Diabetes mellitus

Heterogeneous clinical syndrome in which the central feature is a chronic elevation of the blood glucose concentration - this results in a range of pathologies.

Due to a deficiency of insulin (absolute) or a resistance to insulin (relative).

The chronic hyperglycaemia is associated with long term tissue damage, especially the blood vessels, nerves, heart, kidneys and eyes.

http://en.wikipedia.org/wiki/Diabetes
http://www.diabetes.org/home.jsp
http://diabetes.niddk.nih.gov/
http://www.latrobe.edu.au/podiatry/diabetesresources/diabetes_lecture_1.htm

cf. Diabetes insipidus

Type I diabetes
Results from the body's failure to produce insulin, the hormone that "unlocks" the cells of the body, allowing glucose to enter and fuel them. It is estimated that 5-10% of Americans who are diagnosed with diabetes have type 1 diabetes.

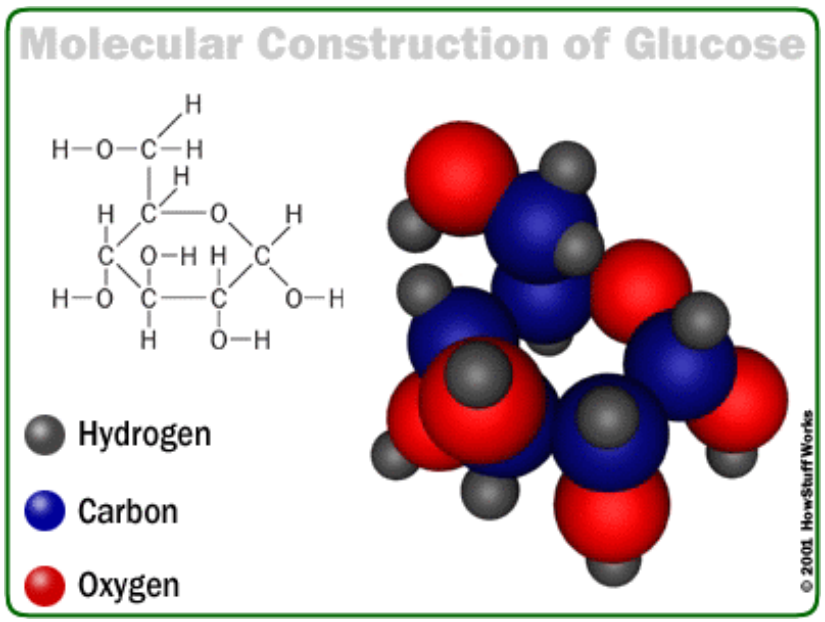
Type II diabetes
Results from insulin resistance (a condition in which the body fails to properly use insulin), combined with relative insulin deficiency. Most Americans who are diagnosed with diabetes have type 2 diabetes.

Gestational diabetes
Occurring during pregnancy. Gestational diabetes affects about 4% of all pregnant women - about 135,000 cases in the United States each year.

Pre-diabetes
Pre-diabetes is a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 diabetes. There are 41 million Americans who have pre-diabetes, in addition to the 20.8 million with diabetes.

Normal blood glucose levels

Normal homeostatic mechanisms maintain blood glucose levels within a narrow range of 3.5-6.5 mmol/l



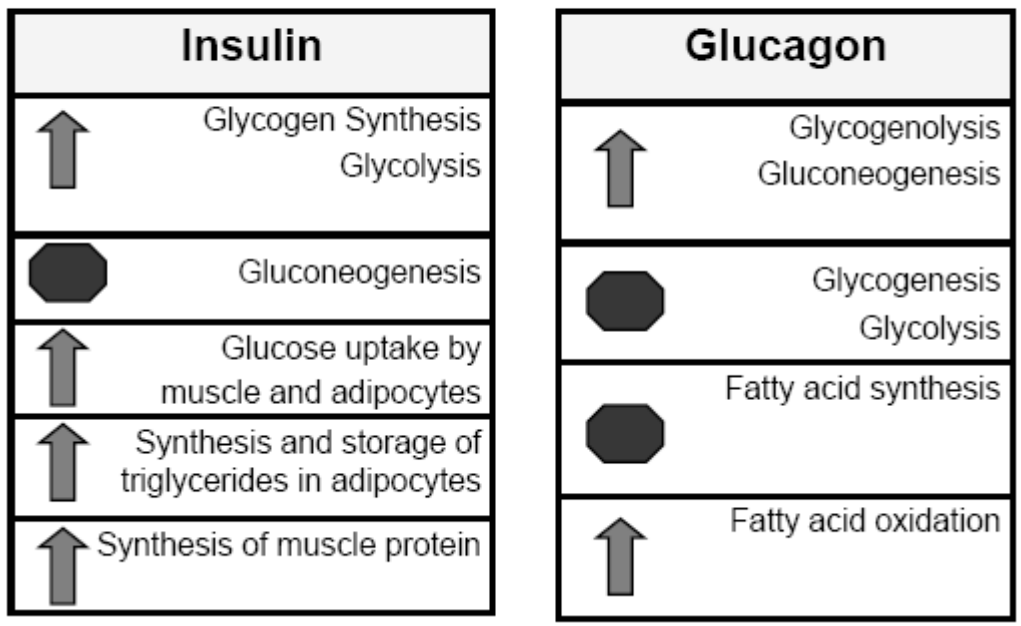
Insulin and Glucagon

- Major hormones that regulate fuel metabolism
- They ensure that cells have a constant source of glucose, fatty acids, and amino acids for ATP generation and cellular maintenance.
- Concentrations of insulin and glucagon in the blood regulate fuel storage and mobilization

INSULIN is released in response to carbohydrate ingestion; promotes the usage of glucose as fuel and storage of glucose as glycogen and fat.

GLUCAGON signals the absence of dietary glucose, and it promotes glucose production by glygogen degradation and gluconeogenesis.

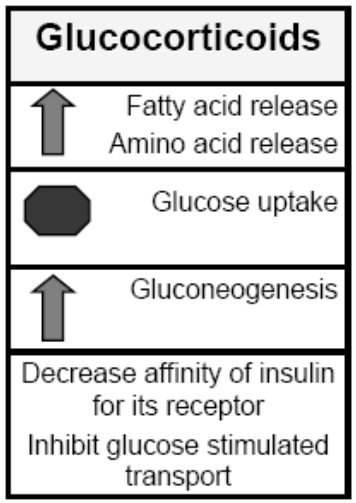
Opposing actions of Insulin and Glucagon



Hormones involved in glucose metabolism

Glucocorticoids

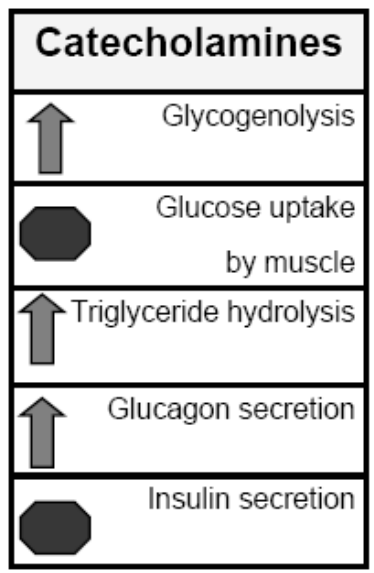
- Cortisol (hydrocortisone) is the major glucocorticoid in humans
- Hormones that raise blood glucose levels- promote survival in times of stress
- Protect body from insulin-induced hypoglycemia

