Metabolism of glucose

D-glucose (dextrose), $C_6H_{12}O_6$, Mw=180g

$$6O_2 + \text{Glucose} \rightarrow 6CO_2 + 6H_2O + 2870\text{kJ}$$

ΔG^0=-2870 kJ/Mol (exergon)

10g/h (resting), RQ=1

Nutrition

carbohydrates (CHO) mono-saccharides, di-saccharrides, poly-saccharrides (starch, glycogen, cellulose)

80% glucose

common glucose pool

Alimentary tract

Salivary and pancreatic amylases (cleavage of α1-4 glycoside bonds) maltose, maltotriose, dextrins

resorption in the small intestine (jejunum)

Plasma glucose

80-90 mg/100ml (4.5-5 mM)

Portal circulation

characteristics of portal blood & circulation

Transport

too big (and polar) for efficient diffusion across cell membrane
glucose-transporters (GLUT)

Transport against concentration gradient

Uptake of glucose into epithelial cells, GLUT-I (co-transport with Na^+), osmotic effects, resorption of water

re-absorption of filtered glucose in the proximal renal tubulus, threshold (≈250 mg/min)

Transport with concentration gradient

GLUT-II (liver, membrane bound and thus insulin-independent)

GLUT-IV (muscle & adipose tissue, insulin-dependent) cycled between cytoplasma (endosomial vesicles) and cell membrane

Intracellular paths

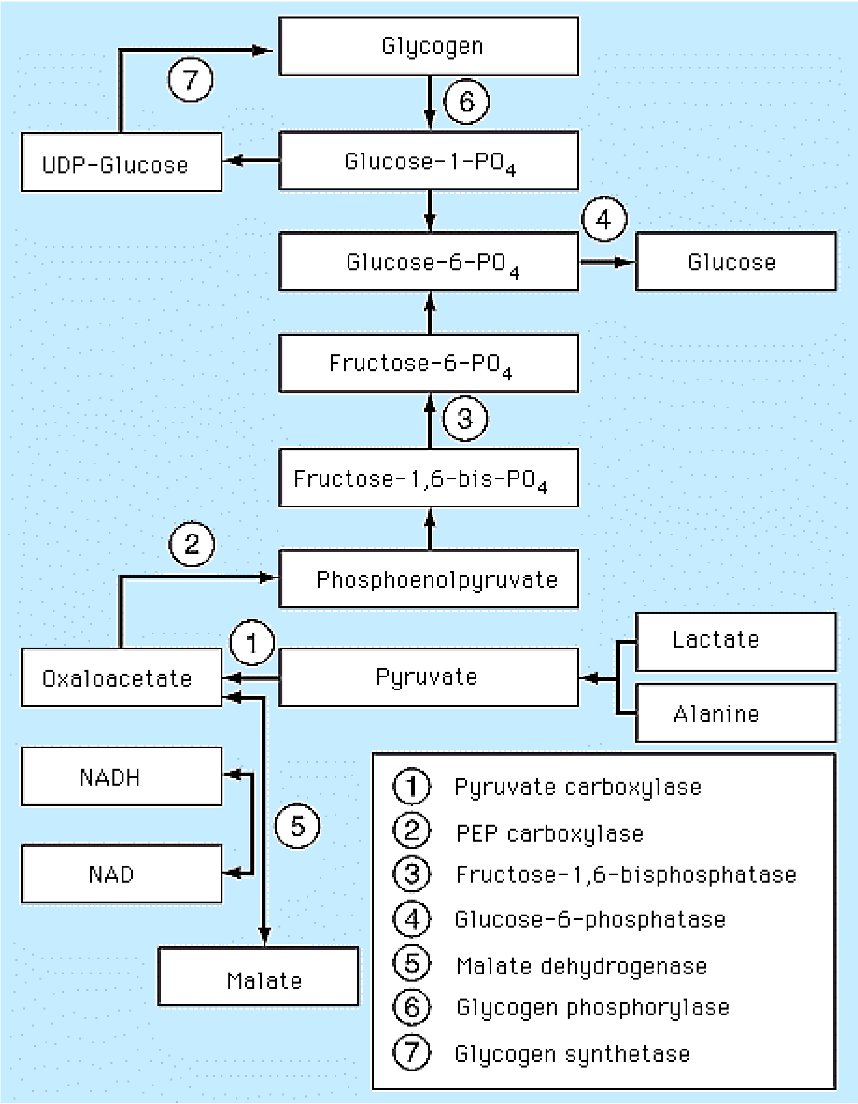
Phosphorylation at C6

glucokinase (Km≈10mM, liver, specific for glucose, insulin controlled)
hexokinase (Km≈100µM, muscle)
clearance of excess glucose, buffer function of the liver

Km (Michaelis constant, substrate concentration at half-maximum reaction rate)

Glu-6-P; activation, trapping of polar molecule in the cell

Glucose-6-phosphatase (liver, activated by glucagon, epinephrine)



Glycolysis (Gluconeogenesis)

Gycogenesis (Glycogenolysis)

