PATHOLOGY OF CARBOHYDRATE METABOLISM. BIOCHEMICAL AND MOLECULAR FUNDAMENTALS OF DIABETES MELLITUS DEVELOPMENT.

LECTURER ALEXANDER KOVAL, PHD

GENERAL, BIOORGANIC CHEMISTRY AND BIOCHEMISTRY DEPT.

CONTENTS

AN ADEQUATE BLOOD GLUCOSE LEVEL MUST BE MAINTAINED AT ALL TIMES

Brain and erythrocytes depend on glucose.

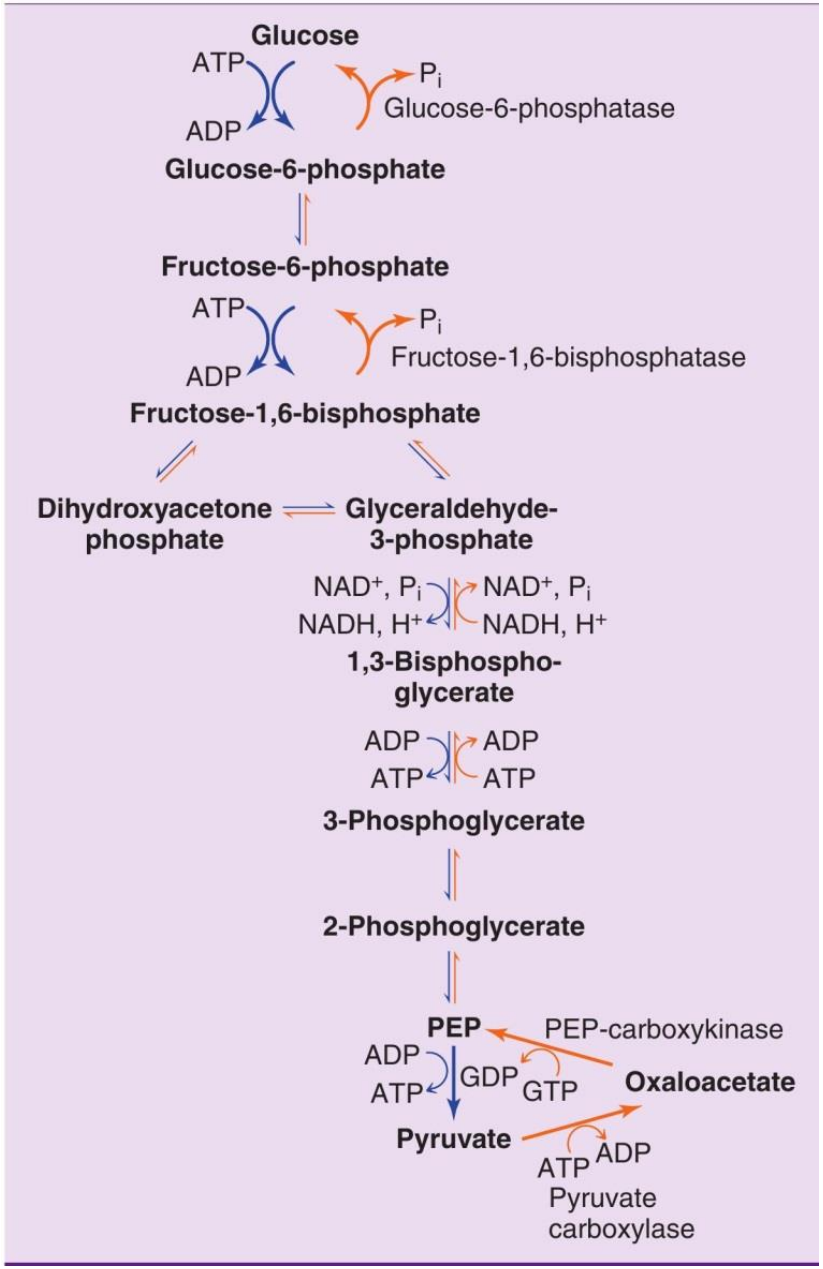
Brain consumes 100 g of glucose per day.

The body maintains a blood glucose level of 4.0 to 5.5 mmol/L (70–100 mg/dL) at all times.

Dietary carbohydrates - for a few hours **after a meal**. The blood glucose concentration can rise up to 8.5 mmol/L (150 mg/dL).

In the **fasting state**, however, the liver has to produce glucose by two pathways:

1. *Glycogen degradation* is fast and cheap. It requires no metabolic energy, but the glycogen reserves of the liver rarely exceed 100 g and therefore are depleted within 24 hours. Only liver glycogen, but not the glycogen of muscle and other tissues, can be used to maintain the blood glucose level.
2. *Gluconeogenesis* produces glucose from amino acids, lactic acid, and glycerol. Liver and kidney both have a complete gluconeogenic pathway, but the liver is the major gluconeogenic organ because of its larger size. Gluconeogenesis is the only source of glucose during prolonged fasting.

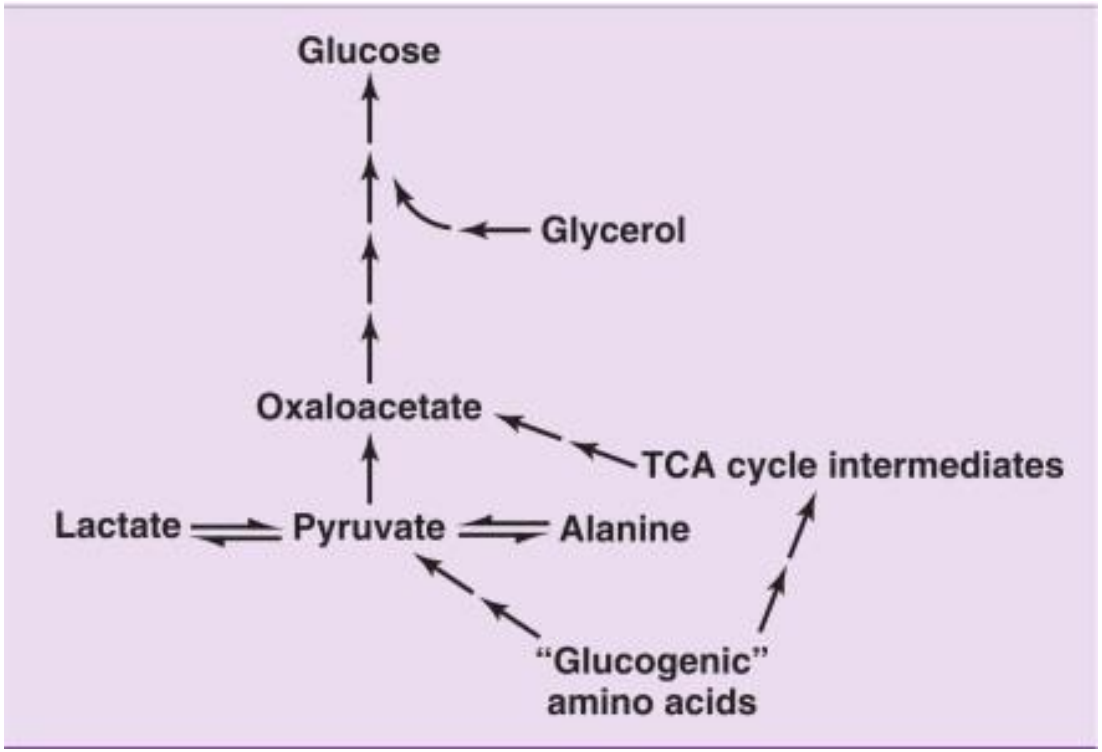


REACTIONS OF GLYCOLYSIS AND GLUCONEOGENESIS

- The easiest strategy for glucose synthesis would be to reverse glycolysis by making glucose from pyruvate and lactate.
- *the gluconeogenic pathway has to bypass the three irreversible reactions of glycolysis: those catalyzed by:*
  1. hexokinase,
  2. phosphofructokinase (PFK), and
  3. pyruvate kinase

