

Index

A

- α -Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors
 - brain ischemic injury, 108–109
 - hippocampal synaptic plasticity regulation, 224
- Acetylcholine (ACh) release
 - Alzheimer's disease, 271–272
 - environmental effects, 269–270
 - septohippocampal cholinergic neurons, 266–267
 - sex-specificity
 - activational effect, 268–269
 - release of, 265–266
 - sex steroids regulation of, 267–268
 - spatial learning and memory, 264
 - spontaneous behaviors, 271
 - synaptic plasticity, 264–265
- Adrenocorticotrophic hormone (ACTH)
 - postnatal development
 - maternal deprivation effect, 371
 - steroidogenic response, 370
 - prenatal restrain stress effects, 379–381
 - suppressor of cytokine signaling (SOCS)-3, 310
- α -fetoprotein (AFP), 372
- Aging, 230–231
- Alzheimer's disease (AD)
 - ACh release effect, 271–272
 - amygdala, 31–32
 - depression, 356–357
- Amygdala
 - brain plasticity, 25
 - central nucleus and dependence
 - brain motivational pathways, 150–151
 - neuroactive peptides, 151–152
 - conditioned aversive properties, 155, 158
 - function and anatomy, 24
 - glia, astrocytes
 - cell division, 37
 - depressive disorder, 28–30
 - epileptic states, 27–28
 - gonadal hormones during adulthood, 34–36
 - gonadal hormones during early development, 33–34
 - other pathologies, 32
 - processes, 26
 - proteinopathies, 30–32
 - receptors, 36
 - structure and function, 25–26
 - glutamate systems and opioid dependence, 148–149
 - location, 24
 - NMDA and μ -opioid receptor, synaptic relationship
 - dendritic distribution, 152–154
 - immunoelectron microscopic analysis, 152–153
 - opioids and dependence
 - conditioned place aversion (CPA), 148
 - pernicious complication, 147
 - withdrawal symptoms, 147–148
 - postsynaptic NR1 deletion
 - Cre-lox technology, 154–156
 - opioid dependence, 155
 - withdrawal-induced place aversion, 155, 157
- Androgen receptors (AR)
 - astrocytes, 35
 - limbic system
 - fire ring, blood–brain barrier, 97–100
 - gene expression, 94–95
- Angiogenesis, 119–120
- Anoxia-induced excitotoxicity, 397–399
- Antidepressant, 329–331
- Anxiety
 - estrogen level and gender, 324–325
 - hyponeophagia test, 8–9
 - neurotrophin role, 190–191
- Apoptosis, 399–401
- AR. *See* Androgen receptors
- Arcuate nucleus (ARC), 204–205
- Arginine vasopressin (AVP)
 - depression
 - chronic stress, 349–351
 - circadian system, 354–356
 - SON and PVN, 351–354
 - vasopressinergic systems, 349
 - IL-6 regulation, 310
- Asphyxia, corticosteroids expression
 - brain injury effects
 - behavioral effects, 409–411
 - unbalanced MR/GR levels, 407–409
 - temperature effects, 406–407
- Astrocytes, 113–114
- Attention-deficit/hyperactivity disorder (ADHD), 394, 409
- Autoradiograms, KAR gene expression, 172
- AVP. *See* Arginine vasopressin

B

- Basal ganglia, subthalamic nucleus (STN)
 anatomy, 54–56
 behavioral changes, 56–57
 high-frequency stimulation, 48–53
- Baseline synaptic transmission (BST),
 progesterone, 234–236
- BDNF. *See* Brain-derived neurotrophic factor
- 17 β -estradiol (E2)
 acetylcholine (ACh) release, 269
 acute ischemic stroke, 119
 GABAergic system, functions and transmission
 developmental stage transmission, 282–287
 matured stage transmission, 287–289
 membrane potential hyperpolarization,
 281–282
 mechanisms of action
 estrogen receptors (ERs), 290
 GABA_ARs subunit expression, 291
 glutamic acid decarboxylase (GAD), 291
 NaKCC₁ cotransporter, 290–291
 receptor clusterization, 293
 synapse reorganization, 292
 rewarding property, 248–249
 synaptic plasticity regulation
 long-term depression (LTD), 230–231
 long-term potentiation (LTP), 225–230
 NMDA, and AMPA receptor regulation,
 222–225
- 11 β -hydroxysteroid dehydrogenase type 2, 370
- Blood–brain barrier
 androgen receptor fire ring, 97, 99–100
 xenobiotic treatment, 95–98
- Brain-derived neurotrophic factor (BDNF)
 anxiety-related behaviors, 190–191
 cognitive benefits, 188–189
 cognitive disorder treatment, 188
 estrogen, 325
 learning and memory, 187–188
 rewarding and addictive behavior, 191–192
 stress adaptation, 192–194
 therapeutic effects, 194
- Brain disorder treatment, 194
- Brain injury, corticosteroids expression
 behavioral effects, 409–411
 unbalanced MR/GR levels, 407–409
- Brain ischemic injury and plasticity
 adult plasticity mechanism
 angiogenesis, 116
 cell renewal, 115
 hormonal effects, 115–116
 neuronal regeneration, 115
 synaptic plasticity, 114–115
 amyloid- β species, 114
 astrocytes, 113–114
 cell death, 109–110
 cyclooxygenase-2 (COX-2), 111, 113
 cytokines and cell adhesion molecules, 113
 effects of, 108
 excitotoxicity, 108
 GABA-related inhibition, 109
 microglial cells, 113
 neuronal death, 110
 postischemic plasticity
 angiogenesis, 119–120
 axonal sprouting, 118–119
 gene and protein expression, 118
 neuroprotective factors, 119
 protein kinase, 117
 reactive synaptogenesis, 116–117
 sequential molecular factors, 120–121
 synaptic remodeling, 116
 tissue plasminogen activator (tPA),
 117–118
 postsynaptic density (PSD), 110–111
 protein synthesis and proteolysis, 109
 reactive oxygen species (ROS), 107
 synaptic transmission, 108–109
 synaptic vesicles (SVs), 111
- Brain motivational pathways, 150–151

C

- Cholecystokinin (CCK), 247
- Chronic unpredictable mild stress (CUS), 9–10
- Cognitive disorder
 nerve growth factor (NGF), 189
 treatment, BDNF, 187–189
- Conditioned place preference (CPP)
 advantages and limitations, 245–246
 conditioning methods, 244–245
 hormones, rewarding property
 corticosteroids, 247–248
 estradiol and progesterone, 248–249
 luteinizing hormone releasing hormone
 (LHRH), 248
 melatonin and substance P, 247
 oxytocin, cholecystokinin, and ghrelin, 247
 testosterone, 250–251
 measurements obtained, 245
- Corticobasal ganglia-thalamocortical limbic
 circuit, 55–56
- Corticosteroids
 mossy fiber synapse, 75–76
 neurons survival and behavioral impairment,
 receptors role
 brain injury effects, 407–411
 detrimental effects, GR activation, 396–401
 hippocampal development, 396
 properties, 394–395
 temperature effects, hypoxia–ischemia,
 405–407
 neuroprotection, MR
 detrimental effect, cerebral ischemia, 405
 injury-induced expression, 401–403

- mechanisms of action, 403–404
 - neuronal stress effect on, 404–405
 - receptor, ontogeny, 373–377
 - rewarding property, 247–248
 - Corticosterone, 326
 - Corticotropin-releasing factor (CRF),
 - transcriptional regulation
 - activator protein 1, 308–310
 - cAMP response element-binding protein (CREB), 303–305
 - estrogens, 306–307
 - glucocorticoid receptor, 308–309
 - inducible cAMP-early repressor (ICER), 306
 - schematic representation, 314
 - suppressor of cytokine signaling (SOCS)-3, 310–313
 - Corticotropin-releasing hormone (CRH)
 - Alzheimer's disease, 356
 - depression (*see also* Depression)
 - and arginine vasopressin (AVP), 349–356
 - HPA axis, hyperactivity and sex difference, 343–348
 - CRF. *See* Corticotropin-releasing factor (CRF), transcriptional regulation
 - Cyclooxygenase-2 (COX-2), 111–113
 - Cytochrome P₄₅₀, 91–92
- D**
- Deep brain stimulation (DBS). *See* High frequency stimulation
 - Depression, 28–30
 - Alzheimer's disease, 356–357
 - arginine vasopressin (AVP)
 - chronic stress, 349–351
 - circadian system, 354–356
 - SON and PVN, 351–354
 - vasopressinergic systems, 349
 - estrogen level and gender, 324–325
 - general considerations in modeling, 2–3
 - glutamate uptake, 28–29
 - human leukocyte antigen, 30
 - hypothalamo-pituitary-adrenal (HPA) axis
 - corticotropin-releasing hormone
 - hyperactivity, 343–344
 - sex difference, 344–348
 - reduced glial number identification, 29
 - stress-based models
 - chronic unpredictable mild stress, 9–10
 - early-life stress, 11–14
 - forced swim test, 6–7
 - hedonic sensitivity, 10–11
 - hyponeophagia test, 8–9
 - learned helplessness, 6
 - risk factors, 4
 - rodent behavioral models, 4–5
 - social defeat, 14–15
 - tail suspension test, 7–8
 - symptoms, 2
- Dynorphin
 - anticonvulsant, 74
 - MF synaptic transmission regulation, 73
- E**
- Early-life stress (ELS)
 - maternal care, 13
 - maternal separation, 12–13
 - models, 11–12
 - prenatal stress, 13–14
 - ELS. *See* Early-life stress
 - Endoplasmic reticulum stress, 136–137
 - Enkephalin, 72
 - Epilepsy
 - amygdala-kindled seizure, 27–28
 - electroconvulsive seizures, 28
 - kainic acid, 27
 - KAR-mediated, 177–178
 - xenobiotic treatment, 95–97
 - Estrogen
 - corticotropin-releasing factor, transcriptional regulation, 306–307
 - limbic system and estrogen receptors (ERs)
 - anatomy, 322–323
 - cyclic E2 administration and stress, 326–328
 - depression and anxiety disorders, 324–326
 - distribution of, 323
 - ER β expression, 323–324
 - intracellular colocalization, 321–322
 - mirtazapine, antidepressant, 329–331
 - neuroplasticity enhancement, 328–330
 - synaptic plasticity
 - glutamatergic synaptic transmission, 221–222
 - long-term depression (LTD), 230–231
 - long-term potentiation (LTP), 225–230
 - NMDA, and AMPA receptor regulation, 222–225
 - Estrous cycle and hippocampal LTP, 227–230
- F**
- Fluoxetine, 75
 - Forced swim test (FST), 6–7
 - Forskolin. *See* Pituitary adenylate cyclase-activating polypeptide
- G**
- GABAergic system
 - 17 β -estradiol, functions and transmission
 - developmental stage transmission, 282–287
 - matured stage transmission, 287–289
 - membrane potential hyperpolarization, 281–282
 - kainate receptors
 - GluR5, 172–173
 - GluR6, 173–174
 - Ghrelin, rewarding property, 247

- Glia, astrocytes
 calcium waves, 26
 depressive disorder
 glutamate metabolism, 28–29
 oligodendrocyte density, 30
 reduced glial number identification, 29–30
 epileptic states
 amygdala-kindled seizure, 27–28
 electroconvulsive seizures, 28
 gonadal hormones
 adulthood, 34–36
 early development, 33–34
 hyperalgesia, 37
 other pathologies, 32
 processes, 26
 proteinopathies
 Alzheimer's disease, 31–32
 Parkinson's disease, 30–31
 serotonin, 36
 sleep disorder, 32
 structure and function, 25–26
- Glucocorticoids
 adult hippocampal neurogenesis, 424–425
 arginine vasopressin (AVP), 349–356
 CRH neurons, hyperactivity, 343
 receptor (GR)
 activation and detrimental effects, 396–401
 brain injury effects, 407–411
 corticotropin-releasing factor (CRF),
 transcriptional regulation, 308–309
 hippocampal development, 396
 ontogeny, 373–377
 prenatal stress effect, 379–381
 properties, 394–395
 temperature effects on, 405–407
- Glutamate
 immunohistochemical investigation, 71
 kainate
 inhibitory effects, 70–71
 potentiation, 70
 receptors, 69–70
 metabotropic receptors, 71–72
 opioid dependence, 148–149
 receptors, GluR5–7, 172–174
- Gonadal hormones
 adulthood
 estradiol treatment, 34
 MePD astrocytes, 35–36
 testosterone, 35
 early development, 33–34
- H**
- Hedonic sensitivity, 10–11
 HFS. *See* High-frequency stimulation
 High-frequency stimulation (HFS)
 limbic effects of
 animal studies, 52–53
 cognitive and behavioral effects, 50
 depression disorder, 50–51
 hypomania, 50–51
 postoperative behavioral changes, 52
 mossy fiber synapse, 72
 and stereotaxy
 neuronal mechanisms, 49–50
 T1-weighted postoperative MRI, 48–49
- Homeostasis
 brain motivational pathway, opioids, 150
 CRF gene regulation (*see* Corticotropin-releasing factor (CRF), transcriptional regulation)
- HPA axis. *See* Hypothalamo–pituitary–adrenal (HPA) axis
- Hyperthermia, corticosteroids expression, 405–407
 Hypomania, 50–51
 Hyponeophagia tests, 8–9
 Hypothalamic inflammation. *See also* Obesity
 anorexigenic signal resistance
 hormone resistance, 137–138
 serine-kinase, 138
 SOCS3, 138
 tyrosine phosphatase PTP1B, 138–139
 diet-induced obesity, 129–130
 feeding and energy expenditure control
 endogenous cannabinoid system, 133
 first-order neurons, 130–132
 insulin receptor, 135–136
 leptin (ObRb) receptors, 133–135
 MCH neurons, 132
 orexin, 132
 nutrient-induced dysfunction
 endoplasmic reticulum stress, 136–137
 fatty acids, 136
- Hypothalamo–pituitary–adrenal (HPA) axis
 corticosteroid receptors alteration, brain injury
 behavioral effects, 409–411
 unbalanced MR/GR effect, 407–409
 depression
 corticotropin-releasing hormone
 hyperactivity, 343–344
 early-life stress, 11–14
 sex difference, 344–348
 social defeat, 14–15
 postnatal development
 adrenal hyporesponsiveness, 369–370
 advantages, 371
 11 β -hydroxysteroid dehydrogenase activity,
 370–371
 leptin levels, 370
 maternal deprivation, 371
 sex-differences, HPA axis activity, 371–373
- Hypothermia, corticosteroids expression,
 405–407
- Hypoxia, MR and GR expression
 detrimental effects, 396–397
 temperature effects, 405–407

I

Inducible cAMP-early repressor (ICER), 306

Insulin

- anorexigenic signal resistance, 137–139
- feeding and energy expenditure, 135–136

K

Kainate receptors (KARs)

anatomical localization

- GluR5, 172–173
- GluR6, 173–174
- GluR7, 174
- ³H KAR binding, 171
- KA1 gene expression, 172, 174–175
- KA2 gene expression, 172, 175

disease

- epilepsy, 177–178
- hippocampal neurotoxicity, 178–179
- mental disorders, 179

electrophysiological function

- glutamatergic transmission, 175
- MFT–CA3 synaptic plasticity, 175–176
- MFT LTP, 176–177

glutamate receptors, 168

ionotropic GluRs, 168

molecular structure, 169–170

mossy fiber synaptic transmission

- inhibitory effects, 70–71
- kainate-induced potentiation, 70
- long-term plasticity, 71

native form composition, 170–171

role in neural transmission, 169

Kainic acid, 27

KARs. *See* Kainate receptors

L

Learned helplessness (LH) tests, 5–6

Leptin

- arcuate nucleus (ARC), 204–205
- brain development, 205–206
- isoforms, 204
- neurotrophic actions, 209
- postnatal development, SHP, 370
- postnatal surge, 206–208
- receptor (ObRb), 133–135
- regulation, 203

Leptin receptors

- body weight regulation, 202
- developmental roles
 - brain development, 205–206
 - developmental changes, 209–210
 - early postnatal period, 207–209
 - neurotrophic actions, 209
 - postnatal leptin surge, 206–207
- energy balance regulator, CNS, 204–205
- neonatal leptin signaling, role of altered

- metabolic benefits, 212
- neonatal nutrition, 211
- severe maternal UN, 211–212

sources and regulation

- gene expression, 203
- leptin isoforms, 204
- obesity, 203
- signaling pathways and binding, 204

Limbic system

biochemical properties

- cytochrome P450, 91–92
- steroid hormones and receptors, 92–93

blood–brain barrier, 102

downstream effects from blood–brain barrier

- androgen receptor fire ring, 97, 99–100
- disintegrated brain network function, 100–101

- epilepsy and tumours, xenobiotic treatment, 95–97

effects, HFS

- animal studies, 52–53
- cognitive and behavioral effects, 50
- depression disorder, 50–51
- hypomania, 50–51
- postoperative behavioral changes, 52

and estrogen receptors (ERs)

- affective disorders and gender, 324–325
- anatomy, 322–323
- antidepressant, 329–331
- cyclic E2 administration and stress, 326–328
- distribution of, 323
- estrogen and ER β expression, 323–324
- hippocampus and amygdala, 325–326
- intracellular colocalization, ER α and ER β , 321–322
- stress and neuroplasticity, 328–330
- synthesis and actions of, 320–321

molecular circuits

- AR and CYP3A4 expression, 93–94
- drug–hormone cross talk, 93
- treatment with chemotherapeutic drugs, 95

neuroactive steroids, 88–89

structure, 88

and xenobiotic uptake

- side effects, 90–91
- sources of, 89–90

Lithium, neurogenesis, 425–426

Long-term depression (LTD)

- estrogen, hippocampus regulation, 230–231
- mossy fiber synapse, 67–68
- progesterone, hippocampus regulation, 232–233

Long-term plasticity, 67–68

Long-term potentiation (LTP)

- acetylcholine (ACh) role in, 264–265
- estrogen, hippocampus regulation
 - estrous cycle, 227–230
 - highfrequency stimulation, 225–227
 - src inhibitor effect, 226

- Long-term potentiation (LTP) (*cont.*)
 ischemia, 116
 kainate receptors, 175–177
 mossy fiber synapse
 Eph receptor–ephrin system, 67–68
 glutamate, 69–72
 monoamines, 74
 progesterone, hippocampus regulation,
 232–233
 Luteinizing hormone releasing hormone
 (LHRH), rewarding property, 248

M

- Magnetic resonance imaging (MRI), PD, 48–49
 Melatonin, rewarding property, 247
 Mental disorders, 179
 Microglial cells, 113
 Mineralocorticoid receptor (MR)
 brain injury effects, 407–411
 hippocampal development, 396
 neuroprotective role, 401–405
 ontogeny, 377–378
 properties, 394–395
 temperature effects on, 405–407
 Mirtazapine, antidepressant activity, 329–331
 Molecular circuits
 AR and CYP3A4 expression, 93–94
 drug-hormone cross talk, 95
 Monoamines, 74–75
 Mossy fiber (MF) synaptic transmission
 CA3 pyramidal cells, 66
 and hormones, 75–76
 kainate receptors
 long-term potentiation (LTP), 176–177
 presynaptic KARs, 176
 modulation
 advantages, 68–69
 glutamate, 69–72
 monoamines, 74–75
 neuropeptides, 72–74
 neuromodulators, 66
 physiological characteristics
 excitatory interneurons, 68
 long-term plasticity, 67–68
 short-term plasticity, 66–67
 stress effects and experience on, 76–77

N

- Nerve growth factor (NGF)
 aggressive behavior, regulation, 190
 cognition enhancer, 189
 plasma, 192
 Neurochemistry, central amygdala (CeA),
 151–152, 158–159
 Neurogenesis, adult hippocampus
 lithium action, 425–427
 postmitotic maturation phase, 423–424

- precursor cell phase, 422–423
 stress and glucocorticoids actions, 424–425
 Neuropeptides, 73–74
 Neuroprotection
 mineralocorticoid receptor (MR)
 detrimental effect, cerebral ischemia, 405
 injury-induced expression, 401–403
 mechanisms of action, 403–404
 neuronal stress effect on, 404–405
 Neurotoxicity, 178–179
 Neurotrophins
 aggressive and defensive behavior, 189–190
 anxiety-related behaviors, 190–191
 behavioral process, 186–187
 brain disorder treatment, 194
 cognition-enhancing effects of
 BDNF, 187–189
 NGF, 189
 leptin actions, 209
 NT-3 and NT-4/5, 189
 rewarding and addictive behavior, 191–192
 role and types, 186
 stress adaptation, 192–194
 NGF. *See* Nerve growth factor
 N-methyl-D-aspartate (NMDA) receptors
 central nucleus and dependence
 brain motivational pathways, 150–151
 neuroactive peptides, 151–152
 conditioned aversive properties, 155, 158
 dendritic outgrowth, 119
 glutamate-responsive, 148–149
 kainate receptors (*see* Kainate receptors)
 mossy fiber synapse, 69
 opioids and dependence
 conditioned place aversion (CPA), 148
 pernicious complication, 147
 withdrawal symptoms, 147–148
 postsynaptic CeA NR1 deletion
 Cre-lox technology, 154–156
 opioid dependence, 155
 withdrawal-induced place aversion, 155,
 157
 synaptic plasticity regulation, 224–225
 synaptic relationship with μ -opioid
 dendritic distribution, 152–154
 immunoelectron microscopic analysis,
 152–153
 Noradrenaline, 74
 Novelty induced hypophagia (NIH), 8
 Novelty-suppressed feeding (NSF), 8

O

- Obesity
 epidemiology, 129–130
 feeding and energy expenditure, hypothalamic
 control
 endogenous cannabinoid system, 133
 first-order neurons, 130–132

