90

V

van del Waals (VDW), 77
Virus fusion, 18–20

W

Water-soluble molecule, 4
Water-soluble sterol-binding proteins, 92

X

X-ray crystallography, 13, 145
X-ray free-electron lasers (XFELs), 95, 97