G. Meisenberg, W. Simmons, 2017

IMPORTANT SUBSTRATES OF GLUCONEOGENESIS



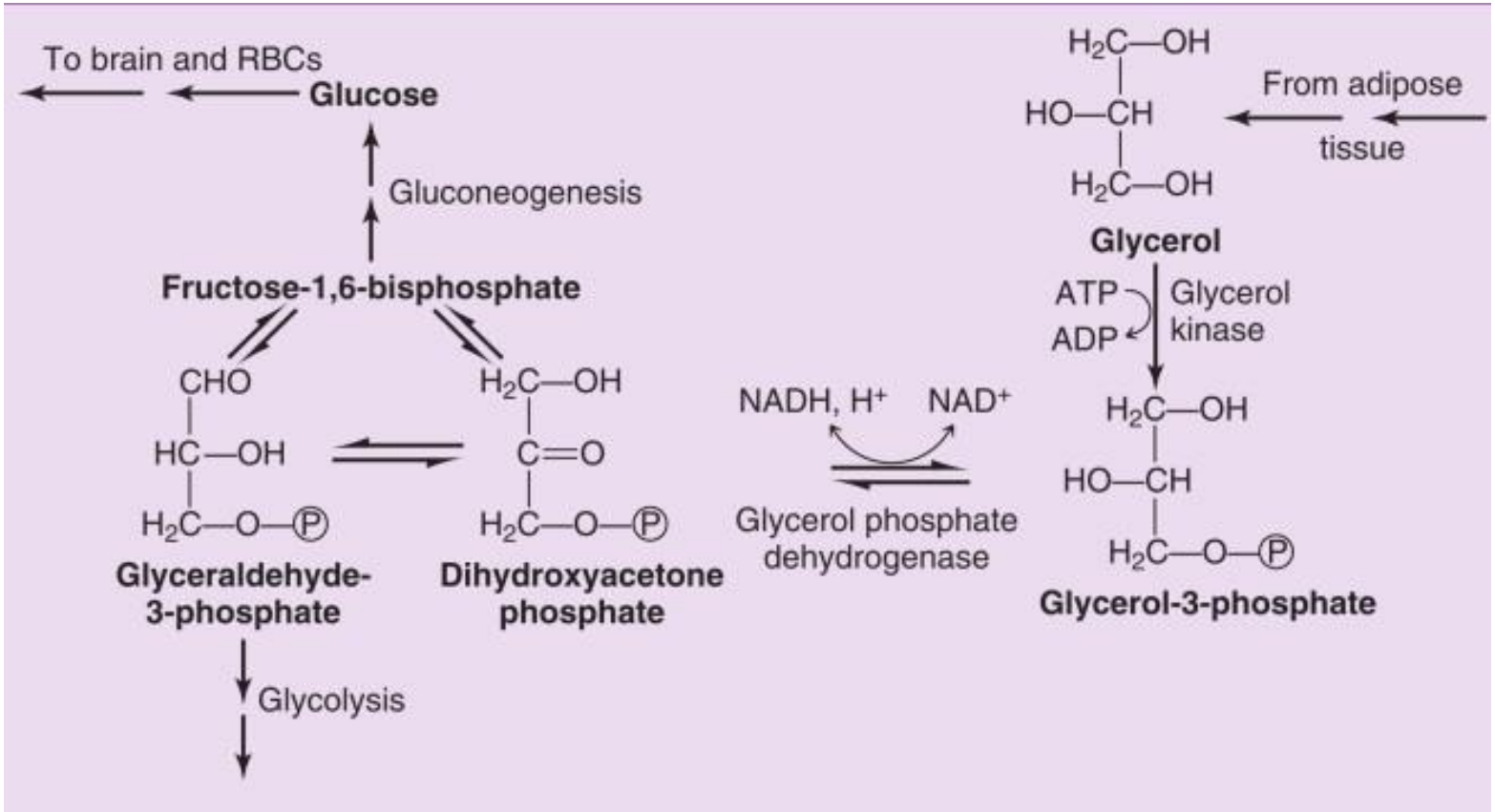
G. Meisenberg, W. Simmons, 2017

Lactate and **alanine** are convenient substrates of gluconeogenesis because they are readily converted to pyruvate by lactate dehydrogenase and by transamination, respectively.

Oxaloacetate is not only a gluconeogenic intermediate but also a member of the TCA cycle. This is important because most amino acids are degraded to TCA cycle intermediates.

Through the TCA cycle, these "*glucogenic" amino acids* feed into gluconeogenesis.

GLYCEROL ENTERS GNG OR GLYCOLYSIS



Glycerol is another substrate of gluconeogenesis. It enters the pathway at the level of the triose phosphates.

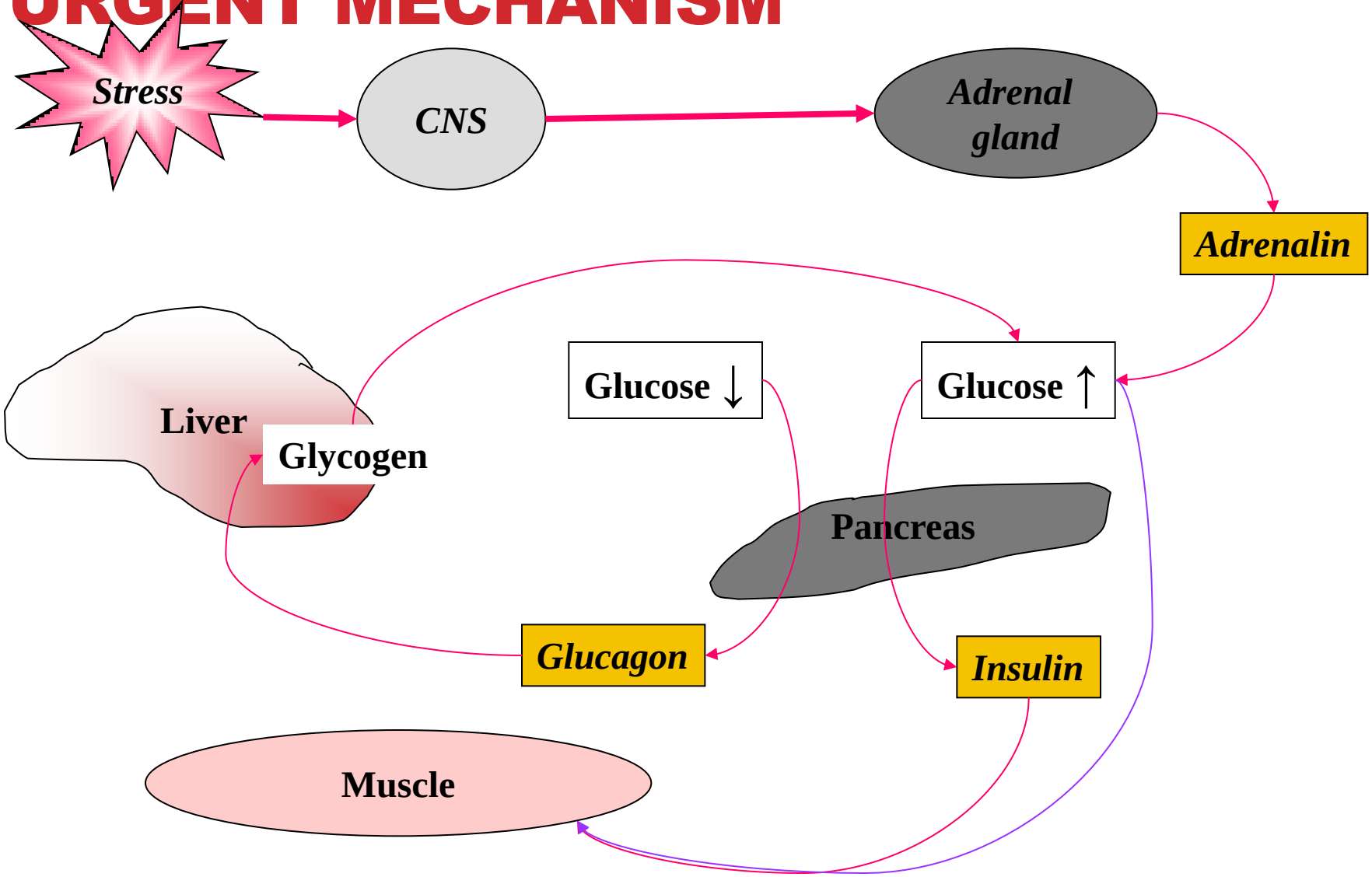
G. Meisenberg, W. Simmons, 2017

MECHANISMS OF BLOOD GLUCOSE LEVEL REGULATION

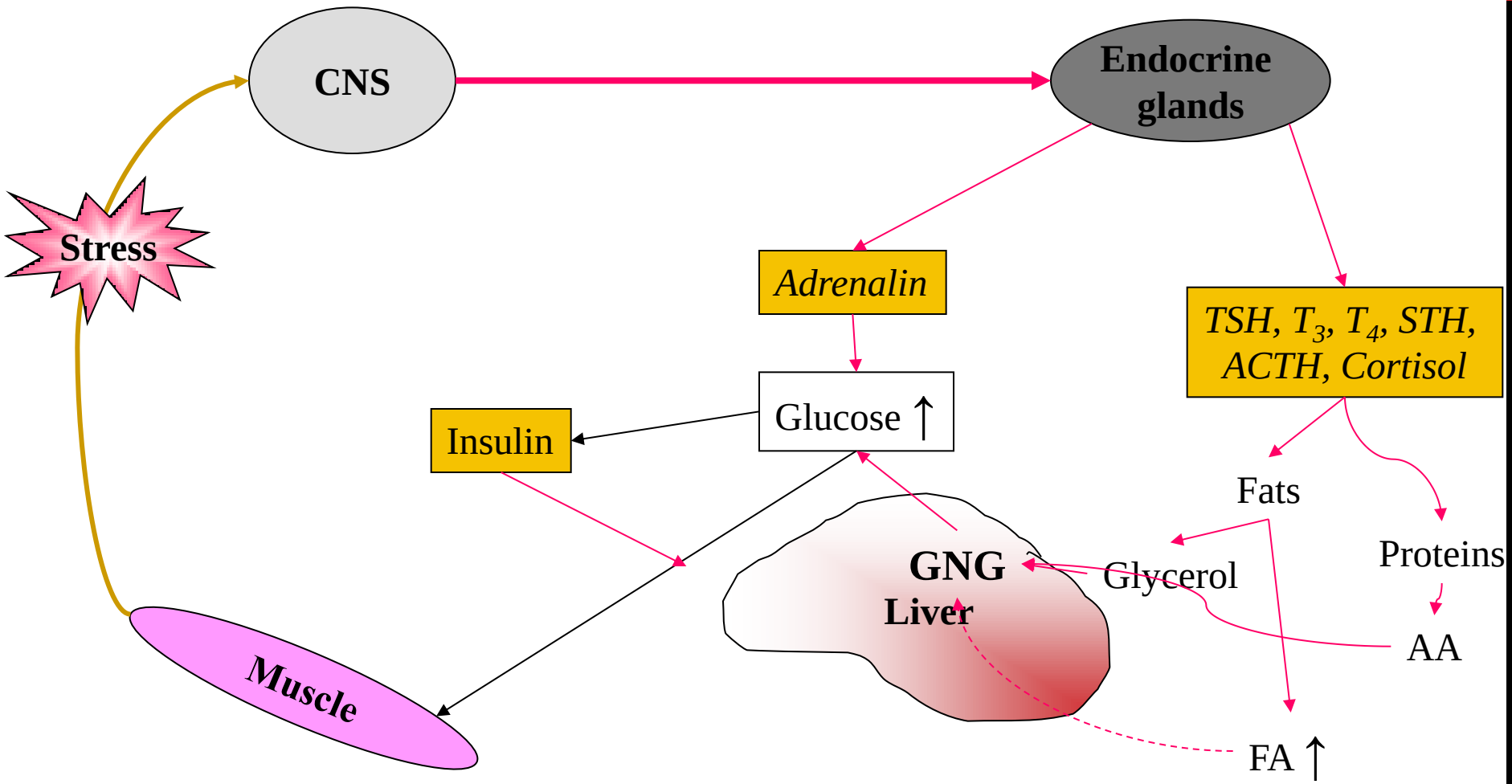
Urgent mechanism – when there is a glycogen in liver and muscles: post-absorptive (fed) state.