- insulin receptor, 135–136
 - leptin (ObRb), 133–135
 - MCH neurons, 132
 - orexin, 132
 - hypothalamic resistance, anorexigenic signals
 - hormone resistance, 137–138
 - serine-kinase, 138
 - SOCS3, 138
 - tyrosine phosphatase PTP1B, 138–139
 - nutrient-induced dysfunction of hypothalamus
 - endoplasmic reticulum stress, 136–137
 - fatty acids, 136
 - Opioids
 - central amygdala (CeA) NR1 deletion
 - conditioned emotional properties, 155, 158
 - Cre-lox technology, 154–156
 - naloxone withdrawal-induced place aversion, 155, 157
 - synaptic coding, 158–159
 - and dependence
 - antagonist-precipitated withdrawal, 147
 - central nucleus, 149–152
 - conditioned place aversion (CPA), 148
 - glutamate receptors, 148–149
 - pernicious complication, 147
 - withdrawal symptoms, 147–148
 - NMDA and μ -opioid receptor, synaptic relation
 - dendritic distribution, 153–154
 - ultrastructural distribution, 152–153
 - Orexin, 132
 - Oxytocin, rewarding property, 247
- P**
- Parkinson's disease (PD)
 - glia, 30–31
 - high-frequency stimulation
 - limbic effects of, 50–53
 - and stereotaxy, 48–50
 - surgical therapy, 48
 - Peroxiredoxin, 6, 31–32
 - Pituitary adenylate cyclase-activating polypeptide (PACAP). *See* Corticotropin-releasing factor (CRF), transcriptional regulation
 - cAMP production, 303
 - IL-6 mRNA expression, 310–311
 - Positive affective (PA) state. *See* Sexual reward
 - Prenatal stress, 13–14
 - Progesterone
 - rewarding property, 248–249
 - synaptic plasticity of
 - baseline synaptic transmission (BST), 234–236
 - LTP and LTD, 232–233
 - receptors, 232
 - Pro-opiomelanocortin (POMC), 370
 - Proteinopathy
 - Alzheimer's disease, 31–32
 - Parkinson's disease, 30–31
- R**
- Reactive oxygen species (ROS), brain ischemic injury, 107
- S**
- Septohippocampal cholinergic neurons, ACh release, 266–267
 - Serotonin
 - astrocytes, 36
 - mossy fiber synapse potentiation, 74
 - Sexual reward
 - conditioned place preference (CPP)
 - advantages and limitations, 245–246
 - conditioning methods, 244–245
 - and hormones, 246–251
 - measurements obtained, 245
 - female sexual behaviour
 - clitoral stimulation (CLS), 256
 - opioids, 255
 - paced mating, 254–255
 - vaginal stimulation, 255
 - male sexual behaviour
 - brain area involved, 252
 - DA-mediated reward, 253
 - endogenous opioids modulation, 251–252
 - positive affective (PA) state
 - definition, 242–243
 - evaluation methods, 243–244
 - Social defeat, 14–15
 - Spatial learning and memory, ACh release effect, 264
 - Stereotaxy, HFS
 - neuronal mechanisms, 49–50
 - T1-weighted postoperative MRI, 48–49
 - STN. *See* Subthalamic nucleus
 - Stress
 - CRF, transcriptional regulation, 303–312
 - cyclic E2 administration
 - corticosterone levels, 326
 - paraventricular (PVN) activity, 326–328
 - depression, 341
 - mossy fiber synaptic transmission, 76–77
 - neurotrophins function, 192–194
 - Stress-hyporesponsive period (SHR), postnatal development
 - adrenal hyporesponsiveness, 369–370
 - advantages, 371
 - 11 β -hydroxysteroid dehydrogenase activity, 370–371
 - leptin levels, 370
 - maternal deprivation, 371
 - sex-differences, HPA axis activity, 371–373
 - Substance P, rewarding property, 247

Subthalamic nucleus (STN)

anatomy

basal ganglia-thalamocortical limbic circuit,
55–56

functional subdivisions, 54–55

primates *vs.* rats, 54

behavioral changes, 56–57

high-frequency stimulation

limbic effects of, 50–53

and stereotaxy, 48–50

surgical therapy, 48

Suppressor of cytokine signaling (SOCS)-3

corticotropin-releasing factor (CRF) regulation

anti-IL-6 Ab effects, 311

JAK and PKA inhibitors effects, 312

negative regulation, 310

promoter activity, 313

obesity, 138

Synaptic plasticity

acetylcholine (ACh) release, 264–265

adult brain, 114–115

estrogen regulation

long-term depression (LTD), 230–231

long-term potentiation (LTP), 225–230

NMDA, and AMPA receptor regulation,
222–225

progesterone regulation, 232–233

α -Synuclein, 30–31

T

Tail suspension test (TST), 7–8

Testosterone

acetylcholine (ACh) release, 268

and ACh release, 268–269

amygdala glia, 34–35

limbic system, molecular circuits, 93–95

rewarding property, 250–251

Tissue plasminogen activator (tPA), 117–118

U

Unfolded protein response (UPR), 137

X

Xenobiotics, limbic system

blood-brain barrier, 102

cytochrome P450, 91–92

downstream effects

androgen receptor (AR) fire-ring, 97,
99–100

disintegrated brain network function,
100–101

epilepsy and tumors, 95–97

molecular circuits

AR and CYP3A4 expression, 93–94

drug-hormone crosstalk, 93

treatment with chemotherapeutic drugs, 95

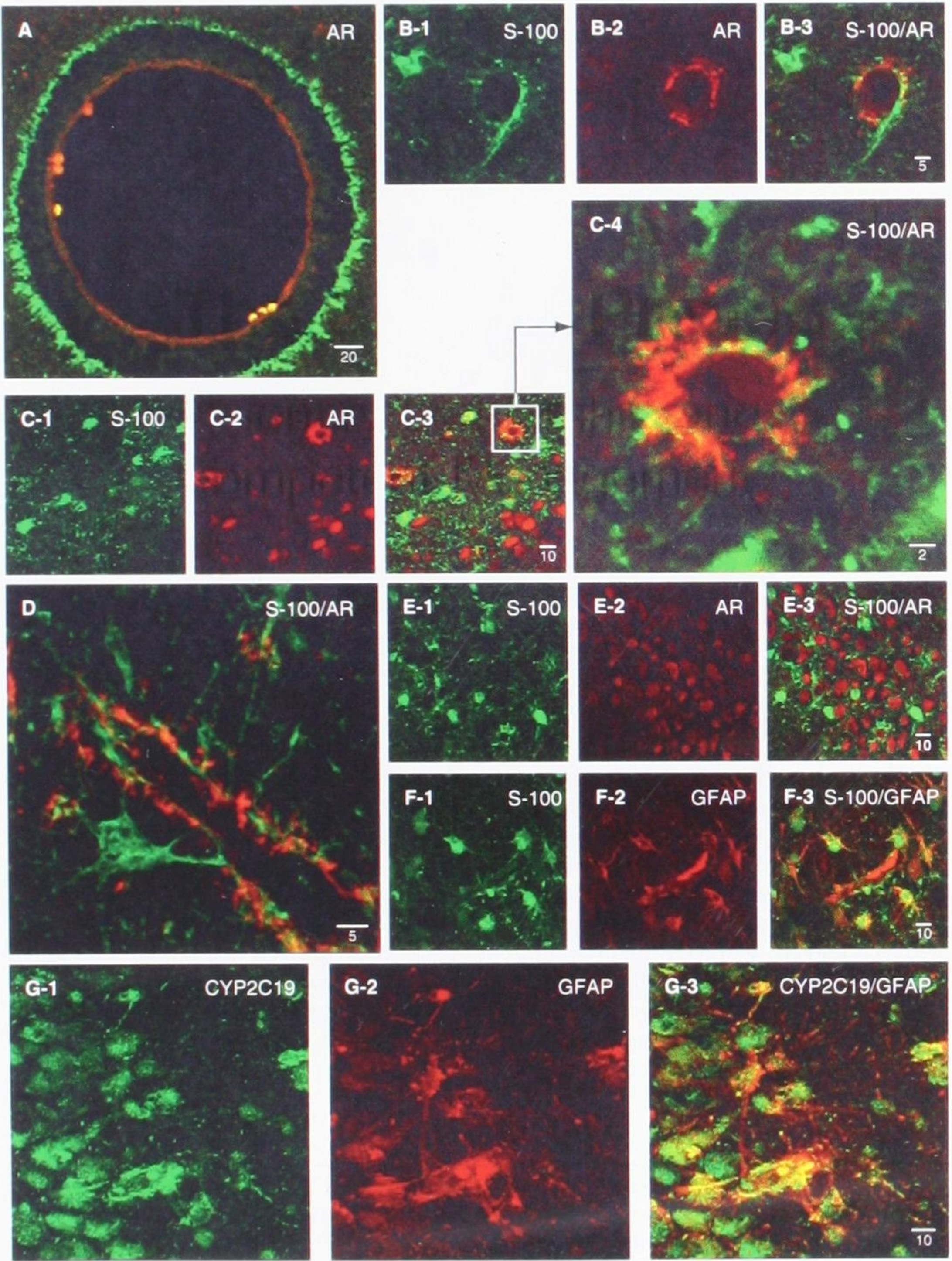
network homeostasis, 101

neuroactive steroids, 88–89

side effects, 90–91

sources of uptake, 89–90

steroid hormones and receptors, 92–93



Ralf P. Meyer *et al.*, Figure 5.4 Characterization of AR expression at the capillaries of the limbic system. High-power confocal images of double-labeled sections illustrating expression and colocalization of AR, the glial markers S-100 and GFAP, and CYP2C19. Colocalization of the antigens appears yellow in the overlay mode (B-3, C-3, C-4, D, E-3, F-3, and G-3). All sections were derived from paraffin embedded biopsy or autopsy samples of epilepsy patients treated with P450-inducing AEDs (carbamazepine, oxcarbazepine, or phenytoin) (see legend of Fig. 5.1 for details). (A): AR expression (green) around a capillary vessel in the subventricular zone of

Index

A

- Accessory olfactory system (AOS)
 accessory olfactory bulb (AOB), 334
 gonadotropin-releasing hormone (GnRH), 336
 hypothalamic and limbic regions, 335
 pheromonal control
 female sexual behavior, 306
 male sexual behavior, 342–343
 mate discrimination, 341–342
 pheromonal processing
 2-heptanone detection, 340
 MHC peptide detection, 340
 nonvolatile pheromones, 337
 pregnancy block effect, 338–339
 volatile pheromones, 336–337
 pheromone detection, 335
 reproductive function, 334–335
 schematic organization, 334
 vomeronasal organ (VNO), 335
- Acyl-CoA binding proteins (ACBP), 434–435
- Additive/synergistic effect, 613–614
- Alarm pheromones
 alarm-eliciting effect, 467–468
 animal systems, 217–220
 ants
 aggressive and panic alarms, 224
 aliphatic carbon chains, 224
 Camponotus obscuripes (Formicinae), 225
 formicidae, 224
 aphids
 alate and apterous *Myzus persicae*, 221
 behavioral effect, 223
 (E)- β -farnesene (Ebf), 222–223
 Germacrene A, 222
 volatile emissions, 222
 applications
 aquatic pests, 232
 grass-cutting ants, 232
 non-insect alarm pheromones, 232
 behavioral impacts, 216–217
 chemical composition, 217
 components, 467
 definition, 467
 effective sting and functional venom, 470–471
 evasive/aggressive, 217
 fishes, 228–229
 honeybees
 (Z)-11-eicosen-1-ol, 226
 guard bees, 225
 isopentyl acetate, 226
 kairomones, 226–227
 mammals, 229–230
 marine invertebrates, 227–228
Mischocyttarus immarginatus, 470
 plants, 230–231
 Stenogastrinae family, 470–471
 venom glands, 469
 venom volatiles, 470
 visual and auditory components, 216
 yellowjackets, 467
- Alarm pheromones, aphid
 aphid colonization reduction, 554
 secondary plant metabolite, 555
- Amygdala
 chemosensory division (*see* Chemosensory amygdala)
 multimodal division, 169
- Amygdalo-piriform transition area (APir)
 calretinin immunoreactivity, 173–174
 layer II, 172–173
 medial and lateral divisions, 173
- Androstenes
 human social interactions
 androstenone thresholds, 74
 chemical signals, 69–70
 compound concentrations, 70–71
 compound-specific effects, 69
 ecological validity, 72
 female perceptions, male odor, 72–73
 intrasexual signaling system, 72
 odor controls, 73
 odor specificity, 73–74
 sex difference, 71–72
 mood changes
 emotional contexts, 64
 erotic fiction, 63–64
 eugenol, 63
 olfactory thresholds
 bimodal distribution, 55–56
 heritability and genetic variation, OR7D4, 55
 menstrual cycle, 56
 sexually dimorphic effect, 56
 production
 age and sex, 50
 axillary region, 49–50
 metabolism, 49
 quantitative assessments, 51–52

Androstenes (*cont.*)

- psychological effects
 - behavioral effects, 64
 - brain imaging, 65–68
 - interpersonal perception, 58–62
 - mood changes, 62–64
 - physiology, 65
- psychophysical research
 - hedonic perception, 57–58
 - olfactory thresholds, 55–56
 - sensitization, 56–57
 - specific anosmia, 52–55
- skin microflora, 50–51

Androsthenol and androstenone

- high concentration, 33
- inconsistent findings, 33
- intersexual contact, 34
- menstrual cycle, 33
- social interactions, 32

5- α -Androstenone, 313–315

Anosmia, 311

Anterior amygdaloid area (AA), 179–180

Anterior cortical nucleus (ACo), 175–176

Ants, alarm pheromones

- aggressive and panic alarms, 224
- aliphatic carbon chains, 224
- Camponotus obscuripes* (Formicinae), 225
- formicidae, 224

Aphid pheromones

- alarm pheromones, 554–555
 - alate and apterous *Myzus persicae*, 221
 - behavioral effect, 223
 - (E)- β -farnesene (Ebf), 222–223
 - Germacrene A, 222
 - volatile emissions, 222
- characteristics, 552
- semiochemicals
 - definition, 553
 - gas chromatography-mass spectrometry (GC-MS), 554
 - volatile collection methods, 553
- sex pheromone components
 - age dependence, 558
 - aggregation pheromone, 566
 - applications, 563–566
 - dolichodial, 561–562
 - dynamic headspace analysis, 556
 - iridoid ratio, 557
 - mature sexual female aphids, 555
 - phenylacetonitrile, 561
 - plant volatile synergism, 562–563
 - spacing pheromone, 566
 - stereochemistry role, 558–560

Attracticide strategy

- mass trapping, 508
- olfactory attractants, 508
- protein degradation, 509

B

Baeyer–Villiger reaction, 612

Bed nucleus of the accessory olfactory tract (BAOT), 179

Bermuda grass infusion fermentation, 617

(E)- β -farnesene (EBF), 555

Biodegradable lethal ovitrap (BLO), 619

Blackflies. *See Simulium damnosum*

Blood feeding bugs, oviposition

- aggregation activity, 608
- alarm signal, 609
- odor, 609
- synchronization signal, 610

Body odor

- apocrine glands, 4
- central processing
 - behavioral effects, 4–5
 - vs.* common odors, 5
 - olfactory stimulation-induced visual activations, 6–7
 - posterior cingulate cortex (PCC), 5–6
- eccrine glands, 4
- fear, neuronal processing
 - acoustic startle reflex, 8
 - ambiguous emotional expression, 8
 - amygdala, 10–11
 - chemosensory system, 9
 - cortical network, 9–10
 - glandular sources, 11–12
 - hidden warning signals, 12
 - neuroimaging studies, 9
 - odor sample collection, 7
 - parachute jump, 8–9
- kin recognition
 - human leukocyte antigen, 15
 - MHC and mating preference, 15
 - self-referential mechanism, 16
- mate choice
 - fluctuating asymmetry (FA), 38–39
 - major histocompatibility complex, 36–38
- microsmatic animals, Broca's
 - description, 2–3
- olfactory system
 - neuroimaging analysis, 14
 - olfactory brain, 12–13
 - olfactory cortex, 13
 - sensory pathway, 12
- perception, 3
- sebaceous glands, 4
- sex differences
 - male body odor, female (*see* Male body odor, female perceptions)
 - olfactory sensitivity, 29–30

Bombyx mori pheromonogenesis

- bombykol biosynthesis
 - fatty-acyl desaturase, 431

- PG-specific fatty-acyl reductases (pgFAR), 431–432
- LD dynamics
 - acyl-CoA binding proteins, 434–435
 - B. mori* FATP homolog (BmFATP), 433–434
 - constituents, 432–433
- PBAN signal transduction cascade
 - BmSTIM1 and BmOrai1B, 439
 - model, 439–440
 - PBAN receptor (PBANR), 435–437
 - store-operated channel activation, 436–438
- PG expressed-sequence tag (EST) database, 430–431
- pheromone gland, 427
- Bruce effect. *See* Pregnancy block effect

C

- Calmodulin-binding domains, 202–203
- Ca²⁺ release-activated Ca²⁺ channel modulator 1 (CRACM1), 439
- Carnivores
 - mammary odor
 - odor learning, 110–111
 - pheromones, 111
 - sources, 109–110
 - odor-mediation, 108
- Chemical communication, MUP
 - behavioral and physiological response, 155
 - individual identity signature, 155–156
 - volatile pheromone carriers, 155
- Chemosensory amygdala
 - active pumping mechanisms, 168
 - evolutionary relevance, 186–189
 - mixed chemosensory amygdala (MxCA)
 - functional anatomy, 184–186
 - olfactory predominance, 175–178
 - vomer nasal predominance, 180
 - olfactory amygdala
 - amygdalo-piriform transition area (APir), 172–174
 - functional anatomy, 180–182
 - posterolateral cortical nucleus (PLCo), 170–172
 - vomer nasal amygdala
 - functional anatomy, 182–184
 - posteromedial cortical nucleus (PMCo), 174
 - posteromedial part of the medial BST (BSTMPM), 174–175
- Chin glands, rabbit
 - chemical composition, 353–354
 - chin-marking, males and females
 - biological significance, 360–361
 - neuroendocrine regulation, 355–359
 - ontogeny and sexual differences, 354–355
 - sensory regulation, 358–360
 - lobes, 353

- sexual dimorphism, 353
- steroid hormones, 353
- Cis-vaccenyl acetate (cVA), 274
- Cone-nose bugs, 608
- Corticoamygdaloid transition area (CxA), 176
- Cue-lure/raspberry ketone, 579–580
- Cue-lure (C-L) technology
 - environmental impact, 586–588
 - fruit flies, 579–580
 - HAWPM program, 583–587
 - vs.* male behavior
 - male *Bactrocera*-parapheromone association, 581
 - mating enhancement, 582
 - sensory trap, 583
 - sexual selection hypothesis, 580
- Culex* oviposition pheromone (CuOP), 611–612
- Cuticular hydrocarbons (CHCs), 453

D

- DAG effect, TRPC2
 - pore-dead TRPC2 mutants, 208–209
 - sensory signals, 209
 - SNARE-like activity, 208
 - TRPC3/6/7 subclade, 209
 - TRP_2 domain mutation, 208
- Dolichodial, 561–562
- Drosophila* CheB proteins
 - CheB42a, 277–278
 - secretion, extracellular compartment, 282
 - cis-vaccenyl acetate (cVA), 274
 - copulation attempts, males to female cuticular hydrocarbons, 278
 - courtship-activating pheromones, 282
 - expression patterns, 275–277
 - CheB42a, CheB93a, and CheB38c, 275–276
 - gustatory detection, pheromones, 277
 - GM2-activator protein, ML family, 279–281
 - gustatory specific pheromone-binding proteins
 - detection models, 283–284
 - function, 281–283
- Dual olfactory hypothesis, 168

E

- EBF. *See* (E)- β -farnesene
- Electroantennogram (EAG), 554, 603
- Estradiol benzoate implants, 358–359

F

- Farma Tech (FT) mallet MC wafer, 586
- Fatty-acyl desaturase, 431
- Fear, neuronal processing
 - acoustic startle reflex, 8
 - ambiguous emotional expression, 8
 - amygdala, 10–11

- Fear, neuronal processing (*cont.*)
 chemosensory system, 9
 cortical network, 9–10
 glandular sources, 11–12
 hidden warning signals, 12
 neuroimaging studies, 9
 odor sample collection, 7
 parachute jump, 8–9
- Female pheromones, pregnancy
 anxiety, postpartum mice
 decreased neurogenesis, 146–147
 decreased serum prolactin levels, 144–145
 impaired maternal behavior, 142–144
 suppressed prolactin, 144–146
 unfamiliar female pheromones, 141–142
- materials and methods
 anxiety testing, 139–140
 maternal behavior testing, 140
 neurogenesis, 140–141
 serum prolactin levels, 140
 statistical analysis, 141
 subjects, 139
- Female sex pheromones, 464–465
- Fertility/rank pheromones, 461–463
- Fetal olfactory learning, 294
- Flight behavior, oviposition, 613
- Frontal gland, isoptera
 function
 alarm pheromones, 529
 primer pheromone production, 530
- occurrence and morphology
 apical and basal differentiations, 526
 nasus, 526–527
- secretion chemicals
 chemical components, 528–529
 classification, 527
 defense secretion components, 528
- Fruit flies
 economic importance
 attractive component, 579
 bactrocera species, 578–579
 chemical structure, 579
 kairomone responses, 580
- HAWPM program
 agricultural chemicals registration, 584–585
 environmental impact, 587–588
 fruit fly monitoring and control technologies, 583
 invasive fruit fly detection, 584–586
 MAT, 586–587
 insect pheromones and parapheromones definitions, 577
vs. natural fruit fly, 578

G

- GLVs. *See* Green leaf volatiles (GLVs)
- Gonadotropin-releasing hormone (GnRH), 336

- Gray short-tailed opossum
 communication and reproduction
 accessory olfactory system, 382–384
 chemosignal diversity, 380–381
 dimorphic scent marking behavior, 379–380
 odors and pheromones, 379
 signal transduction, 381–382
 sniffing and nuzzling, 380
vs. didelphid marsupials, 378
- male estrus-inducing pheromone
 estrus induction, 384–385
 nonvolatile nature, 386
 nuzzling behavior, nonvolatile pheromone, 385
 scent marks, 385
 volatile components, 385–386
- metatherian and eutherian, 378
- reproductive activation
 copulation and ovulation, 389
 estrogenic effects, 387
 GnRH neuronal system stimulation, 386–387
 postlactational estrus, 390–391
 prepubertal exposure, 387–389
 progesterone, 389–390
- reproductive and behavioral ecology
 adult female opossums, 392–393
 ecology and natural history, 391
 young opossums, 392
- Green leaf volatiles (GLVs), 507–508

H

- Harder's glands, 363–364
- Hawaii area-wide pest management (HAWPM) program
 agricultural chemicals registration, 584–585
 fruit fly monitoring and control technologies, 583
 invasive fruit fly detection, 584–586
 MAT, 586–587
 ME and C-L/RK technology (*see* Methyl eugenol (ME) technology)
- HAWPM. *See* Hawaii area-wide pest management program
- Hedonic perception, androstenes
 menstrual cycle, 57–58
 verbal labels, 57
- Hepatic gluconeogenesis, MUP, 158
- Homers, 206–207
- Honeybees
 alarm pheromones
 (Z)-11-eicosen-1-ol, 226
 guard bees, 225
 isopentyl acetate, 226
- Honey bees, pheromones
 future aspects, 417

- gene regulation
 - long-term regulation, 409–410
 - pheromone-regulated transcription factors, 411–412
 - short-term regulation, 410–411
 - hormone regulation, 403
 - pheromone language, 415–416
 - pheromone regulation, 403
 - physiological and behavioral regulation
 - defense mechanism, 406–407
 - learning, 408
 - longevity, 407–408
 - reproduction, 404–405
 - task allocation, 405–406
 - social regulation
 - colony growth, 414–415
 - reproduction, 413–414
 - Human social interactions, androstenes
 - androstene thresholds, 74
 - chemical signals, 69–70
 - compound concentrations, 70–71
 - compound-specific effects, 69
 - ecological validity, 72
 - female perceptions, male odor, 72–73
 - intrasexual signaling system, 72
 - odor controls, 73
 - odor specificity, 73–74
 - sex difference, 71–72
 - Hydrophobic inner-shell domain, 201
- I**
- IA. *see* Isoamyl-acetate
 - Insect control strategies
 - attract-and-kill
 - mass trapping, 508
 - olfactory attractants, 508
 - protein degradation, 509
 - chemical communication inhibitors
 - structures, 503
 - TFMKs, 504
 - transition-state analogues, 503
 - upwind flight inhibition, 501–502
 - definition, 494
 - IPM programs, 494
 - mating disruption
 - insect population management, 500
 - lepidopteran pests, 495–499
 - minimum trapping area, 501
 - valving mechanism, 500
 - plant-based volatiles
 - global mixture, 504–506
 - GLVs, 507
 - ORNs, 507
 - push-pull strategies, 509–510
 - Integrated pest management (IPM) programs, 494
 - Integrated pest management (IPM) scheme, 565
 - Invasive fruit fly detection
 - Farma Tech (FT) mallet MC wafer, 586
 - Jackson traps, 584
 - IPM. *See* Integrated pest management (IPM) programs
 - Isoamyl-acetate (IA), 322
 - Isoptera, exocrine glands and pheromone
 - classification, 522–523
 - communication signals
 - releaser pheromones, 523
 - social interactions/activities, 524
 - frontal gland
 - function, 529–530
 - occurrence and morphology, 526–527
 - secretion chemicals, 527–529
 - mandibular glands
 - function, 531
 - occurrence and morphology, 530
 - secretion chemicals, 530–531
 - recognition mechanism
 - cuticle-exocrine gland semiochemical interactions, 540
 - eusocial colony ability, 541
 - salivary glands
 - function, 533–534
 - occurrence and morphology, 525, 531–532
 - secretion chemicals, 532–533
 - salivary or labial glands, 531–534
 - source
 - epidermal cells, secretory capacity, 524
 - extracellular space development, 526
 - glands, 525
 - sternal gland
 - function, 535–538
 - occurrence and morphology, 525, 534–535
 - secretion chemicals, 535–537
 - tergal gland
 - function, 539–540
 - occurrence and morphology, 525, 538–539
 - secretion chemicals, 539
- J**
- Jackson traps, fruit fly detection, 584
 - Jacobson's organ. *See* Vomeronasal organ (VNO)
- K**
- Kairomones
 - habitat associated, 603
 - pray/predator-released, 607–608
 - Kissing bugs, 608
- L**
- Labial glands, isoptera. *See* Salivary glands, isoptera
 - Lagomorphs
 - mammary odor
 - odor learning, 101–102

