Chapitre 6
Métabolisme 1

Métabolisme 1: finalité et utilité

- Gestion des besoins énergétiques
- Transformation Matière – Energie - Information
- Equilibre Stockage - Consommation
- Régulation selon besoins: repos ⇄ effort ; carence ⇄ pléthore
- Régulation de la température corporelle

Métabolisme 1: structure générale

- Gestion intracellulaire énergie biochimique: Transformation énergétique
  Stockage *Utilisation*
- Transport évolué de matière, d'énergie et d'information
- Interaction milieu externe (environnement) ↔ milieu interne (organisme)
- Ajustement aux conditions évolutives Espace (quantité) – Temps (durée)
- Régulation et limites: Boucle ouverte/fermée

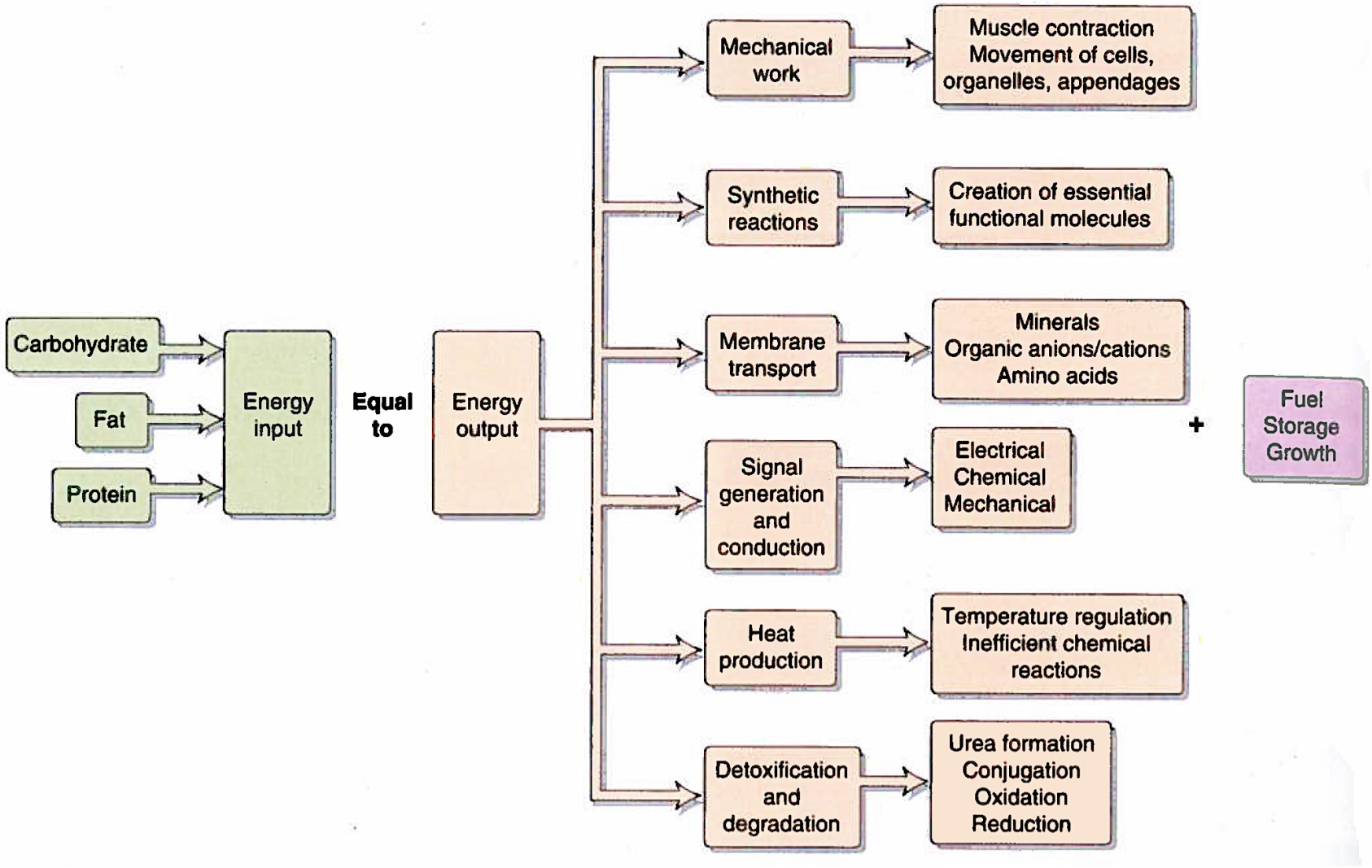
Métabolisme 1: principes généraux

- Organisation système régulation du métabolisme
- Grandeurs physiques: Glycémie, température
- Capteurs: cellules sensorielles spécifiques
- Intégrateur: Système central – périphérique – cellulaire
- Effecteurs: Unités de productions ⇄ Stockage Tissus – cellules

Métabolisme 1: problèmes principaux

- Problématique:
  - Besoin énergétique basal
  - Homéostasie
  - Ajustements selon besoins externes Efforts – repos ; diète – prise alimentaire

Métabolisme 1 Bilan énergétique général



Métabolisme 1 Comparaison des sources d'énergie glucose-lipides

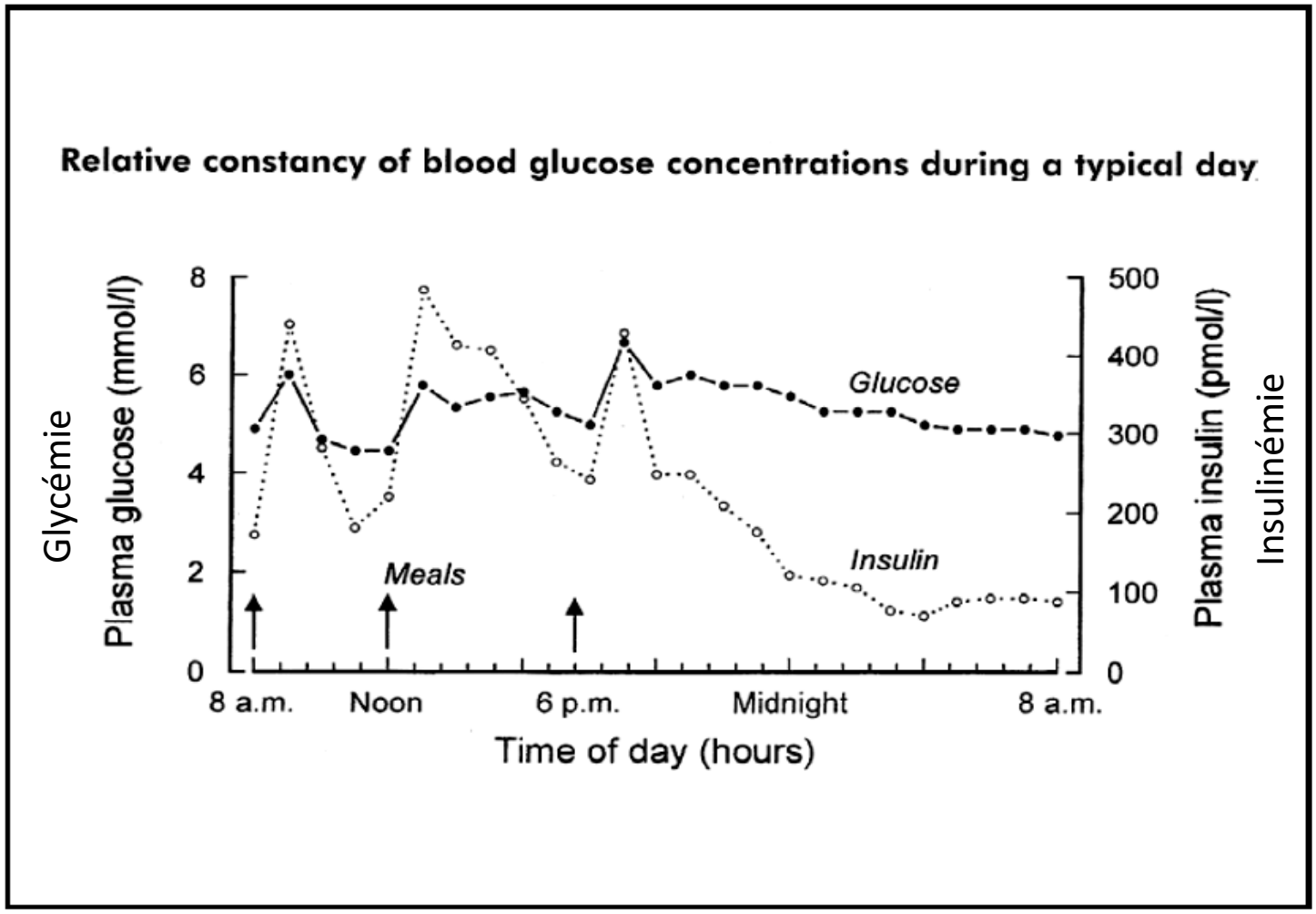
Box 6.1 Glucose and lipids as energy sources

Glucose and lipid fuels in the plasma are compared in terms of their potential yield of energy in the postabsorptive state. First, we will use typical concentrations in the plasma (given in the text) and look at the potential yield of energy per litre of plasma.

Substrate	Typical concentration (mmol/l)	Energy yield on complete oxidation (kJ per g)	Relative molecular mass	'Energy concentration' in plasma (kJ per litre)
Glucose	5	17	180	14
NEFA	0.5	38	280	5
TAG	1	40	850	34

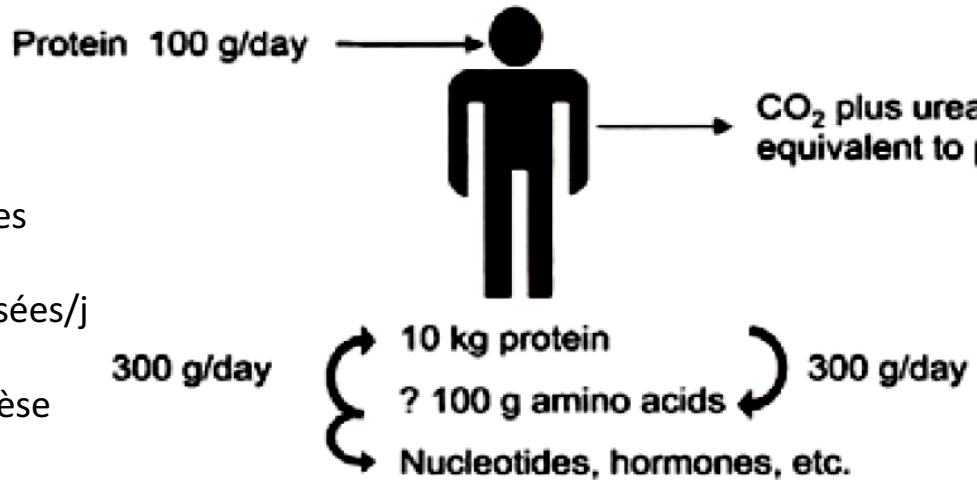
NEFA= non-esterified fatty acids, TAG=triacylglycerides

Métabolisme 1 Homéostasie de la glycémie au cours du temps



Métabolisme 1 Bilan des besoins en protéines et acides aminés

Overview of protein and amino acid turnover in the body



100 g prot. exogènes
+
200 g prot. endogènes
=
300 g prot. métabolisées/j

Protéolyse ↔ Synthèse

Dégradation a.a.