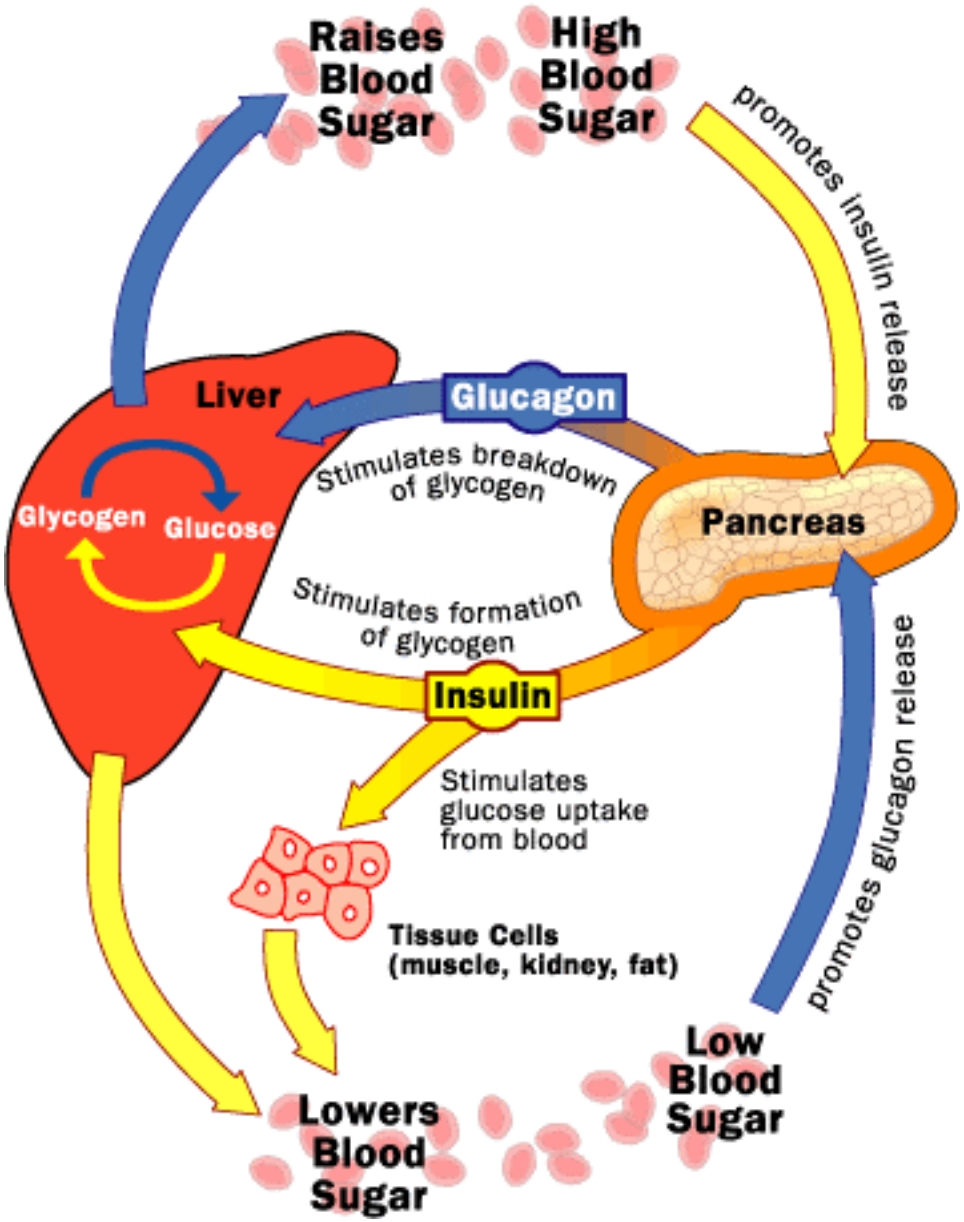


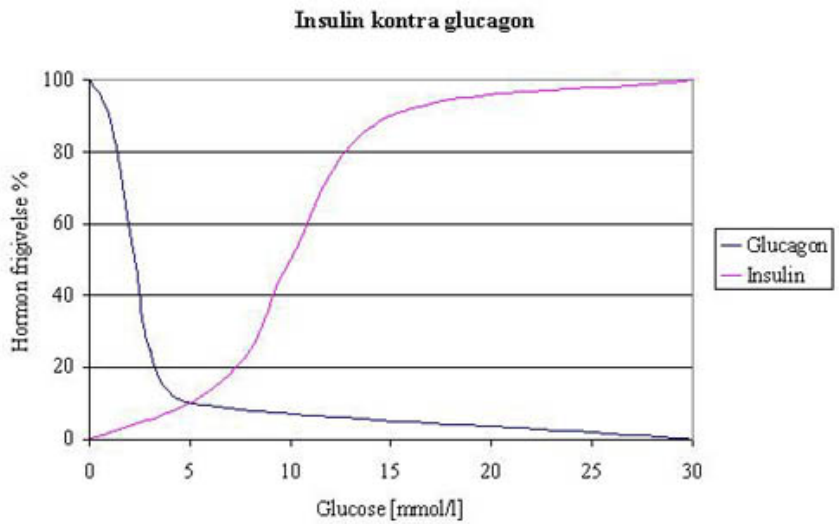
neurotransmitters

Catecholamines: Epinephrine and Norepinephrine

Secreted in response to LOW BLOOD GLUCOSE LEVELS




Raises Blood Sugar
High Blood Sugar
promotes insulin release
Liver
Glucagon
Stimulates breakdown of glycogen
Glycogen
Glucose
Pancreas
Stimulates formation of glycogen
Insulin
Stimulates glucose uptake from blood
Tissue Cells (muscle, kidney, fat)
promotes glucagon release
Low Blood Sugar
Lowers Blood Sugar


Insulin kontra glucagon
Hormon frigivelse %
100
80
60
40
20
0
0
5
10
15
20
25
30
Glucose [mmol/l]
Glucagon
Insulin