- Lagomorphs (*cont.*)
 pheromones, 102–103
 sources, 100–101
 odor-mediation, 100
- Lekking behavior, 599
- Lipid droplet (LD) dynamics, *B. mori*
 pheromonogenesis
 acyl-CoA binding proteins
 β -D-glucosyl-O-L-tyrosine, 435
 pgACBP and mgACBP, 434–435
B. mori FATP homolog (BmFATP), 433–434
 bombykol precursors, 432–433
 staining, 432
 triacylglycerols (TAGs), 432–433
- Lipotoxicity and insulin resistance, MUP, 158
- Lutzomyia longipalpis*, 600
- ## M
- Main olfactory system (MOS)
 gonadotropin-releasing hormone (GnRH),
 336
 main olfactory bulb (MOB), 333–334
 main olfactory epithelium (MOE), 333
 mate discrimination, pheromonal control, 341
 pheromonal control
 female sexual behavior, 343–344
 male sexual behavior, 342–343
 mate discrimination, 341
 schematic organization, 334
 volatile pheromonal signals
 androstenone, 337–338
 2-heptanone detection, 340
 (methylthio)-methanethiol (MTMT), 337
 MHC peptide detection, 340
 reproduction, 337–339
- Major histocompatibility complex, mate choice
 characteristics, 36–37
 HLA-dissimilarity, 37–38
 HLA-similarity, 37
- Major urinary protein (MUP)
 chemical communication
 behavioral and physiological
 response, 155
 individual identity signature, 155–156
 volatile pheromone carriers, 155
 future aspects, 159–160
 nutrient metabolism
 glucose metabolism, 157–158
 hepatic gluconeogenesis, 158
 lipid metabolism, 158
 lipophilic molecules, 158–159
 lipotoxicity and insulin resistance, 158
 nutrient sensing, 156–157
 structure and polymorphism
 androgen, 153–154
 multiple paralogous genes, 154
 pheromones, central β -barrel cavities, 153
 wild or outbred mice, 154
- Male annihilation technique (MAT)
 environment friendly developments, 586–587
 history, 586
- Male body odor, female perceptions, 30–31.
See also Olfaction, humans
- androstadienone
 male facial attractiveness, 35
 mood and physiological arousal, 34–35
 mood state, 34
 negative emotions, 34
- androstenol and androstenone
 high concentration, 33
 inconsistent findings, 33
 intersexual contact, 34
 menstrual cycle, 33
 social interactions, 32
- mate choice
 fluctuating asymmetry (FA), 38–39
 major histocompatibility complex, 36–38
- olfactory sensitivity
 androstenone, 29
 m-xylene, 30
 n-butanol and pyridine, 30
 olfactory detection thresholds, 29
 semiochemicals, 30
 physiological and behavioral impacts, 32–36
 sex determination, 31–32
 sexual behavior, 35–36
- Male estrus-inducing pheromone
 estrus induction, 384–385
 nonvolatile nature, 386
 nuzzling behavior, nonvolatile pheromone, 385
 scent marks, 385
 volatile components, 385–386
- Male sex pheromones
 rubbing behavior, 465–466
 scent-marking behaviors, 466
- Male-specific exocrine gland-secreting
 peptide 1, 337
- Mammalian reproduction
 communication, pheromone
 ablation or disruption, 375
 modulators, 374
 primer pheromone, 374–375
 releaser pheromones, 374
 signaler pheromones, 374
- female mammals
 ovarian activation, 377
 reproductive cycle, 375–376
 seasonal breeding, 376–377
 gray short-tailed opossum (*see* Gray short-tailed
 opossum)
- Mammary gland, rabbit
 mammary pheromone, 363
 nipple-search behavior, 361
 NSP emission, 361–362
- Mammary odor

- abdominal odor, endocrine control, 116–117
 attractant potency, 117–118
 carnivores
 odor learning, 110–111
 odor-mediation, 108
 pheromones, 111
 sources, 109–110
 chemoemission and chemoreception, 122
 chemoreception, newborns, 118
 cognitive mechanisms, 120–121
 lactation, evolution
 communicative function, 86
 exocrine structures, 86
 protective function, 86
 protolactation, 85–86
 lagomorphs
 odor learning, 101–102
 odor-mediation, 100
 pheromones, 102–103
 sources, 100–101
 mammary-based pheromone, 121
 mammary chemical signalization, newborns, 119
 mammary semiochemical system, 119–120
 marsupials
 bulbous swelling, macropodids, 93–94
 imminent parturition, 93
 learning evidence, 94
 odor-mediation, 92–93
 pheromones, 94
 self-licking, 93
 mother-to-newborn transmission, 84
 neonatal attraction, milk, 84
 neonatal localization effort, 85
 nursing-related variations, 117
 primates
 colostrum and milk, 112–114
 nipple/areolar region, 112
 odor learning, 115–116
 odor-mediation, 111–112
 pheromones, 116
 sebaceous and lacteal sources, 113
 volatile compounds, 114–115
 rodents
 biological secretions, 98
 experimental odorants, 97
 milk, 96
 neonatal olfactory abilities, 98
 nipple texture, 95–96
 odor learning, 97–98
 odor-mediation, 94–95
 pheromones, 98–100
 redundant reinforcing agent, 98
 self-licking, 96–97
 ungulates
 odor learning, 106–107
 odor-mediation, 104
 pheromones, 107
 sources, 105–106
- Mandibular glands, isoptera
 function, 531
 occurrence and morphology, 530
 secretion chemicals
 chemical analysis, 531
 mandibular gland ultrastructure, 530
- Marsupials
 mammary odor
 bulbous swelling, macropodids, 93–94
 imminent parturition, 93
 learning evidence, 94
 pheromones, 94
 self-licking, 93
 odor-mediation, 92–93
- MAT. *See* Male annihilation technique
- Mating disruption method
 insect population management, 500
 lepidopteran pests, 495–499
 minimum trapping area, 501
 valving mechanism, 500
- Medial amygdala (Me), 178–179
- Methyl eugenol (ME) technology
 environmental impact
 male lure traps, 588
 scavengers, 587
 fruit flies
 attractive component, 579
 bactrocera species, 578–579
 chemical structure, 579
 kairomone responses, 580
 HAWPM program, 583–587
vs. male behavior
 male Bactrocera–parapheromone
 association, 581
 mating enhancement, 582
 sensory trap, 583
 sexual selection hypothesis, 580
 shikimic acid/shikimate pathway, 577
- Mixed chemosensory amygdala (MxCA)
 functional anatomy, 184–186
 olfactory predominance
 anterior cortical nucleus (ACo), 175–176
 corticoamygdaloid transition area, 176
 nucleus of the lateral olfactory tract,
 176–178
 vomeronasal predominance
 anterior amygdaloid area, 179–180
 bed nucleus of the accessory olfactory
 tract, 179
 medial amygdala, 178–179
- Monodelphis domestica*. *See also* Gray short-tailed
 opossum
 communication and reproduction
 accessory olfactory system, 382–384
 chemosignal diversity, 380–381
 dimorphic scent marking behavior,
 379–380
 odors and pheromones, 379

- Monodelphis domestica*. See also Gray short-tailed opossum (*cont.*)
 signal transduction, 381–382
 sniffing and nuzzling, 380
 reproductive activation
 copulation and ovulation, 389
 estrogenic effects, 387
 GnRH neuronal system stimulation, 386–387
 postlactational estrus, 390–391
 prepubertal exposure, 387–389
 progesterone, 389–390
 reproductive and behavioral ecology
 adult female opossums, 392–393
 ecology and natural history, 391
 young opossums, 392
 Mother–infant interactions, volatile signaling
 olfaction and maternal behavior, 297
 precocious olfactory interaction, 296
 sociobiological remarks, 295–296
 Mother–infant relationship, postpartum anxiety.
 See Female pheromones, pregnancy
 Mother recognition, volatile signaling
 fetal olfactory learning, 294
 humans, 293–294
 nonhuman mammals, 292–293
 Moth sex pheromone production
 bombykol biosynthesis, 428–429
Bombyx mori (see *Bombyx mori* pheromonogenesis)
 cyclic nucleotides, 430
 extracellular Ca^{2+} , 429–430
 type II pheromone components, 428
 type I pheromone components, 428
- N**
- Nestmate recognition pheromones
 colony level, 455–457
 insignificant hypothesis, 460
 males and brood CHCs, 458–459
 population level, 454–455
 recognition mechanism, 457–458
 species level, 452–454
 Neuroendocrine regulation, chin-marking, rabbit
 chinning frequency, 357–358
 estradiol benzoate implants, 358–359
 progesterone receptor (PR), 356–357
 TP implants, 358–359
 Neurogenesis, pheromone exposure. See Female pheromones, pregnancy
 Nipple-search pheromone (NSP), 361–362
 Nucleus of the lateral olfactory tract (NLOT), 176–178
 Nutrient metabolism, MUP
 glucose metabolism, 157–158
 hepatic gluconeogenesis, 158
 lipid metabolism, 158

- lipophilic molecules, 158–159
 lipotoxicity and insulin resistance, 158
 nutrient sensing, 156–157

O

- O BPs. see Odorant-binding proteins
 3-octylthio-trifluoropropanone (OTFP), 503
 Odorant-binding proteins (OBPs)
 chemosensory proteins (CSPs), 242–243
 diversity of
 amino acid sequences, 243–244
 cladograms, 245
Drosophila melanogaster and *Anopheles gambiae* genome, 247
 Lepidopteran OBPs sequence, 246
 Lepidopteran PBPs alignment, 248–249
 three-dimensional structure, BmorPBP1 and BmorGOBP2, 244
 function of
 LUSH suppressing electrophysiological recording, 263–264
 pheromone removal and odorant concentration reduction, 263–264
 signal transduction, 262–263
 pheromone and ligand binding
 affinity constants (KD), 251–252
 cold-binding assay, ApolPBP1, 256–257
 components, 253
 fluorescent displacement-binding assay, 254–255
 identification, 258
 insect olfaction system, 257
 selective binding studies, 253–254
 sequence comparison, 255–256
 structures of, binding cavity establishment
 BmorGOBP2, 261
 BmorPBP1, 259
 LmadPBP, 260
 mosquito OBPs, 261
 subfamilies, 242
 Olfaction, humans
 body odor production
 apocrine glands, 27–28
 axillary microflora, 28
 axillary secretions, 28–29
 eccrine glands, 27
 sebaceous glands, 27
 olfactory communication
 human olfactory bulb, 26–27
 nonhuman animals, 26
 olfactory signals, 26
 Olfactory amygdala
 amygdalo-piriform transition area (APir)
 calretinin immunoreactivity, 173–174
 layer II, 172–173
 medial and lateral divisions, 173
 functional anatomy, 180–182

- posterolateral cortical nucleus (PLCo)
 axonal degeneration, 170
 layers, 171–172
 location, 171–172
- Olfactory functioning
 identification, orbitofrontal processes, 308–309
 sensitivity and schizophrenia
 abnormal steroid secretion, 312–313
 abnormal sweat, 311–312
 Anosmia, 311
 identification deficits, 309–310
 negative symptoms and olfactory deficits,
 318–323
 odorants acuity, 316–318
 steroid secretion and olfactory acuity, 313–315
 structural organisation, 307–309
 terminology, 307–308
- Olfactory receptor neurons (ORNs), 507
- Olfactory signals, rabbit
 anal gland, 364
 chin glands and their secretions
 chemical composition, 353–354
 lobes, 353
 sexual dimorphism, 353
 steroid hormones, 353
 chin-marking, males and females
 biological significance, 360–361
 neuroendocrine regulation, 355–359
 ontogeny and sexual differences, 354–355
 sensory regulation, 358–360
 Harder's glands, 363–364
 inguinal gland secretions, 364
 mammary gland
 mammary pheromone, 363
 nipple-search behavior, 361
 NSP emission, 361–362
 urine, 353–354
- Olfactory systems
 mate recognition and sexual behavior
 accessory olfactory system (*see* Accessory
 olfactory system (AOS))
 main olfactory system (*see* Main olfactory
 system (MOS))
- Olfactory thresholds, androstenes
 bimodal distribution, 55–56
 heritability and genetic variation, OR7D4, 55
 menstrual cycle, 56
 sexually dimorphic effect, 56
- ORNs. *See* Olfactory receptor neurons (ORNs)
- Oviparae, 555
- Oviposition, 613–614
- Oviposition pheromones, haematophagous
 insects
 blood feeding bugs
 aggregation activity, 608
 alarm signal, 609
 odor, 609
 synchronization signal, 610
- egg origin
 aggregation pheromone, 600
Culex tarsalis coquillett, 599
 semiochemical component separation, 601
Simulium damnosum, 600
- evaluation
 additive/synergistic effect, 613–614
 bioactive molecular-controlled release, 614
 field trials, 614–616
 flight behavior, 613
 habitat associated kairomones, 603
- larval origin
 axenic larvae effect, 602
 electroantennogram (EAG), 603
 electrophysiology, 602
 holding waters, 601
- microbial volatiles
 aqueous fungal infusion (AFI), 604
 kairomones stimulation, 605
- parapheromones
 aggregation pheromone, 605
 allelochemicals, 605
 attractants and stimulants, 606
 deterrent/repellent effect, 606
- predator/prey released kairomones, 607–608
- synthesis
 reaction sequence, 612
 sharpless epoxidation method, 611
- traps and baits, 616–619
 veterinary insects, 610–611
- Ovitrap
 Bermuda grass infusion fermentation, 617
 fermentation age, 618
 microbial volatile deployment, 618
 population dynamics monitoring, 616
 sticky and lethal ovitraps, 618–619
- P**
- 4-(p-acetoxyphenyl)-2-butanone, 579–580
- Parapheromones
 definition, 501
- PEA. *see* Phenyl-ethyl alcohol
- Peripheral lipid-binding signals, 201–202
- Pest management programs, 563
- PG expressed-sequence tag (EST) database,
 430–431
- PG-specific fatty-acyl reductases (pgFAR),
 431–432
- Phenylacetone, 561
- Phenyl-ethyl alcohol (PEA), 316–317
- Pheromone and ligand binding, OBPs
 affinity constants (KD), 251–252
 cold-binding assay, ApolPBP1, 256–257
 components, 253
 fluorescent displacement-binding assay,
 254–255
 identification, 258

- Pheromone and ligand binding, OBPs (*cont.*)
 insect olfaction system, 257
 selective binding studies, 253–254
 sequence comparison, 255–256
- Pheromone antagonists
 structures, 503
 TFMKs, 504
 transition-state analogues, 503
 upwind flight inhibition, 501–502
- Pheromone binding proteins (PBPs), 503
- Pheromone biosynthesis activating
 neuropeptide (PBAN)
Bombyx mori (*see also Bombyx mori*
 pheromonogenesis)
 BmSTIM1 and BmOrai1B, 439
 model, 439–440
 PBAN receptor (PBANR), 435–437
 store-operated channel activation, 436–438
Helicoverpa armigera, 428
- Pheromone degrading enzymes (PDEs), 503
- Pheromones
 alarm pheromones, 466–471
 female sex pheromones, 464–465
 major urinary protein (*see* Major urinary
 protein (MUP))
 male sex pheromones, 465–466
 mammary odor
 carnivores, 111
 lagomorphs, 102–103
 marsupials, 94
 primates, 116
 rodents, 98–100
 ungulates, 107
 mate recognition and sexual behavior
 accessory olfactory system (*see* Accessory
 olfactory system (AOS))
 main olfactory system (*see* Main olfactory
 system (MOS))
 nestmate recognition pheromones
 colony level, 455–457
 males and brood CHCs, 458–459
 population level, 454–455
 recognition mechanism, 457–458
 species level, 452–454
 postpartum anxiety
 anxiety testing, 139–140
 decreased neurogenesis, 146–147
 decreased serum prolactin levels, 144–145
 impaired maternal behavior, 142–144
 maternal behavior testing, 140
 mood disorders, 138
 neurogenesis, 140–141
 serum prolactin levels, 140
 statistical analysis, 141
 subjects, 139
 suppressed prolactin, 144–146
 unfamiliar female pheromones, 141–142
 queen and fertility/rank pheromones, 461–463
 reproduction and communication
 gray short-tailed opossum
 (*see* Gray short-tailed opossum)
 social wasps (*see* Social wasps)
 superorganisms (*see* Superorganisms,
 pheromones)
 TRPC channels, 198–199
 Plant-based volatiles, insect control, 504–508
 Posterior cingulate cortex (PCC), 5–6
 Posterolateral cortical nucleus (PLCo)
 axonal degeneration, 170
 layers, 171–172
 location, 171–172
 Pregnancy block effect, 338–339
 Primates
 mammary odor
 colostrum and milk, 112–114
 nipple/areolar region, 112
 odor learning, 115–116
 pheromones, 116
 sebaceous and lacteal sources, 113
 volatile compounds, 114–115
 odor-mediation, 111–112
 Primer pheromone, 374–375
 Prolactin, pheromone exposure. *See* Female
 pheromones, pregnancy
 Psychophysical research, androstenes
 hedonic perception, 57–58
 menstrual cycle, 57–58
 verbal labels, 57
 olfactory thresholds
 bimodal distribution, 55–56
 heritability and genetic variation,
 OR7D4, 55
 menstrual cycle, 56
 sexually dimorphic effect, 56
 sensitization, 56–57
 specific anosmia
 androstenone nondetection rates, 53–54
 labeled anosmics, 52, 55
 trigeminal system, 55
 Push-pull strategy, insect control
 aggregation and antiaggregation
 pheromones, 510
 insecticide resistance management, 509
- Q**
- Queen pheromones, 461–463
- R**
- Raspberry ketone (RK) technology
 environmental impact, 586–588
 fruit flies, 579–580
 HAWPM program, 583–587
vs. male behavior
 male *Bactrocera*-parapheromone
 association, 581

- mating enhancement, 582
 - sensory trap, 583
 - sexual selection hypothesis, 580
- Releaser pheromones, 374
- Rodents
 - mammary odor
 - biological secretions, 98
 - experimental odorants, 97
 - milk, 96
 - neonatal olfactory abilities, 98
 - nipple texture, 95–96
 - odor learning, 97–98
 - pheromones, 98–100
 - redundant reinforcing agent, 98
 - self-licking, 96–97
 - odor-mediation, 94–95
- S**
- Salivary glands, isoptera
 - function
 - attractive cement pheromone, 533
 - generic pheromone, 534
 - occurrence and morphology
 - pheromone-producing glands, 525, 531
 - salivary acini, worker, 532
 - salivary reservoir ultrastructure, 532
 - secretion chemicals
 - defensive chemicals, 533
 - thin-layer chromatography, 532
- Schizophrenia, olfactory functioning
 - abnormal steroid secretion, 312–313
 - abnormal sweat, 311–312
- Anosmia, 311
 - identification deficits, 309–310
 - negative symptoms and olfactory deficits
 - abnormal secretion of steroids, 321
 - acuity, menstrual cycle, 319
 - control women, 323
 - early psychosis patients, 320
 - hexanoic acid (HA) compound
 - detection, 321
 - IA, 322
 - poor hygiene, 318
 - odorants acuity
 - isoamyl-acetate (IA), 316
 - PEA, 316–317
 - Wiener's hypothesis, steroids, 317–318
 - steroid secretion and olfactory acuity, 313–315
- Semiochemicals, 613–614
- Sex pheromone, aphid
 - applications, control and monitoring systems
 - direct control measures, 564
 - integrated pest management (IPM)
 - scheme, 565
 - mass trapping, 564
 - mating disruption system, 563
 - parasitoid management system, 566
- dolichodial, 561–562
- phenylacetonitrile, 561
- stereochemistry role
 - component structure, 560
 - diastereoisomers, 558
 - enantiomers, 559
 - synergistic effect of, 562–563
- Sharpless asymmetric epoxidation reagent, 611
- Signaler pheromones, 374
- Signature odors, 290
- Simulium damnosum*, 600
- Single cell recording (SCR), 554
- Social wasps
 - alarm pheromones, 466–471
 - colony foundation strategy, 449
 - communication, 450–451
 - defense allomones, 473–476
 - nestmate recognition pheromones
 - colony level, 455–457
 - insignificant hypothesis, 460
 - males and brood CHCs, 458–459
 - population level, 454–455
 - recognition mechanism, 457–458
 - species level, 452–454
- Polistinae, 448
- Polistine social wasps, 448–450
- queen and fertility/rank pheromones, 461–463
- sex pheromones
 - female sex pheromones, 464–465
 - male sex pheromones, 465–466
- Stenogastrinae wasps, 448
- subfamily Vespinae, 450
- termites, 448
- Vespidae, 448, 450
- Specific anosmia
 - androstenone nondetection rates, 53–54
 - labeled anosmics, 52, 55
 - trigeminal system, 55
- Sternal gland, isoptera
 - function
 - locomotion ratio, 536
 - nuptial dancing phase, 537
 - odoriferous trails, 535
 - short-and long-range attractants, 538
 - occurrence and morphology
 - Cornitermes cumulans* worker, 534
 - epidermal thickening, 525, 534
 - posterior sternal gland ultrastructure, 535
 - secretion chemicals
 - sex pheromones, 535, 537
 - trail pheromones, 535–536
- Stromal interaction molecule 1 (STIM1), 439
- Superorganisms, pheromones
 - gene regulation
 - long-term regulation, 409–410

- Superorganisms, pheromones (*cont.*)
 pheromone-regulated transcription factors,
 411–412
 short-term regulation, 410–411
 hormone regulation, 403
 organism hormones, 402–403
 pheromone regulation, 403
 physiological and behavioral regulation
 defense mechanism, 406–407
 learning, 408
 longevity, 407–408
 reproduction, 404–405
 task allocation, 405–406
 social insects, 402–403
 social regulation
 colony growth, 414–415
 reproduction, 413–414
 Swarming behavior, 599
 Synergism, aphid sex pheromone, 562–563
 Synthetic racemic pheromone (SRP), 613