Gluconéogenèse: A.a sauf leucine et lysine

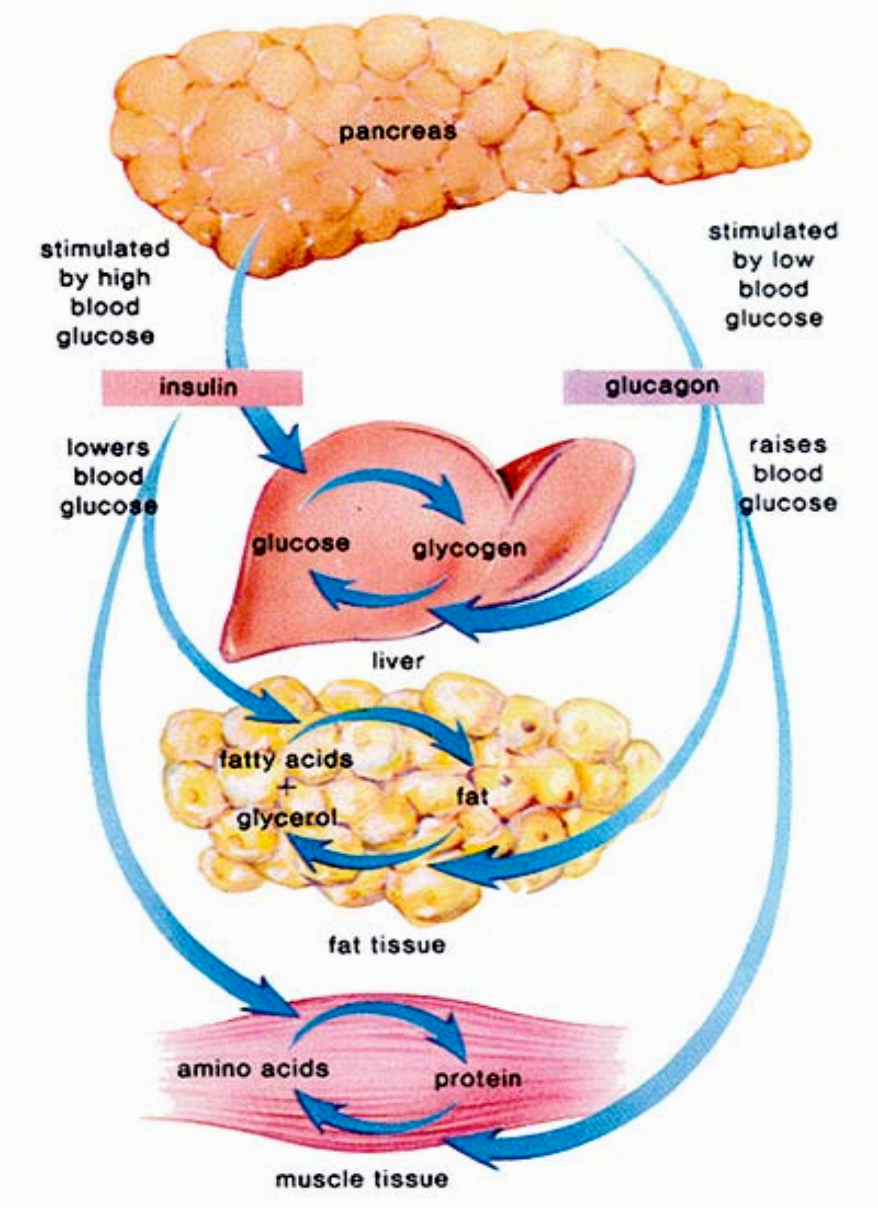
Cétogenèse: A.a isoleucine, leucine, lysine, phénylalanine, tryptophane, tyrosine

Uréogenèse: tous les a.a

We eat (very approximately) 100 g protein per day and therefore (unless we are growing) must dispose of an equal amount, mainly by oxidation of amino acids with generation of CO_2, H_2O, urea and some NH_3. Of the (approximately) 10 kg of protein in the body, there is continuous synthesis and breakdown of (about) 300 g/day (i.e. a 3% 'turnover'), although this varies greatly from tissue to tissue (Table 6.1). Some of the amino acid pool is used for synthesis of purines, pyrimidines and hormones. This may also be put in terms of nitrogen balance. Each 6.25 g protein contains about 1 g nitrogen. Therefore (in round figures) we take in about 16 g N per day. Each day, around 2 g is lost in faeces, 0.5 g in shed skin cells, etc., and the remainder of the 16 g as urea and NH_3 in urine. Reproduced from Frayn (in press).

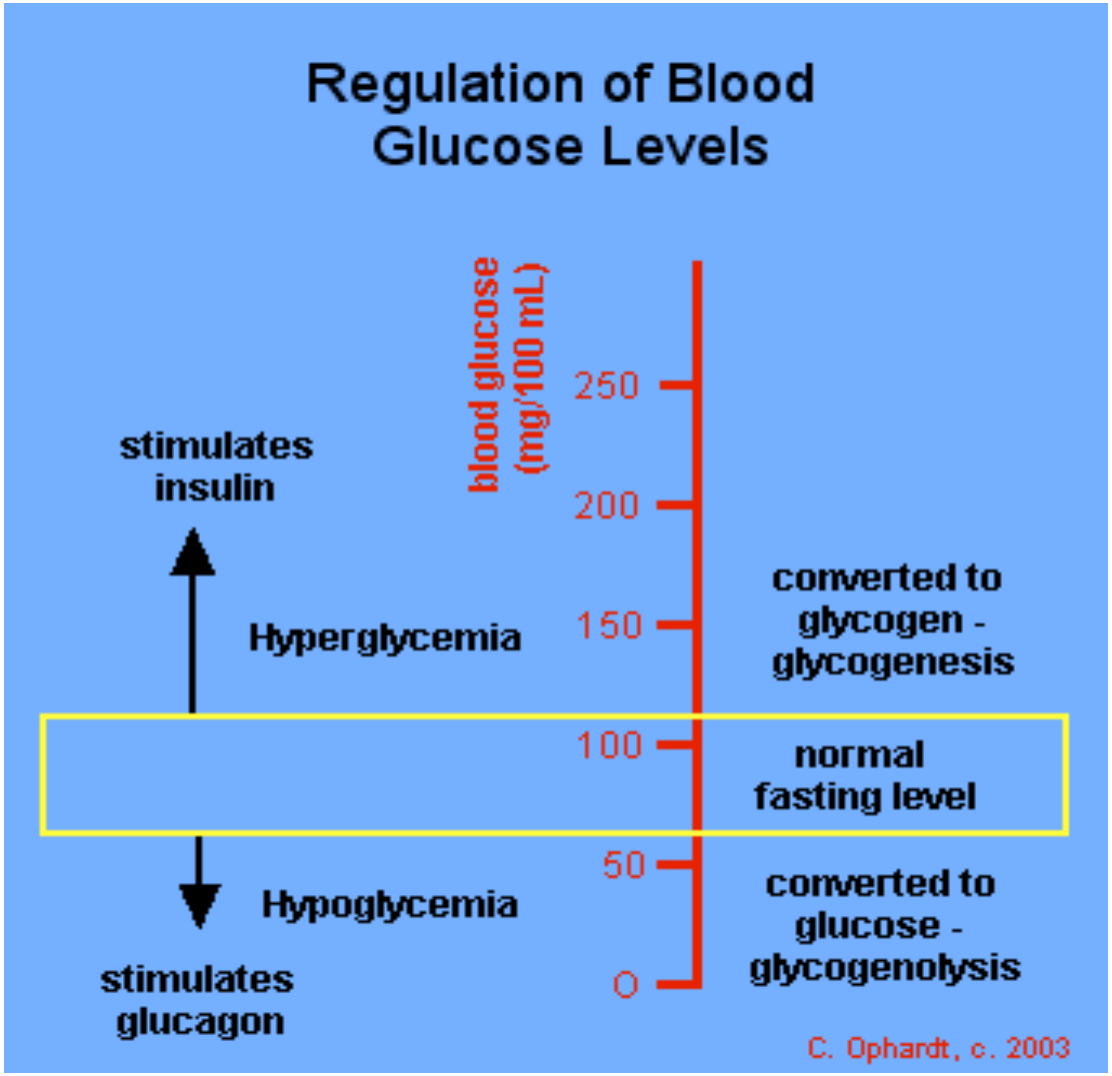
Métabolisme 1 Rôle du pancréas dans l'homéostasie de la glycémie

↑ glycolyse
↑ glycogenèse
↑ lipogenèse
↑ protéogenèse
↓ glycogénolyse
↓ cétogenèse
↓ protéolyse

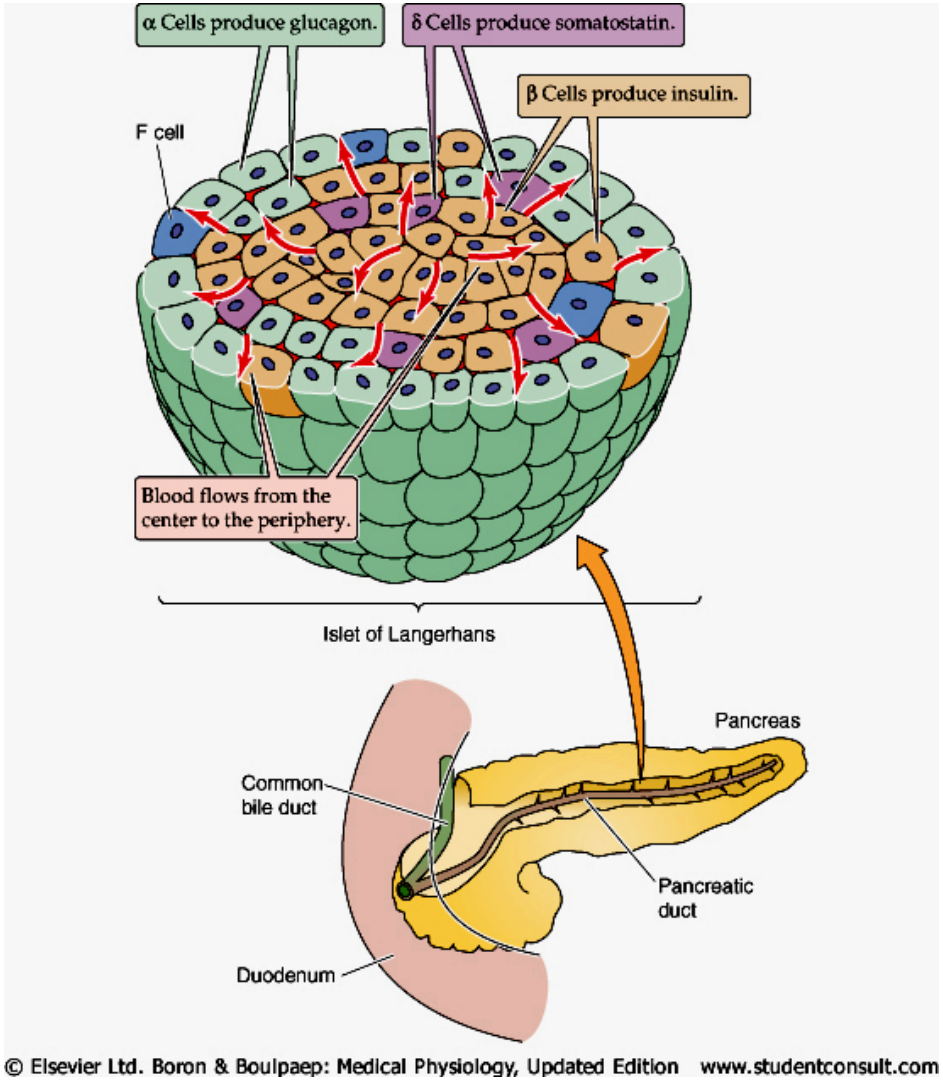


↑ gluconéogenèse
↑ glycogénolyse
↓ glycogenèse
↑ cétogenèse
↑ protéolyse

Métabolisme 1 Homéostasie de la glycémie: Insuline (-) Glugacon (+)