Metabolic homeostasis

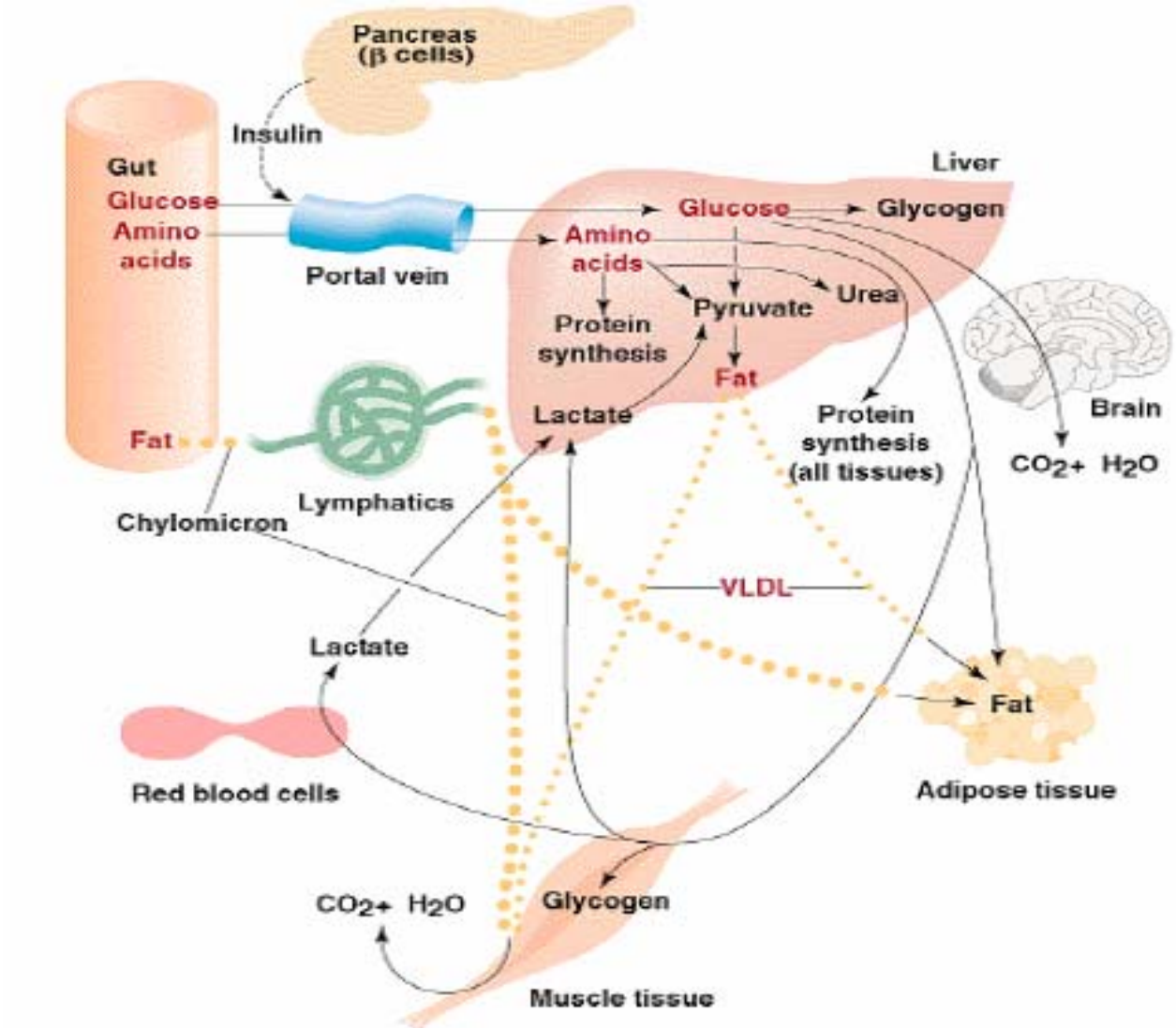
Starch, fat, protein

↓

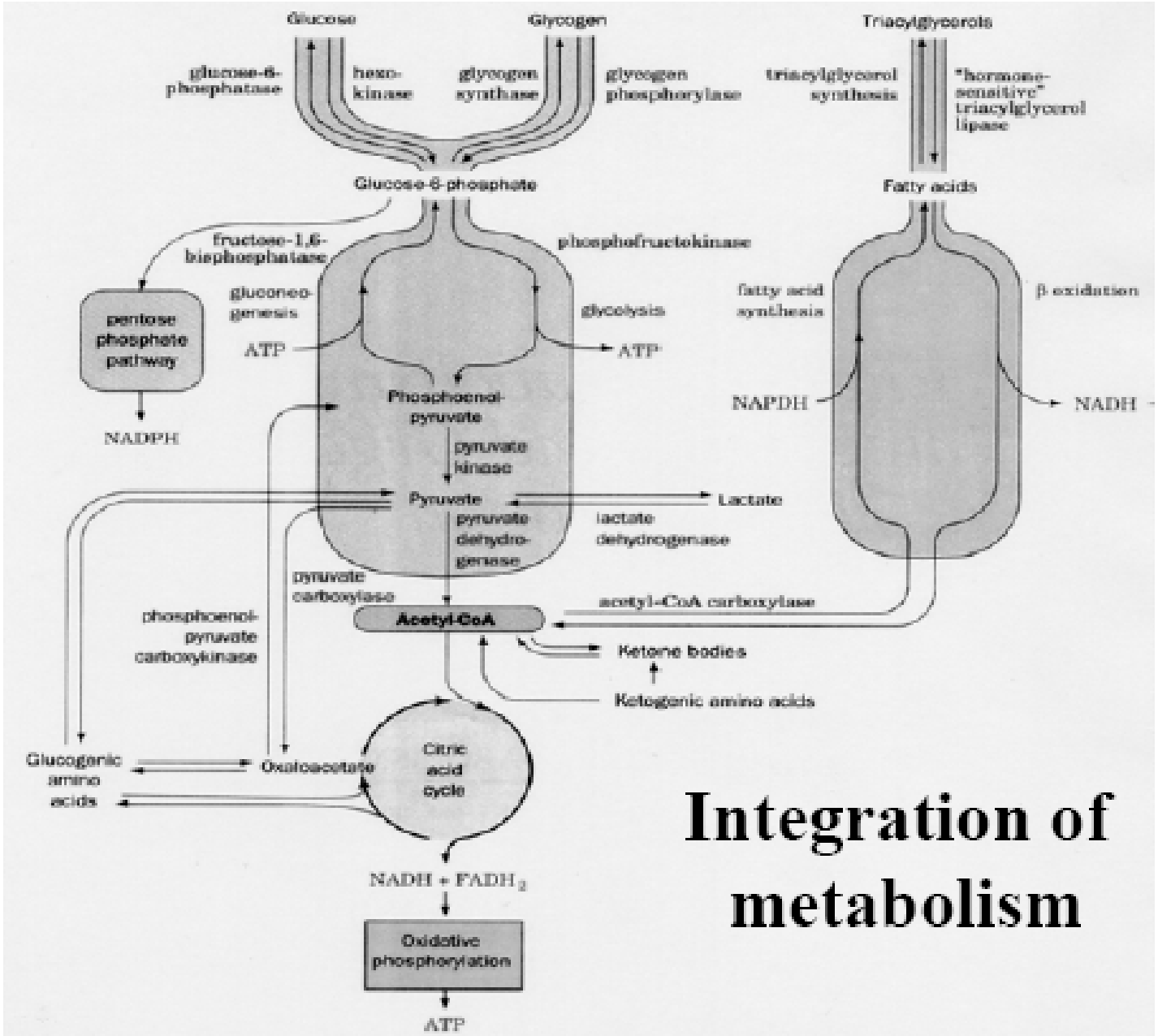
Glucose

↓ ↑

Glycogen, triacylglycerol

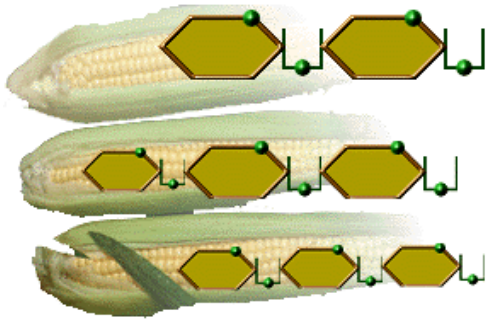


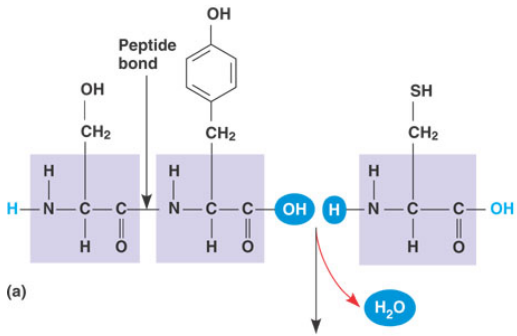
Disposition of glucose, amino acids, and fat by various tissues in the well fed state