T

- Tergal gland, isoptera
 function
 long-range attraction/calling, 540
 tandem behavior/short-range
 attraction, 539
 occurrence and morphology
 epidermal thickenings, 525, 538
 female secretory cells, 538–539
 secretion chemicals, 539
 TFMKs. *See* Trifluoromethylketones (TFMKs)
Toxorhynchites brevipalpis, 606
 Transient receptor potential cation (TRPC)
 channels
 activation mechanisms, TRPC2
 covalent modification, 206
 DAG, 204–206
 phospholipase C (PLC), 204
 DAG effect, TRPC2
 pore-dead TRPC2 mutants, 208–209
 sensory signals, 209
 SNARE-like activity, 208
 TRPC3/6/7 subclade, 209
 TRP_2 domain mutation, 208
 domain architecture, TRPC2
 calmodulin-binding domains, 202–203
 hydrophobic inner-shell domain, 201
 peripheral lipid-binding signals, 201–202
vs. TRPC channels, 201
 pheromone sensing, 199–200
 protein interaction

- Homers, 206–207
 Orai and STIM1 proteins, 207
 Trifluoromethylketones (TFMKs), 503–504

U

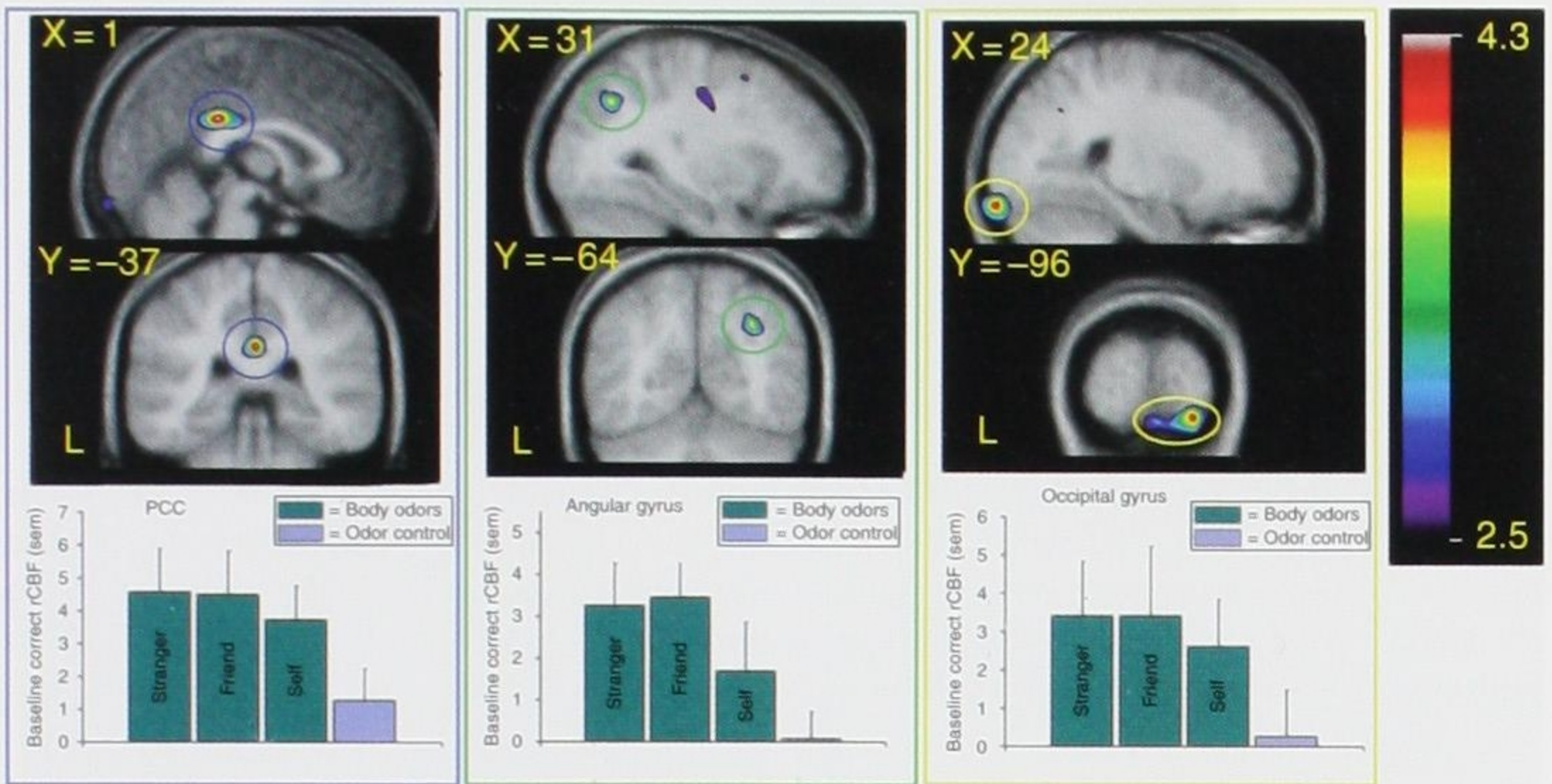
- Ungulates
 mammary odor
 odor learning, 106–107
 pheromones, 107
 sources, 105–106
 odor-mediation, 104
 University of Pennsylvania Smell Identification
 Test (UPSIT), 308–310, 319, 322–323

V

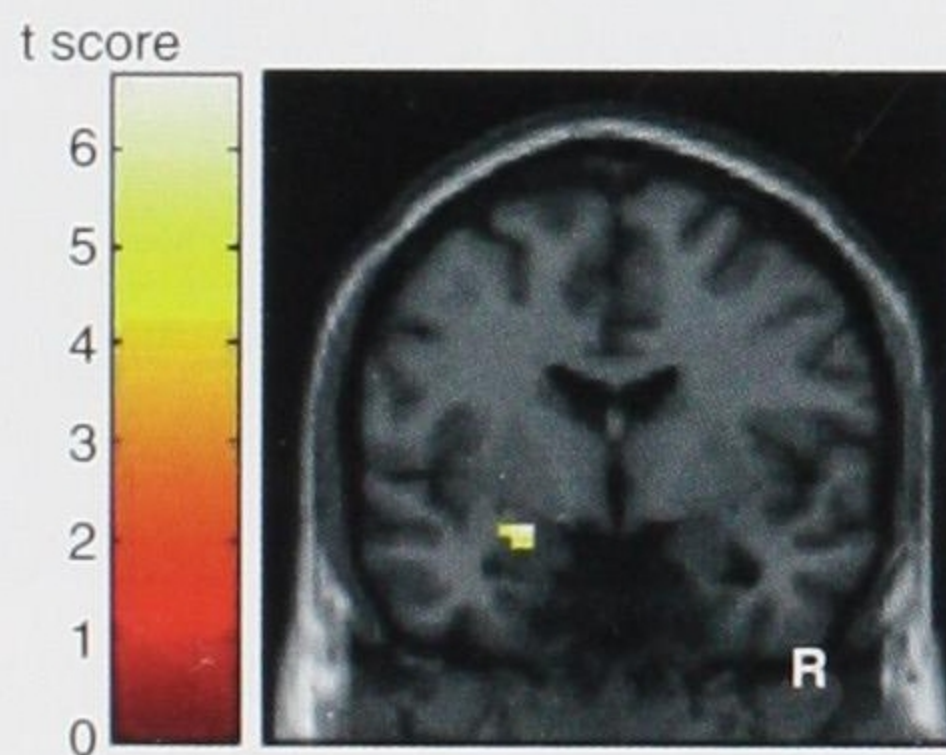
- Volatile signals, pregnancy
 breast-feeding behavior, 300
 chemical profile, 297–298
 mother–infant interactions
 olfaction and maternal behavior, 297
 precocious olfactory interaction, 296
 sociobiological remarks, 295–296
 mother recognition
 fetal olfactory learning, 294
 humans, 293–294
 nonhuman mammals, 292–293
 para-axillary and nipple–areola regions, sweat
 patch samples, 299
 signature odors, pheromones, 290–291
 Vomeronasal amygdala
 functional anatomy, 182–184
 posteromedial cortical nucleus, 174
 posteromedial part of the medial BST
 (BSTMPM), 174–175
 Vomeronasal organ (VNO), 230
 GnRH neurons, 336
 pheromonal control
 female sexual behavior, 344
 male sexual behavior, 342–343
 mate discrimination, 341–342
 pheromonal processing
 2-heptanone detection, 340
 MHC peptide detection, 340
 nonvolatile pheromones, 337
 pregnancy block effect, 338–339
 volatile pheromones, 336–337
 vomeronasal receptors, 335

W

- Willison's lure, 579



Johan N. Lundström and Mats J. Olsson, Figure 1.1 Statistical parametric maps (t statistics as represented by the color scale) of group averaged rCBF responses to processing of body odors superimposed on group averaged anatomical MRI. Blue circles mark increased rCBF in the posterior cingulate cortex (PCC), green circles mark increased rCBF response in the left angular gyrus, and yellow circles mark an increased rCBF response in the right occipital cortex. Coordinates denote center of activation and slice expressed according to the MNI world coordinates system. Left in upper row of pictures represents posterior and left in middle figures represents left side (L). Graphs under each statistical parametric map represent extracted baseline-corrected rCBF values within the activation peak, in each odor category. Error bars represent standard error of the mean (SEM). Reproduced with permission from Oxford University Press.



Johan N. Lundström and Mats J. Olsson, Figure 1.2 Statistical parametric maps (t statistics as represented by the color scale) of group averaged BOLD responses to the processing of fear-related body odors. Note the significant activation in the left amygdala. Reproduced with permission from the authors.

Index

A

- Adipocytes, 54
- Albiglutide, 400
- Alzheimer's disease (AD)
 - diabetes and
 - cognitive impairments, 333–334
 - epidemiological studies, 333
 - GLP-1 analogues, mouse models of
 - APP/PS1, 342, 344–345
 - exendin-4, 342–343
 - liraglutide, 343–345
 - Val(8)GLP-1, 342, 344
- β -Amyloid precursor protein (APP), 342, 344–345
- β -Amyloid, synaptic transmission, 337–338
- Apoptosis, of pancreatic β -cell, 39–44
- Apoptosis signal regulating kinase-1 (ASK1)
 - activation, 41
- Arcuate nucleus (ARC), 309–310
- Arena pharmaceuticals, from GPR119 agonists
 - APD668, 427
 - from central core modifications, 425–426
 - first generation, 424
 - methylpyridine analogs, SAR of, 425–426
 - 4-(piperidin-4-yloxy)pyrimidine, 424–425
- Astellas, from GPR119 agonists
 - AS1535907, 440–441
 - AS1907417, 441
 - fused-pyrimidine-based GPR119 agonists, 440
- ATP-sensitive potassium (K-ATP), 287–288
- Autonomous nervous system role, GIP
 - neuropeptides
 - bombesin, 194–196
 - neuropeptide Y (NPY), 190–192
 - neurotensin (NT), 192–194
 - parasympathetic nervous system, 189–190
 - sympathetic nervous system, 190

B

- Biovitrum, from GPR119 agonists, 436–437
- Blood–brain barrier (BBB), GLP-1 effects, 337
- Bombesin, 194–196
- Bone, GIP and GLP-1, 54–55
- Brain-derived neurotrophic factor (BDNF), 345
- Brain, GLP-1 role, 336–337
- Bristol-Myers Squibb, from GPR119 agonists, 433–434
- Byetta[®], 342

C

- Ca²⁺-induced Ca²⁺ release (CICR) regulation, 291–292
- Cardiovascular effects, GIP and GLP-1, 48–50
- β -Catenin synthesis, Wnt and and incretin
 - connections
 - Gcg expression for
 - 5' flanking regions, comparison of, 365
 - GLUTag cells, 364–365
 - STC-1 cells, 365–366
 - GIP production
 - enteroinsular axis, 368
 - mGip* and *mGcg* promoters, 367
 - TCF/LEF factors, 366–367
 - promoter, 369
- CJC-1134-PC, GLP-1 receptor agonists, 400
- Cytosolic [Ca²⁺] elevation, GSIS, 290–293

D

- Diabetes and Alzheimer's disease, 332–334
- Dietary effects
 - fat sensing, mechanisms, 95–96
 - glucose sensing, mechanisms
 - K_{ATP} channel, 94
 - sodium-glucose cotransporter 1 (SGLT1), 94–95
 - sweet taste receptor, 95
 - incretin hormone secretion
 - carbohydrates, 87–91
 - fat, 91
 - intraduodenal glucose, 85–86
 - protein, 92
 - incretin hormones physiology
 - GIP biological actions, 84–85
 - GLP-1 biological actions, 83–84
 - intestinal L-cells, 82–83
 - obesity and diabetes, 97–98
 - preload concept, 99–100
 - protein sensing, mechanisms, 96–97
 - targeting GIP, 100
 - therapeutic implications, 98–99
- Dipeptidyl peptidase 4 (DPP4), 394
 - inhibitors, incretin-based therapy
 - saxagliptin, 403–404
 - sitagliptin, 402
 - vildagliptin, 402–403
 - inhibitors, with Prosidion, 431

E

- Endocrine pancreas, GIP and GLP-1
 β -cell secretion, 28–29
 glucagon secretion, 29–30
 insulin biosynthesis, 36
 insulin secretion mechanisms
 adenylyl cyclase (AC), 30, 32
 Ca^{2+} -sensitive K^+ (KCa) channels, 30–31
 cyclic AMP, 30–31, 33
 K_v currents, 34
 signaling pathways, 35
 pancreatic islet mass, 36–37
 β -cell apoptosis, 39–44
 β -cell proliferation, 37–39
- Energy metabolism, central GLP-1 actions
 food intake
 exendin 4, 307, 312–313
 ghrelin, 306–307
 GLP-2, 308
 leptin, 306
 lithium chloride, 307
 in obese animals, 307–308
 peripheral administration, 308
 and glucose metabolism
 amide, 310
 arcuate nucleus (ARC), 309–310
 of ATP-sensitive K^+ channels (K_{ATP}), 310
 homeostasis, 309
 and lipid metabolism, 310–311
 metabolic actions of, 312
- Enteroinsular axis, incretin, 356–357, 368
- Epac2-dependent Rap1 activation, islet insulin secretion control
- GSIS
 cytosolic [Ca^{2+}] elevation, 290–293
 phospholipase C-epsilon activation, 285–287
 PIP2 hydrolysis stimulation, 287–289
 protein kinase C-epsilon activation, 289–290
 protein kinases activation, 294
- GTPase
 cAMP, role of, 284
 domain structure of, 284
 guanyl-releasing proteins, 285
 sulfonylureas, 283
 protein kinase A (PKA), 280–282
 secretory granule-associated proteins, interactions of
 exocytosis, 295
 live-cell imaging, 296
 priming of, 295–296
- Exenatide, 398, 401
- Exendin-3, 11, 320
- Exendin-4, 11–12, 307, 312–313, 320
 GLP-1 receptor, ligand recognition
 binding modes of, 261–264

 sequence alignment of, 260
 structure of, ECD of GLP-1R, 261

Exocrine pancreatic secretion, 47–48

F

- Feeding, early events, GIP and GLP-1 effects, 27–28
- Food intake
 central GLP-1 actions, 305–308
 and satiety, GLP-1 effects, 44–46
- Free fatty acids
 FFA₂ and FFA₃ receptors, 171–173
 FFA₁ receptor, 166–171
 sensing receptors, 166

G

- Galvus[®], 402
- Gastrointestinal effects, GIP and GLP-1
 exocrine pancreatic secretion, 47–48
 gastric emptying, 46–47
 gastric secretion, 47
 intestinal absorption, secretion, and motility, 48
- Gastrointestinal regulatory role, GLP-1
 blood glucose rise, inhibitory effect of, 321
 exendin-4, 320
 incretin mimetics, 327
 in metabolism, 321–323
 in motility
 irritable bowel syndrome (IBS), 325–327
 myoelectric complex, 325
 ROSE-010, 326–327
 small bowel manometry, 325
 in satiety, 323–324
- Gastrointestinal system, 227–229
- Genomics Institute of the Novartis Research Foundation (GNF), 438–440
- Ghrelin, 306–307
- Gila monster. *See Heloderma suspectum*
- GlaxoSmithKline, from GPR119 agonists, 434–436
- Glucagon-like peptide-1 (GLP-1), 6–7, 417
 biphasic pattern, 304
 degradation of, 304
 endogenous, 304
 and GIP, incretin-based therapy
 actions of, 394–396
 degradation of, 394
 proglucagon processing in, 392
 secretion of, 393
 receptor agonists
 albiglutide, 400
 CJC-1134-PC, 400
 exenatide, 398, 401
 liraglutide, 398–400
 taspoglutide, 400–401
 receptor, ligand recognition

- binding to ECD, 257–260
 - extendin-4 binding to, 260–264
 - N-terminal extracellular domain (ECD), 255–257
 - structural differences, in ECD, 264–265
 - transmembrane and C-terminal domain, 264–267
- Glucagon-like sequences receptors, 12–14
- Glucagon secretion, 29–30
- Glucose
- homeostasis and GPR119 agonism, 420–423
 - intolerance and disease states
 - antidiabetic agents, 214
 - obesity, 213–214
 - risk of, 213
 - type 2 diabetes, 211–212
 - metabolism, central GLP-1 actions, 308–310
- Glucose-dependent insulinotropic polypeptide (GIP), 392–396
- autonomous nervous system role
 - neuropeptides, 190–196
 - parasympathetic nervous system, 189–190
 - sympathetic nervous system, 190
 - biological actions of
 - actions on pancreatic islets, 126–127
 - extrapancreatic actions of, 127–128
 - GIP receptor (GIPR), 126
 - evolution, 10–11
 - history of, 112–114
 - and K-cells in health and disease
 - after bariatric surgery, 130
 - aging effect, 132
 - autoimmune diseases and inflammatory bowel diseases, 132–133
 - clinical application of, 133–135
 - GIP-producing tumor, 133
 - obesity/diabetes, 128–130
 - reactive hypoglycemia after gastrectomy/gastric bypass, 130–131
 - total parenteral nutrition (TPN), 131
 - neural regulation of, 188
 - regulation and expression
 - GIP gene and evolutionary perspective, 115
 - GIP gene, transcriptional control, 116
 - proGIP, posttranslational processing, 116–117
 - secretion, degradation, and elimination
 - DPP4, 125
 - elimination rates, 126
 - hormonal regulation, 124
 - neural regulation of, 123
 - nutritional stimuli, 119–123
 - secretion from K-cells, intracellular mechanisms, 124–125
 - secretion, regulation of, 188
 - structure and action, 187–188
 - structure of, 5
- Glucose-dependent insulinotropic polypeptide receptor (GIPR), ligand recognition
- binding to ECD, 269–270
 - GLP-1R and, features of
 - model of, 273–274
 - sequence alignment of, 272
 - structural differences, 273
 - N-terminal extracellular domain (ECD), 268–270
 - transmembrane and C-terminal domain, 270–271
- Glucose-stimulated insulin secretion (GSIS),
- Epac2-dependent Rap1 activation
 - Cdc42, 289–290
 - cytosolic $[Ca^{2+}]$ elevation
 - cAMP, 290–291
 - CICR regulation, 291–292
 - insulin secretion, 292–293
 - Stim1, 293
 - voltage-dependent Ca^{2+} channels (VDCCs), 290, 292
 - phospholipase C-epsilon activation, 287
 - domain structures of, 286
 - isoforms, 285
 - PIP2 hydrolysis stimulation
 - ATP-sensitive potassium (K-ATP), model for, 287–288
 - sulfonylureas, 288–289
 - protein kinase C-epsilon activation, 289–290
 - protein kinases activation, 294
- GPR119 agonists, for type 2 diabetes (T2D)
- treatment
 - glucagon-like peptide-1 (GLP-1), 417
 - and glucose homeostasis
 - AR231453, 421–422
 - PSN632408, 422–423
 - structures of, 421
 - medicinal chemistry
 - Arena pharmaceuticals, 423–427
 - Astellas, 440–441
 - Biovitrum, 436–437
 - Bristol-Myers Squibb, 433–434
 - GlaxoSmithKline, 434–436
 - GNF, 438–440
 - Merck, 437–438
 - Metabolex, 432–433
 - Prosidion Ltd., 427–431
 - structure-activity relationship (SAR), 423
 - receptor expression, 418–419
 - signaling and deorphanization
 - endogenous ligands of, 419
 - N-oleoyldopamine (OLDA), 420
 - oleoylethanolamide (OEA), 419–420

G-protein-coupled receptors (GPCRs), ligand recognition
 extracellular domain (ECD), 253–254
 rhodopsin, 252
 secretin, 253
 structural features of, 253
 two-domain model, 254
 Growth factors, neuroprotective effects, 345–346
 GTPase, 283–285

H

Heloderma horridum, 11, 320
Heloderma suspectum, 8, 11, 320
 Hormonal and neuronal pathways, GIP and GLP-1 actions
 GIP/GIPR system, 24–25
 nucleus tractus solitarius (NTS), 26–27
 on stomach and pancreas, 25–26

I

Incretin-based therapy
 DPP4 inhibitors, 401–404
 effect, 391
 GLP-1 and GIP
 actions of, 394–396
 degradation of, 394
 proglucagon processing in, 392
 secretion of, 393
 GLP-1 receptor agonists, 397–401
 glucose-induced insulin secretion, 391
 mimetics and enhancers, 397
 in type 2 diabetes, 396–397
 Incretin hormones, 15–16
 action, 223–224
 anatomy and physiology of
 gastrointestinal system, 227–229
 lymphatic system, 229
 degradation, 226
 discovery, 223
 effect, 356–357
 enteroinsular axis, 356–357
 genes
 exendin, 11–12
 GIP genes, 10–11
 glucagon-like gene family, 5–6
 proglucagon, 7–10
 GIP and GLP-1
 genes, 357, 359
 and target tissues, 358
 lymph fistula model
 fasting and postprandial concentrations of, 232–238
 GIP and GLP-1 secretion, 239–240
 for large animals, 231–232
 lipid and carbohydrate, 238–239
 lymph collection methodology, 240–242
 rat model, 230–231

surgical procedure and recovery protocol, 240–242
 measurement of, 226–227
 mimetics, 327
 pleiotropic actions (*see* Pleiotropic actions, of incretin hormones)
 receptors
 and actions in, 357
 genes, evolution of, 12–15
 ligand recognition (*see* Ligand recognition, incretin receptors)
 response, in health and disease, 359–360
 secretion, 224–226 (*see also* Incretin hormone secretion)
 therapy (*see* Incretin-based therapy)
 in type 2 diabetes, 396–397
 Incretin hormone secretion
 dietary effects (*see* Dietary effects)
 fasting state, 214–215
 GIP and GLP-1 secretion
 after meal ingestion, 204–206
 diurnal variation, 210–211
 dynamic response to each meal, 209–210
 gastric distension, 208
 gastric emptying, 208
 hormones and autonomic nerves, 207
 meal size, 207
 mechanisms, 209
 nutrients regulation, 206–207
 glucose intolerance and disease states
 antidiabetic agents, 214
 obesity, 213–214
 risk of, 213
 type 2 diabetes, 211–212
 Insulin
 biosynthesis, 36
 production of, Wnt and and incretin connections, 372–373
 secretion mechanisms, 30–36
 Irritable bowel syndrome (IBS), 325–327