Métabolisme 1 Pancréas Ilots de Langerhans: cellules α cellules β cellules δ



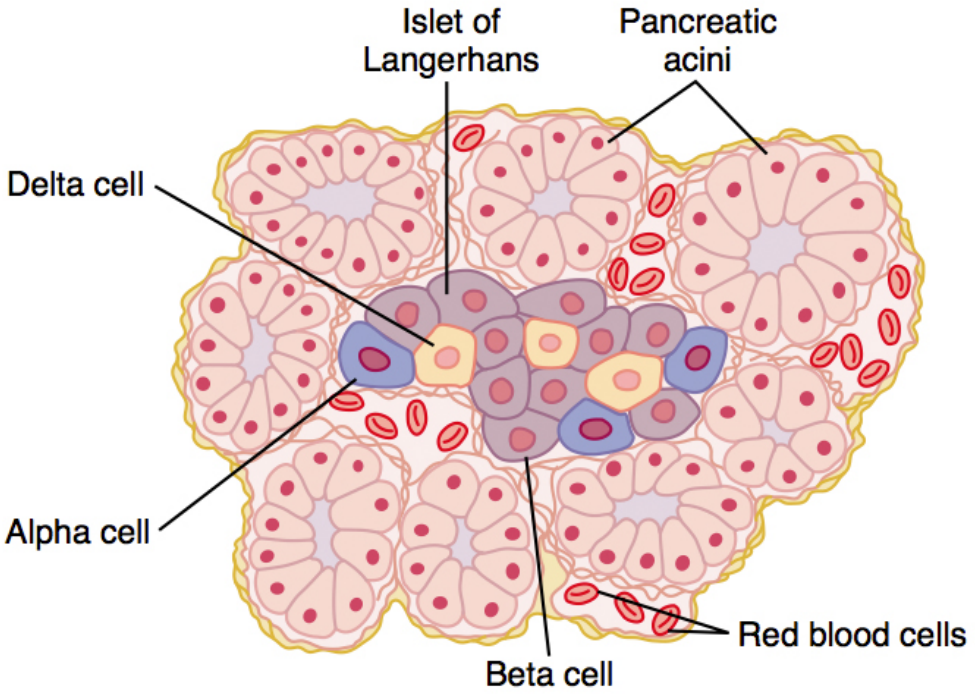


Figure 78–1

Physiologic anatomy of an islet of Langerhans in the pancreas.

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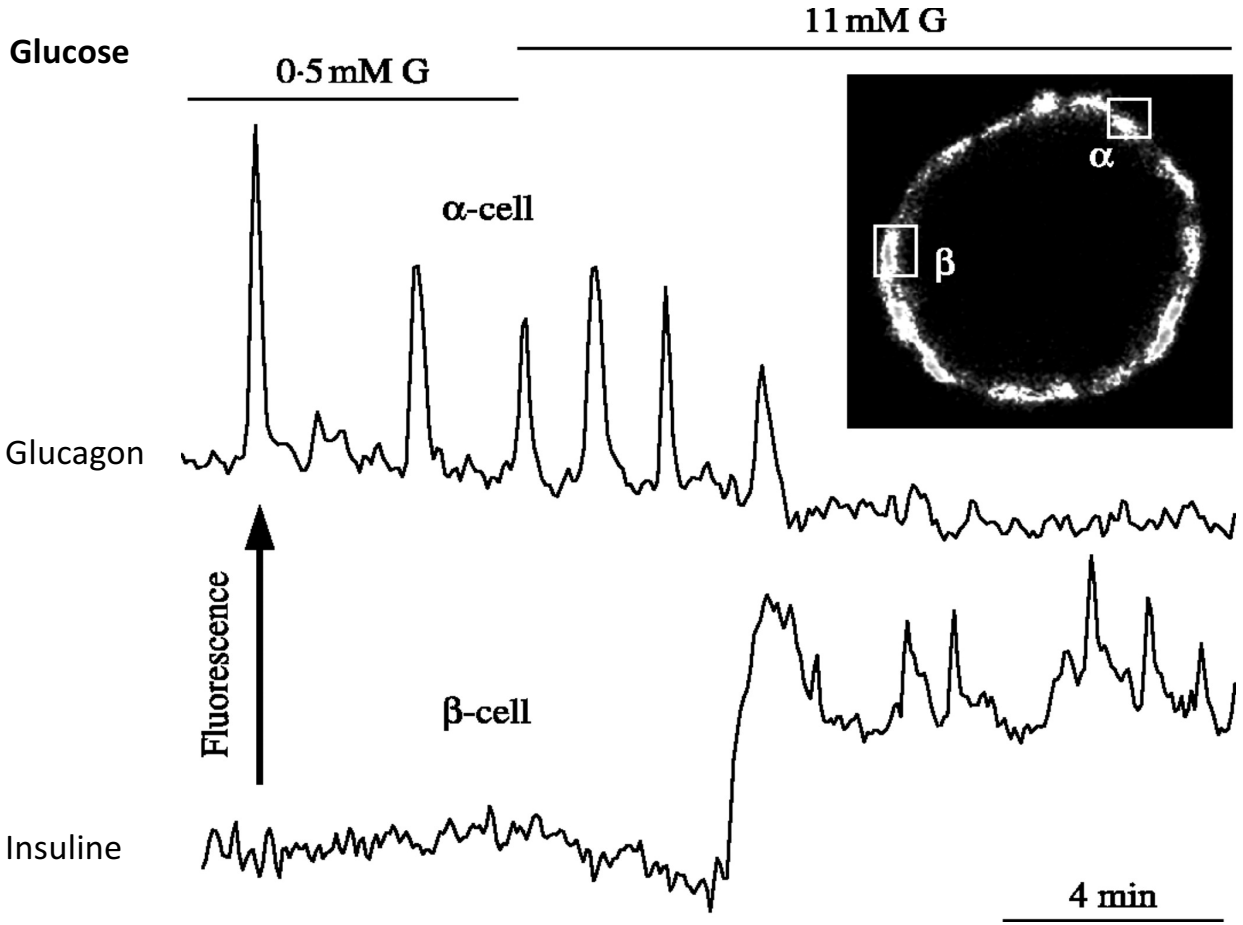
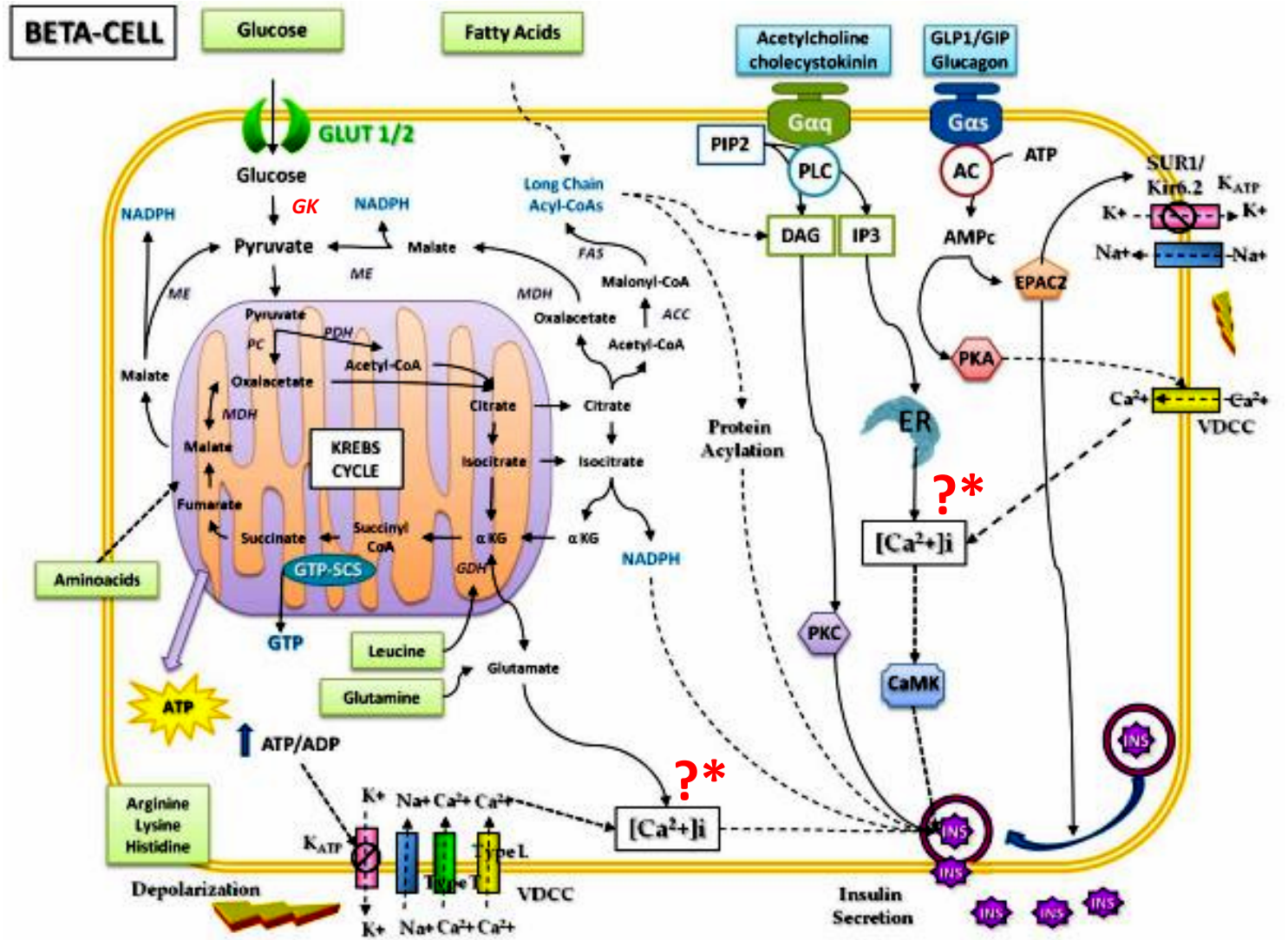
Métabolisme 1 Homéostasie de la glycémie: Activité cellules α cellules β