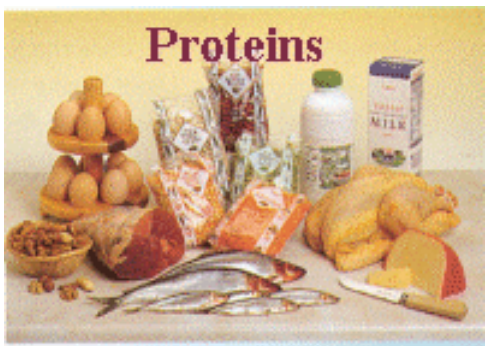


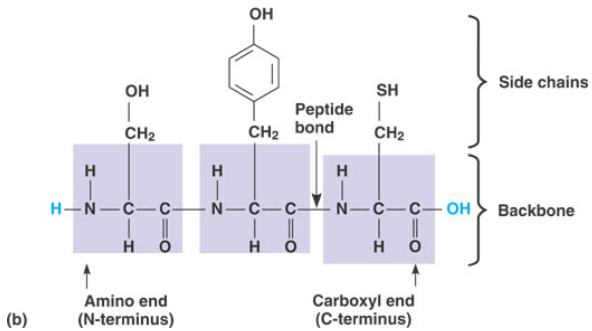
Integration of metabolism

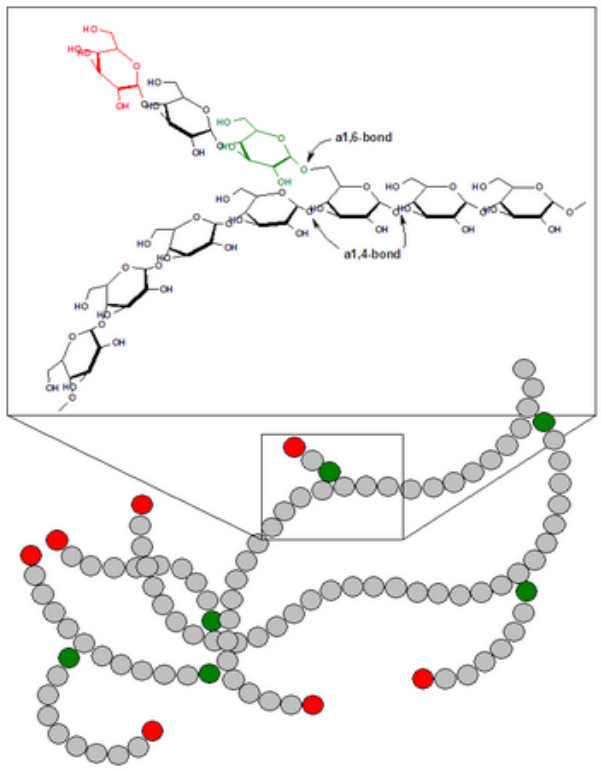
Polysaccharides: starch











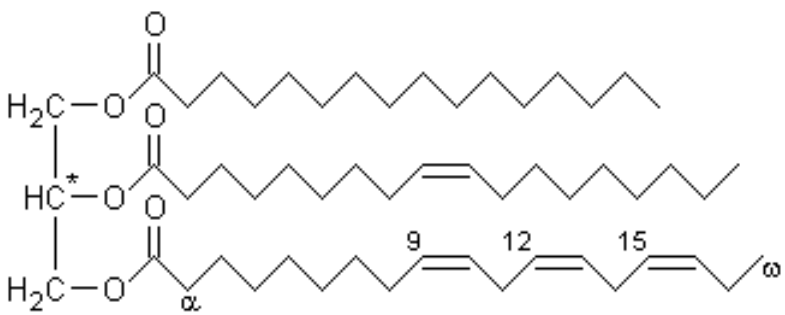


Figure 3.1-1. Glycolysis and Gluconeogenesis

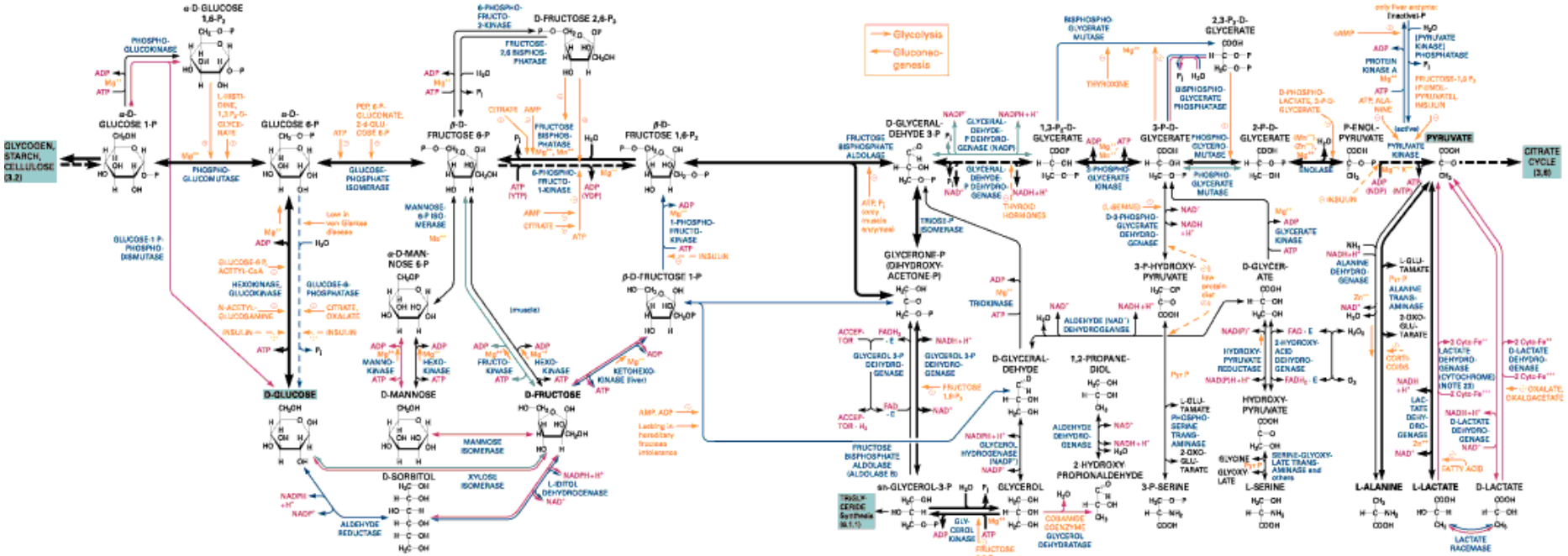
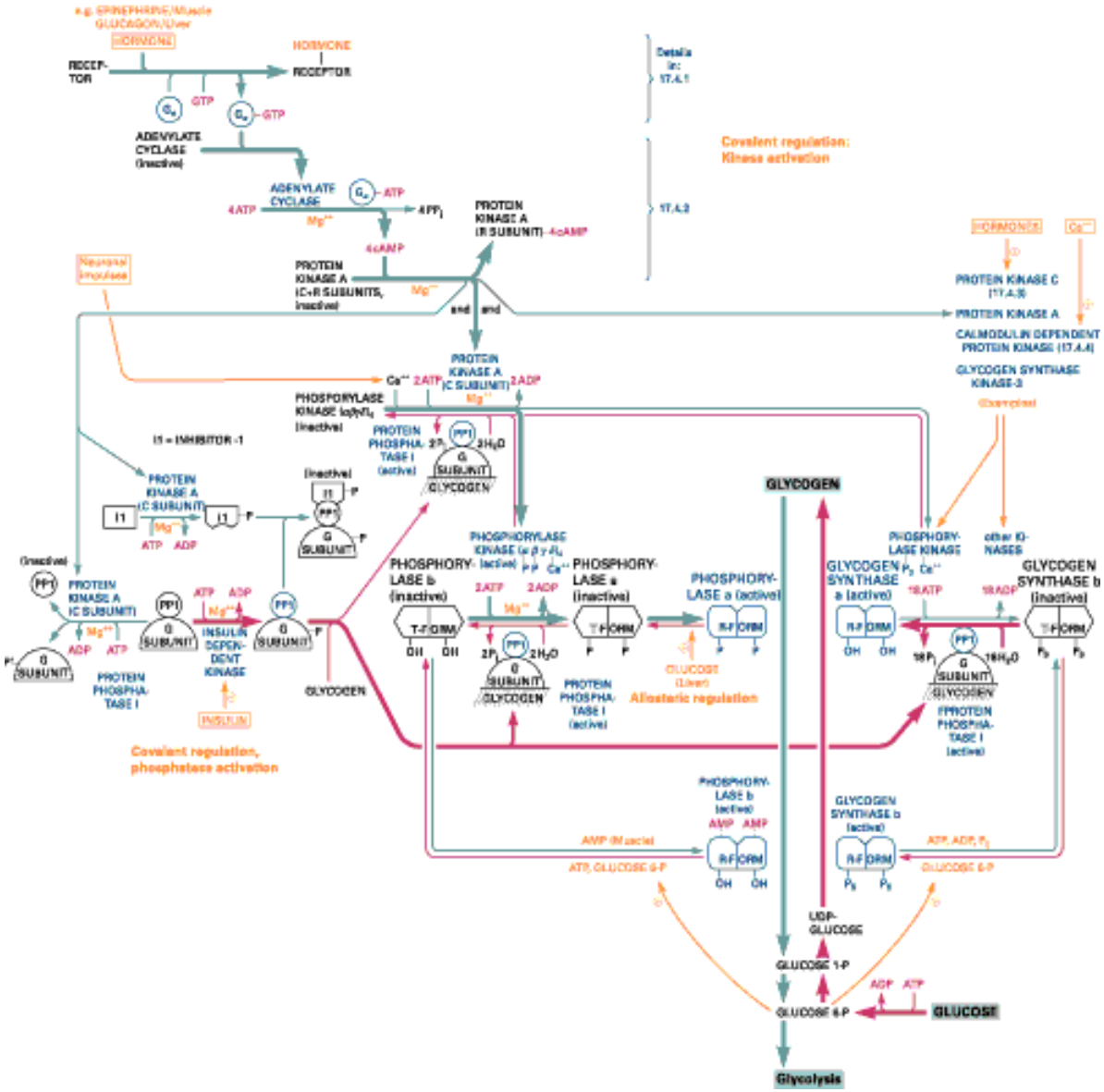


Figure 3.2-5. Regulation of Glycogen Synthesis and Degradation in *Animals*

(Contrary to the arrow colors in other Figures, red arrows indicate here reactions and regulation mechanisms leading to glycogen synthesis, green arrows leading to glycogen degradation)

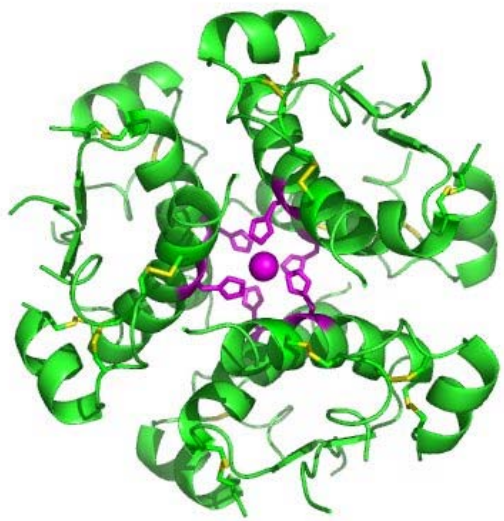


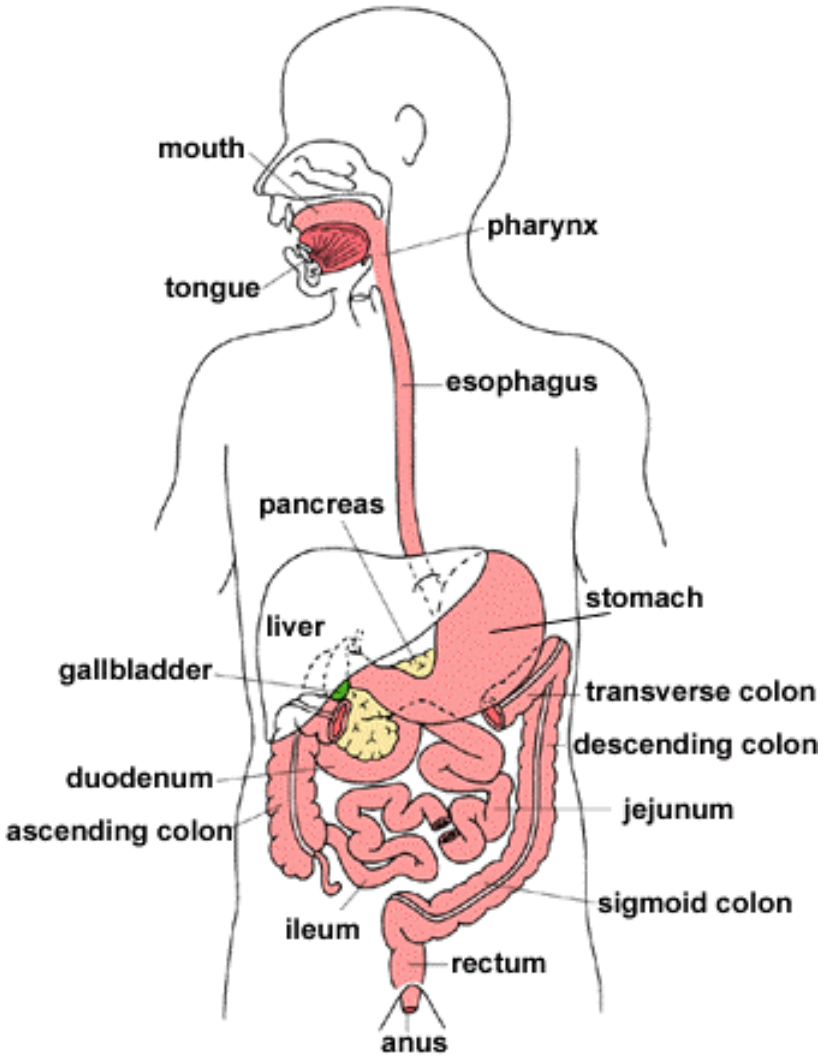
Insulin

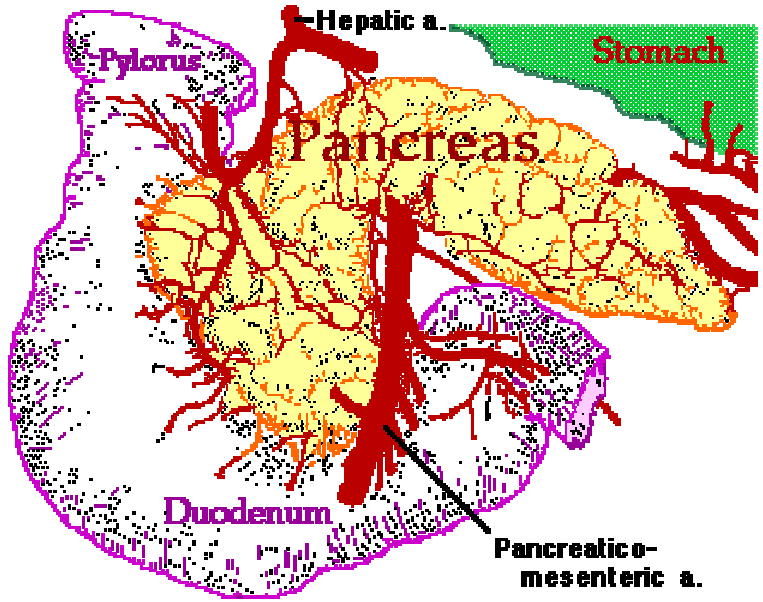
- consists of two amino acid chains linked by two disulfide bridges
- proinsulin in pancreatic beta cell is cleaved to insulin and a connecting peptide (c-peptide levels can be used to measure amount of endogenous insulin production, as commercial insulin preparations do not have c-peptide)
- main stimulus for release is glucose, but release can also be triggered by amino acids, fatty acids and ketone bodies. Activation of beta2-adrenergic receptors in pancreas also stimulate release of insulin whereas stimulation of the alpha-adrenergic receptors in pancreas inhibit insulin release