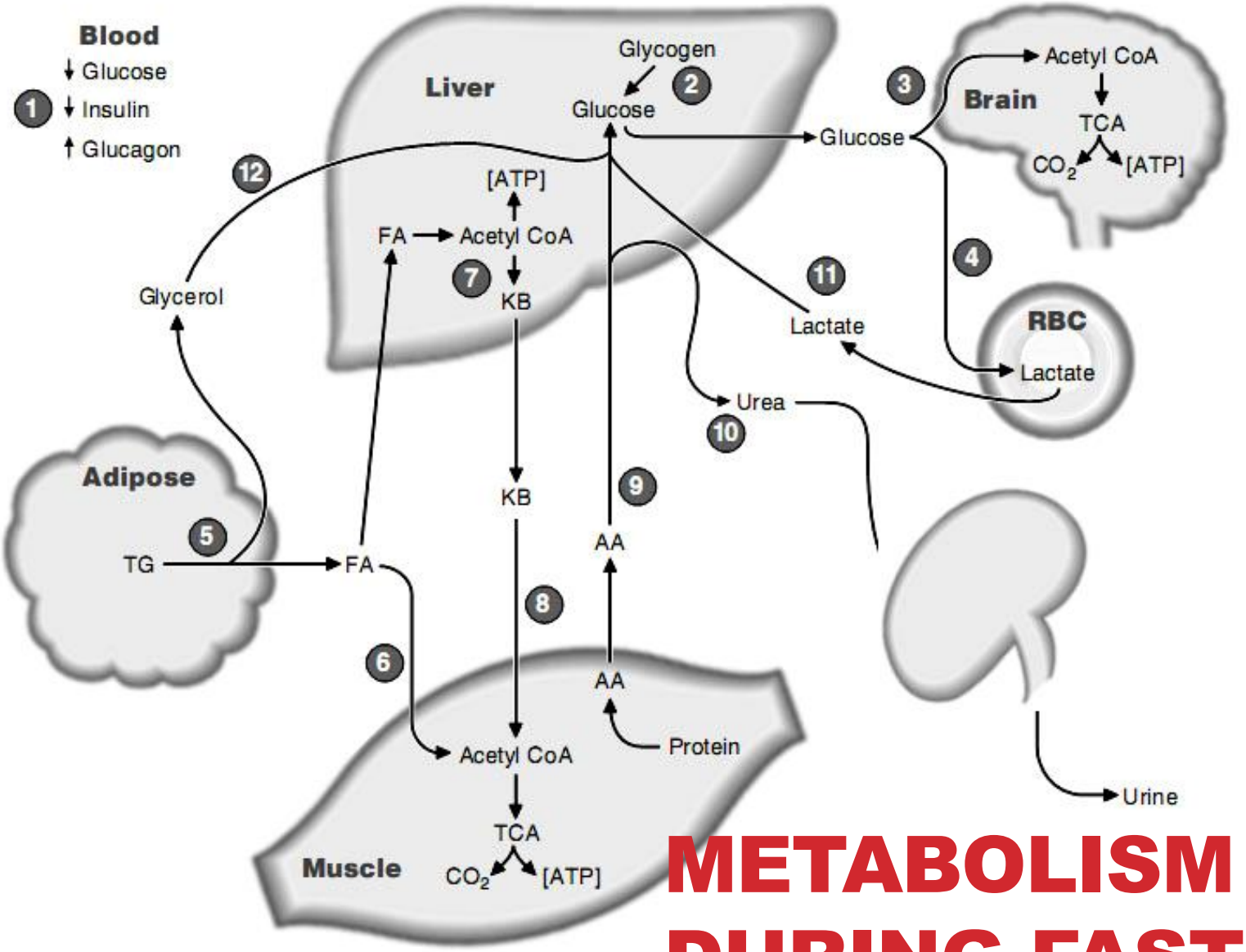
Constant mechanism – when there no glycogen storage in liver and muscles: starving state.

BLOOD GLUCOSE LEVEL REGULATION: URGENT MECHANISM



BLOOD GLUCOSE LEVEL REGULATION: CONSTANT MECHANISM





METABOLISM DURING FASTING

NORMO-, HYPO- AND HYPERGLYCEMIA

Normal blood glucose level – normoglycemia:

3,9 – 6,1 mM (70 – 110 mg/dL)

Decreased blood glucose level – hypoglycemia:

Increased blood glucose level – hyperglycemia:

DISACCHARIDASES AND OLIGOSACCHARIDASES OF THE INTESTINAL BRUSH BORDER

Enzyme	Cleavage Specificity
Glucoamylase	Maltose, maltotriose; acts as exoglycosidase on α-1,4 bonds at the nonreducing end of starch and starch-derived oligosaccharides
Sucrase	Sucrose, maltose, maltotriose
Isomaltase	α-1,6 Bonds in isomaltose and α-limit dextrins
Lactase*	Lactose; also cellobiose†
Cerebrosidase*	Glucocerebroside, galactocerebroside
Trehalase	Trehalose‡

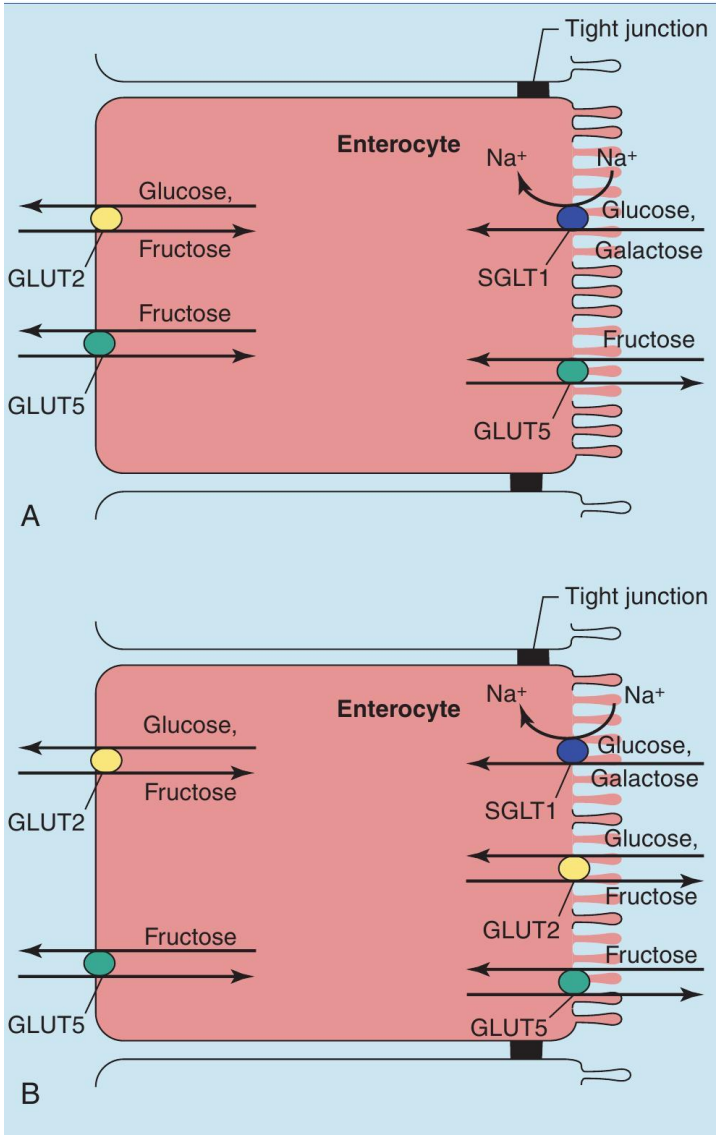
*The lactase and cerebrosidase activities reside in two different globular domains of the same polypeptide (see ***Fig. 19.5***).

† Cellobiose is a disaccharide of two glucose residues in β-1,4-glycosidic linkage.

‡ Trehalose is a disaccharide of two glucose residues in α,α′-1,1-glycosidic linkage; it is common only in mushrooms and insects.

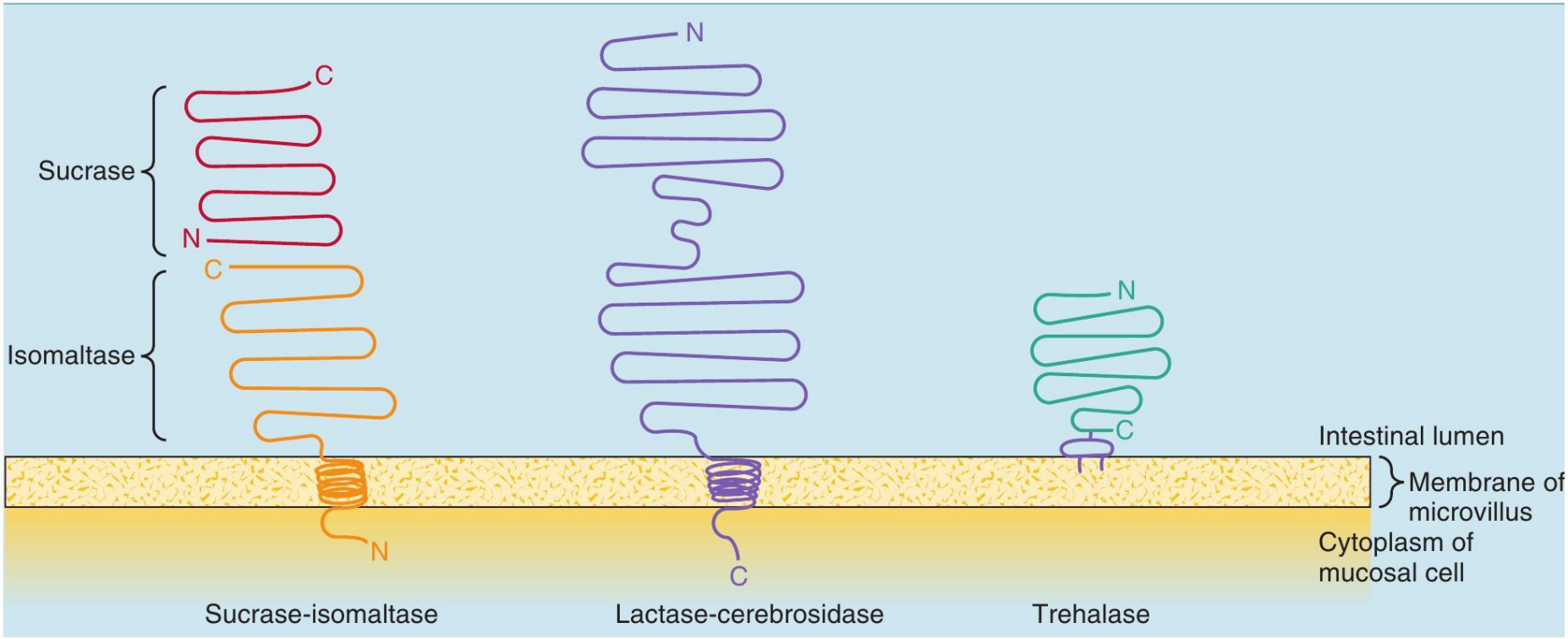
- Disaccharidases and oligosaccharidases hydrolyze sucrose and lactose, as well as the maltose, maltotriose, and α-limit dextrins that are formed by the action of α-amylase on starch.
- The absorption of the monosaccharides requires specialized transporters in the apical (lumen-facing) and basolateral (blood-facing) membranes of the enterocytes.