Quesada I et al. J Endocrinol 2008;199:5-19

Métabolisme 1 Rôles des cellules β dans la sécrétion d'insuline



Vision, smell

Acetylcholine

Glucose in the Small Intestine

GLP-1 Glucagon-like Peptide 1

Glucose-sensors in the portal vein

Acetylcholine

Glucose increase in the blood

Activation of β-cell metabolism

Depolarization of membrane potential

$Ca2^{+}$ increases in cytosol

Exocytose

Insuline release

*** Ca^{2+} is necessary but not sufficient for insulin secretion**

Métabolisme 1 Interaction récepteurs cellulaires-insuline
Rôle de la tyrosine kinase et activité enzymatique

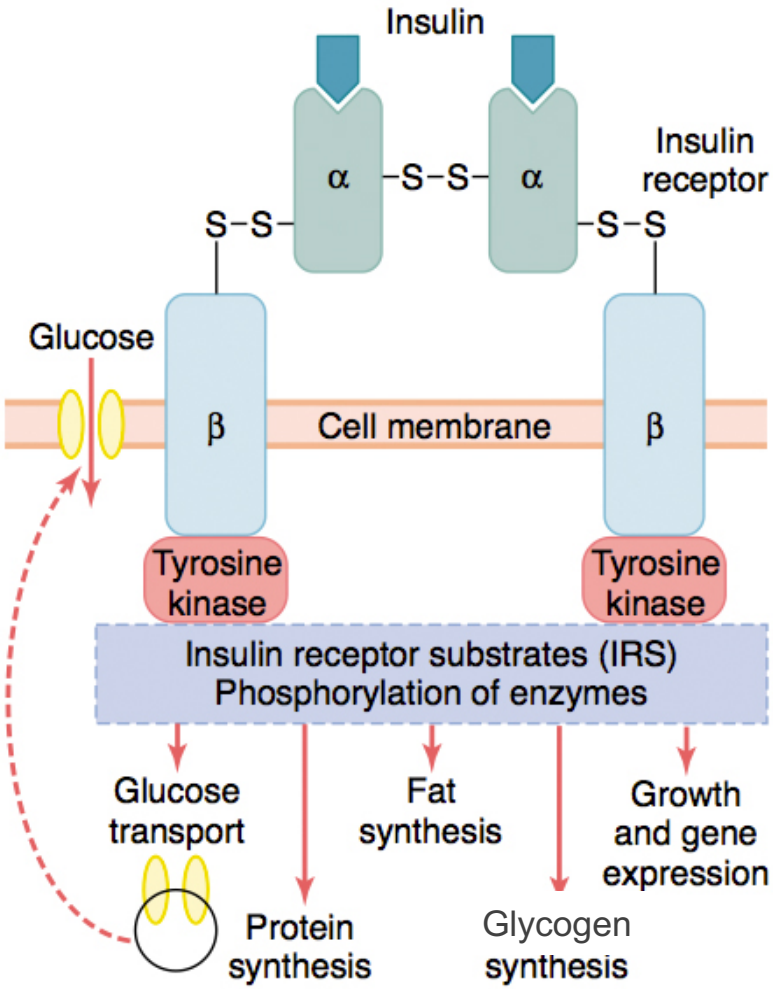
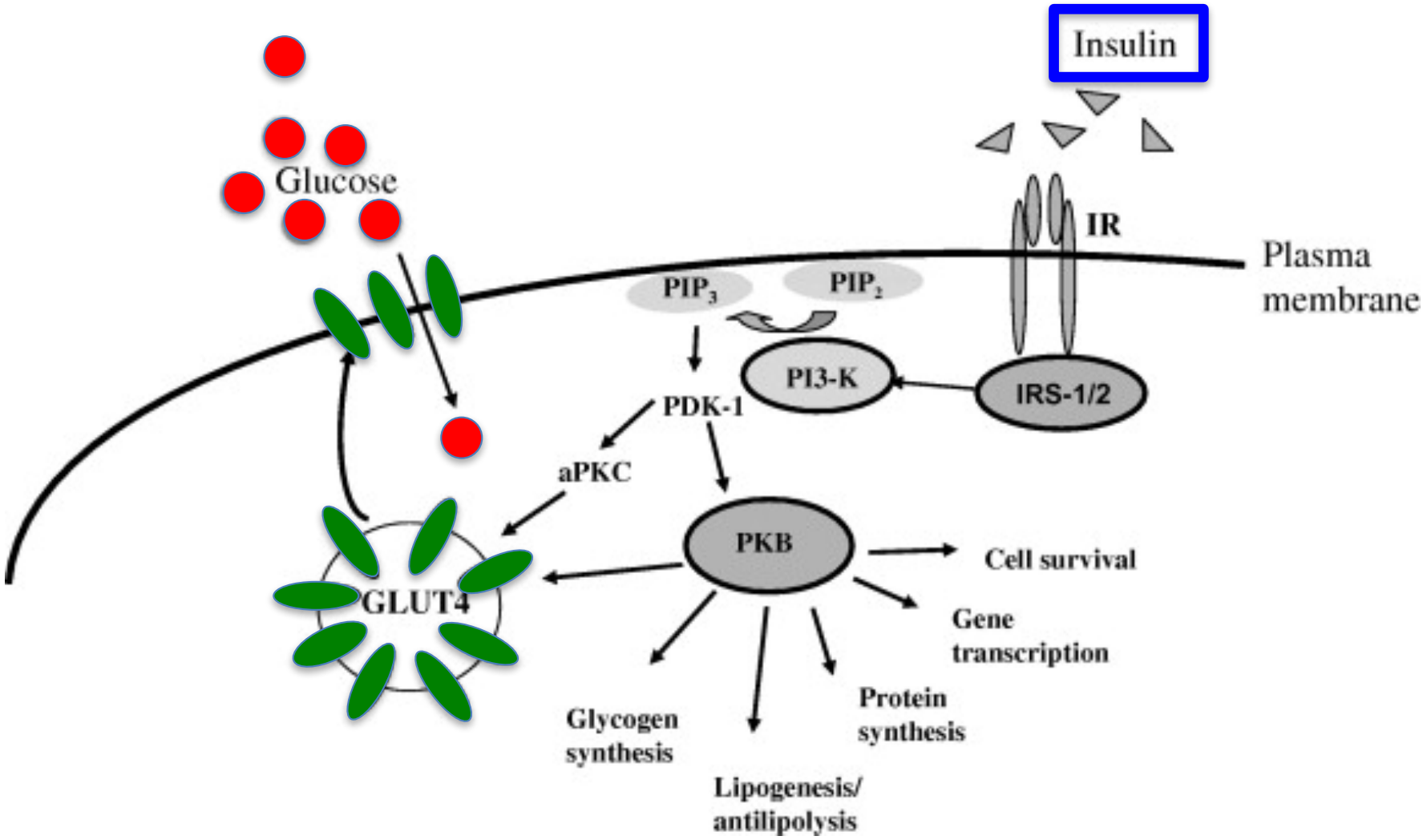


Figure 78–3

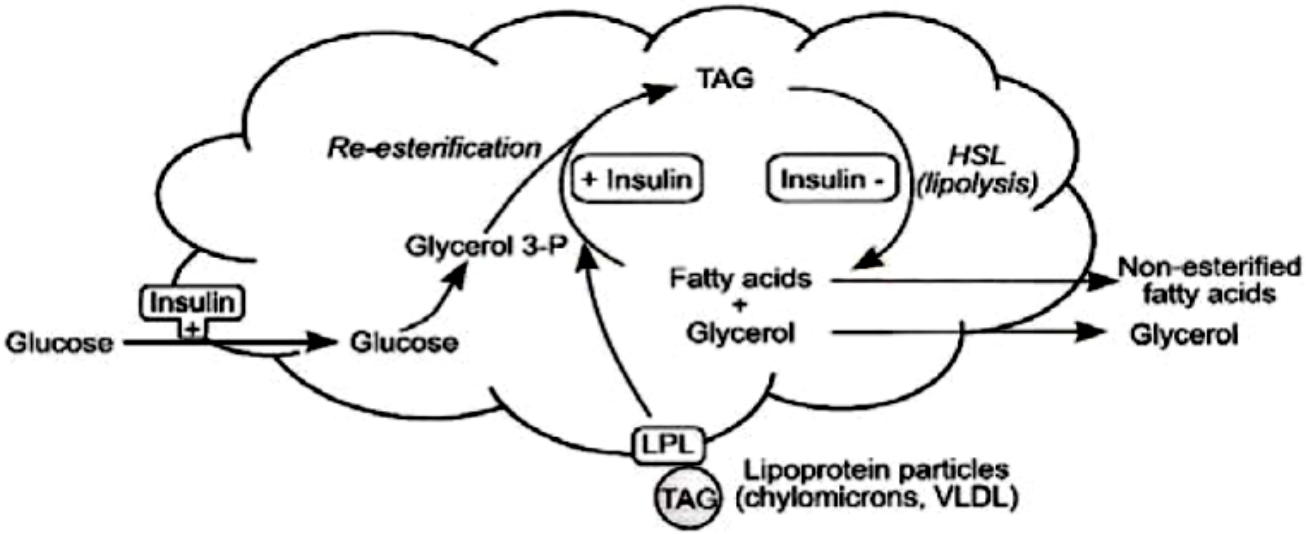
Schematic of the insulin receptor. Insulin binds to the α-subunit of its receptor, which causes autophosphorylation of the β-subunit receptor, which in turn induces tyrosine kinase activity. The receptor tyrosine kinase activity begins a cascade of cell phosphorylation that increases or decreases the activity of enzymes, including insulin receptor substrates, that mediate the effects of glucose on glucose, fat, and protein metabolism. For example, glucose transporters are moved to the cell membrane to facilitate glucose entry into the cell.