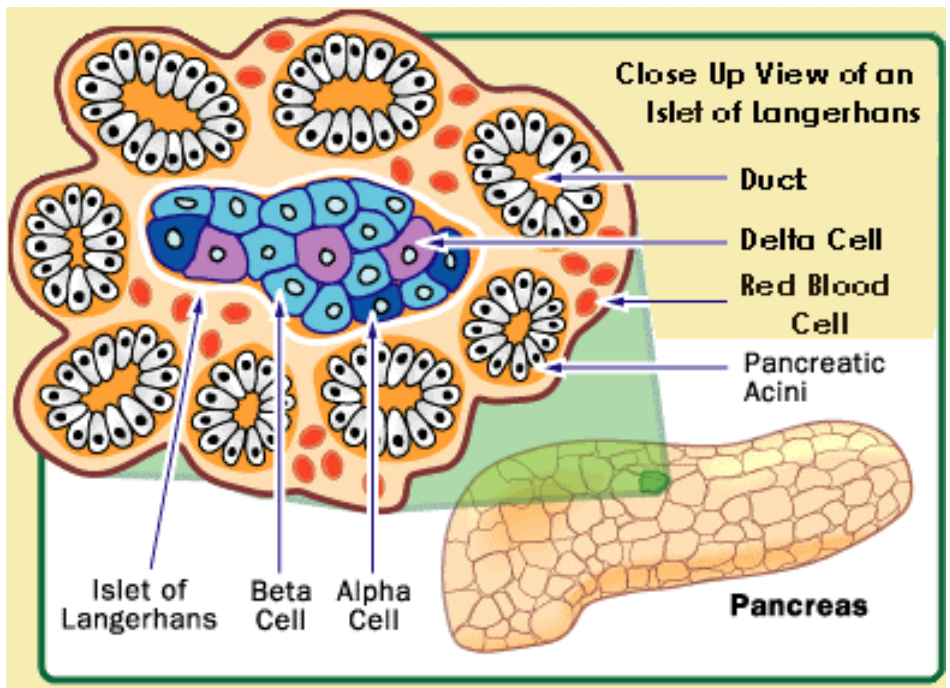
- effects of insulin are anabolic - conservation of energy, promotes cell growth, suppresses gluconeogenesis and promotes glycogenolysis, promotes peripheral uptake of glucose – especially in skeletal muscle cells, encourages storage (as muscle glycogen)

http://en.wikipedia.org/wiki/Insulin
http://en.wikipedia.org/wiki/Glucagon





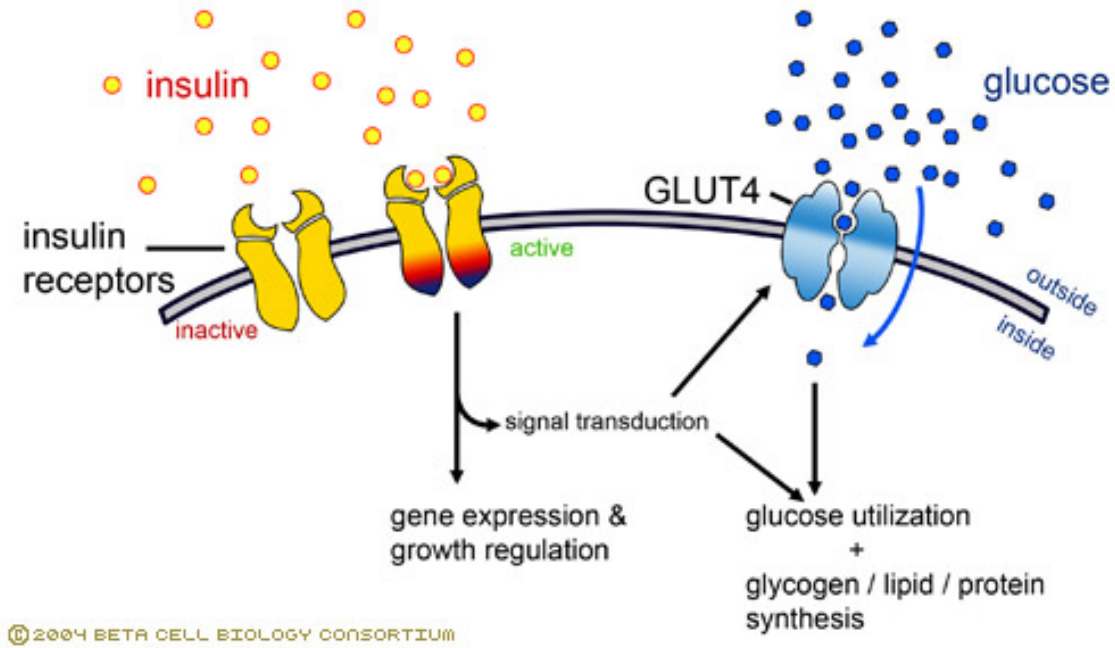


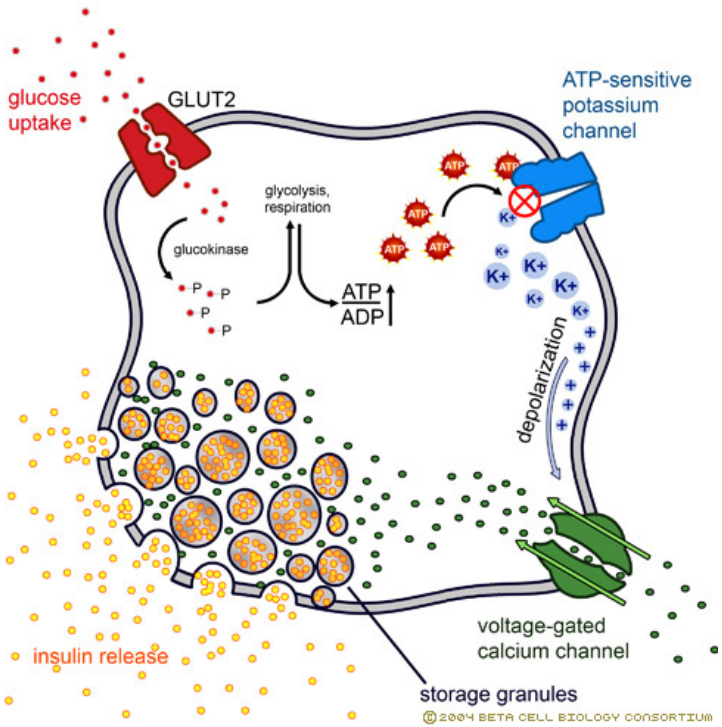


α-cells: glucagon
β-cells: insulin

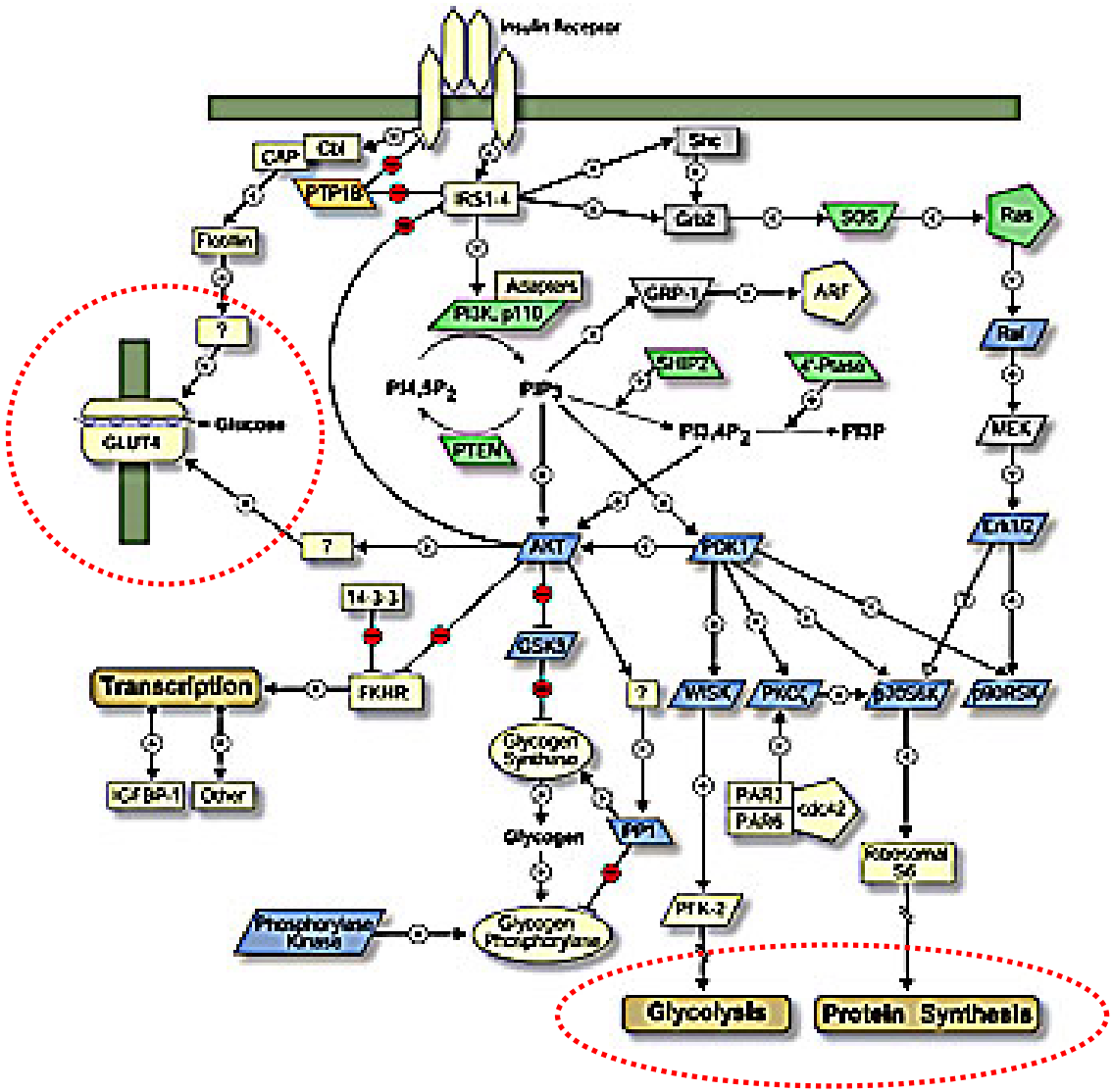
Insulin receptors:

- The receptors for insulin are found on most mammalian cells – action of insulin is mediated through these receptors.
- Impaired action of insulin can result from defects in the receptors or defects in post-receptor events.





Signal transduction



Complications of Diabetes (http://diabetes.niddk.nih.gov/complications/index.htm)

Acute complications:
- ketoacidosis, hypoglycaemia, hyperosmolar non-ketotic coma, intercurrent illness
Chronic complications:
- retinopathy, nephropathy, neuropathy, macrovascular disease, other

Prevalence of complications:
Liebl et al (2002) reported a prevalence's in those with type 2 diabetes of myocardial infarction (10.6%); stroke (6.6%); foot ulcer (3.97%); amputation (2.3%); blindness (1.34%).
Williams et al (2002) reported that at leats 72% of those with type 2 had at least one complication; 19% had only a microvascular complication; 10% had only a macrovascular complication; 24% had both a microvascular and macrovascular complication. The macrovascular complications were – peripheral vascular disease (18%); angina (17%); heart failure (12%); myocardial infarction (9%). The microvascular complications were – neuropathy (28%); renal damage (20%); retinopathy (20%); needing treatment for an eye complication (6%).

Hypoglycaemia
- Most "hypo's" are minor and easily treated
- Prolonged and repeated attacks can result in permanent damage.
- Symptoms occur when blood glucose level drops to about 3.00mmol/l.

Diabetic ketoacidosis (DKA)
- Life threatening - result of severe insulin deficiency - leading to a release of free fatty acids into the circulation and hepatic fatty acid oxidation à forms ketone bodies.
- Biochemical features - hyperglycaemia, hyperketonaemia and metabolic acidosis

Aetiology:
New presentation; intercurrent infection (loose appetite - stop taking insulin); illness (eg stroke); withdrawal of insulin; major dietary indiscretion; significant emotional stress.

Clinical features:
Develops over a few days; polyuria; thirst; weight loss; weakness; leg cramps; hypotension; tachycardia; nausea; vomiting; abdominal pain and tenderness; dehydration; kussmaul respiration; blurred vision; ketotic breath; hypothermia; confusion; coma

Consequences of ketoacidosis - cerebral oedema; acute respiratory distress syndrome; thromboembolism; disseminated intravascular coagulation

Retinopathy

- Main cause of blindness in adults in developed countries.
- Almost all those with diabetes will eventually develop some form of retinopathy (especially those with Type 1).
- Up to 20% of those with Type 2 at time of diagnosis of the diabetes.
- Two basic pathophysiological mechanisms - increased capillary permeability and closure of retinal capillaries vascular leakage retinal oedema and accumulation of lipids seen as hard exudate in the retina and retinal ischaemia.

Other eye conditions in diabetes:

• cataract – develop earlier in those with diabetes; higher risk if also taking corticosteroids
• glaucoma – more common in those with diabetes
• a transient visual disturbance is also common due to osmotic changes

Nephropathy

(http://diabetes.niddk.nih.gov/dm/pubs/neuropathies/index.htm)

- Important cause of morbidity and mortality in those with diabetes.
- Commonest cause of end stage renal failure/disease (ESRF/ESRD) in developed countries.
- Nephropathy is symptom free until it is moderately advanced.
- First sign is a microalbuminuria and elevated blood pressure - progresses to a macroproteinuria with a decline in renal function.

Macrovascular disease

Risk for coronary heart disease, cerebrovascular disease and peripheral vascular disease is higher in those with diabetes - due to premature and accelerated atherosclerosis (major cause of morbidity and mortality).

In type 2 diabetes 'clock starts ticking' for macrovascular disease well before the clinical onset of diabetes due to insulin resistance and dyslipidaemia.

Autonomic neuropathy can reduce the symptoms of chest pain associated with angina and other cardiac complications.

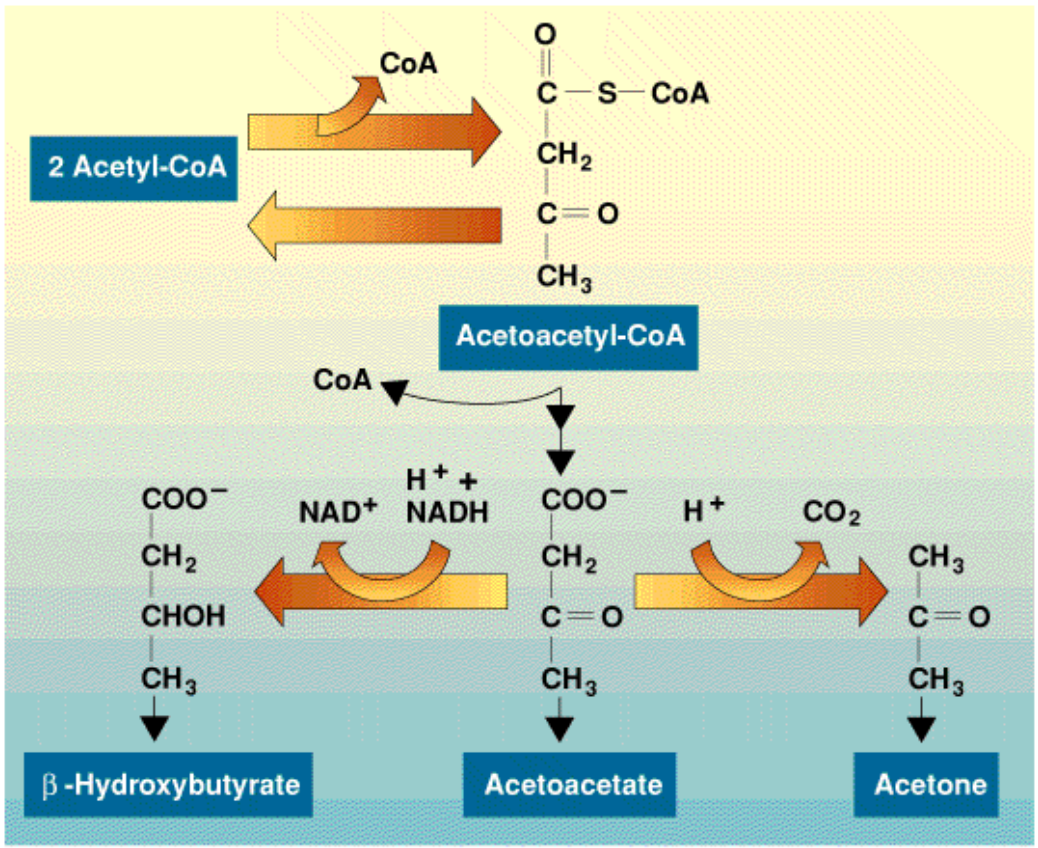
Diabetic Neuropathy

Diabetic neuropathy is a descriptive term covering many clinical types or syndromes of neural damage. It is the most common chronic complication of diabetes and is responsible for a large amount of morbidity

Several types:

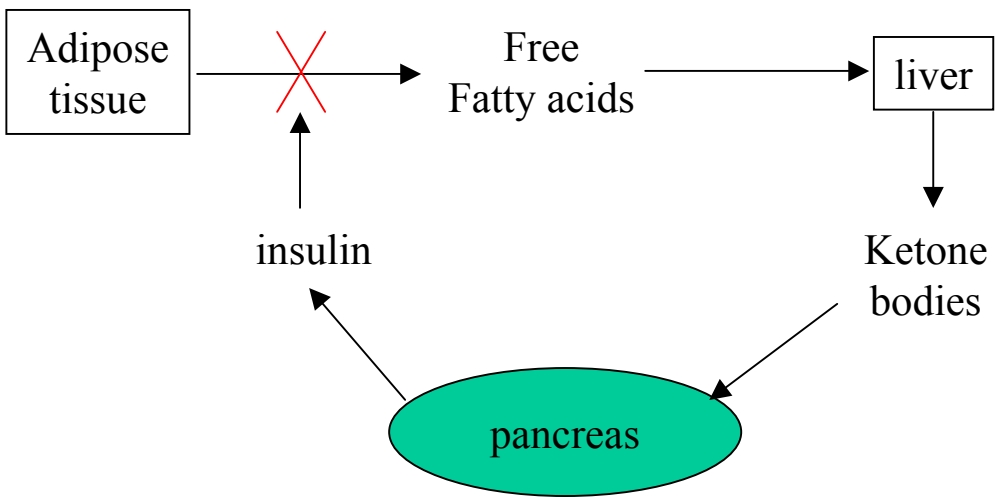
1) Polyneuropathy
    b) Sensorimotor
        a) Acute
        b) Chronic
    a) Autonomic
2) Mononeuropathy
3) Proximal motor neuropathy