SUMMARY THE ABSORPTION OF THE MONOSACCHARIDES



- Glucose and galactose are absorbed into the enterocyte by SGLT1 (sodium-glucose transporter 1), a high-affinity carrier that mediates the coupled transport of two sodium ions into the cell together with the sugar.
- Cotransport of sodium down its electrochemical gradient ensures complete absorption of the sugar from the intestinal lumen, but it requires ATP consumption by the sodium-potassium ATPase to restore the sodium gradient across the plasma membrane

PATHOLOGY OF CARBOHYDRATE DIGESTION AND ABSORPTION



DISACCHARIDASE DEFICIENCY: LACTOSE INTOLERANCE (1/2)

•Lactose (“milk sugar”) is abundant only in milk and milk products.

- Accordingly, the activity of intestinal lactase is maximal in infants.
- Some people maintain abundant lactase throughout life and can digest almost any amount of lactose.
- In other individuals, lactase declines to only 5% to 10% of the original level.

•The result is lactose intolerance, with flatulence and other intestinal symptoms after the consumption of more than 200 to 500 mL of milk.

- Avoiding excessive amounts of milk is the only “treatment” required.
- Also, lactose-free milk products and lactase in pill and capsule forms are commercially available.
- The latter products contain lactases of microbial origin.

LACTOSE INTOLERANCE (2/2)

•In most parts of the world, a majority of the population is lactose intolerant.

- Persistent lactase prevails only in Europeans and in some desert nomads of Arabia and Africa.

•In Europe, lactase persistence is caused by a point mutation in an enhancer 13,910 base pairs upstream of the start of the lactase gene.

•This genetic variant became common only after the introduction of cattle raising and milking; it has not been found in fossil DNA from Europeans dated to between 5000 and 5800 years bc.

•It appears that lactase persistence was selected in Europe because those who could digest the milk of their animals were slightly more likely to survive and reproduce than were those who could not.

- Thus a Roman anthropologist reported about the Germans: “They do not eat much cereal food, but live chiefly on milk and meat.…” (Caesar, Gallic War, 4.1).

APPROXIMATE PREVALENCE OF LACTASE RESTRICTION: (NONPERSISTENT LACTASE) IN VARIOUS POPULATIONS

Population/Country	Percent with Low Lactose-Digesting Capacity
Sweden	1
Britain	6
Germany	15
Greece	53
Morocco	78
Tuareg (Niger)	13
Fulani (Nigeria, Senegal)	0–22
Ibo, Yoruba (Nigeria)	89
Saudi Arabia: Bedouins	23
Saudi Arabia: Other Arabs	56
India (different areas)	27–67
Thailand	98
China	93–100
North American Indians	63–95

CLINICAL CASE

A Chinese student at a U.S. medical school complains to the school physician that he suffers from bouts of flatulence and diarrhea shortly after each breakfast. His usual breakfast consists of two candy bars, a small bag of peanuts, and three glasses of fresh milk. He never had digestive problems in his home country, where his diet consisted only of vegetables, meat, and rice. He has most likely a low level of:

A. Pepsin

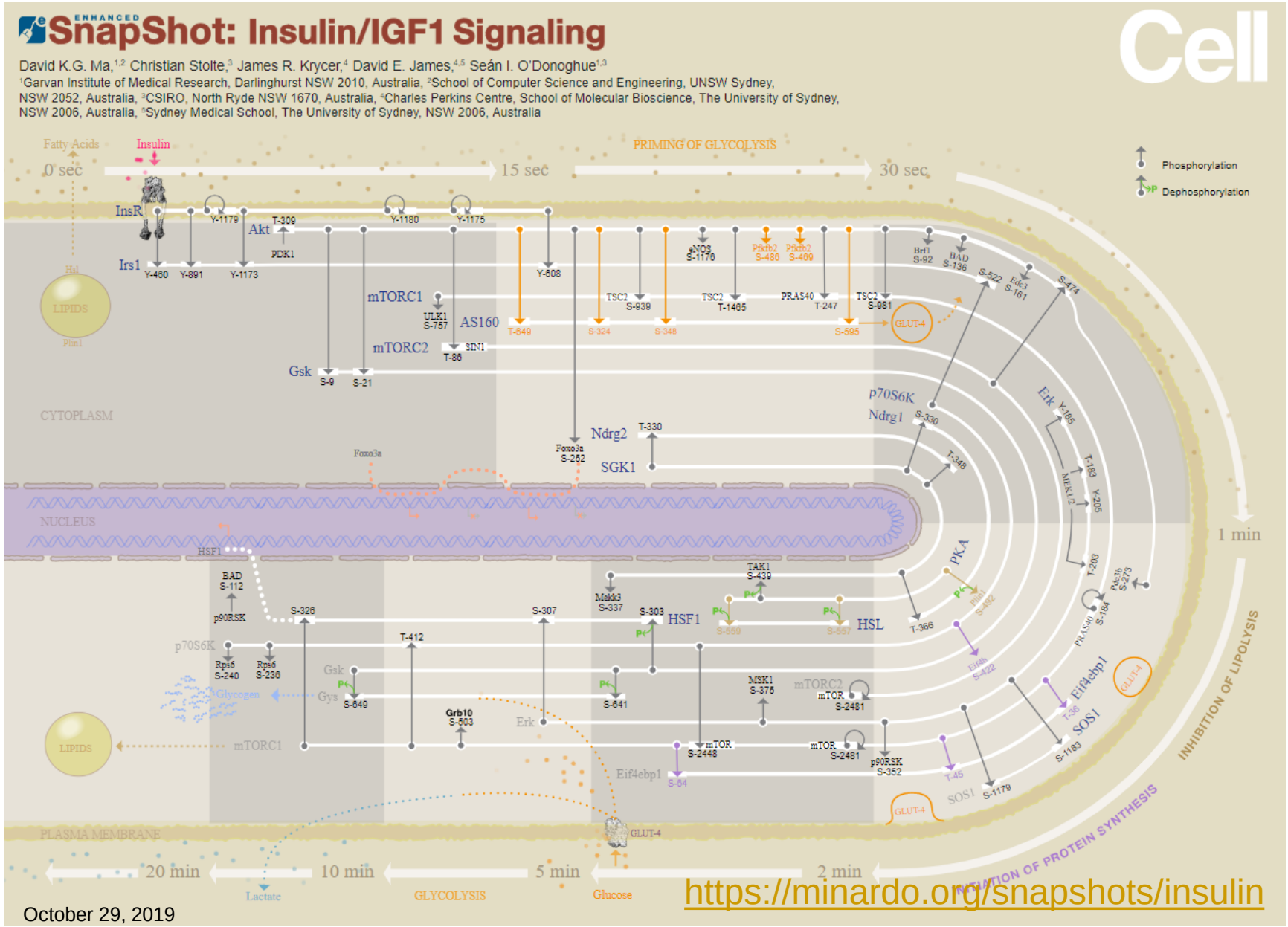
B. Pancreatic lipase

C. Lactase

D. Trypsin

E. α-Amylase

INSULIN SIGNALLING PATHWAY MINARDO



October 29, 2019

Koval AN, 2019 (C)

DIABETES MELLITUS IS CAUSED BY INSULIN DEFICIENCY OR INSULIN RESISTANCE

Diabetes mellitus is caused by a relative or absolute deficiency of insulin action.

Hyperglycemia (abnormally elevated blood glucose) is the biochemical hallmark of **diabetes mellitus**, but the pathways of all major nutrients are deranged.

The two major primary forms of **diabetes** are type 1 and type 2:

Parameter	Type 1	Type 2
Age at onset (years)	≤ 20	> 20
Lifetime incidence	0.2%–0.4%	20–25%
Heritability	≈ 50%	≈ 80%
Pancreatic β-cells	Destroyed	Initially normal
Circulating insulin	Absent	Normal, high, or low
Tissue response to insulin	Normal	Reduced (most patients)
Fasting hyperglycemia	Severe	Variable
Metabolic complications	Ketoacidosis	Nonketotic hyperosmolar coma
Treatment	Insulin	Diet, oral antidiabetics, or insulin

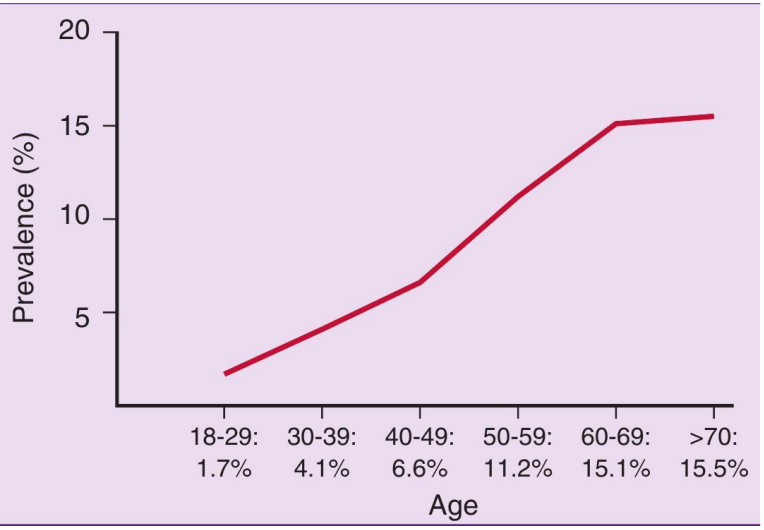
G. Meisenberg, W. Simmons, 2017

TYPE 1 DIABETES

1. Typically starts in childhood or adolescence.
    - It is an autoimmune disease that leads to *destruction of pancreatic β-cells.*
    - Without endogenous insulin production, patients depend on insulin injections for life.
    - Being a protein, insulin is not orally active because it is destroyed by digestive enzymes.
2. Type 1 **diabetes** afflicts perhaps 1 in 400 individuals, and its incidence is not strongly related to lifestyle.

