DIABETES

The new pandemic in Western countries.
DIABETES IS A WHOLE BODY DISEASE

The study of diabetes emphasizes the inter-relatedness of different tissues in maintaining cellular homeostasis and fulfilling life functions.
• TYPE 1 DIABETES: the pancreas does not secrete enough insulin.

• TYPE 2 DIABETES: the pancreas supplies blood insulin normally but the cells do not respond to this stimulus.
NEUROPATHY

OCCURS IN 50% OF DIABETICS DUE TO LOSS OF NERVE CELLS
RETINOPATHY AND DIABETES.
OTHER CONSEQUENCES OF DIABETES.

VASCULAR EFFECTS INCLUDING PLAQUE FORMATION.

LIVER DYSFUNCTION.

HEART EFFECTS DUE TO BLOOD FLOW PROBLEMS AND DIRECT EFFECTS ON MYOCYTE METABOLISM.
Ca^{2+}
AMP kinase

PGC 1 α(β)
AMP kinase

PGC 1α(β)

NRF 1 & 2

Tfam
mt DNA replication

ERR α

nuclear mt genes

Oxidative stress SOD, glutathione

PPARs
Fatty acid oxidation

GR
FOXO
HNF4α

gluconeogenesis
The Cori Cycle

Liver:
- Glucose → 2 Pyruvate → 2 Lactate
  - 6 ATP

Muscle:
- Glucose → 2 Pyruvate → 2 Lactate
  - 2 ATP

Blood
Glucose Production by Liver During Fasting Conditions (Gluconeogenesis and Glycogenolysis)

Fasting State

- Glucagon
- Decreased insulin

Pancreas:
- Fat cell
- Muscle cell
- Other substrates

Glycogenolysis
- Glycogen chain
- Increased glucose production

Gluconeogenesis
- Converted to glucose

Liver

Blood vessel
- Maintains glucose in bloodstream
Figure 16.30
Biochemistry, Seventh Edition
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Molecular mechanisms of insulin signaling.

NO as a second messenger.
THE EVIDENCE IS OVERWHELMING FOR INVOLVEMENT OF MITOCHONDRIAL DYSFUNCTION IN BOTH TYPE 1 AND TYPE 2 DIABETES.
• FOR TYPE 1 DIABETES IT IS THE REQUIREMENT FOR ATP IN ORDER TO SECRETE INSULIN THAT IS THE HEART OF THE ISSUE.

• IN TYPE 2 IT IS A COMBINATION OF NEEDS FOR ATP BUT ALSO LIPID METABOLISM THAT IS CENTRAL.
Genetic factors
- mtDNA mutations
- nDNA mutations
- Common genetic variants

Environmental factors
- Obesity
- Intrauterine malnutrition
- Environmental pollutants

Mitochondrial dysfunction

β-cell dysfunction
- Impaired insulin secretion
- β-cell failure
- Abnormal fusion, fission and autophagy

Insulin resistance
- Decreased mtDNA
- Decreased OXPHOS
- ↑LCAC, ↑DAG, ↑Ceramide

Type 2 diabetes mellitus
INSULIN BINDING

Metabolic arm

- Wortmannin
- PI3-K
- Akt
  - Antilipolysis
  - Glucose internalization
  - Glicogen synthesis
  - Anti-apoptosis
  - Protein synthesis
  - eNOS

Mitogenic/pro-atherogenic arm

- Shc
- Grb
- Sos
- Ras
- Raf
- MEK 1/2
- JNK
- p38
- ERK 1/2

- SB
- PD, UO126

Growth, differentiation,
• The key role of oxidative stress in diabetes.
In the absence of insulin, the principle nodes of regulation within the insulin signaling cascade are kept dephosphorylated via the membrane associated proteins PTP1B, SHP2, and PTEN. Following insulin binding and Tyr-phosphorylation of the insulin receptor and IRS1, the activation of membrane bound NADPH oxidase (potentially mediated by PI3K) results in the accumulation of H2O2 at the level of the plasma membrane to transiently inactivate PTP1B, SHP2 and PTEN, thus allowing propagation of kinase-mediated signaling, leading to GLUT4 translocation and glucose uptake. The global redox state of the cell is maintained by the redox buffering systems i.e 2GSH/GSSG and NADPH/NADP+ couples). Maintenance of global redox ensures that Ser/Thr phosphatase activity, specifically PP2A are maintained. The continued activation of these enzymes ensures that certain Ser/Thr kinases (JNK, ERK, IKKβ) remain inactive and that phosphomoieties are not allowed to accumulate within insulin signaling proteins.
• Chronic elevations in mitochondrial H2O2 emission as a result of a high fat diet serve to reduce the reserve capacity within the redox buffering systems and induce an oxidative shift in the cellular redox. This global shift in cell redox inactivates cellular Ser/Thr phosphatase (PP2A) activity, in turn promoting activation of stress-sensitive Ser/Thr kinases (JNK, ERK, IKKβ) and accumulation of inhibitory phosphomoieties within various insulin signaling proteins. This in turn decreases signal propagation throughout the cascade and impairs glucose uptake.
Metformin reduces gluconeogenesis

