Subject Index

Akt
fructose-2,6-bisphosphate, effects on phosphorylation 265, 266
signaling of glucokinase induction by insulin, beta cells 254–256
Alloxan, glucokinase sulfhydryl group probing 277–279, 282, 283
AMP-activated kinase, hepatoporal glucose sensor modulation 334
Appetite, glucokinase role 321, 322
Beta2, glucokinase neuroendocrine promoter binding 157
Beta cell, see also Insulin
allosteric glucokinase regulation 346, 347
glucokinase activator effects
  glucokinase induction 366
  insulin release 366–369
  metabolism 366
glucokinase expression and activity
  regulation 10, 11, 156–159, 244, 245
glucose metabolism
  glucokinase expression correlation 340, 341
  insulin secretion relationship 342–344, 346
glucose phosphorylation coupling to insulin exocytosis 6, 9, 10
glucose sensing 9, 10
glucose-stimulated insulin release modeling, see Glucose-stimulated insulin release
  maturity-onset diabetes of the young type 2, dysfunction 43, 52, 53
  metabolic fuel hypothesis, glucose sensing 317, 318
  proliferation and hypertrophy, pregnancy 223, 225
Biotin
  beta cell glucokinase induction 245
  hepatic glucokinase regulation 243, 244
Brain glucosensing neurons, see also Hypothalamus
criteria 304, 305
glucokinase glucosensing evidence
  glucokinase presence, glucosensing brain areas 302–304
  physiological evidence 304, 305
  glucose-excited neurons 301, 302, 316, 317
  glucose-inhibited neurons 301, 302, 316, 317
  physiological functions 306, 307
Congenital hyperinsulinism (CHI)
course by gene mutation 86, 87
gene mutations 75
glucokinase-activating mutations, see Persistent hyperinsulinemic hypoglycemia of infancy
  glutamate dehydrogenase gain-of-function mutations,
Congenital hyperinsulinism (continued)
  hyperinsulinism/hyperammonemia syndrome
glucose-leucine interactions
glucose effects on leucine-stimulated insulin secretion 118–120
glutaminolysis pathway 120–122
hyperammonemia 113
hypoglycemia 111, 112
leucine and protein sensitivity 114–116
mutation types 113–115

Cyclic AMP (cAMP)
glucokinase induction 158, 244
islet metabolism, pregnancy 234
Cysteine, see Sulfhydryl groups, glucokinase

Diabetes mellitus, see also Beta cell; Insulin; Permanent neonatal diabetes mellitus
glucokinase activator therapeutic rationale 13, 88, 360, 361
glucokinase activity
  liver 383–385
  muscle 385, 386
glucokinase regulatory protein therapeutic targeting 361, 385
glucose-6-phosphatase activity 382
hepatic glucose metabolism derangements 378, 379
  therapeutic targeting rationale 393
6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase therapeutic targeting 262, 263, 386, 387

Fatty acids, hepatic glucokinase regulation 243
Flux control coefficient
  glucokinase
    adaptive changes, glucose metabolism 212
    feed-forward activation of hepatic glucose metabolism, glucose 219
glucose-6-phosphatase effects 217, 218
glycogen synthesis versus glycolysis 216
  glucokinase regulatory protein balancing, glucokinase 215, 216
Fructose-2,6-bisphosphate
  phosphofructokinase activation 386
  regulation of glucokinase gene expression 263–266, 269, 270