Enzyme kinetics

Rate of reaction (v), turnover of substance per time (µMol/min)

$$E + S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftarrows}} ES \xrightarrow{k_{+2}} E + P$$

$$\left[\dot{E}\right] = -k_1\left[E\right]\left[S\right] + \left(k_{-1} + k_2\right)\left[ES\right]$$

$$\left[\dot{S}\right] = -k_1\left[E\right]\left[S\right] + k_{-1}\left[ES\right]$$

$$\left[\dot{ES}\right] = k_1\left[E\right]\left[S\right] - \left(k_{-1} + k_2\right)\left[ES\right]$$

$$\left[\dot{P}\right] = k_2\left[ES\right]$$

k_2 rate limiting step (Michealis)

$$\left[\dot{S}\right] = 0$$

"quasi – stationary" hypothesis (Briggs & Haldane):

$$\left[\dot{ES}\right] = 0$$

$$v = \frac{v_{\max}\left[S\right]}{K_m + \left[S\right]}$$

$K_m = \left[S\right]_{v_{\max}/2}$; Michaelis constant

$K_m = \dfrac{k_{-1}}{k_{+1}} = \dfrac{\left[E\right]\left[S\right]}{\left[ES\right]}$; dissociation const. of ES

$v_{\max}$ = maximum speed of the reaction

Anabolic/katabolic pathways

anabolic pathways: storage of fuel substrates (insulin)

catabolic pathways: brake-down of fuel stores (glucagon, epinephrine, and „counter-regulatory" hormones)

- glycogenolysis
- lipolysis
- gluconeogenesis
- ketogenesis (alternate fuel source for the brain in absence of glucose)

producing glucose, amino acids, free fatty acids

running fast for 5 min or starving for a week triggers a different hormonal mix

insulin/glucagon ratio switches from storage to utilization of energy

Endocrine Pancreas

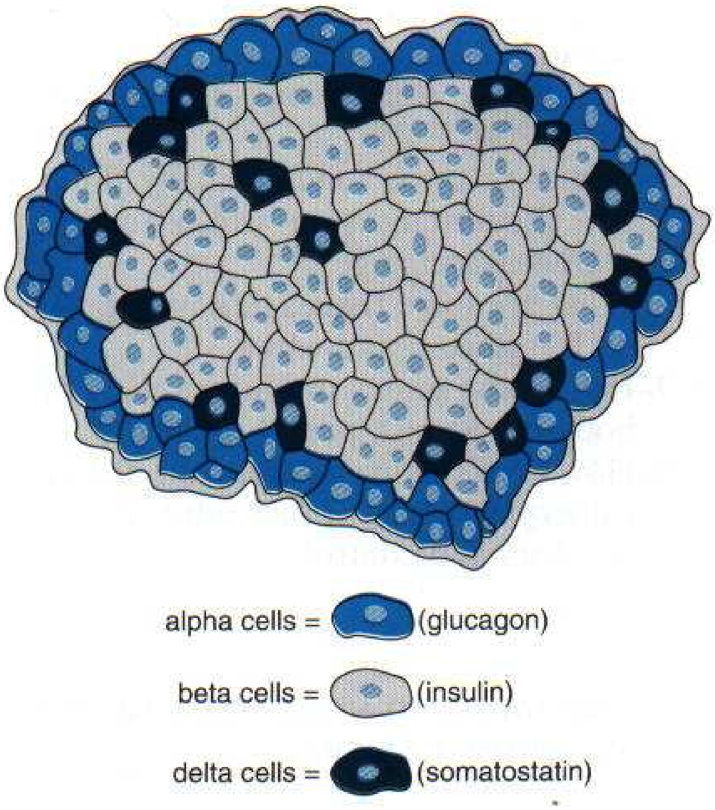
10^6 islets of Langerhans, ≈1000 endocrine cells per islet, interspersed among the acinar tissue and ducts that make up the exocrine pancreas.

α-cells (rim, glucagon), β-cells (center, sole source of insulin), and δ-cells (scattered in-between, somatostatin) form a syncytium (tight junctions), permit for cross-talk between cells (paracrine effects); glucagon and somatostatin are also synthesized by endocrine cells in the gut

insulin secretion into portal blood, liver as first target, cleared by the liver

systematic higher concentration of exogenous insulin, possible cause of long term complications such as arteriosclerosis, hypertension

no direct relationship to α- and δ-cells (fine tuning)



Insulin, "the anabolic hormone"

ER (pre-proinsulin)->Golgi (proinsulin, formation of –S–S– bonds)->secretory granules (cleavage of connecting peptide, C-peptide, no biological function but slow clearance from blood, surrogate for insulin secretion)->secretion into portal blood first protein with known AA sequence (Sanger 1953)

Control of insulin secretion

glucose, and anything increasing [Glu], (+)

intracellular glucose increases ATP levels

ATP used for Na/K-ATPase

excess intracellular ATP inhibits K^+-channel thereby depolarizing the cell

depolarization opens Ca^{2+}-channel

cAMP releases intracellular Ca^{2+} stores

Ca^{2+} promotes fusion of secretory granules with cell membrane

secretion of insulin

aminoacids (+)