J

Januvia[®], 402

K

K-cells
 anatomical localization and development
 of GIP-producing cells, 117–119
 gut, 119–120
 and GIP in health and disease
 after bariatric surgery, 130
 aging effect, 132
 autoimmune diseases and inflammatory
 bowel diseases, 132–133
 clinical application of, 133–135
 GIP-producing tumor, 133
 obesity/diabetes, 128–130

reactive hypoglycemia after gastrectomy/
gastric bypass, 130–131
total parenteral nutrition (TPN), 131
history of, 112–114

L

Leptin, 306

Ligand recognition, incretin receptors

GIP receptor (GIPR)

GLP-1R and, features of, 271–274

N-terminal extracellular domain (ECD),
268–270

transmembrane and C-terminal domain,
270–271

GLP-1 receptor

binding to ECD, 257–260

exendin-4 binding to, 260–264

N-terminal extracellular domain (ECD),
255–257

structural differences, in ECD, 264

transmembrane and C-terminal domain,
264–267

G-protein-coupled receptors (GPCRs)

extracellular domain (ECD), 253–254

rhodopsin, 252

secretin, 253

structural features of, 253

two-domain model, 254

Lipid metabolism, central GLP-1 actions,
310–311

Liraglutide, 398–400

Liraglutide effect and action in diabetes (LEAD),
399

Lymph fistula model

fasting and postprandial concentrations of,
232–238

GIP and GLP-1 secretion, 239–240

for large animals, 231–232

lipid and carbohydrate, 238–239

lymph collection methodology, 240–242

rat model, 230–231

surgical procedure and recovery protocol,
240–242

Lymphoid enhancer factor (LEF), 361–362,
366–367

M

Merck, from GPR119 agonists, 437–438

Metabolex, from GPR119 agonists

five-membered central heterocyclic cores
from, 432

MBX2982, 433

Metabolic diseases, K-cells gene therapy, 135

N

Nerve growth factor (NGF), 346

Neuronal activity and neurodegeneration,

GLP-1 role

analogues of

AD, mouse models of, 342–345

long lasting, development of, 334, 336

memory formation, 341–343

blood-brain barrier (BBB), 337

in brain, 336–337

diabetes and Alzheimer's disease, 332–334

growth factors, 345–346

in pancreatic β -cell, 335

synaptic transmission

β -amyloid, 337–338

and vesicle release, 338–341

Neuropeptides

bombesin, 194–196

neuropeptide Y (NPY), 190–192

neurotensin (NT), 192–194

Neurotensin (NT), 192–194

N-oleoyldopamine (OLDA), 420

Nucleus tractus solitarius (NTS), 304, 312

Nutrient storage and flux, GIP and GLP-1

adipose tissue, 52–54

liver and skeletal muscle, 51–52

O

Oleoylethanolamide (OEA), 419–420

Onglyza[®], 402

P

Pancreatic β -cell

GIP and GLP-1 effects

apoptosis, 39–44

chromatin structure and gene transcription,
43

proliferation, 37–39

GLP-1 receptor role in, 335

Pancreatic islet mass, GIP and GLP-1 effects,
36–37

Parasympathetic nervous system, 189–190

Phosphatidylinositol 4,5-bisphosphate (PIP₂)

hydrolysis, 287–289

Phospholipase C-epsilon (PLC ϵ) activation,
285–287

Pleiotropic actions, of incretin hormones

autonomic nervous systems (ANSs), 25–26

β -cell

apoptosis, 39–41

proliferation, 37–39

secretion, 28–29

bone, 54–55

cardiovascular effects, 48–50

early events during feeding, 27–28

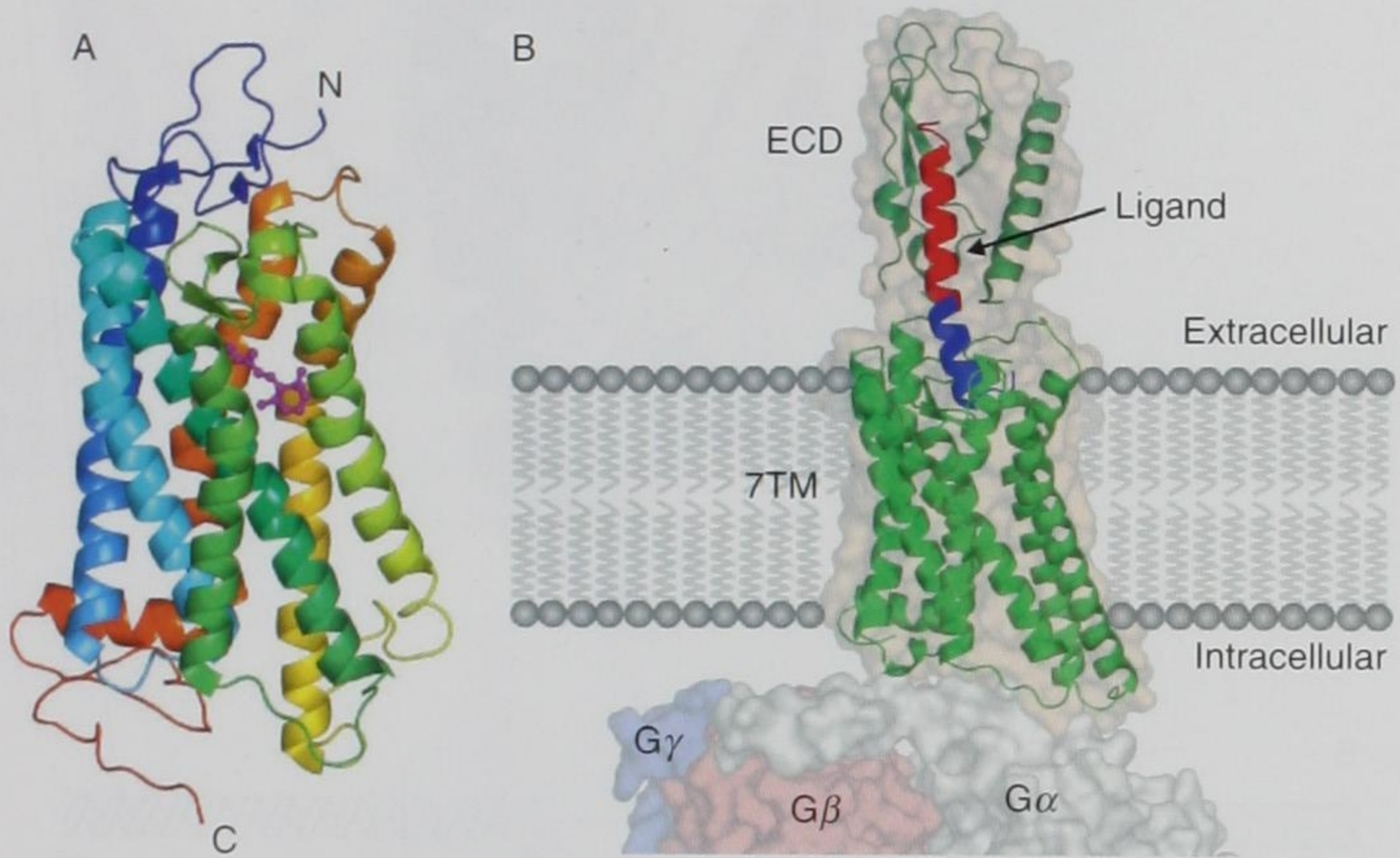
exocrine pancreatic secretion, 47–48

food intake and satiety, 44–46

gastric emptying, 46–47

gastric secretion, 47

- Pleiotropic actions, of incretin hormones (*cont.*)
 glucagon secretion, 29–30
 hormonal and neuronal pathways, 24–27
 insulin
 biosynthesis, 36–37
 secretion mechanisms, 30–36
 intestinal absorption, secretion, and motility, 48
 nutrient storage and flux, 51–54
 pancreatic islet mass, 36–37
 on stomach and pancreas., 26
- Preload concept, 99–100
- Presenilin-1 (PS1), 342, 344–345
- Proglucagon (Gcg) gene
 evolution of, 7–10
 structure and splicing of, 3–4
 WNT/ β -catenin, 364–366
- Prosidion Ltd., from GPR119 agonists
 azetidine, 430
 DPP-IV inhibitors with, 431
 linear core, 429
 oxadiazole, 427–428
 PSN119-1, 428–429
 PSN119-2, 428
 PSN821, 430–431
- Protein kinase A (PKA), 280–282
- Protein kinase C-epsilon activation, GSIS, 289–290
- Protein kinases activation, GSIS, 294
- S**
- Satiety, GLP-1, 323–324
- Saxagliptin, 403–404
- Seven transmembrane (7TM) receptors
 carbohydrate sensing by T1R2/T1R3, 163–164
 family A receptors
 FFA₂ and FFA₃ receptors, 171–173
 FFA₁ receptor, 166–171
 free fatty acid-sensing receptors, 166
 GPR84 and GPR120, 173–174
 peptone sensing by GPR93, 165
 family C nutrient-sensing receptors, 155–157
 human tissues displaying predominant expression, 155
 L-amino acid, Ca²⁺, and peptide sensing, CaR, 157–159
 L-amino acid sensing
 by GPRC6A, 159–161
 by T1R1/T1R3, 161–163
 nutrient substance, 156
 therapeutic perspectives, 174
 T1R1/T1R3 heterodimer, 154
- Sitagliptin, 402
- Small bowel motility, GLP-1, 325
- Sodium-glucose cotransporter 1 (SGLT1), 94–95
- Structure-activity relationship (SAR),
 GPR119 agonists, 423
 Bristol-Myers Squibb, 434
 methylpyridine analogs, 425–426
- Sweet taste receptor, 95
- Sympathetic nervous system, 190
- Synaptic transmission, GLP-1 role
 β -amyloid
 liraglutide, injection of, 338, 340
 long-term potentiation (LTP), 338
 protease resistant derivative, injection of, 338–339
 and vesicle release, 338–341
- T**
- Taspoglutide, 400–401
- T cell factor (TCF), 361–362, 366–367
- Tcf7l2* gene, 372, 374
- Total parenteral nutrition (TPN), 131
- Transmembrane helix (TM2) domain, GLP-1R, 265–266
- Type 2 diabetes (T2D) treatment, 129, 211–213, 332–333, 396–397, 416. *See also* GPR119 agonists, for type 2 diabetes (T2D) treatment
- V**
- Vertebrates
 GIP genes structure, 5
 proglucagon genes, 3–4
- Victoza[®], 343
- Vildagliptin, 402–403
- Voltage-dependent Ca²⁺ channels (VDCCs), 290, 292
- W**
- Wnt and and incretin connections
 β -catenin, synthesis of
 Gcg expression for, 364–366
 GIP production, 366–368
 promoter, 369
 cross talk, 362
 GIP, GLP-1 and target tissues, 358
 GIPR and GLP-1R, 370–371
 for health and disease, 372–375
 knockout mice, 376
 ligands, 360–361
 lrp receptors, 370
 models for, 377
 pathways, 361
 physiological actions, 363–364
 secretion, control of, 369–370
 signaling
 GLP-1, effectors, 371–372
 nutrient detection and insulin production, 372–373
 TCF/LEF effector, 361–362



Christina Rye Underwood *et al.*, Figure 9.1 Structural features of GPCRs: (A) The crystal structure of chromophore-bound bovine Rhodopsin, a class A GPCR. Cartoon representation showing the arrangement of the seven transmembrane α -helices; the bound chromophore retinal is colored in magenta (PDB code: 1U19). (B) A model for ligand binding in class B GPCRs. Peptide ligands are believed to bind to class B receptors according to the “two-domain” model. First, the C-terminal part of the ligand (colored in red) binds the ECD of the receptor (green), followed by binding of the N-terminal part of the ligand (blue) to the transmembrane (7TM) receptor domain. Structural rearrangements in the receptor activate the heterotrimeric G_s-protein, leading to dissociation of the G α subunit, and transduce receptor signaling which results in formation of the second messenger cAMP.

Index

A

Activin

- activin A gene, 260–261
- β_A -subunit, 260
- β_B -subunit, 260–261
- β_D subunit, 261
- bioassays, 258–259
- CNS (*see also* Brain, activin)
 - depression and anxiety-related behavior, 190–193
 - late-phase LTP, 195–196
 - postnatal neurogenesis, 193–195
 - reconsolidation and extinction, 197–200
 - spine formation, 189–190
- definition, 5
- follostatin
 - binding affinity, 263
 - FS288, 263
 - FS315, 263–264
 - FSRP/FSTL3, 264
 - glycosylation, 264–265
 - introns and exons, 262
- gene disruption studies, 6
- glucose metabolism (*see* Glucose metabolism, activins)
- HEK293 and HT22 cells, 6–7
- immune cell migration
 - dendritic cells, 141
 - mast cells, 139–140
 - monocytes, 140–141
- immunohistochemistry, 258
- isoforms, 5–9
- molecular mechanism
 - Smads-dependent cell migration, 132–133
 - Smads-independent cell migration, 133–134
- nomenclature, 260
- pancreatic β -cell line MIN6 cells, 6
- receptors and activin signaling
 - BAMBI, 262
 - betaglycan, 262
 - MAP kinases, 261–262
 - SMAD2/3 signaling, 263
- signaling cascade, postsynaptic region, 186–187
- structure, 186
- synthesis and signaling, 258, 259
- tumor cell migration
 - breast cancer, 135–137

- colon cancer, 138

- prostate cancer, 134–135

Activin A

- bioassays, 258–259
- cachexia, 270–271
- continuous low-level activation, 63–65
- follostatin
 - and FSTL3, 330–331
 - production site and measurement issues, 164–165
- gene, 260
- immunohistochemistry, 258
- immunoregulation, 279
 - asthma, 278–279
 - B cell survival, 275
 - dendritic and natural killer cells, 278
 - IL6 production, 277
 - MHC class II proteins, 275
 - monocyte/macrophage production, 276
 - multipotential progenitor cell development, 275
 - myeloid dendritic cells, 276
 - T cell growth and development, 275
- inflammation and fibrotic response, follistatin
 - β_C -subunit, 274
 - exogenous follistatin, 273–274
 - monocyte/macrophage lineage cell types, 271–273
 - stimulating factors, 273
- inflammation and immunity
 - acute and chronic inflammatory diseases, 265
 - cell types, activin production, 266
 - cytokines, 269
 - interleukin-1, 267–268
 - LPS injection, 266
 - mRNA and protein elevation, 265–266
 - NF- κ B signaling, 268
 - oxidative stress, 269
 - phorbol ester responsive elements, 268–269
 - septicemia and pulmonary hypertension, 265
 - toll-like receptor signaling pathway, 267–268
- intracrine signaling, 71–73
- NAFLD
 - apoptosis and inhibition, hepatocyte growth, 331–332

- Activin A (*cont.*)
 metabolic syndrome (*see* Metabolic syndrome, NAFLD)
 two-hit hypothesis, 332, 333
 nomenclature, 258
 properties, 329
 signal transduction and regulation, 329–330
 Smad2/3 pathway, 331
 synthesis, 258
- Activin B
 inflammation and immunity, 269–270
- Activin receptor
 and BMP
 coreceptors, 110–111
 type II receptors, 110
 type I receptors, 109–110
 function
 activin membrane-bound inhibitor, 85
 BMP, 85
 Cripto, 85–87
 Dapper2, 89
 Dok-PTB containing protein, 88–89
 proteins 1 and 2, 87–88
 regulatory subunits of PP2A, 87
 and their receptors, 107–108
- Activin receptor interacting proteins (ARIPs), 87–88
- Activin receptor-like kinase (ALK), 109–110, 131, 219
 activin/nodal and BMP signaling, 209–210
 activins A and B signal transduction, 303
 ActRIIA and ActRIIB, 30
 ALK4 and 7, 6–7
 BMP-2, 115
 BMP signaling, 4
 BMP2/4/7 signaling, 68, 69
 breast cancer, 137
 Cripto, 86
 CTGF expression, 67
 Dapper2, 89
 dendritic cells, 141
 IL6 production, 277
 inhibitory Smads, 89
 insulin secretion, 220–221
 myostatin signal transduction
 pathway, 223, 274
 nodal and activin pathway, 47
 nodal signaling, 9
 pancreatic endocrine cells, 7–8
 prostate cancer cell, 132
 SB-431542 and GW788388, 201
 Smad2 and 3 phosphorylation, 14, 15
 Smads-dependent cell migration, 132
 stimulation, intracellular TGF- β signaling, 68
 structure, 4
 white adipose tissue, 224
- Activin receptor type IB (ActRIIB)
 FKBP12 and dorsomorphin, 31–32
 TGF- β RI kinase domain structure, 31
- Activin receptor type IIB (ActRIIB)
 active site of, 33–35
 catalytic domain of, 32–33
 vs. type IB domain structures, 35–36
- Anti-Mullerian hormone (AMH)
 follicular phase, 307
 FSH
 human studies, 310
 inhibin B, 307–308
 inhibins and LH, 310
 ovulatory cycles, 307
- Anxiety-related behavior. *See* Depression and anxiety-related behavior
- Apoptosis, 328, 335
- B**
- B cells, activin A, 239–240
- Betaglycan
 inhibins A and B
 ActRII complex, 314–316
 β -subunits, 313
 vs. diglycosylated (34-kDa) inhibins A and B, 312–313
 epitope, 313–314
 inhibin B specific accessory protein, 314, 315
 mRNA expression, 169
- Bone marrow-derived mast cells (BMMCs)
 chemoattractant, 245
 MCP-6 and MCP-7, 244
 regulatory effects, 244
 Smad3, 246
- Bone morphogenic proteins (BMPs), 2
 ActRIIB_{ECD}, 111
 ALK1, 2, 3, and 6, 4
 binding affinity, 114–115
 BMP-6, 154
 chimeras, 116, 117
 coreceptors, 110–111
 GDF3, 49
 inhibitory Smads, 89
 ligand flexibility, 112–113
 mouse and human ESCs, 44–45
 negative regulation, 85
 sequence alignment, 114
 Ski and SnoN, 94
 stem cell pluripotency, 51
 structural studies
 architecture of complex structures, 111–112
 available complex structures, 111
 binding epitopes, 113–115
 ligand flexibility, 112–113
 receptor-receptor interaction, 112
 type II receptors, 110
 type I receptors, 109–110
- Brain, activin
 activin type II receptor, 189

- adult neurogenesis
 bromodeoxyuridine, 193
 electroconvulsive therapy, 195
 excitatory and inhibitory postsynaptic potential, 194–195
 follistatin and GDF11, 194
 FSM/ACM-double transgenic mice, 194
 hippocampal culture, 194
 physiological roles, 193
depression and anxiety-related behavior
 antidepressant drugs, 193
 dominant-negative ActRIB, 190–191, 193
 FSM and ACM, 190, 192
GKAP, 189
glutamate, 189
late-phase LTP, 195–196
memory reconsolidation and extinction
 fear conditioning test, 197–200
 posttraumatic stress disorder, 197
 three-week memory testing, 197
NMDA receptor, 189
postsynaptic density 95 (PSD95), 189
spine formation
 plasticity, 189
 presynaptic contacts, 190
 Smad pathway, 190
 spine morphology, 188
Breast cancer, 135–137, 143
Bromodeoxyuridine, 193
Brown adipose tissue, 225
- C**
- cAMP response element (CRE), 12
Canonical Wnt signaling, 210–212
Cell migration
 immune cells
 dendritic cells, 141
 mast cells, 139–140
 monocytes, 140–141
 molecular mechanism of activin signaling
 Smads-dependent cell migration, 132–133
 Smads-independent cell migration, 133–134
 tumors
 breast cancer, 135–137
 colon cancer, 138
 prostate cancer, 134–135
Chaperones, 164
Chimeras
 Activin-like bioactivity, 116–118
 ActRII binding properties, 116
 antagonism, 118–119
 BMP-like bioactivity, 119–121
 design of, 115–116
Colon cancer, 138, 143
Connective tissue growth factor (CTGF), 60–61
Contextual fear-conditioning test, 197, 199
 ABItTA mice, 200
 FBItTA mice, 197, 199
 Cripto, 85–87, 108
- D**
- Dapper 2, 89
Dendritic cells (DCs), 141, 143
Depression and anxiety-related behavior
 antidepressant drugs, 193
 dominant-negative ActRIB, 190–191, 193
 FSM and ACM, 190, 192
Diglycosylated (34-kDa) inhibins A and B, 312–313
Dok-PTB containing protein (Dpcp), 88–89
- E**
- Ectoderm/TIF1g, 91–92
Electroconvulsive therapy (ECT), 195
Embryonic stem cells (ESCs)
 derivation of, 43–44
 induced-pluripotent stem cells, 45–46
 locations of pluripotent cells, 41–42
 mouse and human, 44–45
Endoderm formation
 activin/nodal and BMP signaling, 209–210
 differentiation, 208
 Wnt signaling pathway
 canonical, 210–212
 hepatocyte-like cells (*see* Hepatocyte-like cells (HLCs))
 noncanonical, 211–212
Endoglin, transmembrane protein, 111
Epigenetic regulation, inhibin
 histone modifications, 154–155
 hypermethylation, 154
Epithelial-mesenchymal transition (EMT), 132–133
Erbin protein, 93–94
Evi-1, zinc finger-containing transcriptional factor, 96
Exogenous FSH stimulation, 305
Extracellular antagonists
 follistatin-related gene, 83–85
 inhibin, 82–83
Extragenadal expression, inhibin
 female reproduction, 158–159
 target receptors expression, 158
 tissue and cellular localization, 159
- F**
- Fear conditioning test, 197–200
Fibrodysplasia ossificans progressiva (FOP), 31
Follicle-stimulating hormones (FSHs), 30
 AMH, 309–310
 human menstrual cycle
 follicular phase, 305, 307
 luteal phase, 305

- Follicle-stimulating hormones (FSHs) (*cont.*)
 ovarian and pituitary hormones, changing patterns, 310–311
 inhibin A and, 309
 inhibin B and, 311–313
 inhibins A and B bioactivity
 ALK4 and ALK7 type I receptors, 316–317
 antagonism, 314–316
 betaglycan, 312–314
 glycosylation, 314
 mono and diglycosylated forms, 316
 posttranslational modifications, 316
 LH, 310–311
 male, inhibins and regulation, 311–312
- Follicular phase, human menstrual cycle, 305, 307
- Follistatin
 binding affinity, 263–264
 FS288, 263
 FS315, 263–264
 inflammation and fibrotic response
 β _C-subunit, 274
 exogenous follistatin, 273–274
 monocyte/macrophage lineage cell types, 271–273
 stimulating factors, 273
 production site and measurement issues, 264–265
 structure, 262–263
- Follistatin-related gene (FLRG), 83–85
- G**
- GATA factor, 151, 152
- Glucose metabolism, activins, 227, 334
 activins A, 226
 activins C and E, 226–227
 adipose tissues
 brown, 225
 inflammation, macrophages, 225–226
 white, 223–224
 blood glucose level, 220
 carbohydrates consumption, 220
 hypertrophy, Akt/mTOR pathway
 activation, 228
- liver
 activin A, 221–222
 activins C and E, 222
 gluconeogenesis, 221–222
 glycogenolysis, 221
 mitogen-stimulated growth inhibition, 221
- obesity, 220
- pancreas
 adult ActRIIA- or ActRIIB-null mice, 219–220
 ALK7, insulin gene transcription, 221
 ES cell line, 220
 glucagon expression, 221
 insulin secretion, 220–221
 regeneration model, 220
 phosphatidylinositol-3 kinase (PI3K) pathways, 227
 skeletal muscle
 ActRIIB/Fc fusion protein, 223
 C2C12 myoblast cells, 222–223
 muscle mass preservation, 222
 myostatin, 223
 tibialis anterior muscle, 222
- Gonadal steroids, 300
- Gonadotrophins, inhibin
 cAMP levels, 151–153
 CREB phosphorylation, 151–152
 FSH production, 153
 gonadotrophin-releasing hormone, 153
- Granulosa cell tumors, 169
- Guanylate kinase domain-associated protein (GKAP), 189
- H**
- Hepatic fibrosis
 matrix metalloproteinases, EMC, 336
 paracrine and autocrine signaling, 336
 tissue homeostasis, 335–336
- Hepatocyte-like cells (HLCs)
 bioartificial liver device, 213
 human drug toxicity, 213
 human liver function model, 212–213
 isolation, 212
- Histone modifications, inhibin, 154–155
- Human embryonic stem cells (hESCs), 44–45
- Humoral immune responses, activin A
 B cells, 239–240
 macrophages
 cytokines and chemokines, 240
 iNOS and arginase, 242, 243
 monocyte-derived dendritic cells, 240–241
 peripheral blood myeloid dendritic cells, 240–241
 TGF- β gene transcripts, 241
 type IV collagenase production, 241–242
- mast cells
 modulation, 244–246
 upregulation, 242–244
- TGF- β , 236–237
- Th2 cells
 activin β A promoter, transactivation, 238
 CD4⁺ CD4 T cells, 237–238
 expression, T helper cells, 237
- Hypermethylation, inhibin, 154
- Hypothalamic pituitary gonadal axis (HPG), 158
- I**
- Immune cell migration
 dendritic cells, 141
 mast cells, 139–140
 monocytes, 140–141
- Induced-pluripotent stem cells (iPSCs), 45–46