G. Meisenberg, W. Simmons, 2017

TYPE 2 DIABETES



In the United States the prevalence of diabetes among adults aged 20 years and older rose from 5.5% in 1991 to 9.3% in 2005 to 2010.

- The disease of middle-aged and older individuals.
  - It is far more common than type 1, is less severe, and has more complex origins.
  - The pancreatic β-cells are intact in the early stages, and the plasma level of insulin can be normal, reduced, or elevated.
  - These patients have either *reduced insulin secretion* or *insulin resistance,* or a combination of both.
- According to one estimate, worldwide 382 million people had **diabetes** in 2013, and the prevalence rises steeply with rising affluence.

G. Meisenberg, W. Simmons, 2017

DIABETES AND OBESITY

- Most patients with poorly controlled type 1 **diabetes** are thin, but most type 2 patients with **diabetes** are obese.
  - In one study, the age-adjusted risk for developing type 2 diabetes was increased by a factor of 2.7 for the overweight and 7.3 for the obese, compared with normal-weight men.
- *Obesity is not a consequence of diabetes, but precedes the onset of type 2 diabetes by many years or decades.*
- Insulin is an anabolic hormone.
  - Without intervention, loss of insulin action reduces body weight.
  - Conversely, most type 2 diabetics gain weight when they are placed on insulin treatment.

G. Meisenberg, W. Simmons, 2017

OBESE PATIENTS WITH TYPE 2 DIABETES ARE INVARIABLY INSULIN RESISTANT

- Even nondiabetic obese individuals have, on average, higher insulin levels than do thin people, and their tissue responsiveness is proportionately reduced.
- Impaired intracellular insulin signaling, rather than reduced receptor number, is the main cause of insulin resistance.
- Insulin resistance is compensated for by increased insulin secretion, and many obese people can remain normoglycemic for decades because hyperinsulinemia compensates for their insulin resistance.
- Type 2 **diabetes** results only when the β-cells cannot keep up with the demand.
  - As the disease progresses, the β-cells tend to “burn out”.
  - In early-stage obese type 2 diabetics, a balanced weight-reduction diet can restore tissue responsiveness to insulin and reduce blood glucose and insulin levels.

G. Meisenberg, W. Simmons, 2017

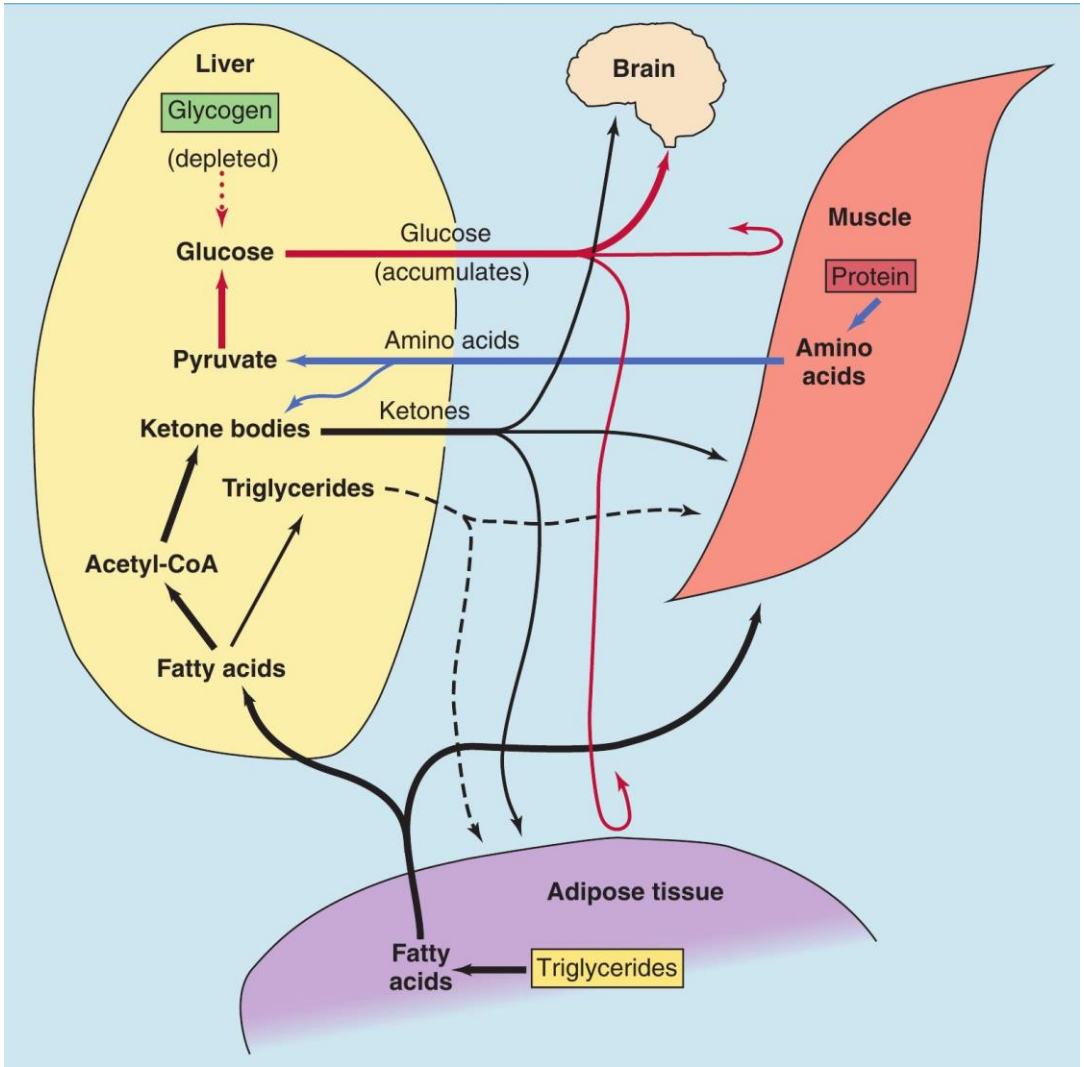
ISLET AMYLOID 1/2

- Most type 2 diabetics who live with their disease for many years develop progressive β-cell dysfunction and reduced β-cell mass, leading to declining insulin levels and the need for insulin injections.
- One likely reason for the “burnout” of β-cells is the progressive deposition of **islet amyloid** in the islets of Langerhans.
  - Islet amyloid is an abnormally folded form of the hormone amylin, which is secreted by the β-cells together with insulin and C peptide.
  - Amylin has hormonal effects that are synergistic with those of insulin.
  - It delays gastric emptying, and it acts on the brain to reduce appetite.
  - In insulin-resistant patients, the secretion of both amylin and insulin is increased.
  - This raises the local concentration of amylin and favors its aggregation into amyloid fibrils.

ISLET AMYLOID 2/2

- Unlike human amylin, mouse amylin does not form amyloid.
  - Normal laboratory mice do not become diabetic spontaneously.
  - However, transgenic mice that produce human amylin instead of mouse amylin do develop diabetes that is frequently (but not always) accompanied by amyloid deposition in the islets.
  - The diabetogenic effect is attributed to soluble oligomers of the islet amyloid rather than the insoluble deposits. Whether transgenic humans expressing the gene for mouse amylin would be resistant to type 2 diabetes is unknown.

IN DIABETES, METABOLISM IS REGULATED AS IN STARVATION



The declining level of plasma insulin mediates most of the metabolic adaptations to food deprivation. Therefore the metabolic changes of **diabetes** resemble those of starvation.

THE HYPERGLYCEMIA OF DIABETES MELLITUS IS CAUSED BY *OVERPRODUCTION AND UNDERUTILIZATION OF GLUCOSE*

- The liver makes rather than consumes glucose, and muscle and adipose tissue fail to take up glucose from the blood.
  - There is also *excessive lipolysis in adipose tissue.*
  - The levels of plasma free fatty acids rise, and the liver turns excess fatty acids into ketone bodies.
  - These are the same changes that occur in starvation, when liver and adipose tissue keep everyone else alive by doling out glucose, fatty acids, and ketone bodies.
- *The oversupply of fatty acids reduces glucose catabolism in liver and skeletal muscle.*
- As we saw before, this is achieved both by allosteric actions of the products of fatty acid catabolism and by actions on insulin signaling that are mediated by protein kinases.
- Because a high-fat diet induces insulin resistance, *dietary treatment of obese type 2 diabetics is based on the restriction of total calories, not the replacement of carbohydrates by fat.*

THE ACUTE COMPLICATIONS OF DIABETES

- The acute complications of **diabetes** include **diabetic ketoacidosis**in type 1 **diabetes** and **nonketotic hyperosmolar coma** in elderly patients with type 2 **diabetes**.
- The latter is caused by excessive glucosuria with osmotic diuresis.
- If the patient forgets to drink, dehydration can become sufficiently severe to affect the brain.

DIABETIC KETOACIDOSIS (1/2)

- The complete absence of insulin in type 1 diabetes => diabetic ketoacidosis, which presents with malaise, nausea, hyperventilation, sweating, tachycardia, postural hypotension, and neurological derangements.
  - Untreated it can lead to circulatory collapse, loss of consciousness, and death.
- Ketoacidosis develops when the liver produces ketone bodies (acetoacetic acid and β-hydroxybutyric acid) faster than they can be oxidized.
  - Being acids, the ketone bodies acidify the blood.
  - Ketosis is accompanied by blood glucose levels that can be as high as 1000 mg/dL.
  - Large amounts of glucose and ketone bodies are lost in the urine, and osmotic diuresis causes dehydration and electrolyte imbalances.