GIP, glucose dependent insulinotropic hormone

small intestine hormone secreted with carbohydrate load

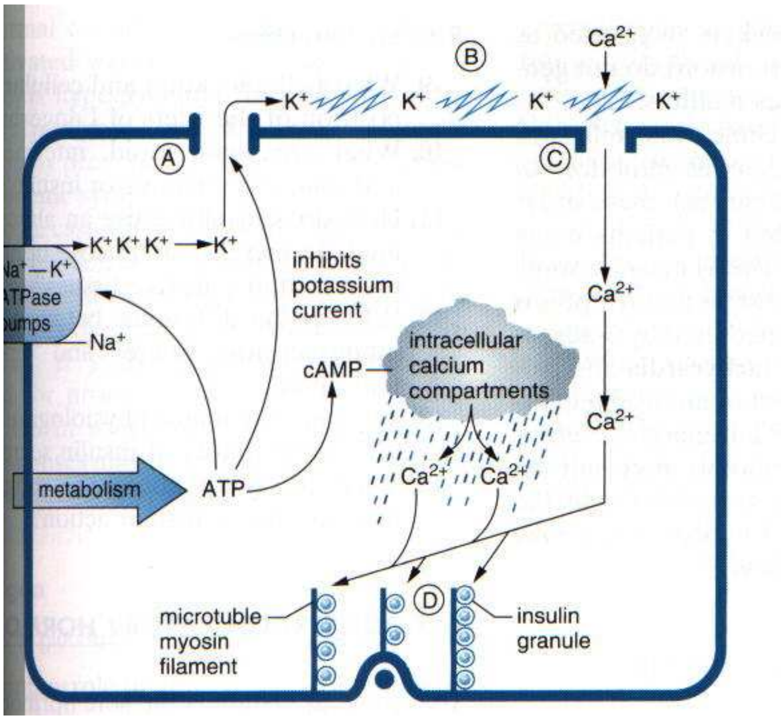
glucagon (+)

specific glucagon receptor

catecholamines

α_2-receptors (inhibitory) primary effect

β-receptors (stimulating) secondary effect (β-blockers usually do not worsen hypoglycemia but suppress important symptoms such as tachycardia, palpitations)



Actions of insulin

Timing

fast

effects on existing proteins, insertion of GLUT-IV in muscle cell membrane;
activation of glucokinase by glucokinase

intermediate

effects on transcription, translation and protein synthesis

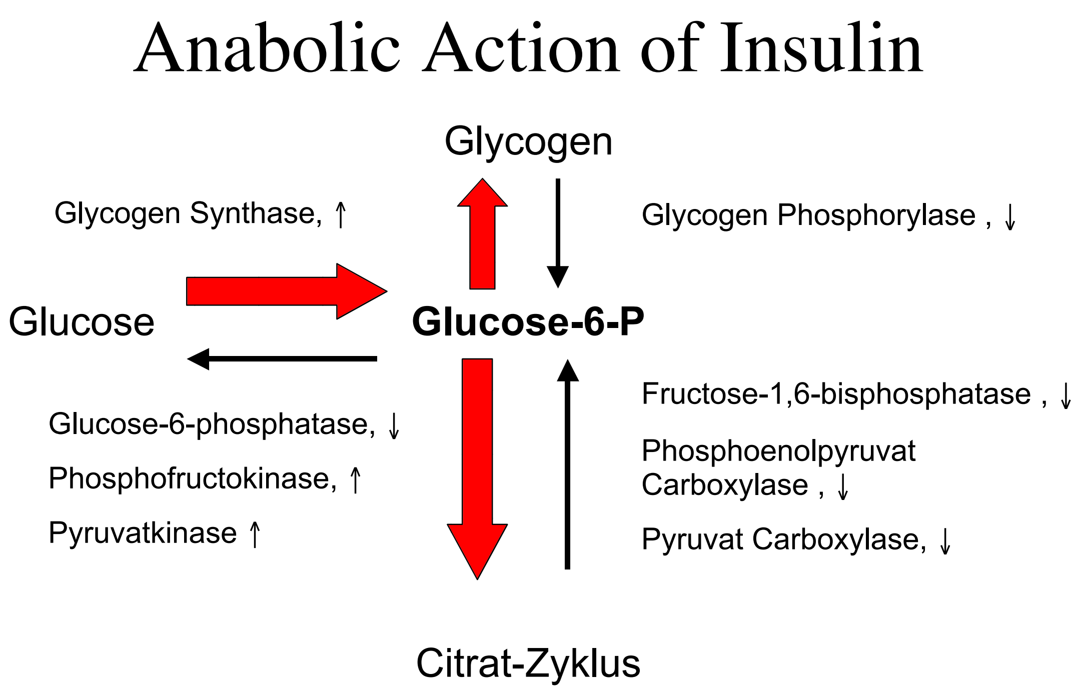
delayed, long-term effects (positive feedback)

other steps and metabolic pathways
other control mechanisms taking time
other receptors; ILGF receptor (insulin-like growth factor) responds to long and high insulinconcentrations
entrenching "anabolic" program (insulin resistance)

Substrate

promotes storage of energy

CHO



glucogenesis (+), glycolysis (+), glycogenolysis (-), gluconeogenesis (-)

why is glycolysis activated?