Métabolisme 1 Translocation du GLUT4 favorisé par l'insuline



Métabolisme 1 Mobilisation des graisses supprimée par l'insuline
Stockage des graisses favorisé par l'insuline

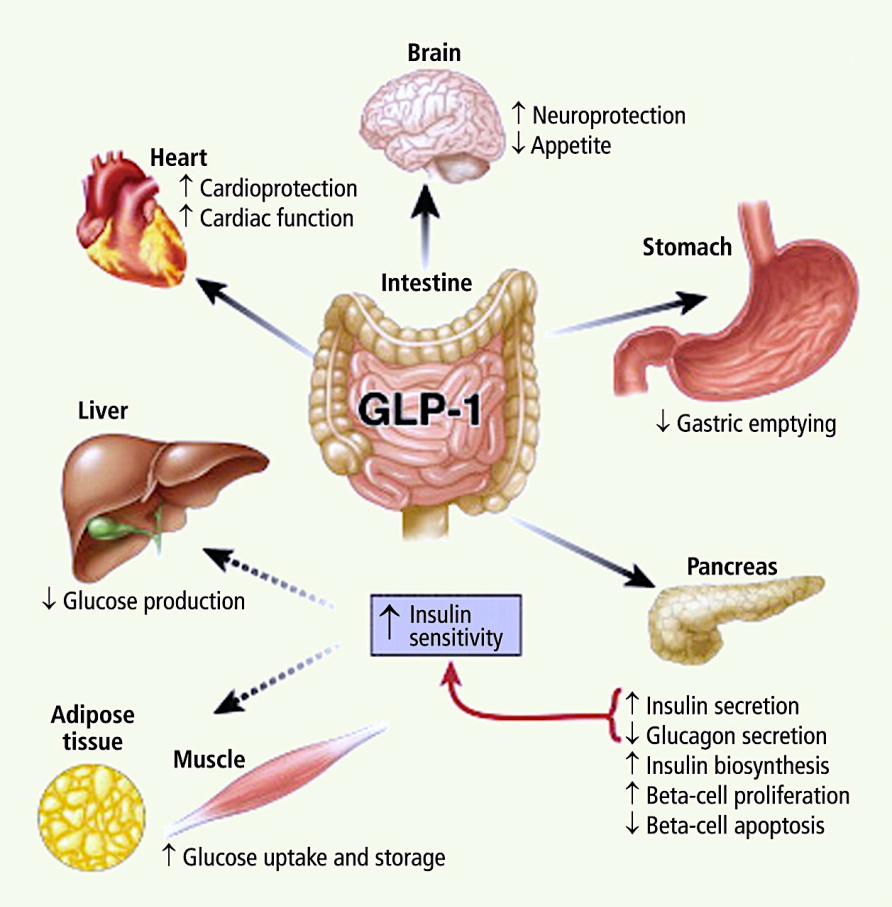
Suppression of fat mobilisation by insulin.

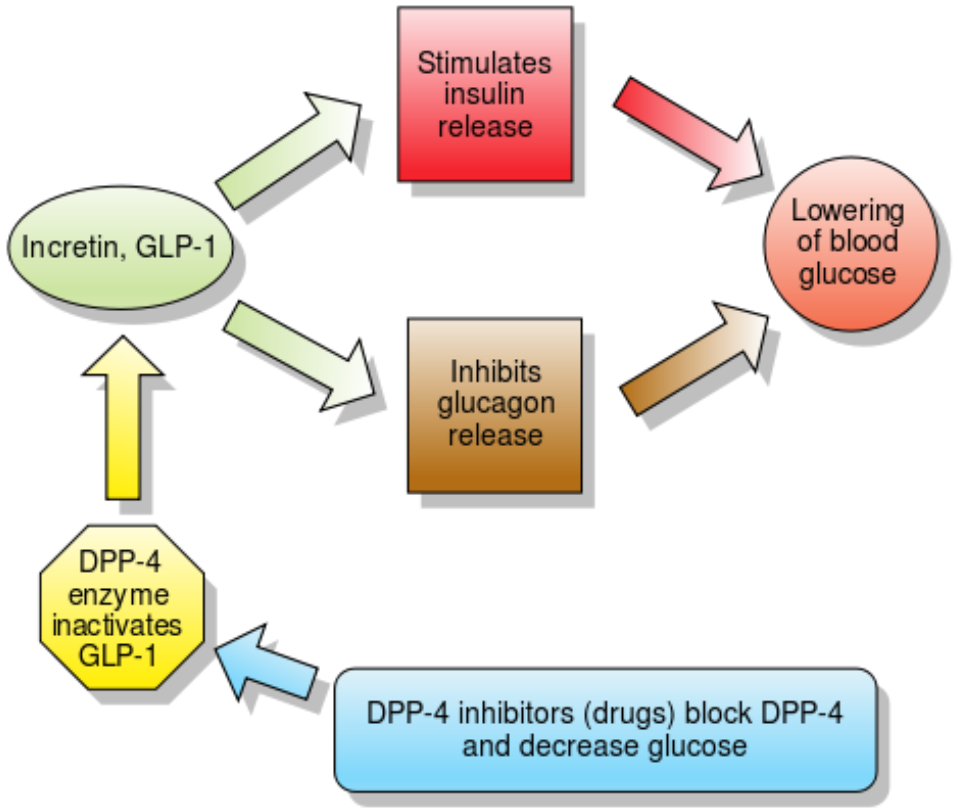


Favorise le stockage des graisses dans les adipocytes

Suppression of fat mobilisation by insulin. Insulin restrains fat mobilisation by two mechanisms: suppression of the activity of hormone-sensitive lipase (HSL), and stimulation of the re-esterification of fatty acids within the adipocytes. (The same process of esterification will also be simultaneously incorporating fatty acids from circulating triacylglycerol, released by lipoprotein lipase (LPL), into stored triacylglycerol.)

Métabolisme 1 Rôle du Glucagon-like Peptide-1 dans le contrôle de la glycémie



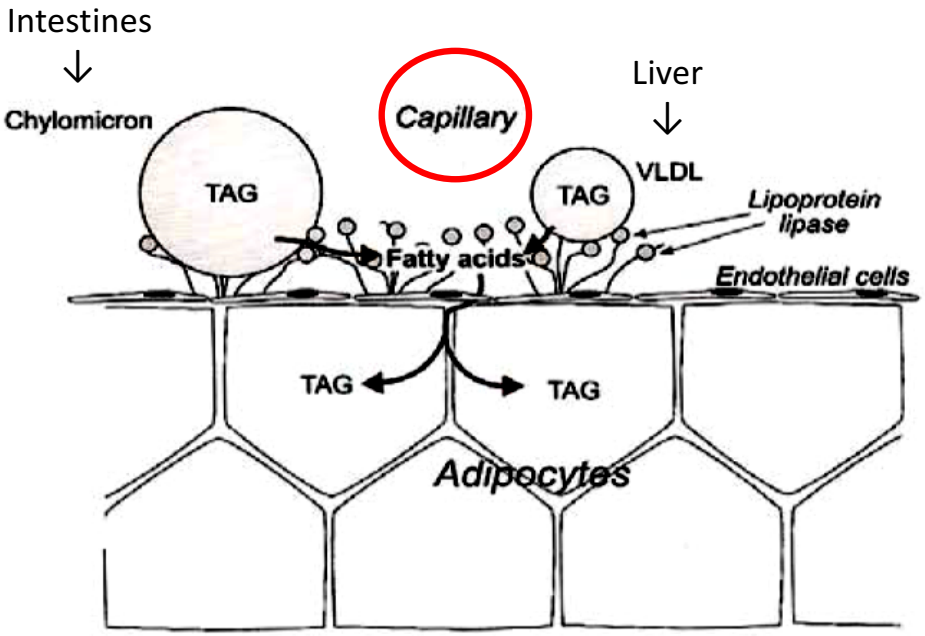


DPP-4: Dipeptidylpeptidase-4

Métabolisme 1 Rôle de la lipoprotéines-lipase dans le tissu adipeux blanc

The action of lipoprotein lipase in white adipose tissue.

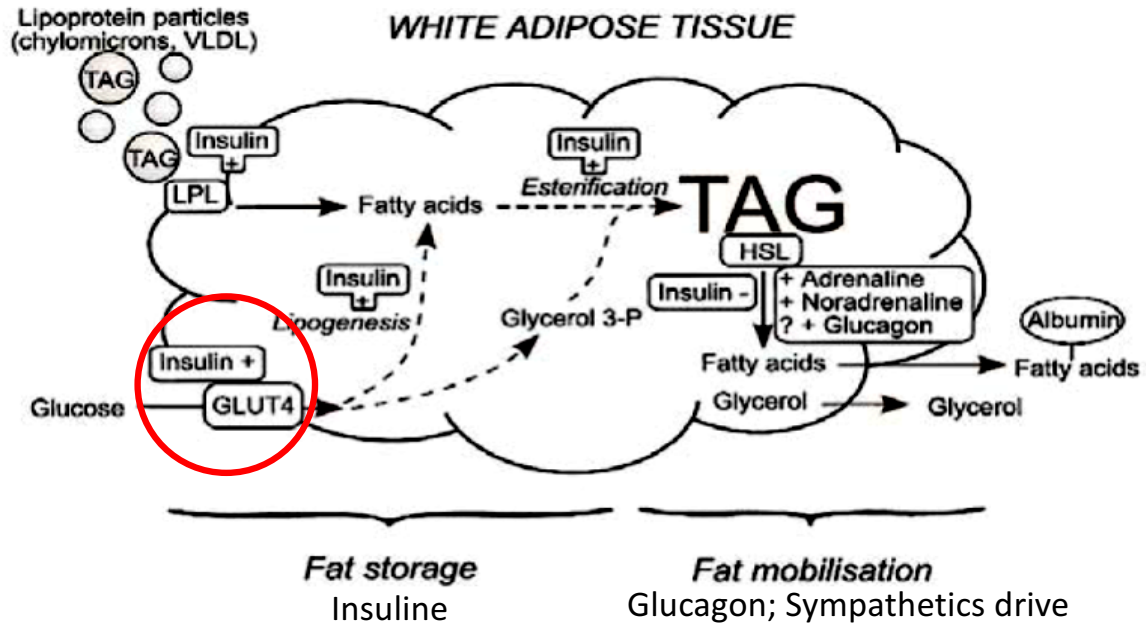
TAG
↓ ← Lipoprotein lipase
Fatty acids
↓
Fatty acids
↓ ← Esterification
TAG



The action of lipoprotein lipase in white adipose tissue. Lipoprotein lipase is attached to the branching glycosamino-glycan chains that form the *glycocalyx* (a fuzzy surface lining the capillary, attached to the endothelial cells). It acts on lipoprotein particles in the capillaries which contain triacylglycerol (TAG), hydrolysing this TAG to release fatty acids which are taken up into adipocytes and re-esterified for storage as TAG. More than one molecule of the enzyme acts on a lipoprotein particle at once.