Glucagon
glucose regulation 1
  liver glucokinase suppression 164, 243
  sterol regulatory element binding protein-1c, control of expression 171, 172
Glucagon-like peptide-1, hepatoportal
  glucose sensor modulation 331, 332, 335
Glucocorticoids
  beta cell glucokinase induction 244
  liver glucokinase induction 164, 243
Glucokinase (GK)
  activators, see Glucokinase activators
  allosteric activator site 6, 7
  appetite and body weight regulation 321, 322
  ATP affinity 5, 128, 129
  cooperativity
    glucose binding 5, 37, 38, 125
    models 129–131
    physiological role 131, 132
    sugar substrates 126–128
crystal structure of liver enzyme, bound activator
  activating mutations around allosteric site 147–149
  activator structure 147
  allosteric site features 146
  hexokinase I structure homology 150, 151
  recombinant enzyme expression and crystallography 152
  synergism of activator and activating mutations 149, 150
definition 18, 125, 126
  flux control coefficient
    adaptive changes, glucose metabolism 212
    feed-forward activation of hepatic glucose metabolism, glucose 219
glucose-6-phosphatase effects 217, 218
glycogen synthesis versus glycolysis 216

glucose-6-phosphate sensitivity 150, 151

glucose sensing
brain, see Brain glucosensing neurons; Hypothalamus
concept 4, 5, 93

glucose affinity 2, 3, 5, 92

glucose phosphorylation coupling to insulin exocytosis 6, 9, 10

glucose-stimulated insulin release modeling, see Glucose-stimulated insulin release

hepatoportal sensor, see Hepatoporal glucose sensor

history of study 2–4

overview 1, 2

glucose transporter coexpression 6

hexokinase I crystal structure modeling, conformational change
activating mutations and hypoglycemia 141, 142
allosteric sites 140, 141
ATP-binding site 140
computations and modeling 136, 137
defective mutations and hyperglycemia 141

hexokinase-binding site, closed
conformation 139, 140
open versus closed conformations 137–139
overview 135, 136

mutations in disease, see Maturity-onset diabetes of the young type 2; Permanent neonatal diabetes mellitus; Persistent hyperinsulinemic hypoglycemia of infancy
pregnancy changes, see Pregnancy regulation of expression, see Glucokinase gene
specie distribution 36, 37
subcellular localization control, glucokinase regulatory protein 199–201, 209–212, 350

sugar substrate specificity 6, 32–34, 365, 366
sulfhydryl groups, see Sulfhydryl groups, glucokinase
tissue distribution 2, 3, 7, 8, 31, 36, 37

Glucokinase activators
animal studies
blood glucose reduction 369–371
liver effects 372, 373
obesity studies 373–375
oral glucose tolerance testing 371

beta cell effects
glucokinase induction 366
insulin release 366–369
metabolism 366

binding site 364
clinical prospects 376, 377

crystal structure of liver glucokinase, bound activator
activating mutations around allosteric site 147–149
activator structure 147
allosteric site features 146
hexokinase I structure homology 150, 151
recombinant enzyme expression and crystallography 152
synergyism of activator and activating mutations 149, 150
mechanism of action 362, 363
stereochemistry 362
substrate specificity studies 365, 366
therapeutic rationale, diabetes 13, 88, 360, 361

Glucokinase gene
chromatin structure 186, 187
deletion, see Knockout mice, glucokinase
developmental expression 240, 241
dual promoter identification and significance 155, 169, 170, 185, 186
expression regulation overview
beta cells 10, 11, 34
dietary adaptation 38, 39
liver 12, 13, 34
fructose-2,6-bisphosphate regulation 263–266, 269, 270
Glucokinase gene (continued)