Campbell, Biochemistry, 3/e
Text Figure 17.09



Harcourt Brace & Company

Normal prevention of ketosis and events leading to ketosis



Insulin deficiency

↓

Mobilize free fatty acids from adipose

↓

Increased fats to liver

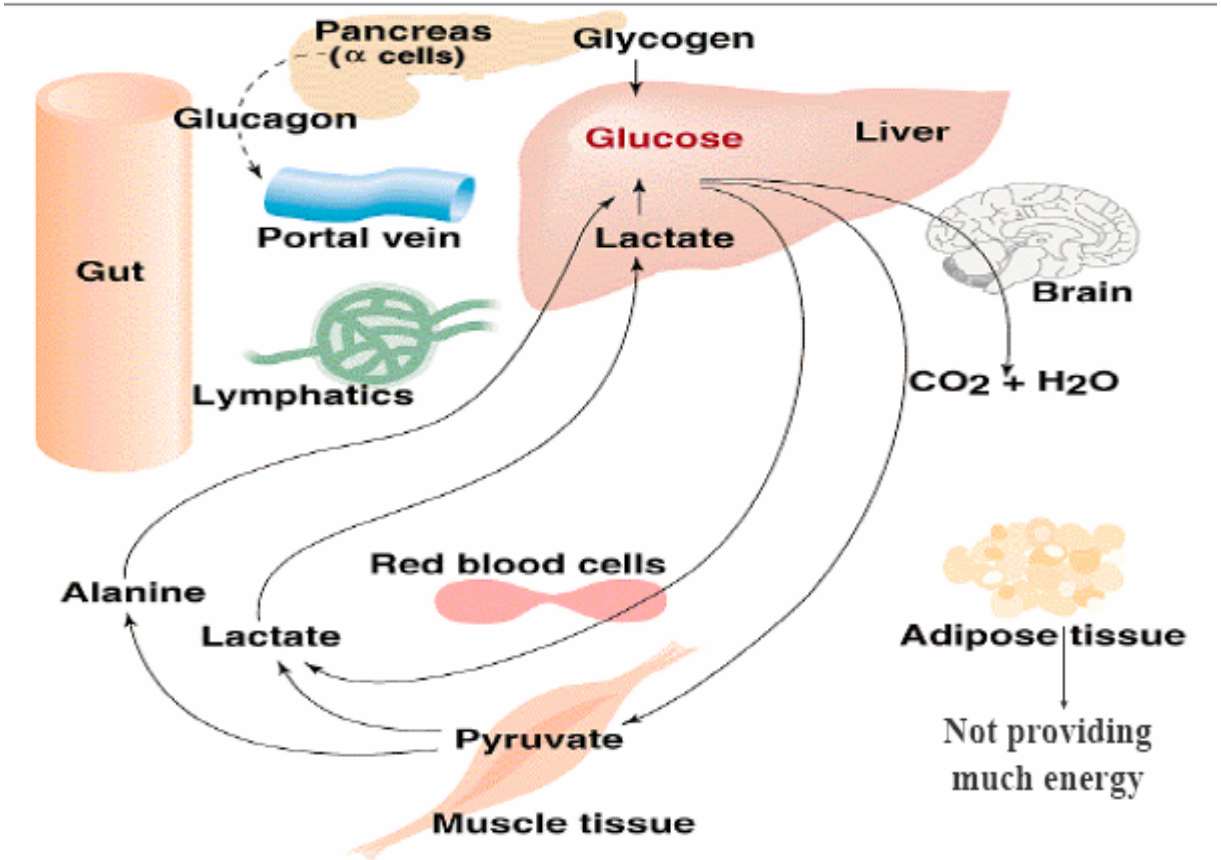
↓

Increased uptake and oxidation of fats

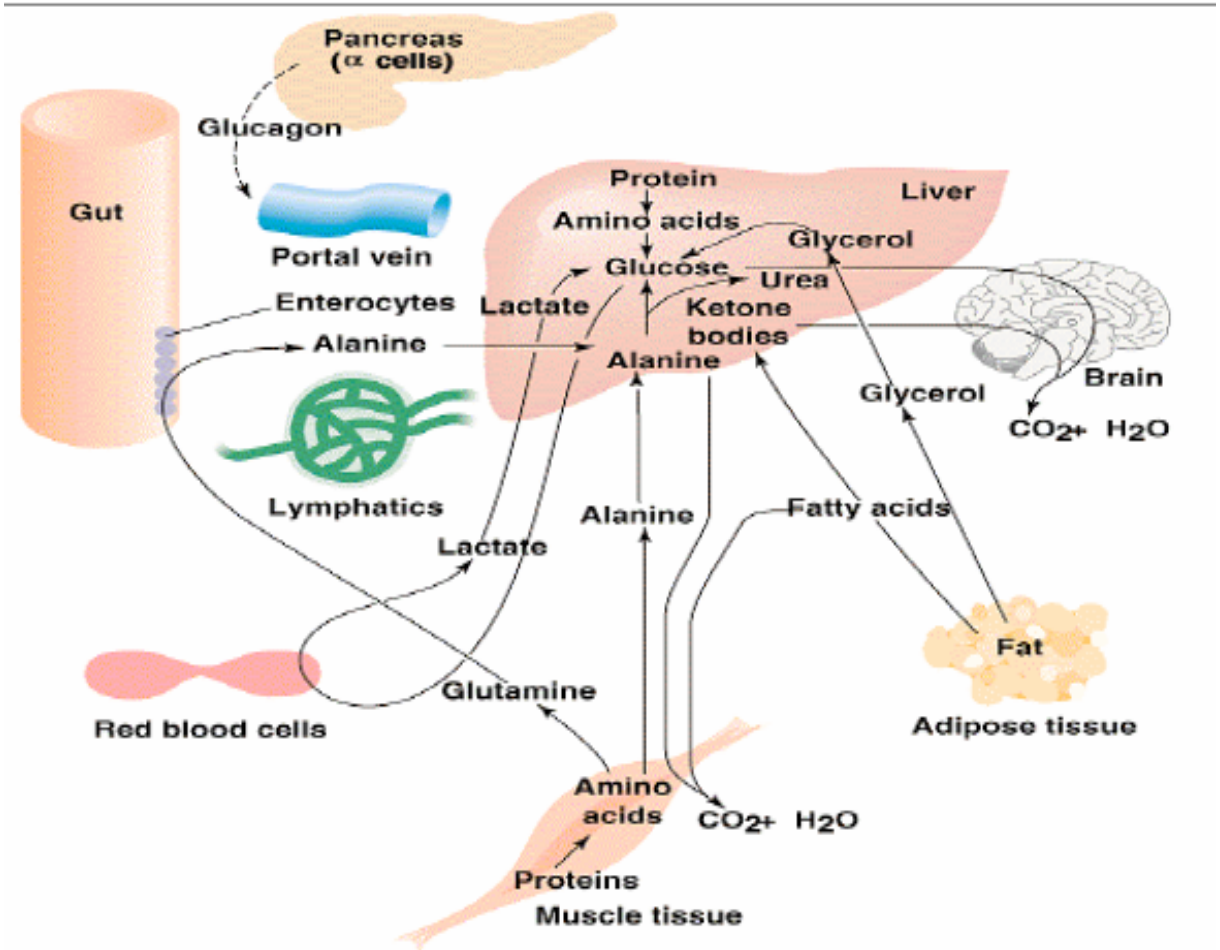
↓

Increased production of ketone bodies

Metabolic interrelationships in the early fasting state (fig. 22.3)