- Inflammation, 336–337
- activins
 - β B-subunit, 269–270
 - interleukin-1 (IL1), 267–270
 - LPS injection, 266
 - mRNA expression and protein localization, 265–266
 - toll-like receptor, 267–270
 - folliculin, 270
- Inhibin, 82–83, 302
- biological actions, 150
 - chaperones, 164
 - circulating forms
 - B forms, men, 170
 - ovarian cancer, 166, 169
 - women, 166–168
 - expression and regulation
 - β B-subunit, 155–154
 - BMP-6, 154
 - epigenetic regulation, 154–155
 - GATA factor, 151, 152
 - gonadotrophins, 151–153
 - human inhibin, 151
 - inhibin synthesis, 151
 - posttranscriptional regulation, 155, 170–171
 - Smad-binding element, 153
 - TATA boxes, 151, 152
 - 5' untranslated regions (UTRs), 151, 152
 - FSH suppression (*see* FSH suppression, inhibin)
 - human tissues
 - adult, 155, 156
 - extragonadal expression, 158–159
 - females, 154, 157
 - HPG axis, 158
 - males, 157–158
 - inhibin A, molecular mass, 167–168
 - mechanism of action
 - activins A and B signal transduction, 303
 - antagonism, 303–304
 - FSH β subunit synthesis, 304
 - LH β subunit synthesis, 305
 - posttranslational modifications, 163–164
 - prodomains, sequence alignment, 160, 162
 - protein structure, 159–162
 - proteolytic processing, 162–163
 - regulation, 150
 - structure
 - glycosylation sites, 302
 - heterodimers, 301–302
 - homodimers, 302
 - precursor inhibin molecule, 300
 - TGF β isoform, 302–303
 - subunits, 150
 - synthesis and secretion, 160, 161
- Inhibitory Smads (I-Smads), 47, 89–90
- Insulin gene regulation
- cAMP response element (CRE), 12
 - C element, 12–13
 - E element, 13–14
 - A element, 10
 - GG element, 11–12
 - Smad-binding element (SBE), 14
- Intracrine signaling mechanism
- Activin A, 72–73
 - aspects of, 65–66
 - TGF- β
 - continuous low-level activation, 63–65
 - external and internal inhibitors, 65
 - inhibitory pathway, 70–72
 - intracellular activation, 61–63
 - stimulatory pathway, 66–70
- Ionotropic glutamate receptors, 189
- L**
- Latent TGF- β binding proteins (LTBPs), 164
- Late-phase LTP, 195–196
- Liver
- activin A
 - gluconeogenesis, 221–222
 - glycogenolysis, 221
 - mitogen-stimulated growth inhibition, 221
 - activins C and E, 222
- M**
- Macrophages, activin A
- cytokines and chemokines, 240
 - iNOS and arginase, 242, 243
 - monocyte-derived dendritic cells, 240–241
 - peripheral blood myeloid dendritic cells, 240–241
 - TGF- β gene transcripts, 241
 - type IV collagenase production, 241–242
- Mast cells (MCs), 139–140, 143
- BMMC maturation
- chemoattractant, 245
 - MCP-6 and MCP-7, 244
 - regulatory effects, 244
 - Smad3, 246
- upregulation
- antigen receptors, cytosolic Ca²⁺ levels, 243
 - high-affinity IgE receptor, 242–243
 - mast cell maturation, 243
- Matrix metalloproteinases (MMPs), 241, 336
- Metabolic syndrome, NAFLD
- activin A
 - activin A/follistatin ratio, 332
 - apoptosis, 335
 - glucose metabolism, 334
 - hepatic FA metabolism, 333–334
 - hepatic fibrosis, 335–336
 - inflammation, 336–337
 - steatosis, 332–333

Metabolic syndrome, NAFLD (*cont.*)
 type 2 diabetes mellitus, 326–327

Microphthalmia-associated transcription factor (MITF), 244

MicroRNAs (miRNAs), 155

Miscarriage, 159

Monocyte-derived dendritic cells, 240–241

Monocytes, 140–141, 143

Mouse embryonic fibroblasts (MEFs), 43

Mouse embryonic stem cells (mESCs), 44–45

N

Negative regulation
 activin receptor function
 activin membrane-bound inhibitor, 85
 BMP, 85
 Cripto, 85–87
 Dapper2, 89
 Dok-PTB containing protein, 88–89
 proteins 1 and 2, 87–88
 regulatory subunits of PP2A, 87
 gene transcription, 94–97

Neurogenesis, activin
 bromodeoxyuridine, 193
 electroconvulsive therapy, 195
 excitatory and inhibitory postsynaptic potential, 194–195
 follistatin and GDF11, 194
 FSM/ACM-double transgenic mice, 194
 hippocampal culture, 194
 physiological roles, 193

N-linked glycosylation, inhibin, 163

NMDA receptor, 189

Nodal signaling, 9

Nonalcoholic fatty liver disease (NAFLD)
 apoptosis, 328
 diagnosis, 325
 epidemiology, 326
 fibrosis, 328
 hepatic fat accumulation, 326–327
 histology, 324
 lipid and glucose metabolism, insulin, 327
 metabolic syndrome, 326–327
 natural history, 325
 pathophysiology, 326
 prevalence, 326
 systemic inflammation, 328–329
 two-hit model, 326, 340

Noncanonical Wnt signaling, 211–212

Nuclear factor of activated T cells (NFAT), 238

O

Ovarian and pituitary hormones, changing patterns, 310–311

Ovarian cancer, 166, 169

P

Pancreatic endocrine cells, 7–9

Pathogen-associated molecular patterns (PAMPs), 267

Peripheral blood mononuclear cells (PBMC), 337

Peripheral blood myeloid dendritic cells, 240–241

Placentation and pregnancy, inhibin, 158–159

Plasminogen activator inhibitor-1 (PAI-1), 224

Pluripotent cells. *See* Embryonic stem cells (ESCs)

Postsynaptic density 95 (PSD95), 189

Posttranscriptional regulation, inhibin, 155

Posttranslational modifications, inhibin, 163–164

Preeclampsia, 159

Prostate cancer, 134–135, 143

R

Receptor-activated SMADs (R-SMADs), 47, 60

S

Serum response factor (SRF), 96

SMAD anchor for receptor activation (SARA), 210

Smad-binding element (SBE), 14, 153–154

Smad proteins, 47
 cell migration
 Smads-dependent, 132–133
 Smads-independent, 133–134
 function
 ectoderm/TIF1g, 91–92
 Erbin, 93–94
 linker phosphorylation, 92–93
 PPM1A, 91
 transmembrane prostate androgen-induced RNA, 94
 signaling pathway, 190
 Smad2/3 signaling pathway, 331

Spine formation, activin, 189–190

Stem cell pluripotency
 Activin/Nodal/TGF β pathway, 46–48
 TGF β signaling, 50–51

T

TATA boxes, 151, 152

Th2 cells, activin A
 activin β A promoter, transactivation, 238
 CD4⁺ CD4⁺ T cells, 237–238
 expression, T helper cells, 237

Transcription regulation
 cAMP response element (CRE), 12
 C element, 12–13
 E element, 13–14
 A element, 10
 GG element, 11–12
 Smad-binding element (SBE), 14

Transforming growth factor- β (TGF- β)

- connective tissue growth factor, 60–61
 - continuous low-level activation, 63–65
 - external and internal inhibitors, 65
 - intracellular activation, 61–63
 - intracrine signaling mechanism
 - inhibitory pathway, 70–72
 - stimulatory pathway, 66–70
 - mouse embryo, 48–50
 - receptors, 3–5
 - schematics, 48
 - stem cell pluripotency, 50–51
 - type I receptor kinase domain structure, 31
 - Transmembrane prostate androgen-induced RNA, 94
 - Tumor cell migration, activins
 - breast cancer, 135–137
 - colon cancer, 138
 - prostate cancer, 134–135
 - Two-hit hypothesis, 332, 333
 - Type 2 diabetes mellitus, 326–327
 - Type I BMP receptors, 109–110
 - Type II BMP receptors, 110
 - Type IV collagenase production, 241–242
- U**
- 5' Untranslated regions (UTRs), inhibin, 151, 152
- W**
- White adipose tissue, 223–224

Index

A

- Activation-induced cell death (AICD)
 of mature T-cells, 165–169
 of thymocytes, 160–162
- Adaptive immune response
 clinical implications
 autoimmunity inhibition, 9–10
 adverse effects, 11
 tissue transplantation, 10–11
 vitamin D role, 7–9
- Adaptive immunity
 modulation, 265–266
 vitamin D
 B-cell function, 45–46
 cytotoxic T-cells, 43–44
 regulatory T-cells, 44–45
 T-cell activation and proliferation,
 42–43
 T-helper cell, 43–44
- Aflatoxins B₁ (AFB₁)
 aflatoxins and, 288–290
 effect of vitamins A, C, and D, 298
 food contamination by, 288–289
 hepatocellular carcinoma by, 289
 interaction between dietary factors and,
 292–293
 molecular mechanisms of, 290–291
 obligations, 299–300
 roles of vitamins A, C, and E, 299
 toxicity and oxidative stress, inhibition of,
 291–292
 vitamin A, 294–295
 vitamin C, 295–296
 vitamin E, 296–299
- AICD. *See* Activation-induced cell death
- AIDS, 164, 183, 192, 195, 356, 362
- Airway epithelium, 222, 228
- ALDEFLUOR assay, 137–138
- Allergic disease, 250–251
- Alveolar macrophages, 222–223
- Animal models, transplantation
 cardiac transplantation, 443
 islet transplantation, 444
 kidney transplantation, 440–442
 liver transplantation, 442–443
 lung transplantation, 444
- Antibacterial actions, vitamin D
 antibacterial effects
 epithelial cells, 38
 keratinocytes, 37–38
 neutrophils, 37
- antibacterial targets
 bacteriocidal activity, 36
 DEFB4, 34
 LL37, 33–34
 mammalian target of rapamycin (mTOR)
 pathway, 36–37
 NOD2, 34
 reactive oxygen species (ROS), 35–36
- bioavailability
 binding affinity, 29
 LL37 induction, 27–28
 megalin-cubilin, 28
 VDR and CYP27B1 induction, 28
 vitamin D binding protein (DBP),
 28–29
- metabolism regulations
 1,25(OH)₂D synthesis, 29–30
 CYP24A1, 31–32
 CYP27B1 regulation, 30–31
 monocytes, 30
- VDR expression
 binding affinity, 32
 HVDRR, 33
 monocytes, 32–33
- Antiinfective vitamin. *See* Vitamin A
- Appendicitis, 357
- Aspergillus flavus* toxins. *See* Aflatoxins B₁
 (AFB₁)
- Asthma, 229–230, 250–251
- Atopic dermatitis (AD), 194
- Autoimmune diseases
 dendritic cells treatment
 antigen-specific immunoregulation, 74
 immunoregulatory effect, 73–74
 VD3 administration, 73
 VDR expression, 73
 low level of vitamin D and, 268–269
 pregnancy and vitamin D, 251–253
 Sjögren's syndrome, 274
 systemic lupus erythematosus, 274–277
 systemic sclerosis
 characteristics, 271–272
 pathogenesis, 272
 vitamin D status in, 273
 vitamin D/VDR signaling, 272–273
 vitamin D deficiency, causes of, 269–270

- Autoimmunity
 innate immune system, 332
 T cell activation, 333
 vitamin D supplementation, 334–335
- Autosomal recessive metabolic disorder, 355
- B**
- B-cells
 activation, 107–109
 differentiation, 111–114
 proliferation, 109–111
 and vitamin D, 45–46
- Basophils, 143
- C**
- Calcemic effects, vitamin D, 386
 Calcipotriene, 273
 Calcitriol synthesis, 329
 Calcitriol therapy
 kidney transplantation, 446–448
 liver transplantation, 442
 Calprotectin, 264
 Cancer, 254
 Cardiac transplantation, 443
 Cathelicidin, 13, 310–311, 315–316
 Celiac disease, 357
 Chronic allograft injury
 molecular mechanisms, 448–449
 transforming growth factor and vitamin D interactions, 449–450
 vitamin D, 448–449
- Chronic obstructive pulmonary disease (COPD), 231
 airway inflammation, 389–391
 cancer, 393
 causes, 380
 comorbidities, 381
 definition, 380
 diagnosis, 380
 exacerbations, 381
 noncalcemic effects, vitamin D, 388–389
 osteoporosis
 definition, 385
 prevalence, 386–387
 risk factors, 387
 vitamin D and calcemic effects, 386
 vitamin D substitution, 388
 skeletal muscle dysfunction, 391–392
 vitamin D
 deficiency, 382–385
 pathway, 382
- Class switch recombination (CSR), 114–115
 Cod liver oil, 316
 COPD. *See* Chronic obstructive pulmonary disease
 Crohn's disease
 causes, 358
 definition, 357
 OCTNs and their association, 359–360
 treatment, 358
- CYP27B1
 epithelia, 6
 expression, 3
 25-hydroxylase activity, 5
 keratinocytes, 6
 kidney cells, activity of, 4
 regulation, in kidney cells, 5, 7
- Cytotoxic T-cells, adaptive immunity, 43–44
- D**
- Deficiency
 vitamin A
 mucosal tissue infection, 86
 tissue inflammation, 94
 vitamin D (*see* Vitamin D)
 vitamin E, 181–184
- Dendritic cells (DC),
 adaptive immunity modulation, 265–266
 autoimmune diseases, treatment of
 antigen-specific immunoregulation, 74
 immunoregulatory effect, 73–74
 VD3 administration, 73
 VDR expression, 73
 1,25-dihydroxyvitamin D generation,
 223–224
 function, 40–42
 immune system
 autoimmune diseases, 65
 immunological tolerance, 65
 lymphoid cells, 64
 myeloid cells, 64
 peripheral tissues, 64–65
 maturation, 39–40
 modulation
 indoleamine 2,3-dioxygenase (IDO), 72
 migration, 71
 myeloid lineage, 72
 NF- κ B signaling, 72
 receptor expression, 71
 receptor inhibition, 70
 T cell differentiation, 70–71
 VDR ligands effect, human myeloid, 68–69
 retinoid acid production, (*see* Dendritic cells,
 retinoid acid production)
 VD3-modulated DC therapy, 74–76
 vitamin D metabolism
 T cell activation, 66–67
 VD3 binding, 66
- Dendritic cells, retinoid acid production
 degradation, *in vivo* and *in vitro*, 143
 gut-homing receptors, 132–133
 gut-related lymphoid organs, 131–132
 identification
 ALDEFLUOR assay, 137–138
 pathway of RA biosynthesis, 137

- imprinting of gut homing specificity
 imprinting process, 132–134
 RAR and RXR, 134
 retinal dehydrogenase (RALDH), 134–135
- induction
 basophils, 143
 GM-CSF and IL-4, 140
 GM-CSF-induced RALDH2 expression, 142
 LXR and PPAR γ , 140–141
 mesenteric lymph node stromal cells, 142
 mucosal epithelial cells, 142–143
 toll-like receptor ligands, 143
- lymphocytes, functional differentiation
 IgA production, 136
 primed T cells, 136
 regulatory T cells and Th17 cells, 135
 Th1 and Th2 cells, 136
- origin
 E-cadherin-mediated adhesion, 139
 lamina propria-dendritic cell subsets, 138–139
 mesenteric lymph node-dendritic cells, 139–140
- 1,25-Dihydroxyvitamin D₃ (VD₃)
 airway epithelium, 222
 alveolar macrophages, 222–223
 autoimmune diseases, treatment, 73–74
 catalysis of, 220
 dendritic cells, 223–224
 immune homeostasis maintenance, 368
 its influence on DC function, 66–67
 local production and effect of, 220–222
 lymphocytes, 224–225, 266–267
 modulation, 70–71
- Diverticulosis, 357
- E**
- Effector T cells, RA
 Th17 cells, 91–92
 Th1/Th2 cells, 90–91
- Estimated average requirement (EAR), vitamin E,
 183, 185–186
- F**
- Fas-induced cell death, 169–170
 FoxP3⁺ T cells, 92–93
 Free radicals, 186–187
 Friedreich's ataxia, 182–183
- G**
- Gastroenteritis, 357
 Glucocorticosteroids, 230
 Granulocyte/macrophage colony-stimulating factor (GM-CSF), 140
- Gut-homing receptors, 132–133
 Gut-related lymphoid organs, 131–132
- H**
- Heliotherapy, 316
 Hemolysis, 185
 Hereditary vitamin D resistant rickets (HVDRR), 33
 HIV, 164–165, 168–169, 172–173, 183, 195
 Hygiene hypothesis, 372
 1 α -Hydroxylase, 218, 220, 222–224, 226, 231
 Hypercalcemia, 318
- I**
- IgA production, 136
 IL-4. *See* Interleukin (IL-4)
 Immunological use
 vitamin D, 246
 vitamin E
 in animals, 196, 198–200
 in humans, 191–197
- Immunomodulatory effects
 vitamin A, 154
 vitamin D, tuberculosis, 309–310
 vitamin E
 antioxidant functions, 186–188
 Immunologic mechanisms, 188–191
- Indoleamine 2,3-dioxygenase (IDO), 72
 Infectious disease, 253–254
- Inflammatory bowel disease
 immune responses vitamin D, 48–49
 vitamin D
 animal models, 372–373
 Crohn's disease activity index, 374
 hygiene hypothesis, 372
 immune system, 368–371
 immunomodulatory effects, 373
 vitamin D status, 371–372
- Innate immune response, vitamin D role, 12–15
- Interferon regulatory factor-3 (IRF-3), 12
 Interleukin (IL-4), 140, 267
- Intestinal epithelia and dietary systems, 129–130
- Intestinal inflammation
 pathological processes, 356–358
 treatment, 358
- Irritable bowel syndrome (IBS), 357
- Islet transplantation, 444
- K**
- Keratinocytes, 14–15
 Kidney transplant recipients
 chronic allograft injury
 molecular mechanisms, 448–449
 transforming growth factor and vitamin D interactions, 449–450
 vitamin D, 448–449

- Kidney transplant recipients (*cont.*)
 graft function and rejection, 446–448
 infections
 infection defense and antimicrobial peptides, 451–452
 prevention, infectious diseases, 453–454
 vitamin D and innate immune system, 452–453
 vitamin D deficiency and supplementation, 445–446
- Kidney transplantation, 440–442

L

- L-carnitine
 antioxidant activities, 360–361
 deficiency, 355–356
 function
 chemical structure, 354
 transportation, 354–355
 immunosuppressive properties
 glucocorticoid receptor alpha (GR α), 362
 in vitro, 361–362
 in vivo, 362
 intestinal epithelial barrier protection, 362–363
 therapeutic applications, 356
- Lamina propria-dendritic cell subsets, 138–139
- Ligands of liver X receptor (LXR), 140–141
- Liquid chromatography–tandem mass spectrometry (LC–MS/MS), 331–332
- Liver transplantation, 442–443
- LL-37, 13, 310–311, 315, 452, 453
- Lung
 immune functions
 activation of, 219–220
 pattern recognition receptors, 218–219
 infections and vitamin D
 mycobacteria, 225–227
 respiratory infections, 227–229
 transplantation, 444
- LXR. *See* Ligands of liver X receptor
- Lymphocytes, 224–225, 266–267
- Lymphoid organs, 131–133

M

- Macrophages, 13–14
- Maternal nutrition. *See* Pregnancy, vitamin D
- Mature T cell death regulation
 death by neglect of, 162–163
 on ACAD of, 163–165
 on AICD of, 165–169
- Mesenteric lymph node stromal cells, 142
- Mesenteric lymph node-dendritic cells, 139–140
- Mucosal epithelial cells, 142–143
- Multiple sclerosis (MS)
 1,25(OH) $_2$ D effects, EAE, 417–418
 characteristics
 primary progressive MS, 403

- relapsing remitting MS, 402
 secondary progressive MS, 403
- immune responses vitamin D, 47–48
in vitro effects, 1,25(OH) $_2$ D, 410–417
- Maternal vitamin D, 252–253
 metabolism, vitamin D, 409–410
- T-cell compartment, 403–404
 and vitamin D status, 418–420
- treatment, 404
- vitamin D
 metabolism, 409–410
 receptor expression, 408
 supplementation, 420–421
- Mycobacteria, 225–227
Mycobacterium tuberculosis, 26–27
- Myeloid cells
 development, 86–90
 role in immune system, 64
- Myeloid differentiation factor-88 (MyD88), 12

N

- National Health and Nutrition Examination Survey (NHANES), 228
- Noncalcemic effects, vitamin D, 388–389
- Nuclear factor- κ B (NF- κ B), 228

O

- Obstructive lung disease and vitamin D
 asthma, 229–230
 COPD, 231
- Organic cation transporters (OCTNs), 354
- Osteoporosis, Vitamin D role
 and calcemic effects, 386
 definition, 385
 prevalence, 386–387
 risk factors, 387
 substitution, 388

P

- Parathyroid hormone (PTH), 4
- Pattern recognition receptors (PRRs), 218–219
Post hoc analysis, 454
- PPAR γ , 140–141
- Pregnancy, vitamin D
 dietary guidelines and maternal intake, 248–250
 disease outcome in offspring, 250–254
 forms and sources of, 241
 functions, 245
 immunological functions, 246
 metabolism, 241, 244–245
 role of maternal, 242–243
 S-25-OHD assessment, 246–247
- Primed T cells, 136
- Psoriasis and associated arthritis, 342