substrates and metabolites of glycolysis and the Krebs cycle are important building blocks for fatty acids, triglycerides, and VLDL thereby increasing the capacity to store excess energy as lipids

Protein

facilitates uptake of AA, stimulates protein synthesis

Fat

synthesis of fatty acids, triglycerides, and VLDL

inhibits the hormone-sensitive lipase in fat tissue which has a normal basal activity

Location

different effects on various tissues

insulin dependent tissue (muscle, adipose tissue)

insulin-independent tissue (brain, renal medulla, RBC, liver)

Insulin (anabolic program)

liver: glycogenesis, VLDL synthesis

muscle: glycogenesis, protein synthesis

fatty tissue: triglyceride synthesis

Insulin absence (catabolic program)

liver: glycogenolysis, gluconeogenesis, ß-oxidation, ketogenesis

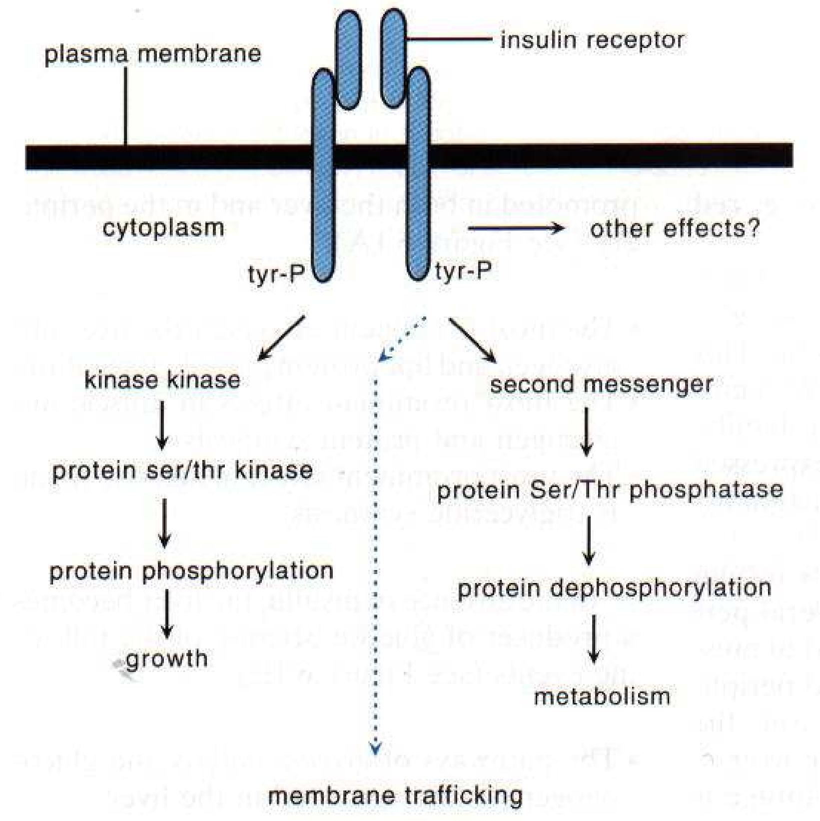
muscle: protein degradation, AA for gluconeogenesis in the liver

adipose tissue: hormone-sensitive lipase activated, fatty acids, glycerin for gluconeogenesis

Insulin receptor

hetero-dimeric, 2a & 2ß sub-units, binding of insulin on a-sub-unit, activation of a tyrosin-kinase located on the ß-sub-unit, cascade of phosphorylations and de-phosphorylations, various second messengers affecting

- vesicle trafficking
- enzyme activation, de-activation
- translation (protein synthesis)
- transcription (m-RNA synthesis)
- DNA synthesis



Counterregulatory hormones

Anabolic metabolism is essentially controlled by a single hormone (insulin) whereas an array of hormones defends the body against hypoglycemia.

Catabolic metabolism is controlled by a decrease in insulin concentration and by five main counter-regulatory hormones

- glucagon, epinehprine (primary)
- cortisol, growth hormone (secondary)
- placental lactogen (fetal protection)
- (somatostatin, thyroid hormone, estrogen, progesterone)

glucose receptors in the hypothalamus

a) sympathetic activation (epinephrine), stimulation of α-cells, glucagon release, inhibiting hypoglycemia

b) hypophysis, STH & ACTH secretion, cortisol (gluco-corticoid, adrenal glands), gluconeogenesis

the counter-regulatory system is also compromised in the diabetic patient (paracrine effect of β-cells on α- and δ-cells)

Glucagon

liver (exclusively)

glycogenolysis (+), gluconeogenesis (+), β-oxidation (+)

glycolysis (-), glycogenesis (-), FA-synthesis (-)

Hypoglycemia (abundance of insulin)

tumor (insulinome), excessive insulin dosage

low blood sugar (arterial, venous, capillary blood)

symptoms depend on time course, no clear threshold

autonomic symptoms (sympathetic activation: sweating, tachycardia, anxiety, palpitations, mydriasis)

neuroglycopenic symptoms (dizziness, blurred vision, difficulty thinking, cramps, unconsciousness)

treat with glucose (often significant amounts)