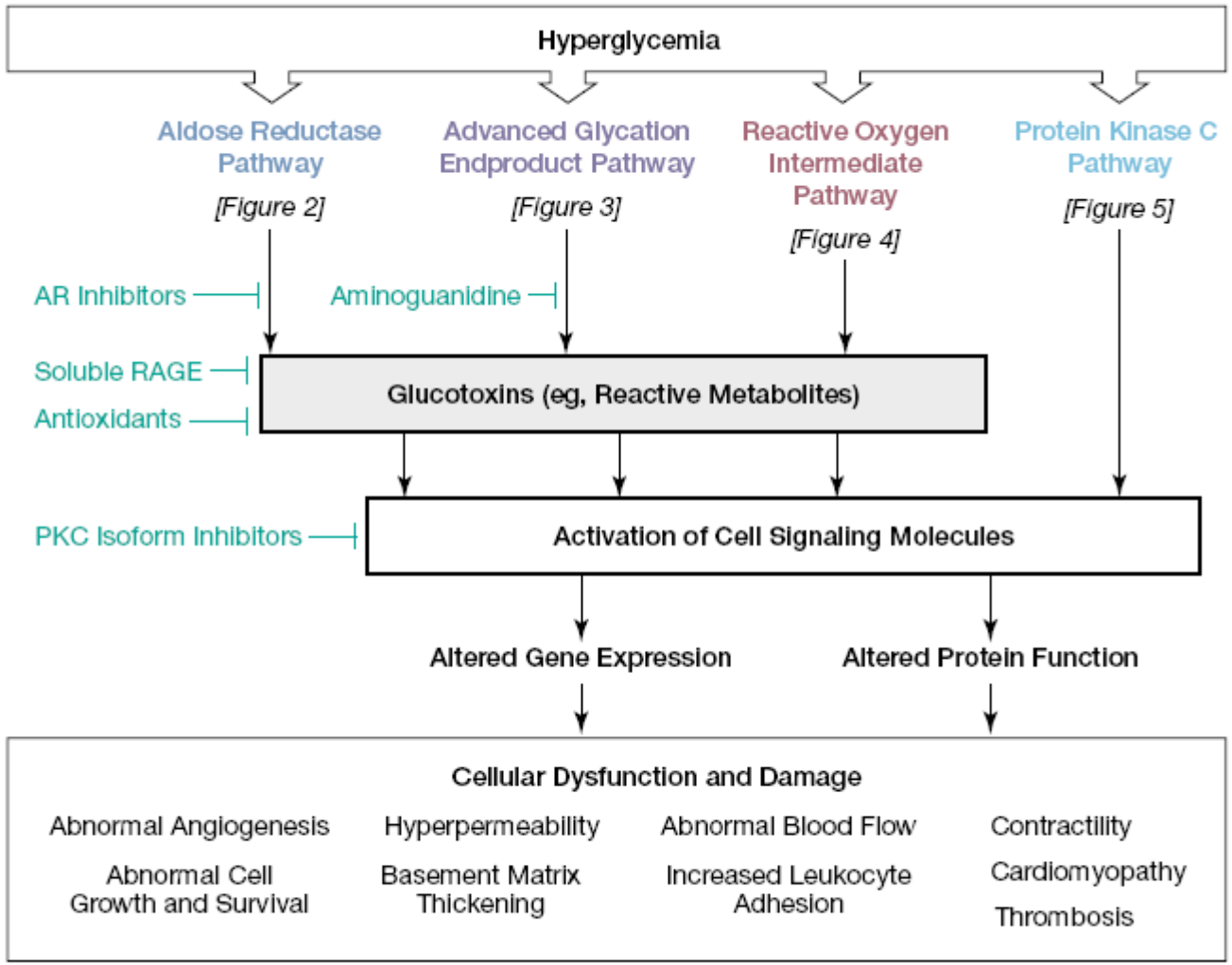


Metabolic interrelationships in the fasting state (fig. 22.4)



JAMA 288:2579-2588 (2002) Molecular understanding of hyperglycemia's adverse effects for diabetic complications

Figure 1. Overall Categorization of Signaling Pathways Involved in Diabetic Complications



AR indicates aldose reductase; RAGE, receptor for advanced glycation endproducts; PKC, protein kinase C.

Figure 2. Aldose Reductase Pathway Theory

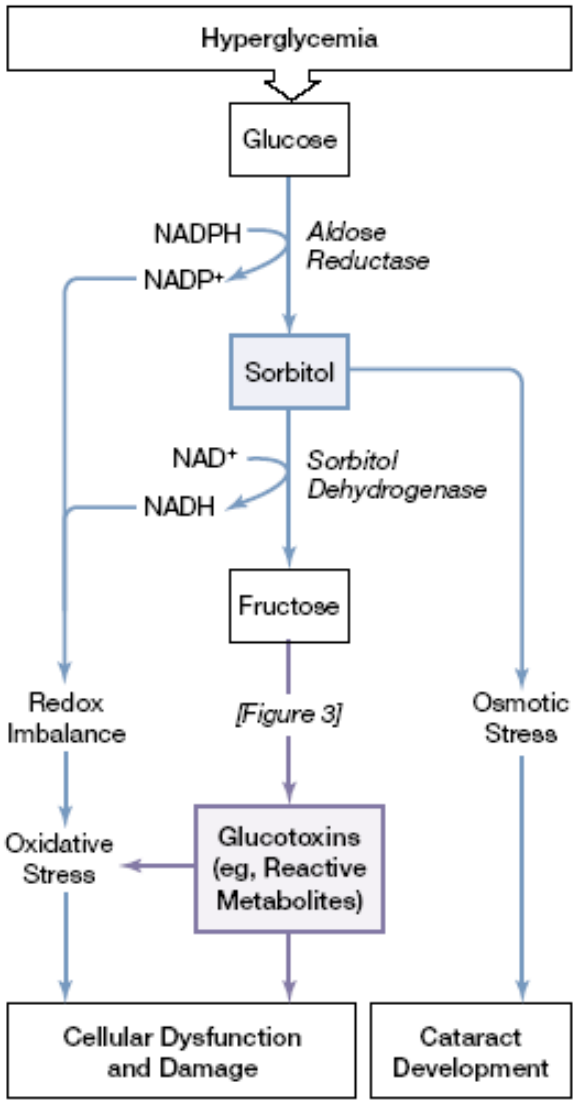


Figure 3. Advanced Glycation Endproduct (AGE) Pathway Theory

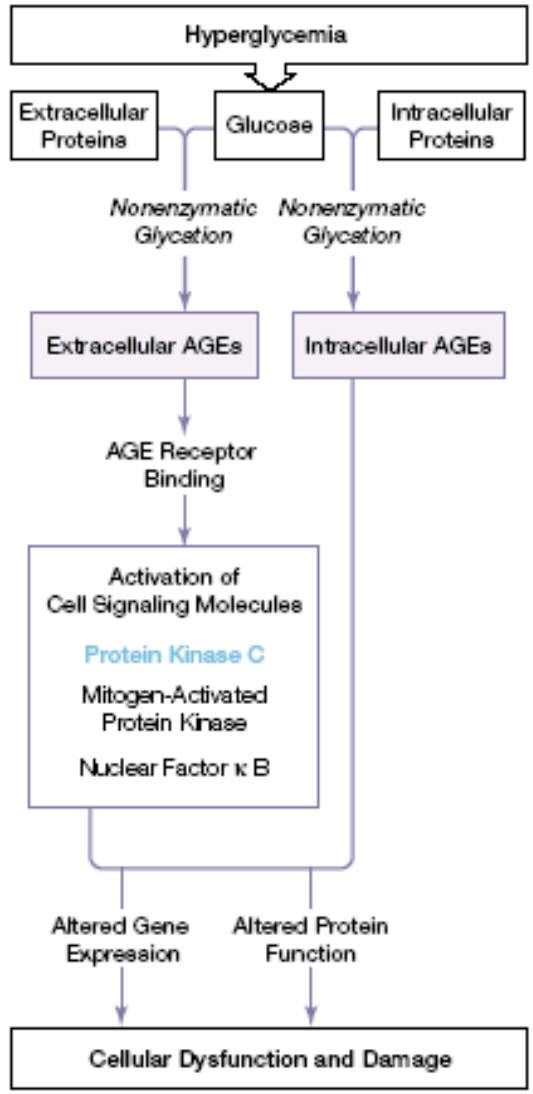


Figure 4. Reactive Oxygen Intermediate Pathway Theory

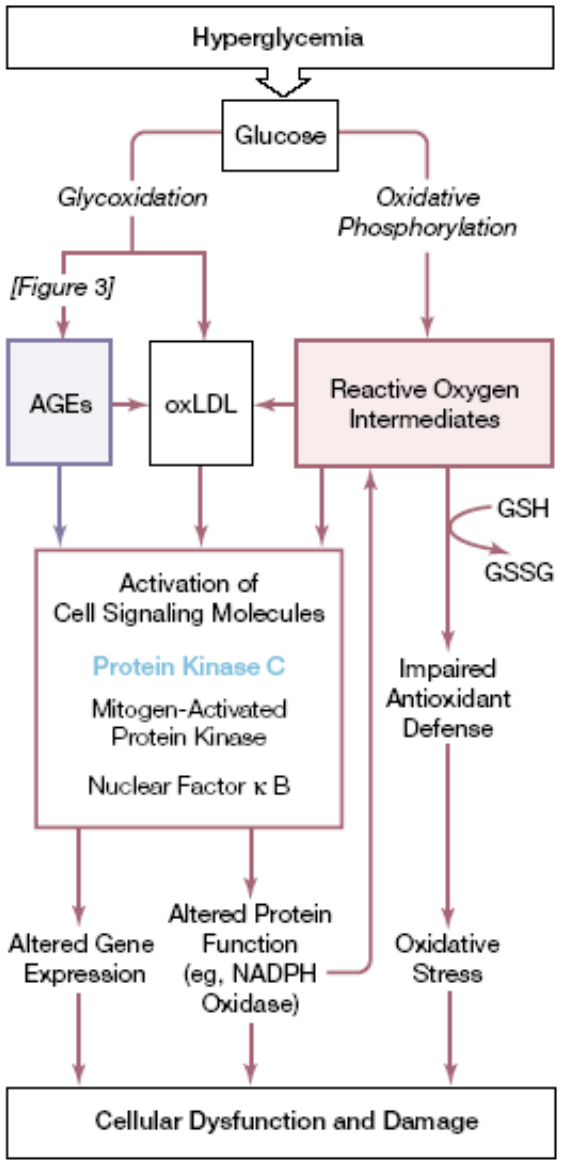


Figure 5. Protein Kinase C Theory