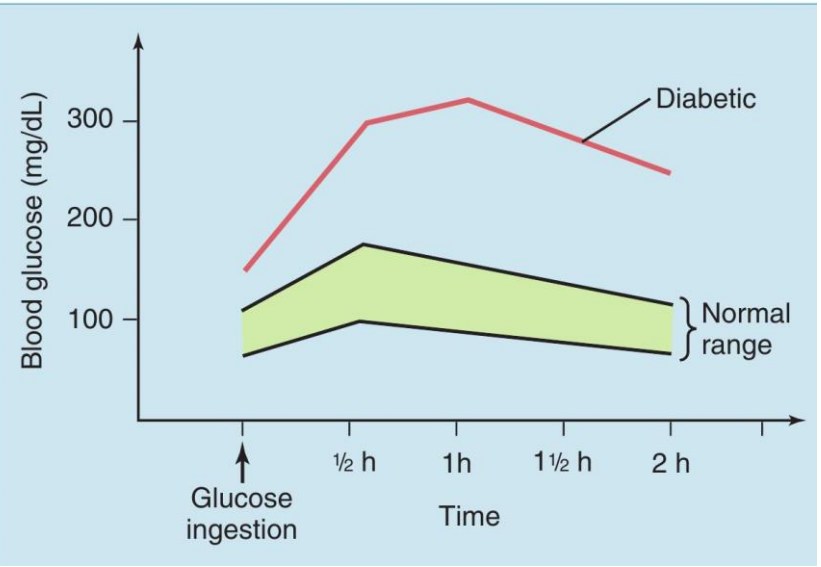
DIABETIC KETOACIDOSIS (2/2)

- Osmotic diuresis and acidosis reduce the blood pressure through hypovolemia and peripheral vasodilation, respectively.
  - Hypotension activates the sympathetic nervous system, which attempts to restore a normal blood pressure by stimulating the heart and contracting peripheral resistance vessels.
  - However, it also stimulates fat breakdown in adipose tissue and thereby supplies the liver with even more substrate for ketogenesis.
- Because of this vicious cycle, *ketoacidosis is fatal if untreated.*
  - Proper treatment includes fluid replacement, correction of the acidosis, and generous insulin injections.
  - The CNS depression in diabetic ketoacidosis is not caused by excess glucose.
  - Hyperglycemia is not acutely damaging to the brain.
  - It rather is caused by dehydration, electrolyte disturbances, and acidosis.

DIABETES IS DIAGNOSED WITH LABORATORY TESTS

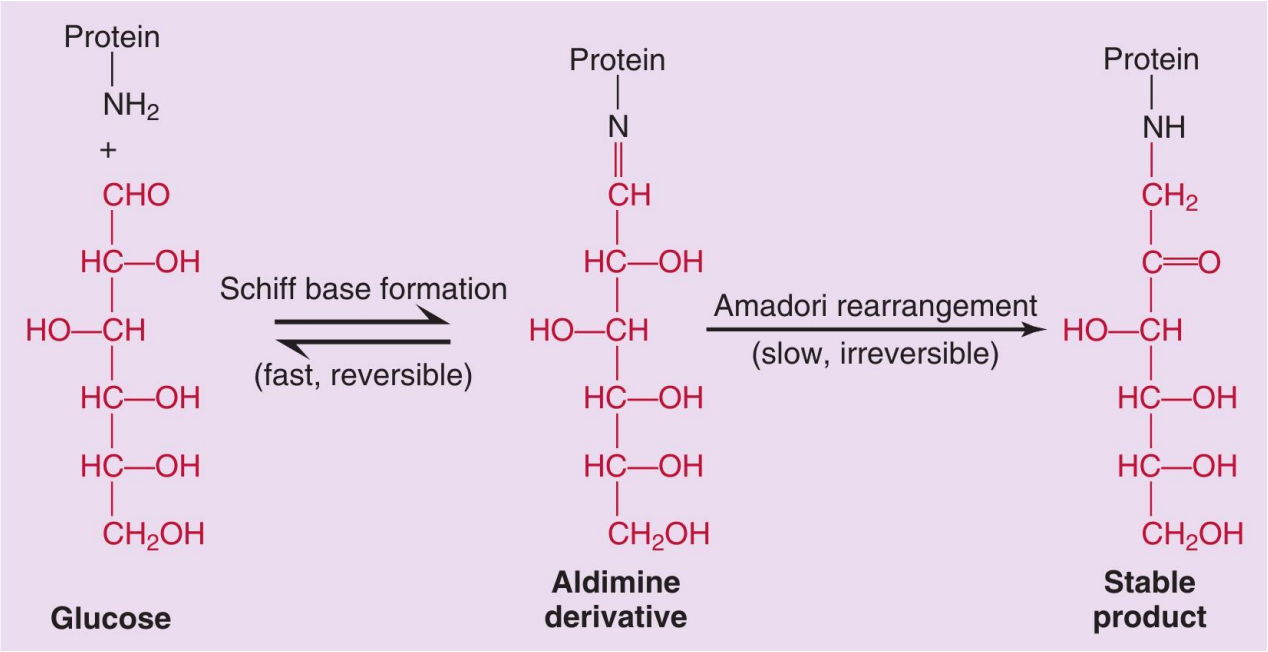
- **Urinalysis** is a quick screening test for diabetes mellitus.
  - *Whenever the blood glucose level exceeds 9 to 10 mmol/L (160–180 mg/dL), glucose appears in the urine.*
  - Also ketone bodies are excreted in diabetic urine and are measured routinely in addition to glucose.
- Blood tests provide quantitative results.
- A *fasting blood glucose level* greater than 7.8 mmol/L (140 mg/dL) on two different occasions frequently is used as a diagnostic cutoff.
  - Borderline cases can be evaluated with the **glucose tolerance test**.

GLUCOSE TOLERANCE TEST



- It involves repeated measurements of blood glucose both immediately before and at different intervals after ingestion of a glucose solution.
- Both the fasting blood glucose concentration and, to a far greater extent, the glucose tolerance test show wide variations among healthy individuals.
- Therefore the diagnostic cutoff between “normal” and “diabetic” is as arbitrary as that between “pass” and “fail” on a biochemistry examination.

GLYCOSYLATED HEMOGLOBIN, HBA_{1c}



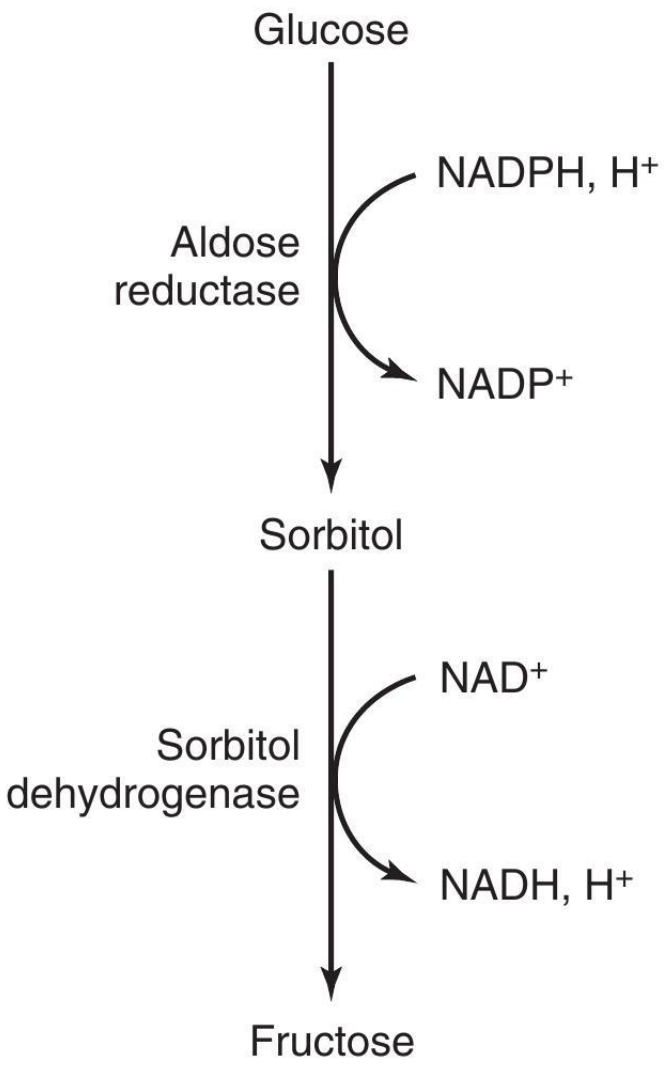
- **Hemoglobin A_{1c}** is formed by nonenzymatic glycosylation of the terminal amino groups in the α-chains and β-chains.
  - It is measured to assess long-term metabolic control of diabetes.
- *The concentration of glycosylated hemoglobin is proportional to the blood glucose level.*
  - It is 4% to 5.9% in normal individuals and greater than 6% in diabetic patients.
  - A target value of 7% is frequently cited for diabetes treatment, but is difficult to achieve without serious risks of hypoglycemia.
  - Because hemoglobin has a life span of 4 months, *hemoglobin A_{1C} provides information about the average severity of hyperglycemia during the weeks to months preceding the test.*

LATE COMPLICATIONS IN DIABETES (1/2)

- Many diabetic patients develop accelerated atherosclerosis, nephropathy, retinopathy, cataracts, and/or peripheral neuropathy many years after the onset of their disease.
  - Diabetes is an important cause of blindness, renal failure, and excess cardiovascular mortality.
- Two biochemical mechanisms have been proposed for diabetic complications:

1. *Nonenzymatic glycosylation of terminal amino groups* impairs the normal function or turnover of proteins.
   - This mechanism has been suggested for the thickening of basement membranes that is observed in the renal glomeruli of diabetic patients.

LATE COMPLICATIONS IN DIABETES (2/2)



- *Increased formation of sorbitol and fructose by the polyol pathway* is favored by hyperglycemia:
- The K_m of aldose reductase for glucose is near 200 mmol/L, which is 40 times higher than the normal blood glucose level. Therefore the reaction rate depends directly on the glucose concentration.
- Sorbitol and fructose not only are osmotically active but also interfere with the metabolism of inositol.
- Aldose reductase is abundant in Schwann cells of peripheral nerves, papillae of the kidney, and lens epithelium, sites that are affected by diabetes.