Hyperglycemia (lack of insulin)

osmotic diuresis & glucosuria = diabetes mellitus

glucose tolerance test: 75-100g of glucose, elevated basal glucose concentration, elevated peak concentration, prolonged elevation

Acute symptoms

lack of appetite, nausea, vomiting

hyperglycemia (insulin resistance)

diabetic ketoacidosis (metabolic acidosis)

ketogenesis (acetone breath)

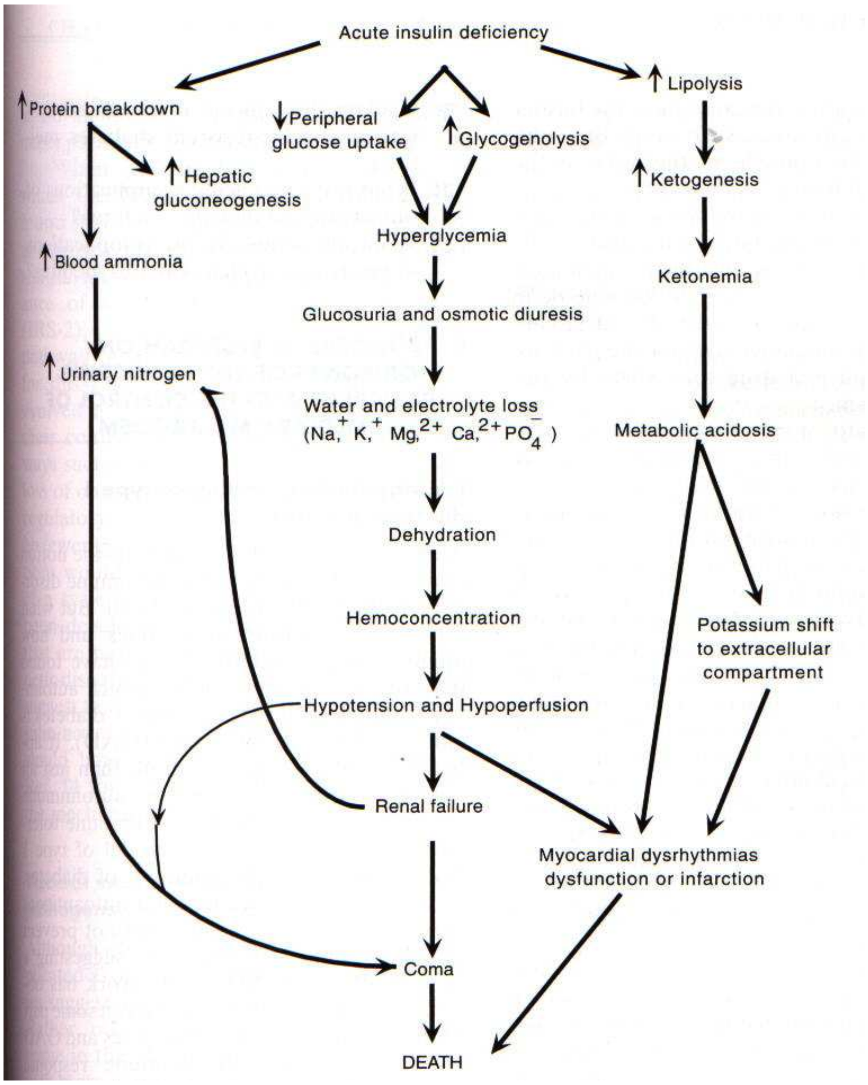
Kussmaul respiration (deep ventilation, at times reduced frequency, to compensate for acidosis)

volume loss (diuresis) polyuria

coma

hyperosmolar coma (complication, extreme hyperglycemia 55 mmol/L, no ketone formation, 50% mortality) volume effects on the brain

treat with volume, insulin, electrolytes, HCO_3-



Long term complications

cardiovascular system, microcirculation, eye, kidney, peripheral nervous system

arteriosclerosis (oxidized LDL)

arterial occlusions

hypertension

Diabetes mellitus

Type 1 diabetes (IDDM)

destruction of islet cells (in young patients with complete lack of insulin), most likely an autoimmune disorder

related to antibodies against certain viruses, BSA from cow milk, glutamic acid decarboxylase (GAD)

similarities between the GAD gene and of viral genes apparently leads to cross-reactions in some patients with certain major histocompatibility complex (MHC) genes

Type 2 diabetes (NIDDM)

defective insulin secretion, peripheral insulin resistance (after the age of 40, in obese individuals with normal or high levels of insulin)

ß-cell exhaustion

amyloid deposits

glucose toxicity

advanced glycosylation end products (AGE)

activation of sorbitol pathway, sorbitol accumulation (cataract)