liver promoter
  biotin induction 243, 244
developmental regulation of liver expression 181–184
difficulty of study 180
glucagon suppression 164, 243
glucocorticoid induction 164, 243
insulin induction 162–164, 172–175, 184, 185, 190, 241, 243
microsatellites 188
nutritional and hormonal effects 162, 169, 184, 185
regulatory regions 159, 160
retinoic acid induction 244
thyroid hormone induction 164, 165, 243
transacting factors
  hepatic nuclear factor-3β 189
  hepatic nuclear factor-4α 160, 189
  hepatic nuclear factor-6 161, 189
  STAT5 161
  upstream stimulatory factor 160, 161
neuroendocrine promoter
  activation, different tissues 156
  inducers
    cyclic AMP 158, 244
    glucose 158, 159
    insulin, see Insulin
  transacting factors
    Beta2 157
    Nkx2.2 157
    Pax6 157
    Pdx-1 156, 157
    PPARγ 157, 158
overexpression, see Transgenic mice, glucokinase
sterol regulatory element binding
  protein-1c regulation, see Sterol regulatory element binding protein-1c
Glucokinase regulatory protein (GKR)
  adaptive changes in glucose phosphorylation affinity, fasting and feeding 212
discovery 193, 194
  flux control coefficient balancing, glucokinase 215, 216
gene structure 195
glucokinase kinetics effects 196, 197
  glucokinase subcellular localization control 199–201, 209–212, 350
  glucose competitive inhibition 196, 208
  knockout mouse studies 201, 202
  liver enzyme regulation 13
  mechanism of action 197–199
  physiological significance 202–204
  sequence homology between species 194, 195
  therapeutic targeting, diabetes 361, 385
  tissue distribution 195, 196
  transgenic mouse studies 385
Glucose-6-phosphatase, activity in diabetes 382
Glucose-stimulated insulin release (GSIR)
glucokinase sensing of glucose, see Glucokinase
  mathematical modeling of threshold accuracy, disease states 106, 107
  adaptation effects on threshold 103
  assumptions 93, 94
  contributions of individual
    glucokinase kinetic parameters 103, 104
    enzyme expression coefficient 94, 96
    enzyme stability coefficient 96, 97
    glucokinase wild-type and mutant enzymes
      kinetic characteristics 95–97
      missense mutations and disease 105, 106
      threshold predictions 97–99, 101–103
  minimal model 94
  relative activity index 97
Glucose transporters
glucokinase coexpression 6
hepatoportal glucose sensor
  GLUT4 modulation 333, 334
  transgenic and GLUT2 knockout mouse studies 329, 330
Glutamate dehydrogenase, see Congenital hyperinsulinism
Growth hormone, glucokinase regulation 245
Hepatic glucose metabolism
balance between glucose
phosphorylation and glucose-6-
phosphate hydrolysis
glucokinase activity, diabetes
liver 383–385
muscle 385, 386
glucose-6-phosphatase activity,
diabetes 382
regulatory steps 380, 381
derangements, diabetes 378, 379
fructose-2,6-bisphosphate activation of
phosphofructokinase 386, 387
protein phosphatase-1 glycogen-targeting
subunits, effects on glycogen synthesis
and glucose disposal 387–393
therapeutic targeting rationale 393
Hepatic nuclear factor-1α (HNF-1α),
fructose-2,6-bisphosphate induction 264
Hepatic nuclear factor-3β (HNF-3β),
glucokinase liver promoter binding 189
Hepatic nuclear factor-4α (HNF-4α),
glucokinase liver promoter binding
160, 189
Hepatic nuclear factor-6 (HNF-6),
glucokinase liver promoter binding
161, 189
Hepatocyte
glucokinase expression regulation, see
Glucokinase gene
glucose-6-phosphate, lack of feedback
inhibition of glucose phosphorylation
218
glucose sensing 11, 12
Hepatoportal glucose sensor
activation 328
AMP-activated kinase modulation 334
cellular structure 334, 335
glucagon-like peptide-1 modulation 331,
332, 335
glucose transporter transgenic and
knockout mouse studies 329, 330
GLUT4 modulation 333, 334
hypoglycemia induction by portal vein
glucose infusion 328
muscle insulin receptor modulation 333
neurocircuitry 328, 329, 332, 333
signal transduction 332, 333
Hexokinases, see also Glucokinase
actin fold sequence motifs 19, 21
catalytic reaction 32
classification 18, 19, 31, 32
conformational changes, plant glucose
sensing 13, 14
cysteine patterns, glucokinase versus
hexokinases 277
definition 18
discovery 2
evolution of mammalian isozymes 22,
23, 35, 36
gene cloning and sequence availability
19–21
genes of mammalian isozymes
exon size comparison 24–26
intron-exon structure 24
promoter structure and transcriptional
regulation 26, 27
hexokinase I crystal structure modeling
of glucokinase
activating mutations and hypoglycemia
141, 142
allosteric sites 140, 141
ATP-binding site 140
computations and modeling 136,
137
defective mutations and hyperglycemia
141
glucose-binding site, closed
conformation 139, 140
open versus closed conformations
137–139
overview 135, 136
posttranscriptional regulation and
3′-untranslated region 27, 28
substrate specificity 32–34
Hypothalamus
glucokinase, appetite and body weight
regulation 321, 322
glucose, nutritional feedback signal
313–316
glucose-excited neurons 316, 317
glucose-inhibited neurons 316, 317
metabolic fuel mechanism, glucose
sensing 318–321
Insulin, see also Beta cell
  amino acid stimulated secretion 110, 118–120
  glucokinase association with granules
evidence 351, 352, 354
  nitric oxide synthase interactions 356
  physiological significance 354–356
  glucokinase induction
    beta cells
    liver 162–164, 172–175, 184, 185, 190, 241, 243
  overview 158, 159, 249
    glucose/insulin-sensitive cis elements 256, 258
    immediacy of response 250
    insulin receptor B-type signaling, role 252–256
    insulin stimulation studies 250–252
  glucose metabolism and secretion
    relationship 342–344, 346
  glucose phosphorylation coupling to
    insulin exocytosis 6, 9, 10
  glucose regulation 1
  glucose-stimulated insulin release
    modeling, see Glucose-stimulated insulin release
  hepatoporal glucose sensor, muscle
    insulin receptor modulation 333
  pregnancy
    glucokinase glucose sensing and
      insulin secretion increase 229–235
    secretion 225–227
    sterol regulatory element binding
      protein-1c, control of expression 171, 172, 175, 176