DAMAGE OF TISSUES BY HYPERGLYCEMIA

- In diabetic patients, the intracellular glucose concentration is not elevated in muscle and adipose tissue, whose glucose uptake is insulin dependent.
- However, **nerve sheaths**, **endothelial cells**, **kidneys**, and the **retina** have insulin-independent glucose uptake. These tissues are **most vulnerable to diabetes**.
- *Most of the late diabetic complications are related to vascular changes.*
  - thickening of subendothelial basement membranes,
  - increased capillary permeability, and accumulation of plasma proteins in interstitial spaces below the endothelium.
- Proteinuria caused by abnormalities of the glomerular basement membrane and macular edema in diabetic retinopathy are examples of the role of vascular changes.
- Therefore *cardiovascular risk factors such as hypertension and dyslipidemia should be treated aggressively in diabetic patients.*

MANY DRUGS ARE AVAILABLE FOR DIABETES TREATMENT

- Patients with **type 1 diabetes** can only be treated with insulin, administered by injection or infusion pump.
  - The main treatment challenges are adjustment of the insulin dose and patient education to ensure proper timing of insulin administration with meals.
- There is a greater variety of treatment options for **type 2 diabetes**.
  - **Lifestyle change** is the first treatment modality to be tried in early-stage, mildly affected patients.
  - **Weight reduction** by caloric restriction increases insulin sensitivity and lowers both glucose and insulin levels, especially in combination with regular physical exercise.
    - For nonobese patients, substantial weight reduction is not an option but regular exercise is recommended.

ORAL ANTIDIABETIC DRUGS ARE THE NEXT LINE OF TREATMENT (1/2)

- **Metformin** is a weak inhibitor of respiratory complex I in the mitochondria.
  - It causes a mild reduction in the cellular energy charge, not enough to cause functional impairment but enough to trigger adaptive changes.
  - *Its most important effect is inhibition of hepatic gluconeogenesis.*
  - Reduced energy charge inhibits pyruvate carboxylase and fructose 1,6-bisphosphatase directly, and the AMP-activated protein kinase suppresses the expression of gluconeogenic genes by phosphorylating several transcription factors.
  - Other effects of AMP kinase activation include reduced fatty acid synthesis in the liver and enhanced activity of GLUT4 transporters in muscle and adipose tissue.
- **Sulfonylureas** are insulin releasers.
  - They bind to a component of the K_{ATP} channel in pancreatic β-cells, favoring its closure and thereby causing membrane depolarization, calcium entry, and insulin release.
  - Unlike metformin, the sulfonylureas lead to weight gain as a result of increased insulin levels.

ORAL ANTIDIABETIC DRUGS ARE THE NEXT LINE OF TREATMENT (2/2)

- **Thiazolidinediones (glitazones)** sensitize cells to insulin by activating the transcription factor **PPAR-γ (peroxisome proliferator activated receptor-γ).**
  - They may increase the risk of acute myocardial infarction, possibly by stimulating the uptake of oxidized lipoproteins by macrophages.
- **DPP-4 inhibitors (gliptins)** inhibit **dipeptidyl peptidase-4.**
  - This enzyme inactivates the two incretins GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory polypeptide).
  - The effects are increased insulin secretion and reduced appetite.
- **GLP-1 agonists** activate the GLP-1 receptor.
  - Like the DPP-4 inhibitors, they tend to reduce food intake and body weight in addition to raising insulin.
- **SGLT2 inhibitors** block sodium-glucose transporter-2 (SGLT2), the sodium-dependent glucose carrier that reabsorbs most of the glucose from the proximal renal tubules.
  - Rather than improving the body's capacity to metabolize glucose, these drugs remove excess glucose by increasing its renal excretion.

DIABETES TYPE 2 TREATMENT WITH INSULIN

- Type 2 diabetics whose condition cannot be controlled adequately with orally active drugs require insulin, administered by injection or infusion pump.

GLYCOGEN STORAGE DISEASES (GLYCOGENOSES)

- **Glycogen accumulates in several enzyme deficiencies**
- **Glycogen storage diseases** are rare (overall incidence 1 in 40,000), recessively inherited diseases in which the deficiency of a **glycogen**-degrading enzyme causes abnormal accumulation of **glycogen**.
  - Because different isoenzymes are present in different tissues, most deficiencies are limited to one or a few organ systems.
  - The most useful distinction is among *hepatic, myopathic,* and *generalized* types

GLYCOGEN STORAGE DISEASES

Type	Enzyme Deficiency	Organ(s) Affected	Clinical Course
I (von Gierke disease)	Glucose-6-phosphatase	Liver, kidney	Severe hepatomegaly, severe hypoglycemia, lactic acidosis, ketosis, hyperuricemia
II (Pompe disease)	α-1,4-Glucosidase ("acid maltase")	All organs	Death from cardiac failure in infants
III (Cori disease)	Debranching enzyme	Muscle, liver	Like type I but much milder
IV (Andersen disease)	Branching enzyme	Liver, myocardium	Death from liver cirrhosis usually before age 2 years
V (McArdle disease)	Phosphorylase	Muscle	Muscle cramps and pain on exertion, easy fatigability, normal life expectancy
VI (Hers disease)	Phosphorylase	Liver	Like type I but milder, with less severe hypoglycemia
VII (Tarui disease)	Phosphofructokinase	Muscle, red blood cells	Like type V
VIII	Phosphorylase kinase*	Liver	Mild hepatomegaly and hypoglycemia

* There is also an X-linked form of phosphorylase kinase deficiency that affects muscle and several autosomal recessive forms that affect liver, muscle plus liver, or muscle plus heart. The enzyme contains four different subunits, one of which is encoded by a gene on the X chromosome.

- Hepatic **glycogen storage** diseases present with fasting hypoglycemia.
  - This is expected because the primary function of liver glycogen is maintenance of an adequate blood glucose level during fasting.
- The myopathic forms present with muscle weakness and muscle cramps during exertion but no symptoms during rest.
  - This is expected because during vigorous exercise, glycogen is a major fuel for both oxidative metabolism and lactate formation.

VON GIERKE DISEASE

- Of all glycogen storage diseases, deficiency of glucose-6-phosphatase (von Gierke disease) leads to the most severe fasting hypoglycemia, starting 2 to 4 hours after the last meal.
  - This is because glucose-6-phosphatase is required for the formation of glucose by glycogen breakdown as well as gluconeogenesis.
- Patients present with life-threatening hypoglycemia and acidosis within months after birth.
  - The acidosis is caused by the overproduction of both lactic acid and the “ketone bodies” (acetoacetic acid and β-hydroxybutyric acid).
  - Lactic acidosis develops because the liver is unable to convert lactic acid into glucose, and ketoacidosis develops because the severe hypoglycemia reduces insulin secretion while stimulating sympathetic nervous activity.
  - This combination causes excessive fat breakdown in adipose tissue and conversion of the fatty acids to ketone bodies in the liver.
  - The liver is massively enlarged with accumulating glycogen and fat.
- Patients can be kept alive only by regular carbohydrate feeding day and night.
- von Gierke disease shows that *without synthesis of glucose by the liver, we would die of hypoglycemia within hours after the last meal.*

MCARDLE DISEASE

- Deficiency of glycogen phosphorylase in skeletal muscle, known as McArdle disease, leads to muscle weakness and painful cramps on exertion.
  - Patients are otherwise in good health although some experience acute episodes of myoglobinuria, and some develop persistent muscle weakness and muscle wasting as they grow older.
  - This disease shows that *muscle glycogen is not essential for life but is necessary for normal performance during physical exercise.*
- Patients with McArdle disease do not show the expected rise in the blood level of lactic acid after muscular activity.
- This demonstrates that *the most important source of lactic acid during muscular activity is not glucose from the blood but stored muscle glycogen.*

POMPE DISEASE

- Although most glycogen is degraded by glycogenphosphorylase, a small amount is captured by autophagy and degraded by a lysosomal α-glucosidase **(“acid maltase”).**
  - Like most lysosomal enzymes, acid maltase does not have tissue-specific isoenzymes.
  - Therefore its deficiency leads to glycogen accumulation in virtually all tissues.
- In classic cases, diagnosed as **Pompe disease,** the enzyme is virtually absent.
  - Affected infants develop respiratory insufficiency and die of cardiac failure by the age of 2 years.
  - Milder forms with significant residual activity of acid maltase present with proximal muscle weakness that can start at any age and, if fatal, progresses to death by respiratory failure.

MUCOPOLYSACCHARIDOSIS

- **Mucopolysaccharidoses are caused by deficiency of glycosaminoglycan-degrading enzymes**
  - The deficiency of lysosomal enzymes can interrupt GAG degradation => *undegraded GAGs accumulate in the lysosomes.*
  - Partially degraded polysaccharide appears in blood and urine => as diagnostic tests.
- So **mucopolysaccharidosis** is one type of **lysosomal storage disease.**
  - “Mucopolysaccharide” is an obsolete name for GAG, but “glycosaminoglycanosis” does not seem to sound right.
- **The mucopolysaccharidoses are rare diseases: incidence 1 in 10,000 - 1 in 20,000**

SOME FEATURES OF MUCOPOLYSACCHARIDOSES:

1. **The enzyme deficiency is generalized, affecting all organ systems.**
   - lysosomal enzymes do not have tissue-specific isoenzymes.
2. **Inheritance is autosomal recessive or X-linked recessive.**
   - Heterozygotes are healthy, and can be identified by enzyme activity in cultured leukocytes, fibroblasts, or amniotic cells.
3. **Many mucopolysaccharidoses exist in both severe and mild forms.**
   - Total absence of the enzyme activity => **severe disease**; greatly reduced enzyme activity => **milder disease**. The difference between types IH and IS in is an example.
4. **Most mucopolysaccharidoses are not apparent at birth.**
   - Signs and symptoms develop gradually as more and more mucopolysaccharide accumulates.
5. **Defects in the degradation of keratan sulfate and dermatan sulfate cause skeletal deformities and other connective tissue abnormalities.**
   - Typical abnormalities include **coarse facial features (*"gargoylism"*)**, short stature, corneal clouding, hearing loss, stiff joints, valvular heart disease, obstructive lung disease, and hepatosplenomegaly.
6. **Defects in the degradation of heparan sulfate cause mental retardation and neurological degeneration.**
   - Heparan sulfate is the only important GAG in the central nervous system.
7. **Chondroitin sulfate and hyaluronic acid DO NOT ACCUMULATE.**
   - They can be degraded by a lysosomal endoglycosidase when one of the exoglycosidases is missing.