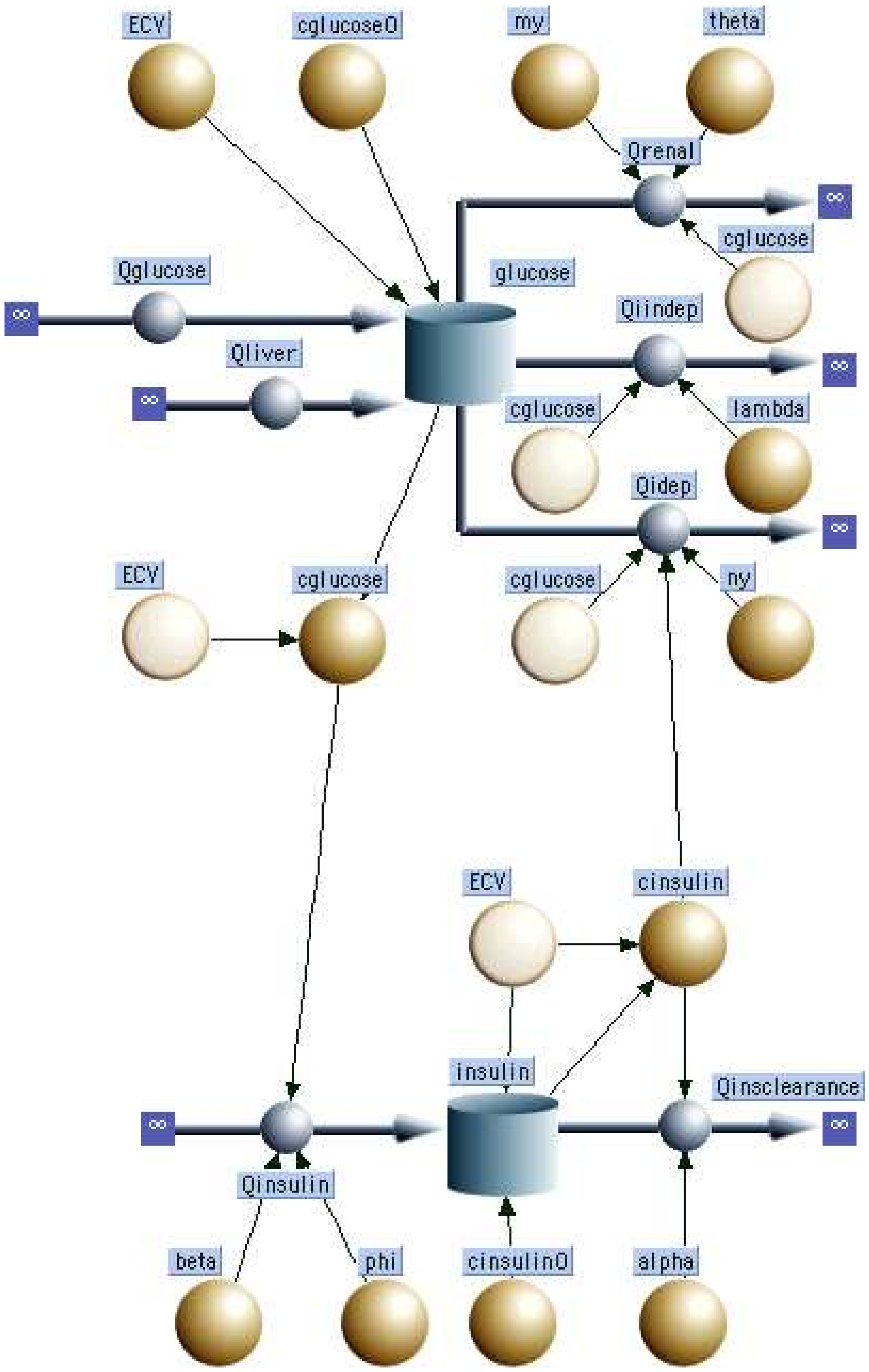
Classification Of Diabetes Mellitus

PRIMARY

- Autoimmune (type 1) diabetes mellitus
  - Non-insulin-dependent diabetes mellitus (type 1 NIDDM—transient)
  - Insulin-dependent diabetes mellitus (type 1 IDDM)
- Non-autoimmune (type 2) diabetes mellitus
  - Insulin-dependent diabetes mellitus (type 2 IDDM—transient)
  - Non-insulin-dependent diabetes mellitus (type 2 NIDDM)
  - Maturity-onset diabetes of the young (MODY)

SECONDARY

- Diabetes caused by pancreatic disease
- Diabetes caused by hormonal abnormalities
- Drug- or chemical-induced diabetes
- Diabetes caused by insulin receptor abnormalities
- Diabetes associated with genetic syndromes
- Diabetes of other causes



Model of glucose control

Stolwijk, JE and JD Hardy. Regulation and control in physiology. In: Medical Physiology, 13th ed. (edited by VB Mountcastle). CV Mosby, St. Louis, 1974; pp. 1343-1358

Assumptions

Plasma volume and interstitial fluid volume are represented in a single compartment (≈3L+12L, in the normal adult) with constant volume

The steady state concentration of glucose in this compartment is x (in mg/mL)

Glucose enters through absorption from the GI tract or through production from the liver at the rate QL (in mg/h)

Glucose is eliminated from the single compartment by three major pathways:

When x is elevated beyond a certain threshold (θ), glucose is excreted by the kidneys

$$Q_r = \mu(x-\theta), \quad x > \theta$$
$$Q_r = 0, \quad x \le \theta$$

Glucose leaves the extracellular volume to enter the cells to be metabolized and/or stored.