Knockout mice, glucokinase
  beta cell specific knockout 294, 295
  global knockouts 293, 294
  glucokinase regulatory protein knockout
effects 201, 202
  liver-specific knockouts 295, 296
  models and phenotypes, overview 290
  neural/neuroendocrine-specific knockout 294
  prospects for study 296–298

Liver
  glucokinase gene promoter, see
    Glucokinase gene
  glucose metabolism, see Hepatic glucose
    metabolism

Maturity-onset diabetes of the young type 2
  (MODY-2)
    clinical features
      diabetes complications 55, 56
      hyperglycemia 55
    glucokinase mutations
      genotype-phenotype correlations and
        clinical implications 59, 60
      pathophysiology
        beta cell dysfunction 43, 52, 53
        hepatic glucose metabolism
          dysfunction 53–55
        types 8, 43–52
    glucose-stimulated insulin release
      modeling, see Glucose-stimulated insulin release
    management
      hyperglycemia 58, 59
      pregnant patients 59
    mouse models 8, 9
    pregnancy
      diagnosis 57
      fetal growth 57, 58
    prevalence of subtypes 42

Metabolic fuel hypothesis
  beta cell glucose sensing 317, 318
  hypothalamic glucose sensing 318–321

Mitogen-activated protein kinase (MAPK),
signaling of glucokinase induction by
insulin, beta cells 253, 254

MODY-2, see Maturity-onset diabetes of
the young type 2

NAD(P)H
  glucokinase expression correlation with
    levels 340, 341
  glucose metabolism correlation 339
  insulin secretion relationship 342–344, 346

Nitric oxide synthase (NOS), glucokinase
interactions, insulin granules 356
Nkx2.2, glucokinase neuroendocrine promoter binding 157

Obesity
brain glucosensing neurons and glucokinase expression 307, 321, 322
glucokinase activator studies 373–375