MUCOPOLYSACCHARIDOSES: TYPES

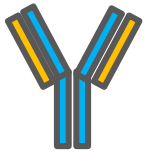
Systematic Name	Common Name	Inheritance	Enzyme Deficiency	GAG(s) Affected	Clinical Features
IH	Hurler	AR	α-L-iduronidase (complete deficiency)	Dermatan sulfate, heparan sulfate	Skeletal deformities, dwarfism, corneal clouding, hepatosplenomegaly, valvular heart disease, mental retardation, death at ≤10 years
IS	Scheie	AR	α-L-iduronidase (partial deficiency)	Dermatan sulfate, heparan sulfate	Corneal clouding, stiff joints, normal intelligence and life span
II	Hunter	XR	Iduronate sulfatase	Dermatan sulfate, heparan sulfate	Similar to Hurler but no corneal clouding; death at 10–15 years
IIIA	Sanfilippo A	AR	Heparan-*N*-sulfatase	Heparan sulfate	Severe to profound mental retardation, mild physical abnormalities
IIIB	Sanfilippo B	AR	α-*N*-acetyl-glucosaminidase		
IIIC	Sanfilippo C	AR	Acetyl-CoA: α-glucosaminide acetyltransferase		
IIID	Sanfilippo D	AR	*N*-acetylglucosamine 6-sulfatase		
IVA	Morquio A	AR	Galactose 6-sulfatase	Keratan sulfate	Corneal clouding, normal intelligence
IVB	Morquio B	AR	β-Galactosidase		
VI	Maroteaux-Lamy	AR	*N*-acetylgalactosamine 4-sulfatase	Dermatan sulfate	Severe skeletal deformities, corneal clouding, normal intelligence
VII	Sly	AR	β-Glucuronidase	Dermatan sulfate, heparan sulfate	Skeletal deformities, hepatosplenomegaly

AR, Autosomal recessive; *CoA*, coenzyme A; *GAG*, glycosaminoglycan; *XR*, X-linked recessive.

ENZYME REPLACEMENT THERAPY FOR LYSOSOMAL STORAGE DISEASES

- Replacement of the missing enzyme is the most direct way of treating lysosomal storage diseases.
  - The enzyme is injected into the bloodstream, endocytosed and targeted to the lysosomes, especially if it contains a **mannose-6-phosphate tag** that directs the enzyme to the lysosomes.
  - **Hurler-Scheie syndrome**, **Hunter syndrome**, and **Maroteaux-Lamy** syndrome all have been treated successfully with enzyme replacement therapy.
- **Limitations:**

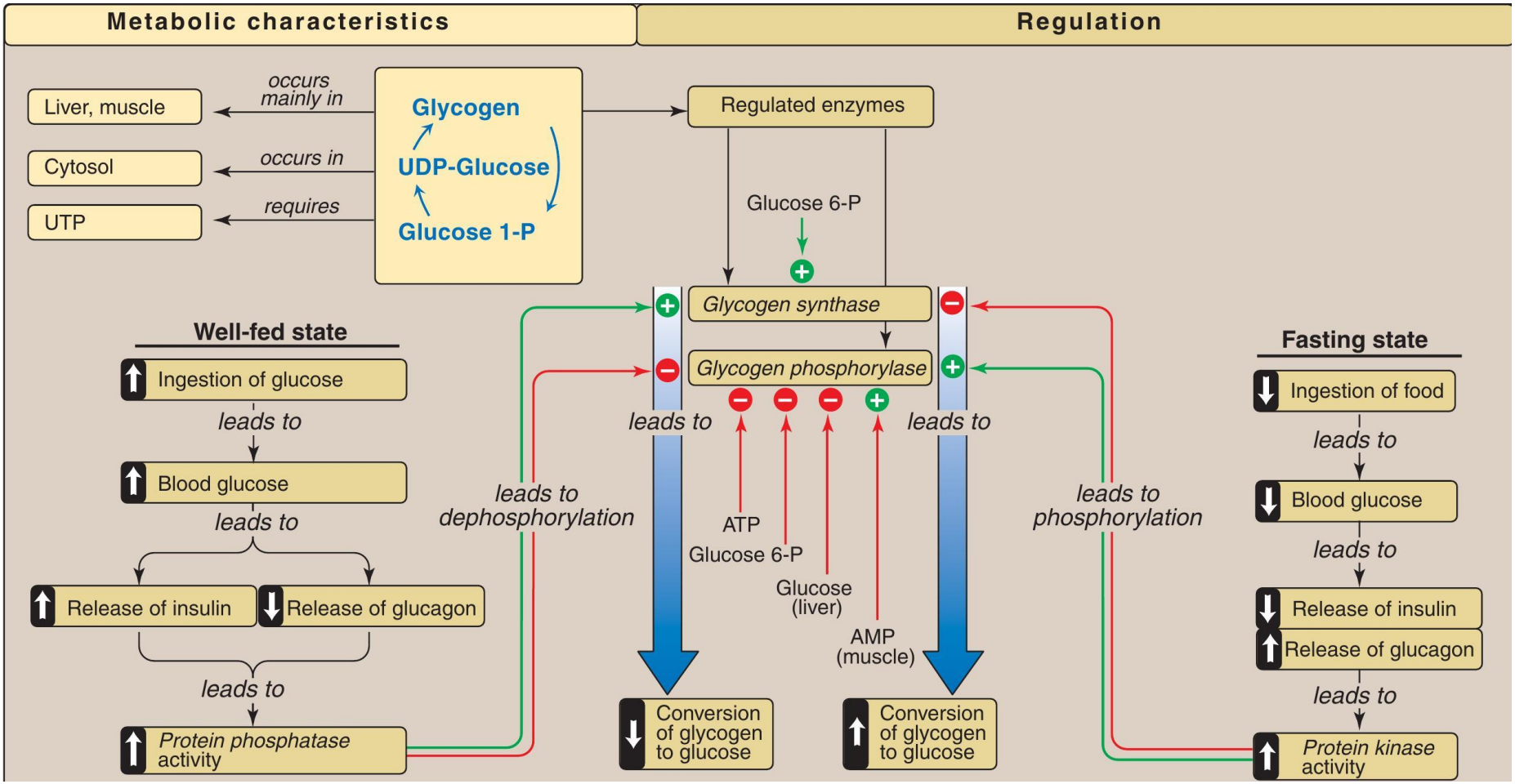
1. **Inability** of the enzymes **to enter the brain** after injection into the blood.

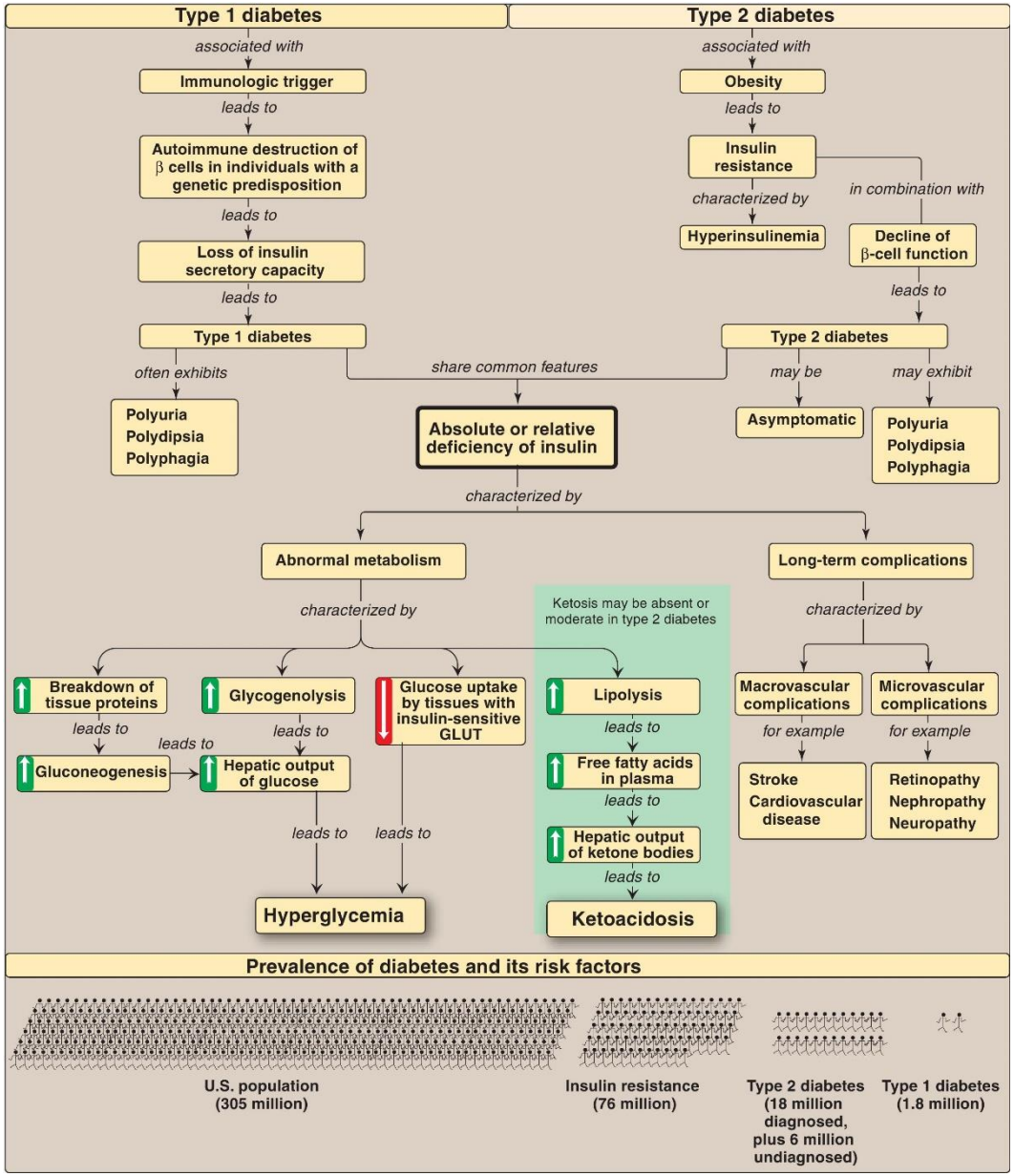


2. **Formation of immunoglobulin G (IgG) antibodies** to the enzyme.
   - Antibody formation is common in patients who lack immunoreactive enzyme but is less common in patients who possess an immunoreactive enzyme whose activity has been knocked out by a missense mutation.

3. **High cost of the enzymes**, which have to be injected in quantities of at least 1 g/day.

CONCLUSION GLYCOGEN





CONCLUCION DIABETES