Métabolisme 1 Métabolisme ac. gras + glucose dans le tissu adipeux blanc
Rôle de l'insuline et du glucagon

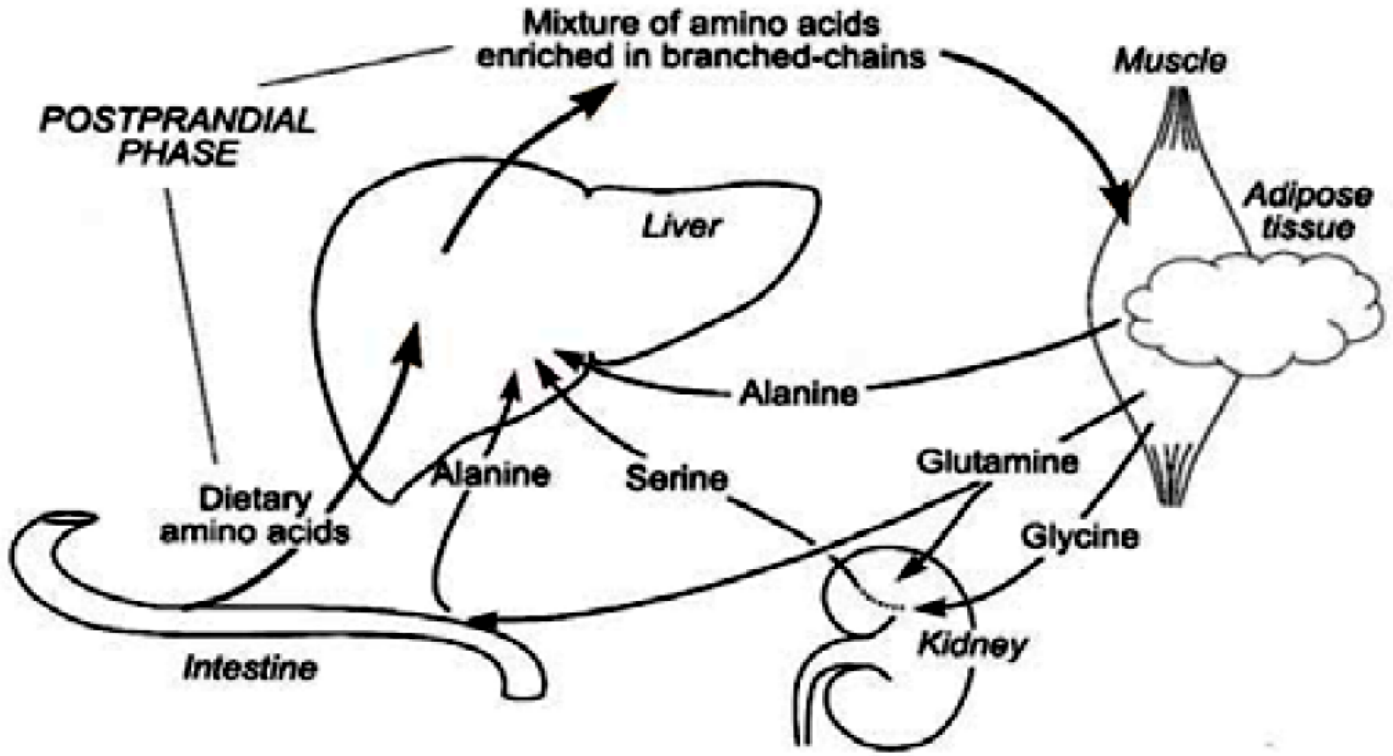
Overview of fatty acid and glucose metabolism in white adipose tissue.



Overview of fatty acid and glucose metabolism in white adipose tissue.
The body's main store of chemical energy is in the form of triacylglycerol (TAG) in white adipose tissue. *Fat storage* is the process of deposition of TAG; *fat mobilisation* (or *lipolysis*) is the process of hydrolysis of the stored TAG to release *non-esterified fatty acids* into the plasma (bound to the carrier protein albumin), so that they can be taken up by other tissues. LPL, lipoprotein lipase; HSL, hormone-sensitive lipase; glycerol 3-P, glycerol 3-phosphate; VLDL, very-low-density lipoprotein. The major pathways and main sites of hormonal regulation are shown: a plus sign indicates stimulation, a minus sign inhibition. Dashed lines show multiple enzymatic steps.

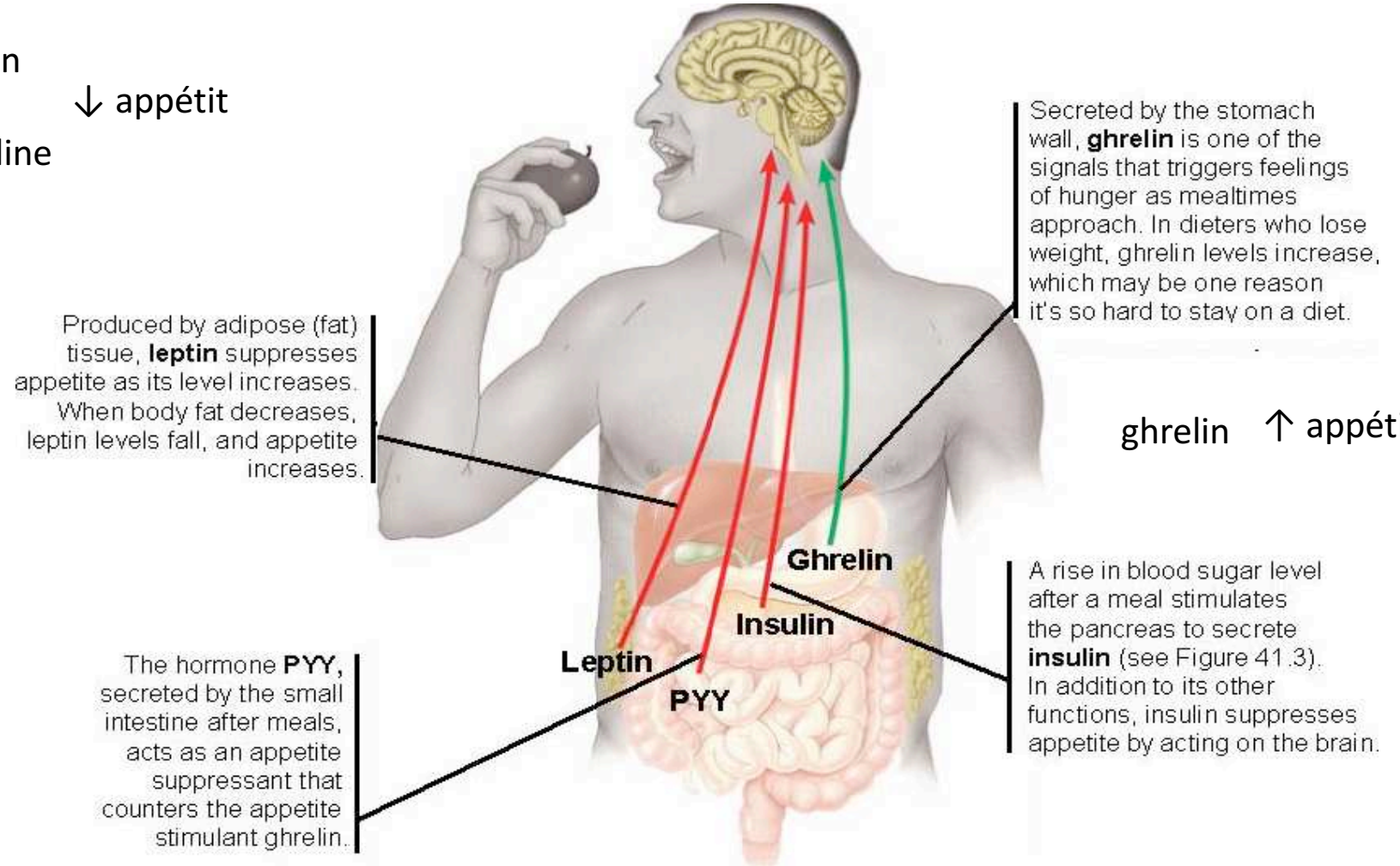
Métabolisme 1 Métabolisme des acides aminés
Circulation foie-muscle-rein