Pax6, glucokinase neuroendocrine promoter binding 157
Pdx-1, glucokinase neuroendocrine promoter binding 156, 157
Permanent neonatal diabetes mellitus (PNDM)
causes 65, 67
clinical features 66–70
glucokinase mutations
kinetics, mutant enzymes 70, 71
screening 72
types 8, 67, 70
glucose-stimulated insulin release modeling, see Glucose-stimulated insulin release incidence 65
mouse models 8, 9, 69
transient disease etiology 65
treatment 71, 72
Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
clinical features
birth weight 82
C-peptide suppression test 80
fasting insulin response 77, 80
insulin secretory rates 77
intravenous glucose test 85, 86
obesity and insulin resistance 83, 84
onset 82
oral glucose tolerance test and reactive hypoglycemia 84, 85
severe hypoglycemic attacks 83
course 86, 87

Prolactin (PRL)
pregnancy
pancreatic islet regulation 227, 228, 235–237
secretion 225–227
PPARγ, glucokinase neuroendocrine promoter binding 157, 158

Placental lactogen (PL)
pancreatic islet regulation 227, 228, 235–237
secretion, pregnancy 225–227

Pregnancy
beta cell proliferation and hypertrophy 223, 225
glucokinase glucose sensing and insulin secretion increase 229–235
insulin secretion 225–227
maturity-onset diabetes of the young

type 2
diagnosis 57
fetal growth 57, 58
management 59
prolactin and placental lactogen pancreatic islet regulation 227, 228, 235–237
prolactin receptor signaling, beta cells 227, 228, 232–234
secretion 225–227

Phosphatidylinositol 3-kinase, signaling of glucokinase induction by insulin, beta cells 253–256
6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase (6PF2K/F26P2ase) functions 262
glucokinase physical interactions 266–271
liver versus islet glucokinase regulation 271
product, see Fructose-2,6-bisphosphate therapeutic targeting, diabetes 262, 263, 386, 387

PPARγ, glucokinase neuroendocrine promoter binding 157, 158

Pregnancy
beta cell proliferation and hypertrophy 223, 225
glucokinase glucose sensing and insulin secretion increase 229–235
insulin secretion 225–227
maturity-onset diabetes of the young

type 2
diagnosis 57
fetal growth 57, 58
management 59
prolactin and placental lactogen pancreatic islet regulation 227, 228, 235–237
prolactin receptor signaling, beta cells 227, 228, 232–234
secretion 225–227

Prolactin (PRL)
pregnancy
pancreatic islet regulation 227, 228, 235–237, 245
secretion 225–227

Subject Index 405
Prolactin (continued)
receptor signaling, beta cells 227, 228, 232–234
Protein kinase B, see Akt
Protein phosphatase-1 (PP1), glycogen-targeting subunits and effects on glycogen synthesis and glucose disposal 387–393
Retinoic acid
beta cell glucokinase induction 245
hepatic glucokinase regulation 244
STAT5, glucokinase liver promoter binding 161, 232, 233
Sterol regulatory element binding protein-1c (SREBP-1c)
comparison of isoforms 170
DNA-binding sites 171
glucagon control of expression 171, 172
glucokinase expression regulation, liver insulin signaling pathway 175
mediation of insulin effects 172–175, 190
physiological significance 176
insulin control of expression 171, 172, 175, 176
nutritional effects on liver expression 171
tissue distribution 170
Sulphydryl groups, glucokinase alloxan probing 277–279, 282, 283 conformational hindrance by oxidation 280, 281
cysteine patterns, glucokinase versus hexokinases 277

cysteine residues, oxidative conformational locking 281, 282
oxidation sensitivity, purified protein 275, 276
redox regulation of activity 284, 285
Thyroid hormone, liver glucokinase
induction 164, 185, 243
Transgenic mice, glucokinase
blood glucose versus gene copy number 292
liver-specific transgenesis 291
models and phenotypes, overview 290
prospects for study 296–298
viral studies, primary hepatocytes 292, 293
Upstream stimulatory factor (USF), glucokinase liver promoter binding 160, 161