TORC2 is deacetylated by SIRT1 and subsequently degraded leading to reduced gluconeogenic gene expression

SIRT1 mediated PGC1α induction is blocked by GCN5 leading to a net inhibition of gluconeogenesis

Pck1 gene expression → Hepatic glucose production → Lower blood glucose + insulin
• When cells use fats e.g. fatty acids for energy metabolism instead of glucose much higher levels of oxygen free radicals are formed which in chronic disease are pathogenic.
KETOGENESIS

- Acetyl CoA
- Acetoacetyl CoA
- Acetoacetate
- Acetone + CO₂
- D-β Hydroxybutyrate
- D-β Hydroxybutyrate dehydrogenase

- HMG CoA reductase
- HMG CoA synthase
- HMG CoA lyase
- ACAT-1 (mit)
- ACAT-2 cyt
- Cholesterol and other sterols
ANAPLEUROSIS AND AMINO ACID METABOLISM

PEPCK1

oxaloacetate

MDH1

malate

MDH2

α ketoglutarate

GOT1

glu./asp. transporter

GOT2

oxaloacetate

malate

Gln. synthetase

Glutaminase

aspartate

asparagine

glutamine

Glutamate

PCCA

MCM

Methylmalonyl CoA

odd chain fatty acids

AGXT

ALD

PEP

glucose

pyruvate

alanine

lactate

citrate

α ketoglutarate

OGDH

FH

glutamate

succinyl CoA

propionyl CoA

malate

oxaloacetate

α ketoglutarate

aspartate

amino acids

PEP

pyruvate

alanine

Nutrition
Exercise
Drug therapy

Mitochondria:
- ROS production
- Electron transport
- Carnitine palmitoyl transferase
- Pyruvate dehydrogenase
- Coenzyme Q

Cellular control of mitochondria function:
- Mitochondrial biogenesis (PGC-1a)
- Fatty acid flux (uptake, acyl-CoA synthase, malonyl-CoA, AMPK, ACC2, MCD)
- Heme oxygenase
- SIRT1
Maternal nutrition and metabolism are critical determinants of adult offspring health. Recent reports describe adverse offspring outcomes associated with the father's diet, indicating nongenetic inheritance of paternal experience. Determining underlying mechanisms may require reconsideration of our understanding of the heritability of epigenetic states.
• Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring.
• Ng SF1, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ.

• The global prevalence of obesity is increasing across most ages in both sexes. This is contributing to the early emergence of type 2 diabetes and its related epidemic. Having either parent obese is an independent risk factor for childhood obesity. Although the detrimental impacts of diet-induced maternal obesity on adiposity and metabolism in offspring are well established, the extent of any contribution of obese fathers is unclear, particularly the role of non-genetic factors in the causal pathway. Here we show that paternal high-fat-diet (HFD) exposure programs β-cell 'dysfunction' in rat F(1) female offspring. Chronic HFD consumption in Sprague-Dawley fathers induced increased body weight, adiposity, impaired glucose tolerance and insulin sensitivity.
Relative to controls, their female offspring had an early onset of impaired insulin secretion and glucose tolerance that worsened with time, and normal adiposity. Paternal HFD altered the expression of 642 pancreatic islet genes in adult female offspring (P < 0.01); genes belonged to 13 functional clusters, including cation and ATP binding, cytoskeleton and intracellular transport. Broader pathway analysis of 2,492 genes differentially expressed (P < 0.05) demonstrated involvement of calcium-, MAPK- and Wnt-signalling pathways, apoptosis and the cell cycle. Hypomethylation of the Il13ra2 gene, which showed the highest fold difference in expression (1.76-fold increase), was demonstrated. This is the first report in mammals of non-genetic, intergenerational transmission of metabolic sequelae of a HFD from father to offspring.
TREATING MITOCHONDRIAL DYSFUNCTION AS AN APPROACH TO TREATING
• DIABETES
• CANCER
• PARKINSONS DISEASE
• ALZHEIMERS
• HUNTINGTONS DISEASE
• AGEING
• AUTOIMMUNE DISEASES