Major pathways for amino acid flow between tissues

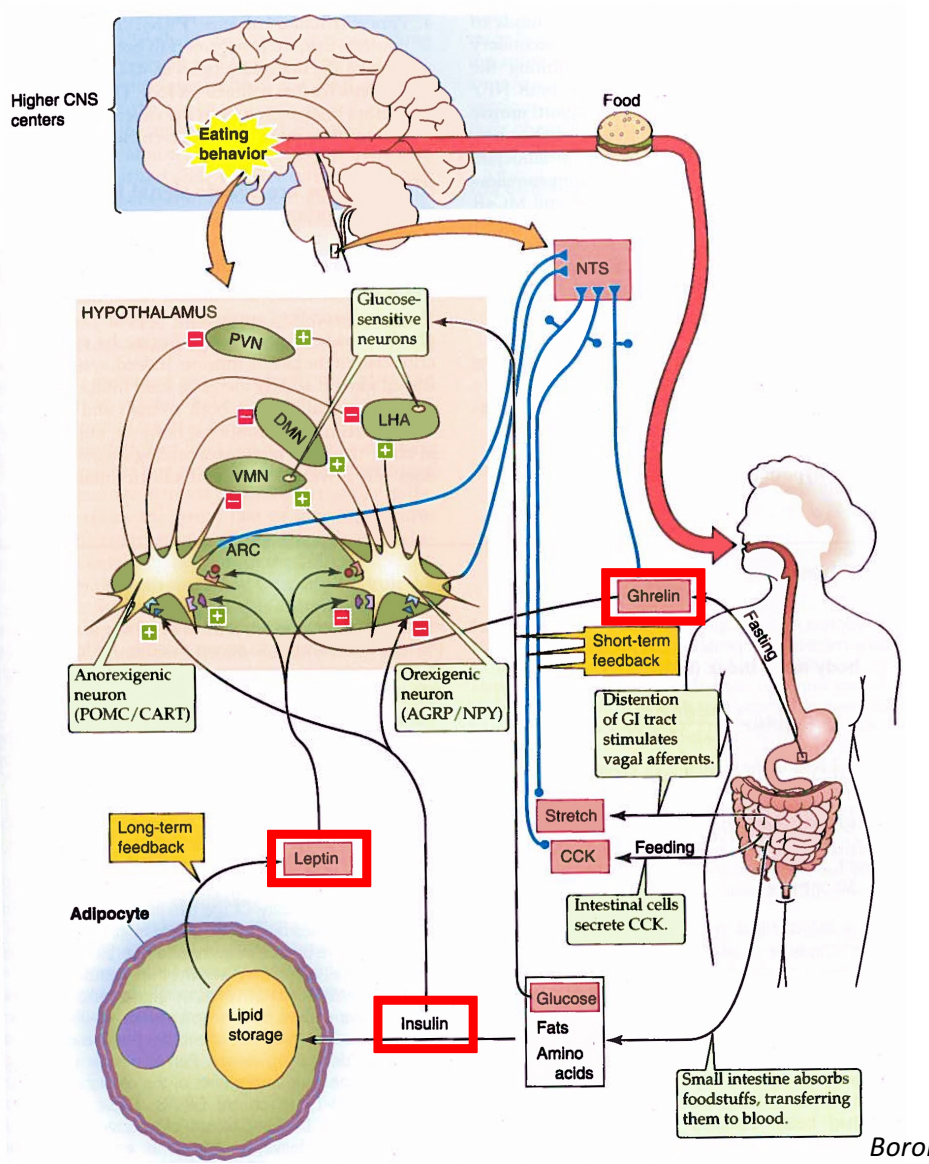


Métabolisme 1 Sensation de faim: rôle des médiateurs

leptin
PPY ↓ appétit
insuline



Métabolisme 1 Contrôle hormonal de l'apport alimentaire



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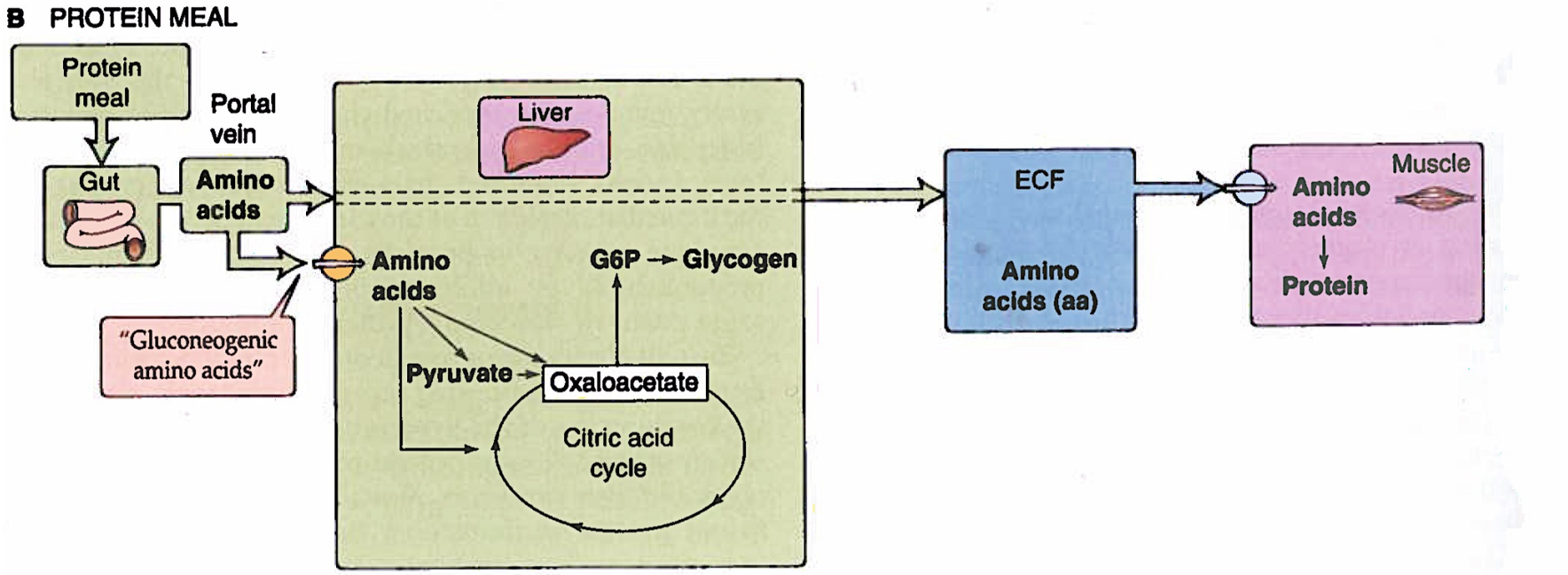
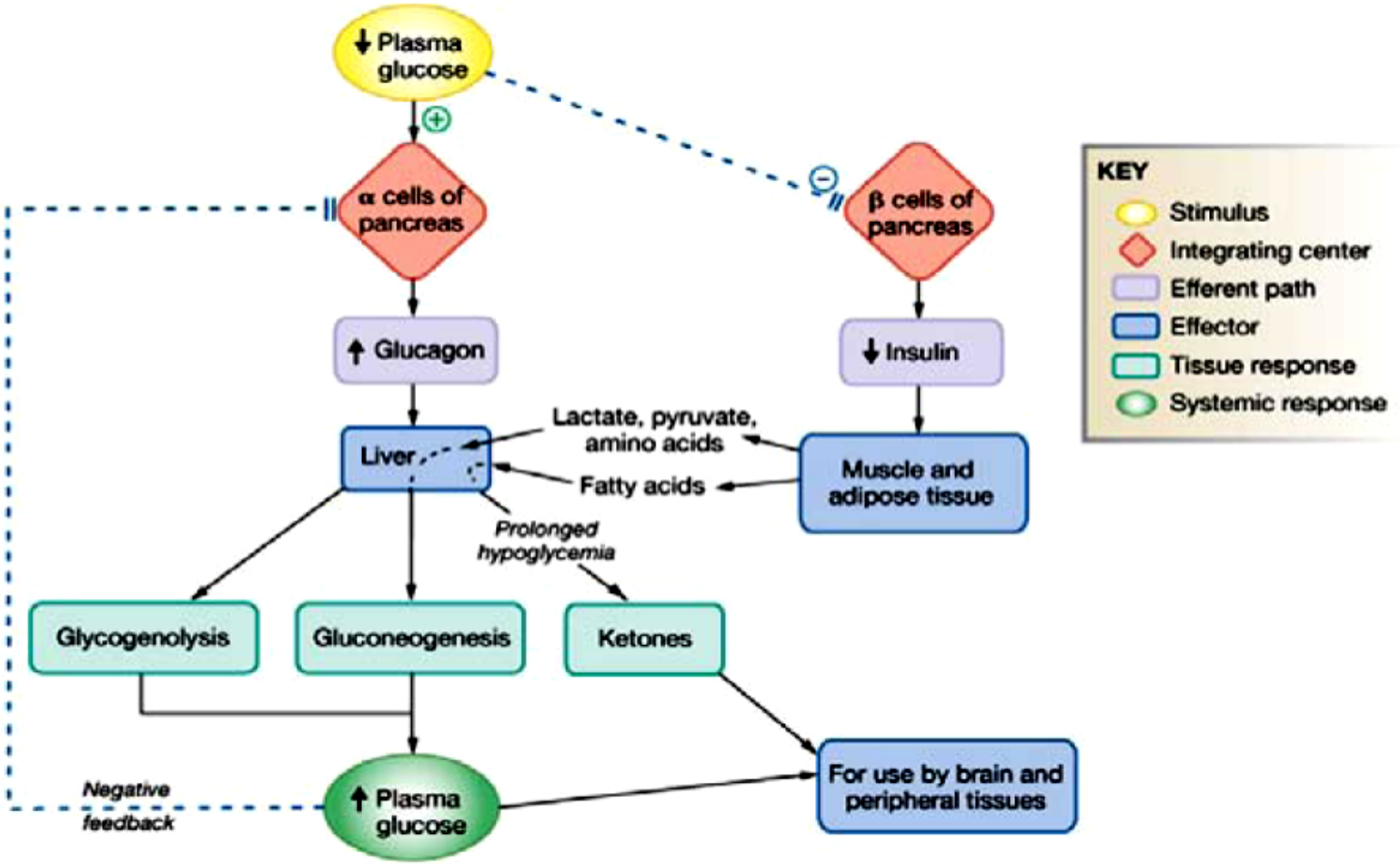
Métabolisme 1 Métabolisme des acides aminés après un repas protéiné



Métabolisme 1 Rôle du glucagon dans le maintien de la glycémie



Métabolisme 1 Rôle du glucagon dans le maintien de la glycémie
Stimulation des hépatocytes

Glucagon= antagoniste de l'insuline

Rôle essentiel dans la gestion du jeûne; carence en glucose exogène

Lieu d'action: les hépatocytes

Action: ↑ gluconéogenèse ⇒ production de glucose
↑ glycogénolyse ⇒ dégradation de glycogène
↓synthèse de glycogène
↑ kétogenèse ⇒ production de corps cétoniques
↑ catabolisme de protéines ⇒ acides aminés ⇒ gluconéogenèse

NB: le Glucagon n'affecte pas le métabolisme des protéines des muscles!

Métabolisme 1 Métabolisme du glucose en phase post nocturne

Glycogen
↓ ← Glycogenolysis
Glucose

Lactate
↓ ← Gluconeogenesis
Glucose

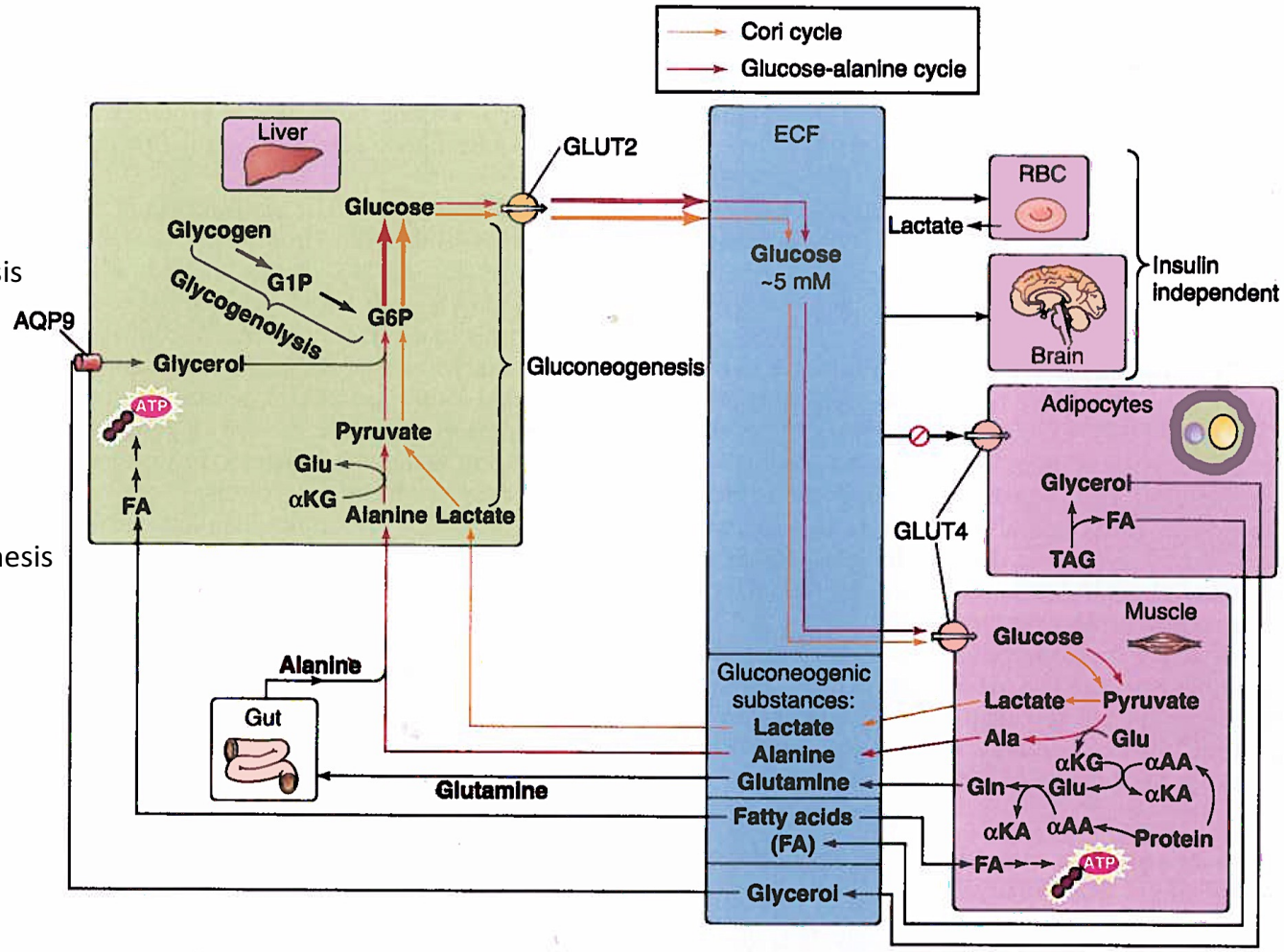
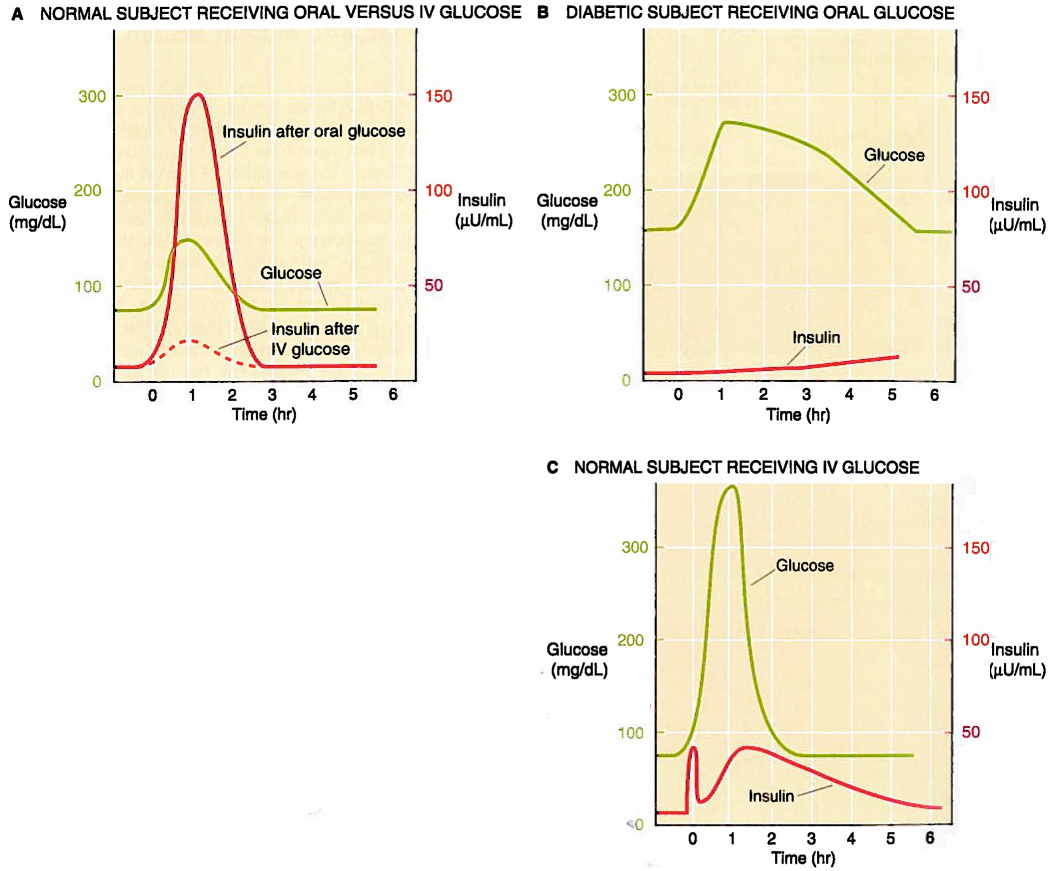