R

- Reactive oxygen species (ROS), 187
- Regulatory T cells, 135
 adaptive immunity, 44–45
 retinoic acid, 92–93
- Relapsing remitting multiple sclerosis (RRMS), 402
- Respiratory infections, 227–229
- Retinal, 130
- Retinal dehydrogenase (RALDH), 134–135
- Retinoid acid (RA)
 antibody responses regulation, 9394
 clinical and experimental uses, 106–107
 effector T cells
 Th1 or Th2 cells, 90–91
 Th17 cells, 91–92
 as factor in B-cell maturation, activation, and proliferation
 immunocompetence and initial activation, 107–109
 proliferation, 109–111
 as factor in germinal center formation, 116–117
 costimulation with RA and PIC, 117–119
 FDC network formation, 118–120
 future directions, 120–121
 myeloid cell development, regulation
 apoptosis and maturation of DCs, 88–89
 bone marrow differentiation, 87–88
 cell division, 87
 dendritic cells, 88
 langerin, 89
 neutrophils, 88
 RAR and RXR, 87
 9-*cis* retinoid acid (9cRA)
 anti-CD3-induced AICD, inhibition of, 167–168
 physiological relevance, 170–171
 production, dendritic cells
 degradation, *in vivo* and *in vitro*, 143
 functional differentiation regulation, 135–136
 gut-homing receptors, 132–133
 gut-related lymphoid organs, 131–132
 identification, 137–138
 imprinting of gut homing specificity, 132–135
 induction, 140–143
 origin, 138–140
 retinoid acid receptor (RAR), 134
 regulatory T cells, 92–93
 synthesis, 85
 tissue inflammation
 mucosal immune system, 95
 vitamin A deficiency (VAD), 94
 vitamin A effects, 130–131
- Retinoid deficiency, 89–90
- Retinoid X receptor (RXR), 134

- Retinol. *See* Vitamin A
- Retinyl esters, 155
- Rheumatic diseases, vitamin D
 autoimmunity
 innate immune system, 332
 T cell activation, 333
 vitamin D supplementation, 334–335
 function and biochemical measures
 calcitriol, 329–330
 liquid chromatography–tandem mass spectroscopy, 331–332
 matrix effect, 330
 overlap syndromes, 343
 psoriasis and associated arthritis, 342
 rheumatoid arthritis, 341–342
 SLE and systemic autoimmune diseases
 25-OH vitamin D inadequacy, 335–339
 bone mineral density (BMD), 335
 UCTD, 340
 supplementation, 343–346
- Rheumatoid arthritis, 277–279, 341–342
- RXR. *See* Retinoid X receptor

S

- Serum-25-hydroxy vitamin D (S-25-OHD), 246–247
- Sjögren's syndrome, 274
- Skeletal muscle dysfunction, 391–392
- Systemic lupus erythematosus (SLE)
 25-OH vitamin D inadequacy, 335–339
 bone mineral density (BMD), 335
 UCTD, 340
 and vitamin D, 274–277
- Systemic sclerosis
 characteristics, 271–272
 pathogenesis, 272
 vitamin D status in, 273
 vitamin D/VDR signaling, 272–273

T

- T cell death
 FAS-induced, 169–170
 forms of
 mature T cells, 158–159
 thymocytes, death of, 157–158
 mature, effects of vitamin A
 death by neglect of, 162–163
 on ACAD of, 163–165
 on AICD of, 165–169
 and 9cRA, 170–171
 pathways, 156–157
 physiological implications, 171–173
 thymocyte, effects of vitamin A
 neglect of, 159–160
 on AICD, 160–162
- T-cell activation and proliferation, 42–43

- T-helper cell, adaptive immunity, 43–44
- TB. *See* Tuberculosis
- Th1/Th2 cells, 90–91, 136
- Th17 cells, 91–92, 135
- Tocopherol. *See* Vitamin E
- Toll-like receptor ligands, 143
- γ -Trimethylamino- β -hydroxybutyric acid. *See* L-carnitine
- Tuberculosis (TB)
 cause for, 308
 vitamin D
 and hypercalcemia, 318
 cathelicidin and, 310–311, 315–316
 cod liver oil, 316
 deficiency of, 314–315
 epidemiological studies, 317–318
 heliotherapy, 316
 immune responses, 46–47
 immunity and, 314
 immunomodulatory role of, 309–310
 metabolism, 309
 pharmacological doses, 316–317
 randomized controlled trials, 317
 receptor, 311–313
 VDR gene polymorphisms, susceptibility and treatment response, 318–319
- Type 1 diabetes, 47, 252
- U**
- UCTD. *See* Undifferentiated connective tissue disease
- Ulcerative colitis (UC), 357, 368
- Undifferentiated connective tissue disease (UCTD), 343
 clinical manifestations, 270–271
 pathogenesis, 271
- V**
- VD3-modulated DC therapy, 74–76
- VDR gene polymorphisms, 312–313, 318–319
- Vitamin A. *See also* Retinoic acid
 aflatoxin B₁-induced oxidative stress, 294–295
 B-cell maturation, activation, and proliferation
 immunocompetence and initial activation, 107–109
 proliferation, 109–111
 cell death pathways, 156–157
 class switch recombination (CSR), 114–115
 deficiency (*see* Vitamin A deficiency)
 effects of
 on ACAD of mature T cells, 163–165
 on AICD of mature T cells, 165–169
 on AICD of thymocytes, 160–162
 on death by neglect of mature T cells, 162–163
 on FAS-induced cell death, 169–170
 on thymocyte cell death, 159–160
 effects on host defense systems
 intestinal epithelia and dietary systems, 129–130
 metabolites, 130–131
 germinal center (GC) formation, 116–117
 costimulation with RA and PI, 117–119
 FDC network formation, 118–120
 future directions, 120–121
 immunomodulatory role, 154
 mechanism of action, 154–156
 metabolism and function, 85–86
 9cRA, 170–171
 physiological implications of, 171–173
 RARs, 155
 retinoic acid, 154–155
- T cell death
 death of thymocytes, 157–158
 mature, 158–159
- transcription factors promoting B-cell differentiation, 111–114
- vitamin A-retinoic acid signaling system
 clinical and experimental uses, 106–107
 nutritional physiology and functions, 105–106
- Vitamin A deficiency (VAD)
 mucosal tissue infection, 86
 tissue inflammation, 94
- Vitamin C, aflatoxin B₁-induced oxidative stress, 295–296
- Vitamin D
 adaptive immune response
 antigen presentation, 7, 8
 antimicrobial activity loss, 11
 autoimmunity inhibition, 9–10
 cytokine regulation, 9
 interleukin production, 8
 tissue transplantation, 10–11
- adaptive immunity
 B-cell function, 45–46
 cytotoxic T-cells, 43–44
 modulation, 265–266
 regulatory T-cells, 44–45
 T-cell activation and proliferation, 42–43
 T-helper cell, 43–44
- antibacterial actions, 26
 antibacterial effects, neutrophils and cell types, 37–38
 antibacterial targets, 33–37
 bioavailability, 27–29
 intracrine pathway, 26
M. tuberculosis, 25–26
 metabolism regulations, 29–32
 monocyte activity, 27
 VDR expression, 32–33
- antigen presentation
 DC maturation, 39–40
 metabolism and DC function, 40–42
- autoimmune diseases and, 268–270

- biologic responses, 263
- biological effects of, 220
- and cathelicidin, 310–311, 315–316
- chronic liver disease patients, 455
- deficiency and calcium metabolism, 406
- deficiency and COPD
 - airway and systemic inflammation, 388–393
 - COPD and osteoporosis, 385–388
 - prevalence and determinants, 382–385
- deficiency and TB, 314–315
- dietary guidelines and maternal intake
 - assessment during pregnancy, 249–250
 - during pregnancy, 248
 - food and supplements, 248–249
- 1,25-dihydroxyvitamin D
 - airway epithelium, 222
 - alveolar macrophages, 222–223
 - catalysis of, 220
 - dendritic cells, 223–224
 - local production and effect of, 220–222
 - lymphocytes, 224–225
 - production, 2–7
- during pregnancy and disease outcomes in offspring
 - allergic disease and asthma, 250–251
 - autoimmune disease, 251–253
 - birth cohort studies, 255
 - cancer, 254
 - infectious disease, 253–254
- environmental factors, 262
- epidemiological studies, 227, 231–232
- extra-calcemic consequences, 407
- forms and sources of, 241
- functions of, 245
- heart transplant recipients, 455–456
- and hypercalcemia, 318
- immune system
 - animal models, transplantation, 440–444
 - dendritic cells, 436–437
 - in vitro* research, 439–440
 - T-cell activation and differentiation, 437, 438
- immune System and human health
 - inflammatory bowel disease, 48–49
 - multiple sclerosis, 47–48
 - tuberculosis, 46–47
 - type 1 diabetes, 47
- immune-regulative role, 263
- and immunity to TB, 314
- immunological functions, 246
- immunomodulatory role of, 309–310
- inflammatory bowel disease
 - animal models, 372–373
 - Crohn's disease activity index, 374
 - hygiene hypothesis, 372
 - immune system, 368–371
 - immunomodulatory effects, 373
 - vitamin D status, 371–372
- innate immune response
 - keratinocytes, 14–15
 - macrophages, 13–14
 - myeloid differentiation factor-88 (MyD88), 12
 - pathogens invasion, 15
 - TLR activation, 12–13
- kidney transplant recipients
 - chronic allograft injury, 448–451
 - graft function and rejection, 446–448
 - infections, 451–454
 - vitamin D deficiency and supplementation, 445–446
- liver transplant recipients, 455
- lung immune functions
 - activation of, 219–220
 - pattern recognition receptors, 218–219
- lung infections and
 - mycobacteria, 225–227
 - respiratory infections, 227–229
- lymphocytes, 266–267
- metabolism, 241, 244–245, 309, 405–406
 - after kidney transplantation, 435
 - chronic kidney disease, 432–435
 - and monocytes/dendritic cells, 265–266
- obstructive lung disease and
 - asthma, 229–230
 - COPD, 231
 - role of, 218
- on innate immunity, 263–264
- pregnancy, status during, 247
- rheumatic diseases
 - autoimmunity, 332–335
 - function and biochemical measures, 329–332
 - overlap syndromes, 343
 - psoriasis/associated arthritis, 342
 - rheumatoid arthritis, 341–342
 - SLE and systemic autoimmune diseases, 335–340
 - supplementation, 343–346
- rheumatoid arthritis and, 277–279
- role of maternal, 242–243
- S-25-OHD assessment, 246–247
- Sjögren's syndrome and, 274
- sources, 404–405
- sources and metabolism, 430–432
- systemic lupus erythematosus and, 274–277
- systemic sclerosis and, 271–273
- T-cell modulator, multiple sclerosis
 - characteristics, 402–403
 - compartment, 403–404
 - treatment, 404
- treatment of TB
 - cod liver oil, 316
 - heliotherapy, 316
 - vitamin D2, 316–318
- undifferentiated connective tissue disease and, 270–271

- Vitamin D (*cont.*)
 vitamin D receptor (VDR)
 and transcription, 312
 gene polymorphisms, 312–313, 318–319
- Vitamin E
 aflatoxin B₁-induced oxidative stress,
 296–299
 antioxidant functions of, 186–188
 daily intakes, 186
 deficiency
 AIDS, 183
 and immune response, 184
 ataxia, 182–183
 classification, 182
 genetic abnormalities, 182
 definition of, 180–181
 for CVD, 186
 IgE-mediated atopic responses, 194–195
 immunologic mechanism of, 188–191
 immunological use
 in animals, 196, 198–200
 in humans, 191–197
 immunomodulatory effects of
 antioxidant functions, 186–188
 Immunologic mechanisms, 188–191
 naturally occurring forms, 180–181
 RDA for, 185
 requirements and reference ranges
 functional criterion, 185
 polyunsaturated fatty acids, 185–186
 recommend daily intakes, 186
 structures of, 180–181
 tocopherol, 180
 tolerable UL, 185

Index

A

- Adipose derived mesenchymal stem cells (ADMSCs)
 - BMSC, 441
 - LIPUS, 458–459
- ADMSCs. *See* Adipose derived mesenchymal stem cells
- Adult cardiac-derived stem cells
 - bone marrow stem cell therapy, 112
 - c-kit-positive
 - GATA₄, 120
 - IGF-1 and Akt pathway, 120
 - LA-PCs *vs.* other stem cells, 115–116
 - left atrium-derived, 115
 - long-term cultures, 113–114
 - microarray and pathway analysis, 116–118
 - myogenesis and adipogenesis, 118–119
 - noggin and cardiac myocyte development, 119–120
 - transcription factors, 116
 - Wnt and TGF- β , 118
 - isolation, 112–113
 - myocardial infarction, 112
 - rodent and murine stem cells, 121
 - spheroid, 112–113
 - TGF- β functions, 121
- Adult stem cells (ASC), 292–293
- Alkaline phosphatase (ALP)
 - activity, 133–134, 437
 - COLI, 451
 - OCN mRNA, 438
- ALP. *See* Alkaline phosphatase
- Alzheimer's disease (AD), 146
- ARNT. *See* Aryl hydrocarbon receptor nuclear translocator
- Aryl hydrocarbon receptor nuclear translocator (ARNT), 368

B

- Bag-of-marbles (Bam) and benign gonial cell neoplasm (Bgen)
 - brain tumor, fused and Dsmurf repression, 409
 - Brat repression, 412
 - cystoblasts, 411
 - decapentaplegic signaling
 - cystoblasts, 408
 - description, 407–408
 - thick veins (Tkv), 408

- “timorous”, 408
- E-cadherin translation, 405
- expression, cysts, 401, 402–403
- extrinsic and intrinsic factors, 401–402
- germline Piwi expression
 - Dpp signaling, 405–406
 - Dsmurf, 406
 - germline, 406
 - piRNAs, 405
- GSC, 400
- microRNAs, Mei-P26, 406–407
- molecular interplay, 409–410
- Nos translation
 - Pum, 403
 - role, 403–404
 - 30'-UTR, 404
- protein expression, 403
- Pum function, 404–405
- somatic niche cells, 400–401
- translational regulation, 411, 412
- Bcl-X_L effects
 - BAX protein, 187
 - cell death
 - brain development, 189
 - embryogenesis, 189
 - immature cells, 189–190
 - oligodendrocytes, 190
 - pathways, 188–189
 - PD model, 190
 - progenitor cells, 189
 - cell proliferation
 - calcium homeostasis, 192
 - cell cycle, 191
 - cytosolic calcium, 192
 - intermediate progenitors (IPs), 191–192
 - neurogenic effect, 190–191
 - p53-p21 pathway, 193
 - p53 role, 192
 - synapse formation, 191
 - hematopoietic system, 187
 - Mcl-1 protein, 186
 - neuronal parameters, 186–187
 - progenitor population, 187
 - proneuronal gene Ngn2, 193
 - rat striatum, 188
 - TH-positive generated neurons, 188
- BMPs. *See* Bone morphogenetic proteins
- Bone marrow MSCs
 - adipose tissue, 128, 129

- Bone marrow MSCs (*cont.*)
 cell types, 128–129
 differentiation potency
 chondrogenic, osteogenic and adipogenic lineages, 129–131
 mesenchymal lineages, 131
 signaling networks, 131
 differentiation, TGF- β 1
 adipogenic, 135
 chondrogenic, 133–134
 embryonic heart development, 135–136
 molecular mechanism, 136
 osteogenic, 134
 SMCs and cardiomyocytes, 135
 and TGF- β signaling, 131–133
 direct plating and heterogeneous nature, 128–129
 plastic-adherent cells, 128
- Bone morphogenetic proteins (BMPs)
 adenoviral expression, 47
 adipogenesis, 49
 chondrogenesis, 48
 components, 299–301
 description, 46
 mediating MSC self-renewal, 52–53
 MSC, commitment, 299–301
 self-renewal process, 42
 signaling (*see* Signaling pathways, pancreatic β -cells)
 survival and proliferation, MSC, 50
 treatment, 301–302
 Wnt pathway, 45–46
- Bulk-cultured cardiac stem cells (CSC-BCs)
 description, 113
 GATA₄, 120
 gene expression, 113, 114
vs. LA-PCs, 115
- C**
- Calcineurin/NFAT signaling (*see* Signaling pathways, pancreatic β -cells)
- Chondrogenesis, MSC
 BMP2, 48
 chondrocyte maturation, 48
 TGF- β , differentiation induction, 48
- c-kit-positive cardiac cells
 GATA₄, 120
 IGF-1 and Akt pathway
 enhancement, cardiac myocytes, 120
 role, 120
 LA-PCs
 cytokine, 115–116
 vs. mesoangioblasts, 115
 vs. peripheral blood mononuclear cells, 115–116
 left atrium-derived, 115
 long-term cultures
 CSC-BCs, gene expression, 113, 114
 description, 113
 RT-PCR, 113
 microarray and pathway analysis
 LA-PCs culture, 116–118
 muscle contraction signaling, 116–118
 Wnt and TGF- β , 116–118
 myogenesis and adipogenesis, TGF- β effect
 LA-PCs, 119
 role, 118–119
 Smad7 activation, 118
 noggin and cardiac myocyte development, 119–120
 transcription factors, 116
 Wnt and TGF- β , 118
- CME. *See* Crushed muscle extract
 Crushed muscle extract (CME), 256–257
 CSC-BCs. *See* Bulk-cultured cardiac stem cells
- D**
- DAn generation. *See* Dopaminergic neurons generation
- DCMMS. *See* Direct cell membrane magnetic stimulus
- D-galactosamine model, 100
- Direct cell membrane magnetic stimulus (DCMMS), 432
- Dopaminergic neurons (DAn) generation
 basal ganglia, 176–177
 cell replacement, PD
 fetal mesencephalic neurons/cells, 178–179
 stem cells, 179–185
 hNSCs differentiation, A9 DA phenotype
 epigenetic cues, 185–186
 genetic manipulations, 186–197
 potency loss, 177
 source, standards, 176–177
 tissue transplantation, 176–177
- E**
- ECM. *See* Extracellular matrix
- Embryonic stem (ES) cell regulation
 BMP pathway
 differentiation, 349–350
 embryos, 349
 ERK, 348–349
 growth differentiation factor, 347–348
 helix-loop-helix proteins, 348
 Id factors, 348
 LIF, 347
 role, 347
 Nodal pathway
 Brachyury expression, 352
 differentiation, 353
 embryo, 352–353
 Id genes, 351–352
 Lefty factors, 352

- Nodal-Smad2 signaling, 351
 - Smad2 signaling, 350–351
 - Embryonic stem (ES) cells, pancreatic β -cells
 - generation
 - endocrine progenitors, 80
 - final stages, 86–87
 - genetic manipulation, 80
 - insulin therapy, 80
 - islet transplantation, 80
 - signaling pathways
 - BMP, 84–86
 - Calcineurin/NFAT, 83
 - Epac, 83–84
 - Hedgehog, 82–83
 - manipulations, 86–87
 - PI3K, 81–82
 - type 1 diabetes mellitus, 79–80
 - Epac signaling. *See* Signaling pathways, pancreatic β -cells
 - ERK. *See* Extracellular receptor kinase
 - Extracellular matrix (ECM)
 - FGF receptors, 258–259
 - fibronectin, 253
 - glycosaminoglycans (GAGs), 253
 - growth control and differentiation, 255
 - IGF-1 and-2
 - expression, 259
 - myoblast proliferation and differentiation, 259
 - in vitro* cultured myoblasts, 260
 - MMPs, 254, 255
 - skeletal muscle repair, 252–253
 - slow-twitch soleus muscle, 249
 - TGF- β , 253, 259–260
 - Extracellular receptor kinase (ERK), 348–349, 354
- F**
- FGF. *See* Fibroblast growth factor
 - Fibroblast growth factor (FGF)
 - receptors, 258–259
 - syndecan-1 and glypican, 255
 - Fluid-induced shear stress (FSS)
 - 2D and 3D, 432
 - description, 430–431
 - differentiation pathways, 456–457
 - 3D perfusion systems, 454
 - 3D scaffold, 431–432
 - effect, 451–454
 - osteogenesis
 - ALP activity, 455–456
 - 2D and 3D, 454–455
 - scaffold pore size, 457
 - Folbp1. *See* Folbp1-folic acid binding protein
 - Folbp1-folic acid binding protein (Folbp1)
 - cell surface proteins, 152
 - folate receptors, 152
 - Folic acid (FA), maternal intake
 - AD, 146
 - asthma, 148
 - autism, 146
 - cardiac diseases, 147–148
 - cerebral ischemia, 147
 - depression, 147
 - mouse models, NTD, 148–149
 - neural crest development, 150–162
 - NTDs, 145–146
 - PD, 147
 - FSS. *See* Fluid-induced shear stress
- G**
- GCPs. *See* Granular cell precursors
 - Gene regulatory networks (GRNs)
 - maternal folate intake, 150
 - NC development, 149–150
 - potential folate responsive, 160–162
 - Germline proliferation, *Caenorhabditis elegans*
 - counter-intuitive assay
 - cell development, 66–67
 - DTC-intrinsic migration program, 66
 - screening strategy, 67–68
 - description, 62
 - development
 - cell nuclei, 63
 - larval stages, 63
 - somatic gonad rearrangement, 63–64
 - sperm production, 64
 - transition zone, 63–64
 - diet/metabolic signaling, 75
 - germline cell cycle arrest, IIR role, 73–74
 - IIR pathway, identification
 - DAF-2 activity, proliferative zone, 68, 69
 - description, 68, 69
 - IIR role, 74
 - IIR signaling, 68–69
 - insulins
 - characteristics, 71
 - ligand-encoding genes, 71
 - larval germline cell division cycle
 - DAF-2 activity, proliferative zone, 69–70
 - daf-2*/IIR mutants, 69–70
 - parameters, 69–70
 - ligand activity, 76
 - Notch-independent soma germline signaling
 - mechanisms, 64–65
 - Notch signaling pathway, 64–65
 - nutrition impacts, 75
 - target tissues, IIR signaling
 - daf-16* activity, 72
 - FOXO transcription factor *daf-16*, 71–72
 - nuclear localization, 72–73
 - sheath cell-ablation phenotype, 72, 73
 - Germline stem cells (GSCs), 400
 - Glucocorticoid hedgehog agonists, neurogenesis
 - cell growth, 210–211

Glucocorticoid hedgehog agonists, neurogenesis
 (*cont.*)
 mood disorders, 208
 potential effects
 β -arrestin-GFP reporter, 209–210
 dexamethasone, 210
 GCP proliferation, 208, 209
 hedgehog signaling pathway, 208
 SAR
 β -arrestin2-GFP translocation assay, 211,
 212, 213
 hydroxyl group, 211–212
 working model, 211–212, 214
 seven transmembrane receptors, 208
 steroids, 210–211
 Granular cell precursors (GCPs)
 cell growth, 210–211
 proliferation
 cerebellum, 209
 dexamethasone, 210
 stem cell population, 209
 treatment, 209–210
 GRNs. *See* Gene regulatory networks