In insulin independent tissue the rate of glucose utilization (Qii) depends only on the extracellular to intracellular glucose gradient. The intracellular concentration is ignored.

$$Q_{ii} = \lambda x$$

Glucose uptake in insulin dependent tissue is facilitated by insulin concentration (y). Therefore, the rate of insulin dependent glucose utilization (Qid) is given as

$$Q_{id} = \nu xy$$

In the above equations, μ, λ, and ν are constant proportionality factors.

The mass balance equation is obtained by the sum of inflows and outflows:

$$Q_l = \lambda x + \nu xy, \quad x \le \theta$$
$$Q_l = \lambda x + \nu xy + \mu(x-\theta), \quad x > \theta$$

Notice two strong non-linearities, first the product of xy and second, the threshold nonlinearity. Also, a negative feedback is embedded in the characteristic since an increase in x requires a decrease in y, and vice versa.

A similar mass balance can be established for plasma insulin concentration. Insulin is produced at a rate dependent on plasma glucose levels. However, if x falls below a certain threshold (p), insulin secretion ceases.

$$Q_i = 0, \quad x \le \phi$$
$$Q_i = \beta(x-\phi), \quad x > \phi$$

Insulin is removed from the plasma involving the insulinase enzyme at a rate proportional to its concentration in blood:

$$Q_{icl} = \alpha y$$

The steady state concentration for insulin (y) is given as

$$y = 0, \quad x \le \phi$$
$$y = \frac{\beta}{\alpha}(x-\phi) \quad x > \phi$$

Aside from the threshold nonlinearity, the insulin response to glucose is basically linear.

The steady state level of glucose and insulin in the blood under a given set of conditions can be predicted from solving these equations simultaneously.

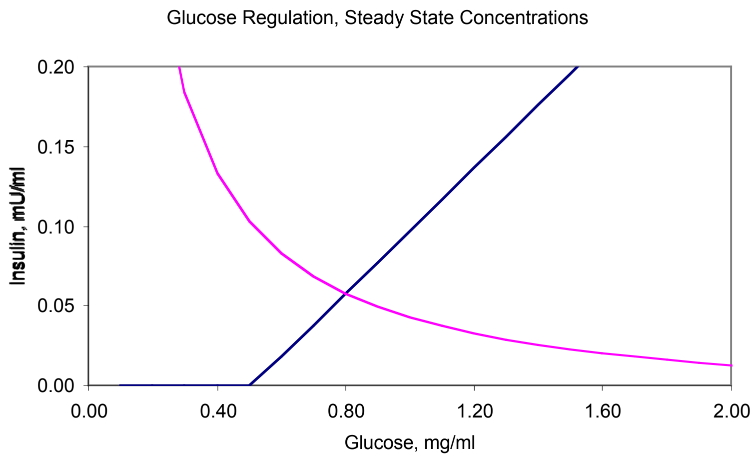
The following values were assumed for the model:

Parameter	Unit	
θ	mg/mL	2.5
μ	mL/h	7200
λ	mL/h	2470
ν	1/(mU h)	139000
ϕ	mg/mL	0.51
β	mU mL/(mg h)	1430
α	mL/h	7600
QI	mg/h	8400

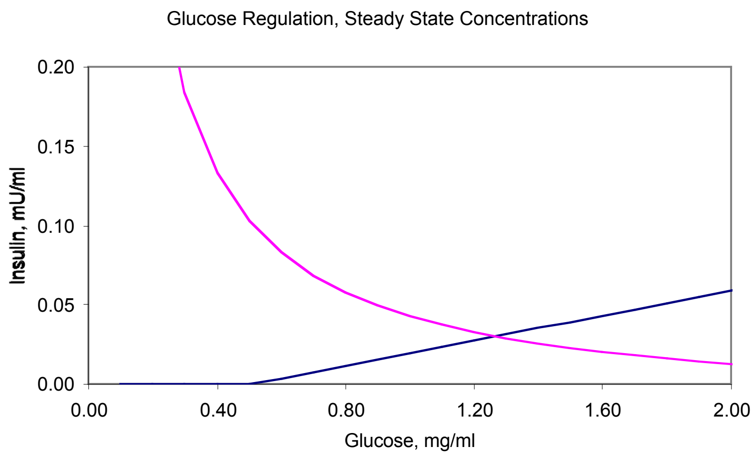
Exercise

Calculate steady state concentrations (glucose and insulin) for the normal case, for 80% β-cell destruction, and for the case when β-cell sensitivity is reduced to 20% of normal.