H

hADSCs. *See* Human adipose tissue derived
 MSCs
 Hedgehog signaling. *See* Signaling pathways,
 pancreatic β -cells
 Hematopoietic stem cells (HSCs), 242, 245–246
 Hepatocyte growth factor (HGF), satellite cells
 activation, ERK1 and ERK2, 256
 cell cycle, 257–258
 c-fos and c-jun genes, 258
 CME, 256–257
 cyclin D1 and CDK inhibitor, 257–258
 exogenous administration, 257
 muscular disorder, 256–257
 proliferation, 255–256
 regeneration, skeletal muscles, 255
 hESCs. *See* Human embryonic stem cells
 hiPS cells. *See* Human induced pluripotent stem
 cells
 HLA-G. *See* Human leukocyte antigen G
 HLSCs. *See* Human liver stem cells
 HSCs. *See* Hematopoietic stem cells
 Human adipose tissue derived MSCs (hADSCs),
 298–299
 Human embryonic stem cells (hESCs)
 challenges, 180
 clinical application, 179
 coculture, 179
 feeder-based protocols, 180
 Human induced pluripotent stem (hiPS) cells
 challenges, 181
 DNA methylation, 181

parkinsonian rats, 181
 transcription factors, 180
 tumor formation, 181
 Human leukocyte antigen G (HLA-G)
 expression, progesterone
 agents, 226–227
 CD4+ T lymphocytes, 226
 cell cultures, 227–228
 cytotrophoblast cells, 226
 endothelial cells, 227
 immune interactions, 228–229
 immunomodulatory factors, 226
 MSCs cultures, 228
 PIBF, 230
 steroid effects, 228
 Human liver stem cells (HLSCs), 299
 Human neural stem cells (hNSCs)
 cell differentiation, 182–185
 cell division-related genes, 181–182
 cultures, precursors, 181–182
 differentiation, A9 DA phenotype
 Bcl-X_L effects, 186–194
 bHLH transcription factors, 195
 cell therapy strategies, 194
 cytokines, 185
 embryonic development, 185
 hVM1 cells, 186
 Lmx1a, 195, 196–197
 notch signaling, 196
 Nurr1 and Foxa2, 196
 orthodentic homeobox 2, 195
 Pitx3, 195
 tissue samples, 185
 transcription factors, 194–195
 VM neurosphere cultures, 197
 Wnts, 195
 hVM1 cell line, 182–185
 Hypertension
 Ca(L), 332
 description, 331–332
 vascular system, 332, 333
 Hypoxia-inducible factors (HIF α) proteins
 angiogenesis therapies, 374
 ARNT, 368
 and cancer
 genetic instability, 369
 proliferation and metastasis, 369–370
 cardiac ischemic diseases, 373
 cell proliferation and differentiation pathways,
 374–375
 description, 368
 neurodegenerative diseases, 372–373
 stem
 cancer, 371–372
 Oct4, 370–371
 Sox2 and Klf4, 370–371

I

- IIR. *See* Insulin/IGF-like receptor
- Induced pluripotent stem (iPS), 358
- Inner cell mass (ICM), mammalian embryos
- blastocyst stage, 4
 - cell lineage segregation mechanisms
 - implantation rodent, 14–15
 - Nanog*, *Cdx2* and *Oct4* expression, 14
 - reciprocal inhibition, 14
- epiblast (EPI) and primitive endoderm (PE) formation
- blastocysts, 12
 - egg cylinder stage, 12
 - FGF signaling, 12–13
 - GATA4 and GATA6, 11–12
 - mosaic “composition”, 12–13
 - Nanog* expression, 11–12
 - positional signals, 11
 - Sox7* expression, 13
- and trophoblast (TE)
- blastomeres division, 4–5
 - Cdx2* mutant cells, 9
 - 8-cell stage, 4–5
 - chromatin remodeling protein BRG1, 6–8
 - FGF/ERK, 10–11
 - KLF5, 9–10
 - lineage, 5–6
 - perturbation, MAPK signaling, 11
 - “polarity” factors, 4–5
 - SOX2, 9
 - TEAD4 and YAP1, 8–9
 - transcriptional networks, 5–6, 7
 - transcription factors, 5–6
- Insulin/IGF-like receptor (IIR)
- germline cell cycle arrest, 73–74
 - larval germline proliferation, role, 74
 - mutants, analysis, 69–70
 - pathway, germline proliferation, 68
 - signaling, *Caenorhabditis elegans*
 - description, 68–69
 - target tissues, 71–73
- iPS. *See* Induced pluripotent stem

K

- Krüppel-like transcription factor (Klf5)
- core pluripotency network, 391–392
 - description, 382
 - expression, 382
 - function, ESCs
 - knockdown (KD), 385–386
 - LIF absence, 386
 - proliferation rate, 386–387
 - gene expression network, ESC pluripotent
 - Nanog*, 385
 - Oct3/4*, *Sox2*, and *Nanog*, 384
 - Sox2*, 384–385
 - STAT3 suppression, 384

- Wnt proteins, 384
- reprogramming, 383
- role, embryonic development
 - blastocyst outgrowth, 387–389
 - expression, 387, 388
 - Klf2 and Klf4, 390
 - phenotype, null blastocysts, 387–389
 - targets, 390–391

L

- LA-PCs. *See* Left atrium-derived pluripotent cells
- Left atrium-derived pluripotent cells (LA-PCs)
- cytokine, 115–116
 - vs.* mesoangioblasts, 115
 - microarray and pathway analysis, 116–118
 - vs.* peripheral blood mononuclear cells, 115–116
 - TGF- β 1, 119
- Leukemia inhibitory factor (LIF)
- BMP4, 348–349
 - presence and absence, 347–348
- LIF. *See* Leukemia inhibitory factor
- LIPUS. *See* Low-intensity pulsed ultrasound
- Low-intensity pulsed ultrasound (LIPUS), 459, 460
- L-type calcium channel [Ca(L)], 332

M

- Mad-homology 2 (MH2), 345
- Mammalian embryos and embryo-derived stem cells
- BMP/SMAD/Id signaling, 22
 - cell fate determination, 26–27
 - FGF2 and TGF β /ActivinA/Nodal signaling
 - culture medium, 25–26
 - differentiation markers, 23–25
 - neural induction, 23–25
 - neuroectodermal differentiation, 25–26
 - self-renewal, 23–25
 - SMAD2/3 transcription factors, 23–25
- human origin, 2–3
- ICM
- blastocyst stage, 4
 - cell lineage segregation mechanisms, 14–15
 - EPI and PE formation, 11–13
 - and TE, specification, 4–11
 - “immortal” stable cell lines, 15–16
- LIF/Jak/STAT3 signaling
- description, 19–21
 - receptor (LIFR), 19–21
 - self-renewal and differentiation, 19–21
- LIF/Ras/MEK/ERK signaling, 21
- lineage choice, 15
- PI3K/Akt and Src signaling, 21–22
- pluripotency, 2
- pluripotent stem cell lines
- embryonic stem (ES) cells, 16–17

- Mammalian embryos and embryo-derived stem cells (*cont.*)
- epiblast stem (EpiS) cells, 17
 - pre- and post-implantation, 15
 - totipotency and pluripotency, 3
 - transcriptional regulators
 - extrinsic and intrinsic factors, 18
 - gene expression, 18–19
 - ground and transient intermediate state, 18
 - OCT4 transcription factor, 18
 - SSEA1 and PECAM1, 18–19
 - WNT/ β -catenin signaling
 - activation, 22–23
 - description, 22–23
 - “3i conditions”, 23
 - self-renewal, 20, 22–23
 - teratoma formation, 23
- MAPK pathway. *See* Mitogen-activated protein kinase pathway
- Matrix metalloproteinases (MMPs), ECM remodeling
 - growth factors, 255
 - MMP-9 and -2 activity, 254
 - TIMPs and enzymes, 254
- Mesenchymal stem cells (MSCs)
- adipogenic differentiation
 - miR-31 and BMP-2, 302–304
 - Wnt signaling, 302–304
 - bone marrow, 422
 - CD271, 222–223
 - cells and tissue, 419–420
 - chondrogenic differentiation
 - in vitro* model, 304–305
 - microarray profile, 304–305
 - compression
 - chondrogenesis, 446–449
 - 3D cultures, 441–446
 - effect, 441–446
 - osteogenesis, 449–451
 - DCMMS, 458
 - definition, 222
 - description, 419
 - differentiation *in vitro*
 - adipogenesis, 424
 - chondrogenesis, 423–424
 - description, 422
 - osteogenesis, 422–423
 - tenogenesis, 424–425
 - features, isolated cells, 223
 - FSS, 451–458
 - function, mechanical regulation, 425–426
 - heterogeneity, 223
 - homogeneous population, 223
 - human endometrium
 - basal layer, 225
 - CD146 and PDGF-R β , 224–225
 - changes, menstrual cycle, 224
 - chimerism, 224
 - clonogenicity, 224–225
 - lymphocytes and NK cells, 224
 - niche, 224
 - reproductive hormones, 225
 - in vivo* loading
 - effect, 462–465
 - LMHF, 465
 - low magnitude, high-frequency vibration, 461
 - mechanical loading
 - compression, 429–430
 - DCMMS, 432
 - description, 427–428
 - FSS, 430–432
 - high frequency, low-magnitude vibration, 433
 - tension, 428–429
 - ultrasound, 432–433
 - mechanotransduction, 426–427
 - osteogenesis
 - adipogenesis, 437
 - ADMSC, 437
 - BMSCs, 441
 - dexamethasone, 437, 438
 - tenogenesis, 441
 - osteogenic differentiation
 - BMPs, 299–301
 - hADSC, 302
 - miR-206 expression, 301–302
 - plasticity
 - HNF4A, 306
 - miR-181, 305
 - neuronal-like cells, 306
 - role, miRNAs, 300, 305
 - progesterone
 - HLA-G expression, 226–229
 - PIBF expression, 229–230
 - SSEA-4 cells, 223
 - Stro-1 antibody, 222
 - TE, 418–419
 - tension
 - cardiomyogenesis, 440–441
 - chondrogenesis, 440
 - description, 433
 - osteogenesis, 437–439
 - tenogenesis, 439–440
 - tensile loading, 433, 434
 - tissue culture, 421
 - types, 420–421
 - ultrasound
 - BMSCs and ADMSCs, 459
 - LIPUS, 458–459
- MicroRNA (miRNA) and vascular smooth muscle cells (VSMC)
- application, 334–335
 - biogenesis and mechanism
 - description, 324–325
 - mRNA arrays, 325–326
 - differentiation

- Dicer, 327
- ES cells, 326
- miR-143/miR-145, 326–327
- diseases
 - aneurysm, 332–334
 - atherosclerosis, 331
 - diabetic vascular complications, 334
 - hypertension, 331–332
- histone modification, 323–324
- neointima hyperplasia
 - description, 330
 - microarray analysis, 330
 - vascular injury models, 330–331
- phenotypic switch
 - KLF4 and KLF5, 329
 - miR-143/145, 328
 - PDGF, 327–328
 - PDGF and TGF β pathways, 328–329
 - proliferation, 327
 - TGF- β and BMP, 328
 - target pairs, 324, 325
- MicroRNAs (miRNAs)
 - ASCs and MSC, 292–293
 - biogenesis, 293, 294
 - cell-to-cell communication
 - MVs, 307–308
 - tissue injury, repair, 306–307
 - description, 292
 - ESCs, 292
 - expression profiles
 - hADSC, 298–299
 - HLSC, 299
 - mammals, 297
 - miRISC, 295
 - MSC differentiation
 - adipogenesis, 302–304
 - chondrogenic, 304–305
 - osteogenic, 299–302
 - plasticity, 305–306
 - role, 299, 300
 - P-bodies, 295
 - profile, MSCs, 298
 - role, stem cell biology, 296–297
- Microvesicles (MVs)
 - biological effects
 - genetic information, 310
 - tissue repair, 310–311
 - description, 307–308
 - miRNA transfer
 - ESCs, 308
 - gene ontology analysis, 308–310
 - human bone marrow, 308–310
- miRISCs. *See* miRNA-induced silencing complexes
- miRNA. *See* MicroRNA
- miRNA-induced silencing complexes (miRISCs), 295
- Mitogen-activated protein kinase (MAPK) pathway
 - components, 10–11
 - MEK1 inhibitors, 21
 - signaling perturbation, 11
- MSCs. *See* Mesenchymal stem cells
- MSCs, molecular mediator
 - adipogenesis
 - adipogenic differentiation, 48–49
 - cell lines, 49
 - BMP, 46
 - canonical Wnt and BMP signaling, 46–47
 - chondrogenesis
 - BMP2, 48
 - chondrocyte maturation, 48
 - TGF- β , differentiation induction, 48
 - definition, murine, 40–41
 - description, 40
 - differentiation, 41
 - ex vivo expansion, HSCs, 53
 - immunomodulatory properties
 - anti-inflammatory role, 43
 - autoimmune encephalomyelitis model, 44
 - clinical trials, 43
 - proinflammatory cytokines, 43–44
 - roles, 44
 - mediating MSC self-renewal
 - description, 52
 - engraftment, 52–53
 - model, sFRP2 role, 52
 - mode of action, 52–53
- MI therapy
 - challenges, myocardial repair, 44
 - myocardial repair and ventricular dysfunction, 44
- osteogenesis
 - adenoviral expression, 47
 - canonical Wnt signaling, 47
- self-renewal process, 42
- sFRP
 - cytoprotection and proliferation, 51–52
 - description, 51
 - netrin (NTR) domain, 51
- survival and proliferation
 - BMP, 49–50
 - enhancement, wound, 50–51
 - Wnt, 49–50
- therapy
 - clinical approaches, 42
 - intracoronary administration, 43
- Wnt pathway
 - BMP and Wnt signaling, activation, 45
 - inhibition, 46
 - noncanonical and canonical, 46
- Muscle stem cells activation
 - ECM, 252–255, 258–260
 - growth and repair
 - Dicer-null satellite cells, 244

- Muscle stem cells activation (*cont.*)
 microRNAs molecules, 244
 MRFs, 244
 MSCs and HSCs, 245–246
 MyoD-positive cells, 242–243
 myofibers, 240–241
 myogenic precursor cells, 240, 241
 myostatin, 242–243
 Pax7 transcription factor, 242–243
 pericytes, 245–246
 “replacement” stem cells, 246
 SDF-1 receptor, 242
 side population (SP) cells and PICs, 244–245
 Sprouty1, 242–243
 transcription factors, 242
 HGF, 255–258
 regeneration, skeletal muscles
 fast-twitch and slow-twitch, 249
 fibrotic tissue, 248–249
 macrophages, 248
 myolysis and reconstruction, 246–247
 neutrophils, 247–248
 protein degradation, 247–248
 recruitment, inflammatory cells, 247–248
 soleus- and edl-derived myoblasts, 249
 satellite cell niche
 aging muscle, 252
 asymmetric stem cell division, 250
 Delta-like protein and Numb, 250–251
 described, 250
 m-cadherin, 250
 myofiber damage, 252
 syndecan-3, 251–252
 Wnt proteins, 251
 MVs. *See* Microvesicles
- N**
- NCSCs. *See* Neural crest stem cells
 Neural crest development, NCSCs and FA role
 Dicer and miRNA
 cell death, 153
 KDM6B expression and chromatin, 153
 EMT, 149
 Fgf4
 expression, 159
 Pax3 downstream, 158–159, 160
 Folbp1
 cell surface proteins, 152
 folate receptors, 152
 GRN genes, 149–150
 Hcy levels, NCC formation, 155
 Hes1 and Neurog2
 H3K9Ac, H3K18Ac and H3K27me2, 157
 stem cell proliferation and neurogenesis,
 158, 159
WT embryos proliferate and neurospheres,
 157, 158
 Lrp6-Wnt coreceptor
 β -catenin levels, 151–152
 mutations, 151–152
 miRNAs, 156–157
 neuroepithelial cells, transformation, 154–155
 Notch signaling
 cell proliferation, 160
 cranial development, 154
 potential folate responsive GRN, 160–162
 p53
 craniofacial defects, 153
 diabetes, 153–154
 expression, 153–154
 Pax3, 155
 Tead2
 Pifithrin- α , 150–151
 transcription factors, 150–151
 transcription factors, 149–150, 151
 Wnt signaling
 β -Catenin, 155–156
 FA supplementation, NTD, 156
 Neural crest stem cells (NCSCs)
 life history, 144
 and maternal FA intake
 folate levels, 144–145
 homocysteine (Hcy) levels, 145
 mouse models, NTD, 148–149
 neural crest development, 149–162
 role, human health, 145–148
 Neural tube defects (NTDs)
 autism, 146
 diabetes, 153–154
 folate nonresponsive genetic mouse models,
 162
 humans, 145–146
 Lrp6 mutations, 151–152
 mutant mice
 FA nonresponsive, 148–149
 folate responsive, 148
 Notch-independent soma germline signaling
 mechanisms
 distal Sh1 sheath, 66
 L3 and L4 stage, structure, 65
 mutant analysis, 65
 NTDs. *See* Neural tube defects
- O**
- Osteogenesis, MSC
 adenoviral expression, 47
 canonical Wnt signaling, 47
- P**
- Parkinson's disease (PD)
 cell replacement, human DAN
 donor tissue and cell composition of the
 grafts, 178–179
 hESCs, 179–180

- hiPS cells, 180–181
 - hNSCs, 181–185
 - host tissue/environment, 178–179
 - limitations, 179
 - transplantation, stem cells, 179
 - safe and functional transplantation, 176–177, 178
 - P-bodies. *See* Processing bodies
 - PD. *See* Parkinson's disease
 - PDGF. *See* Platelet-derived growth factor
 - PIBF. *See* Progesterone-induced blocking factor
 - Platelet-derived growth factor (PDGF), 328–329
 - Pluripotent stem cell lines
 - embryonic stem (ES) cells
 - chimeras and teratomas, 16–17
 - isolation, research groups, 16
 - molecular characteristics, 16
 - population-doubling time, 16
 - epiblast stem (EpiS) cells
 - characteristics, 17
 - description, 17
 - Processing bodies (P-bodies), 295
 - Progesterone
 - extra-reproductive tissues
 - epithelial cells, 219–220
 - experimental data, 220
 - mammary gland, 219–220
 - neuroprotective and promyelinating effects, 220
 - NK cells, 220–221
 - interactions, 218
 - MSCs, 222–223, 224–225, 226–230
 - receptors
 - genomic and nongenomic effects, 221–222
 - knockout approach, mice, 221
 - protein isoforms, 221
 - reproduction
 - decidualization, 219
 - endometrium transformation, 219
 - granulosa cells, 218–219
 - inhibitory effect, 218–219
 - target cell populations, 218
 - Progesterone-induced blocking factor (PIBF)
 - expression
 - cell culture, 230
 - described, 229
 - HLA-G, 230
 - immunomodulatory effect, 229
 - monoclonal antibody, 230
- R**
- Reserve liver progenitor cells, activation and regulation
 - adult rodent, structure, 97, 98
 - cell populations, 97
 - hierarchical responses, liver disease
 - cellular responses, 102
 - description, 102, 103
 - IL6 role, 102
 - mature hepatocytes, liver regeneration
 - description, 94–95
 - gene expression, phases, 95
 - mitogenic growth factors, 96
 - periportal location, 94–95
 - surgical partial hepatectomy (PH), 94–95
 - TGF β and activin, 96–97
 - TNF α , 95–96
 - transcription factors, activation, 95–96
 - oval cells and SHPCs, 97–98
 - and proliferation, oval cells
 - cellular events, 99
 - compartment, 99
 - cytokine-mediated priming stimulus, 100
 - experimental models, 98–99
 - D-galactosamine model, 100
 - pathophysiological circumstances, 98–99
 - Solt-Farber model, 100
 - and proliferation, SHPCs
 - cellular responses and time course, 101
 - molecular mechanisms, 102
 - phenotype, 101
 - proliferative stimulus, 101
 - retrosine, 100–101
 - stem cell lineage system, 94
 - Reverse transcriptase polymerase chain reaction (RT-PCR)
 - long-term culture, 113, 114
 - measurement, TGF-R1 expression, 116–118
 - RT-PCR. *See* Reverse transcriptase polymerase chain reaction
- S**
- SAR. *See* Structure–activity relationships
 - Secreted Frizzled-related protein 2 (sFRP2)
 - cytoprotection and proliferation, 51–52
 - description, 51
 - mediating MSC self-renewal, 52–53
 - NTR domain, 51
 - sFRP2. *See* Secreted Frizzled-related protein 2
 - SHPCs. *See* Small hepatocyte-like progenitor cells
 - Signaling pathways, pancreatic β -cells
 - BMP
 - description, 84–85
 - endocrine differentiation, 85
 - Noggin, inhibitor, 85
 - Pdx1* and *Hnf6* expression, 86
 - Pdx1* and insulin expression, 85
 - Calcineurin/NFAT
 - description, 83
 - NFATc proteins, 83
 - Epac
 - cAMP, 83–84
 - description, 83–84
 - dosage, exendin-4, 84

Signaling pathways, pancreatic β -cells (*cont.*)
 regulation, insulin secretion, 84

Hedgehog
 activation level, 83
 description, 82
 downregulation, Sonic (Shh), 82–83
 inhibition, 82–83

PI3Ks
 activators, 81
 description, 81
 maturation, role, 81
 regulation, 81–82

Small hepatocyte-like progenitor cells (SHPCs)
 cell populations, 102
 description, 97
 proliferation
 cellular responses and time course, 101
 molecular mechanisms, 102
 phenotype, 101
 proliferative stimulus, 101
 retorsine, 100–101

SMCs. *See* Smooth muscle cells

Smooth muscle cells (SMCs)
 development, TGF- β 1 signaling, 135
 transcription factors, 136

Solt–Farber model, 100

SSEA-4 cells. *See* Stage-specific embryonic antigen-4 cells

Stage-specific embryonic antigen-4 (SSEA-4) cells, 223

Structure–activity relationships (SAR)
 β -arrestin2-GFP translocation assay, 211, 212, 213
 hydroxyl group, 211–212
 working model, 211–212, 214

T

TE. *See* Tissue engineering

TGF- β 1. *See* Transforming growth factor- β 1

Thymosin- β 4 (T β 4)
 chemotactic activity
 description, 285
 F₁-F₀ ATP synthase, 285, 286
 classification
 description, 278–279
 structures, 278–279
 extracellular
 Ac-SDKP, 282
 sulfoxide, 281–282
 VEGF, 281
 gene and mRNA expression, 279
 intracellular, 281
 roles, heart regeneration, 282–283
 roles, skin tissue regeneration, 282
 skeletal muscle regeneration
 injury, 283
 myoblasts, 283–284

therapeutic applications, muscular dystrophy, 284–285
 in species, 280
 structure and posttranslational process, 280

Tissue engineering (TE), 418–419

Transforming growth factor- β 1 (TGF- β 1)
 chondrogenic differentiation
 cartilage development, 133
 pellet culture system, 133–134
 type II collagen hydrogel, 133–134
 embryonic heart development, 135–136
 inhibitor, adipogenesis, 135
 molecular mechanism
 MAPK activation, 136
 signaling pathway, 136
 transcriptional activity, Runx2 and TAZ, 136
 osteogenic differentiation
 ALP activity, 134
 bone regeneration, 134
 SMCs and cardiomyocytes, 135
 TGF- β signaling
 biological processes, 132
 downstream target genes, 132–133
 mammalian isoforms, 131–132
 transmembrane receptor, 132–133

Transforming growth factor-beta (TGF-beta)
 epiblast stem cells, 356–357
 ES, 342
 ES cell regulation, 347–350
 human ES cells
 FGF signaling, 356
 LIF and BMP, 354–356
 Nanog expression, 356
 iPS cells, 357–358
 ligands and transmembrane receptors
 BMP and Nodal, 343, 344
 type I and II receptors, 343
 pluripotency pathways, 354, 355
 signaling modulators, 346–347
 smad proteins
 DNA, 345–346
 members, 346
 MH1 and MH2 domains, 345

V

Vascular endothelial growth factor (VEGF), 281
 Vascular smooth muscle cells (VSMC).
See MicroRNA (miRNA) and vascular smooth muscle cells (VSMC)

VEGF. *See* Vascular endothelial growth factor

W

Wnt pathway, MSCs
 BMP and Wnt signaling, activation, 45
 inhibition, 46
 noncanonical and canonical, 46