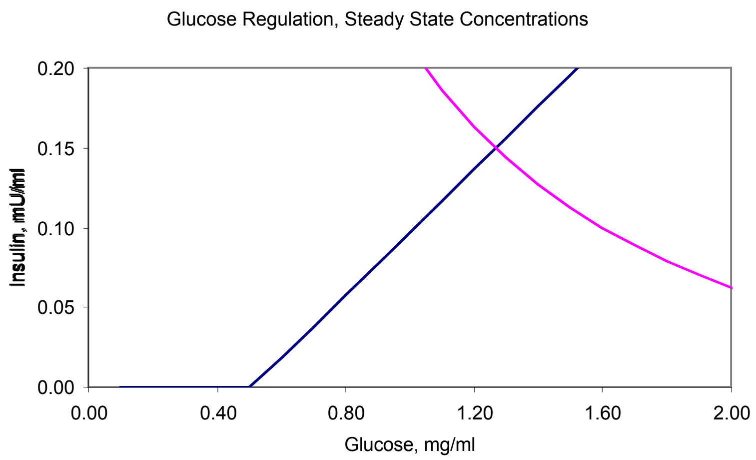
Steady state, normal



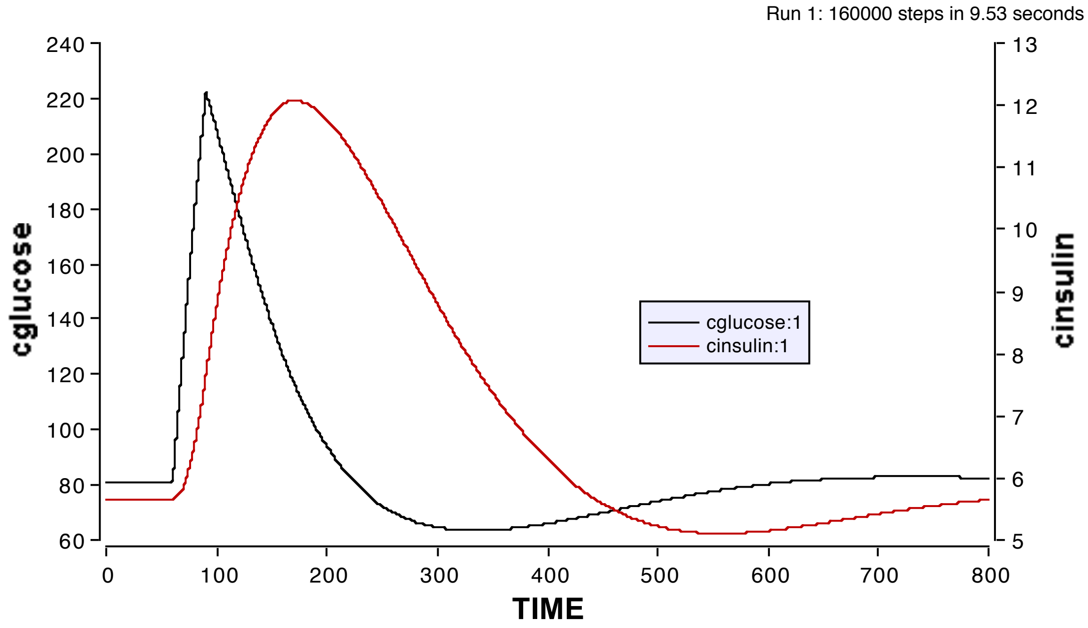
Steady state, 80% ß-cell destruction

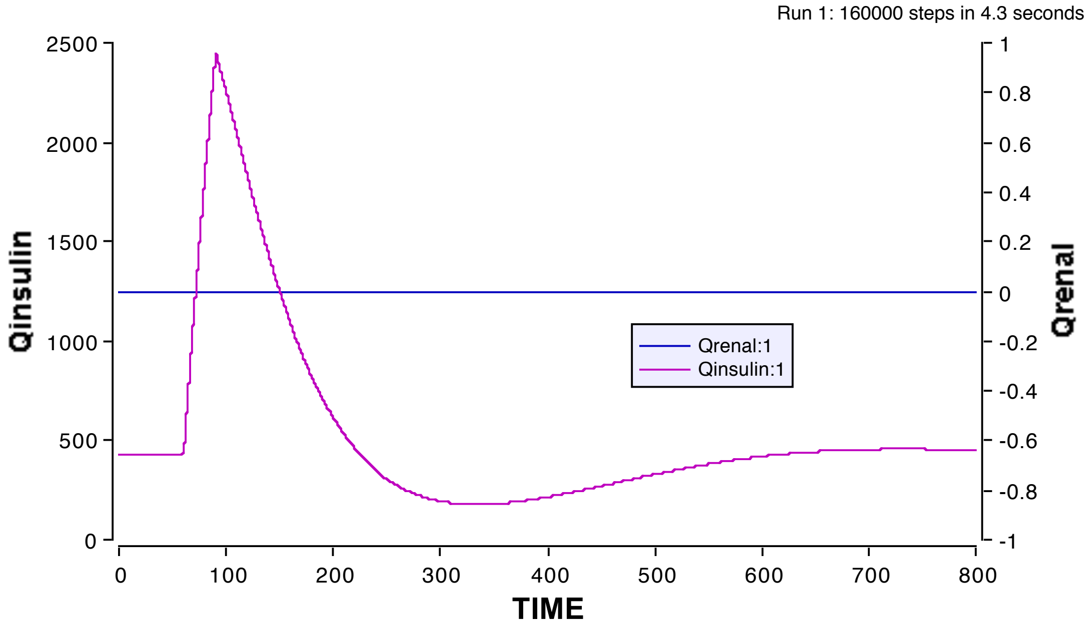


Steady state, 80% insulin resistance



Glucose tolerance test (normal)





Glucose tolerance test (reduced ß-cell secretion)