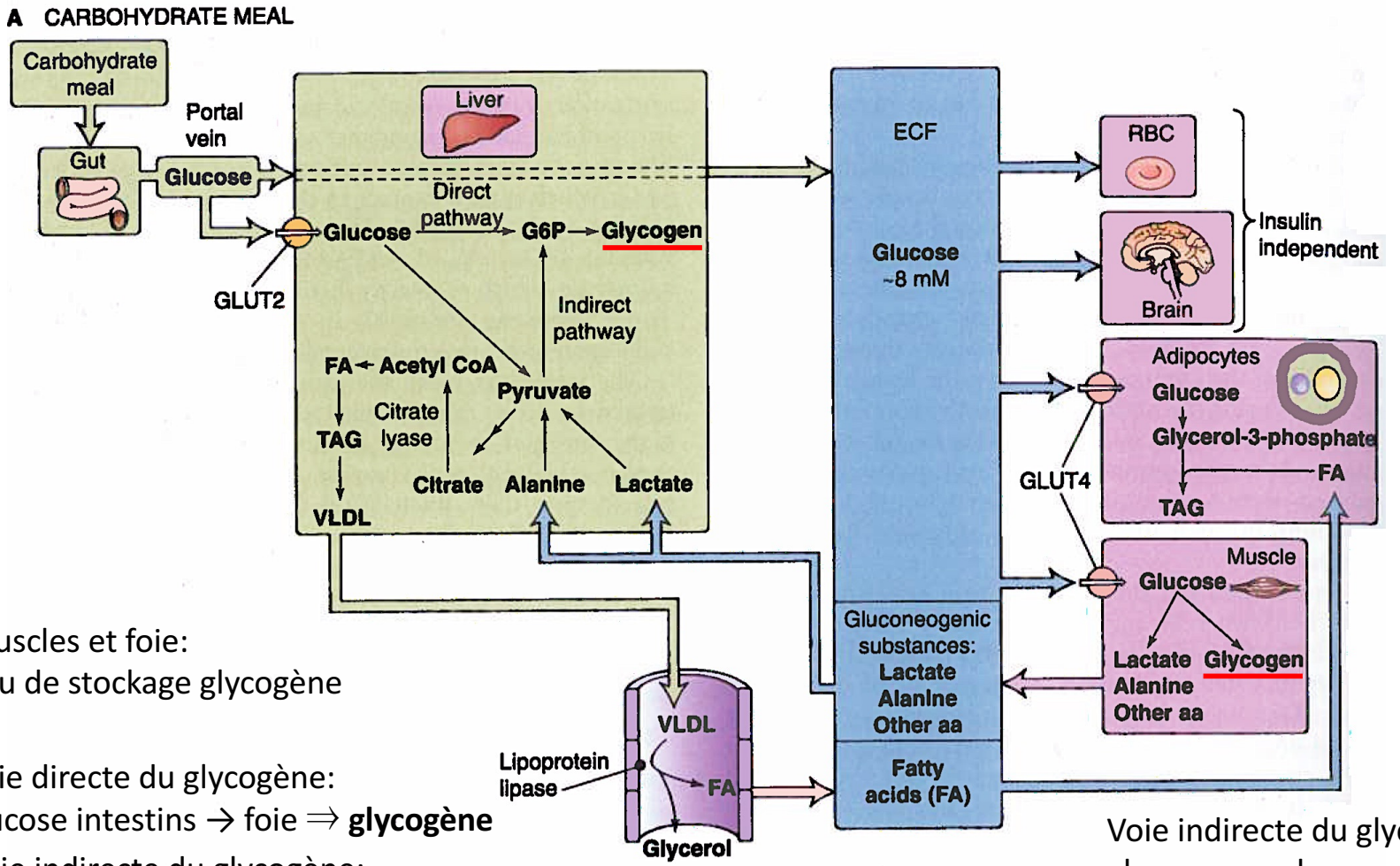
Figure 58-13 Overnight fast. αAA, α-amino acid; AQP9, aquaporin 9; ECF, extracellular fluid; αKA, α-keto acid; αKG, α-ketoglutarate.

Métabolisme 1 Epreuve de tolérance au glucose



Glucose tolerance test. *A*, When a human consumes a load of glucose (75 g), plasma [glucose] rises slowly, reflecting the intestinal uptake of the glucose. In response, the pancreatic cells secrete insulin and plasma [insulin] rises sharply. *B*, In a patient with type 1 diabetes, the same glucose load as that in *A* causes plasma [glucose] to rise to a higher level and to remain there for a longer time. The reason is that plasma [insulin] rises very little in response to the glucose challenge so that the tissues fail to dispose of the glucose load as rapidly as normal. The diagnosis of diabetes is made if the plasma glucose is above 200 mg/dl at the second hour. *C*, If the glucose challenge (0.5 g glucose/kg body weight given as a 25% glucose solution) is given intravenously, then the plasma [glucose] rises much more rapidly than it does with an oral glucose load. Sensing a rapid rise in [glucose], the cells first secrete their stores of presynthesized insulin. Following this "acute-phase," the cells begin to secrete newly manufactured insulin in the "chronic phase," which lasts as long as the glucose challenge. IV, intravenous.

Métabolisme 1 Effets de la prise d'aliments: prise d'hydrates de C



Tissu adipeux:
lieu de stockage
lipogenèse (TAG)

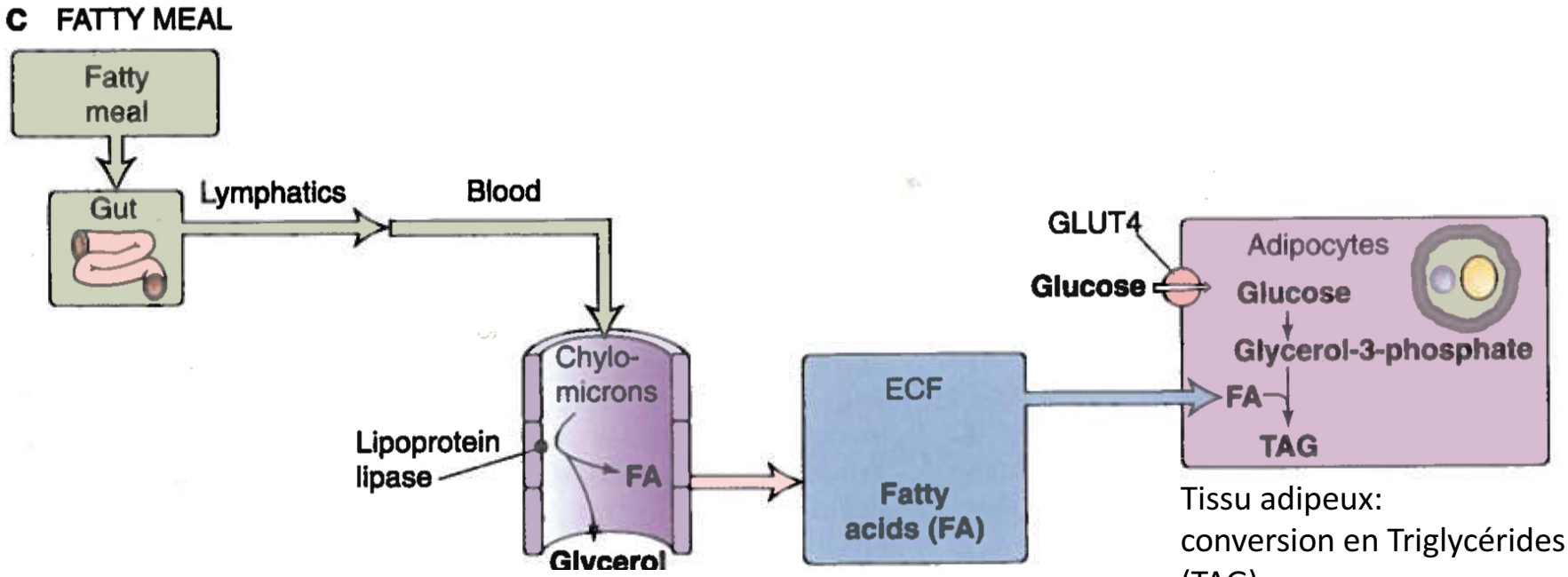
Muscles et foie:
lieu de stockage glycogène

Voie directe du glycogène:
glucose intestins → foie ⇒ **glycogène**

Voie indirecte du glycogène:
glucose intestins ⇒pyruvate
→ foie ⇒ **glycogène**

Voie indirecte du glycogène:
glucose muscles
⇒ lactate → foie ⇒ **glycogène**

Métabolisme 1 Effets de la prise d'aliments: prise de lipides et d'hydrates de C



Tissu adipeux:
conversion en Triglycérides (TAG)

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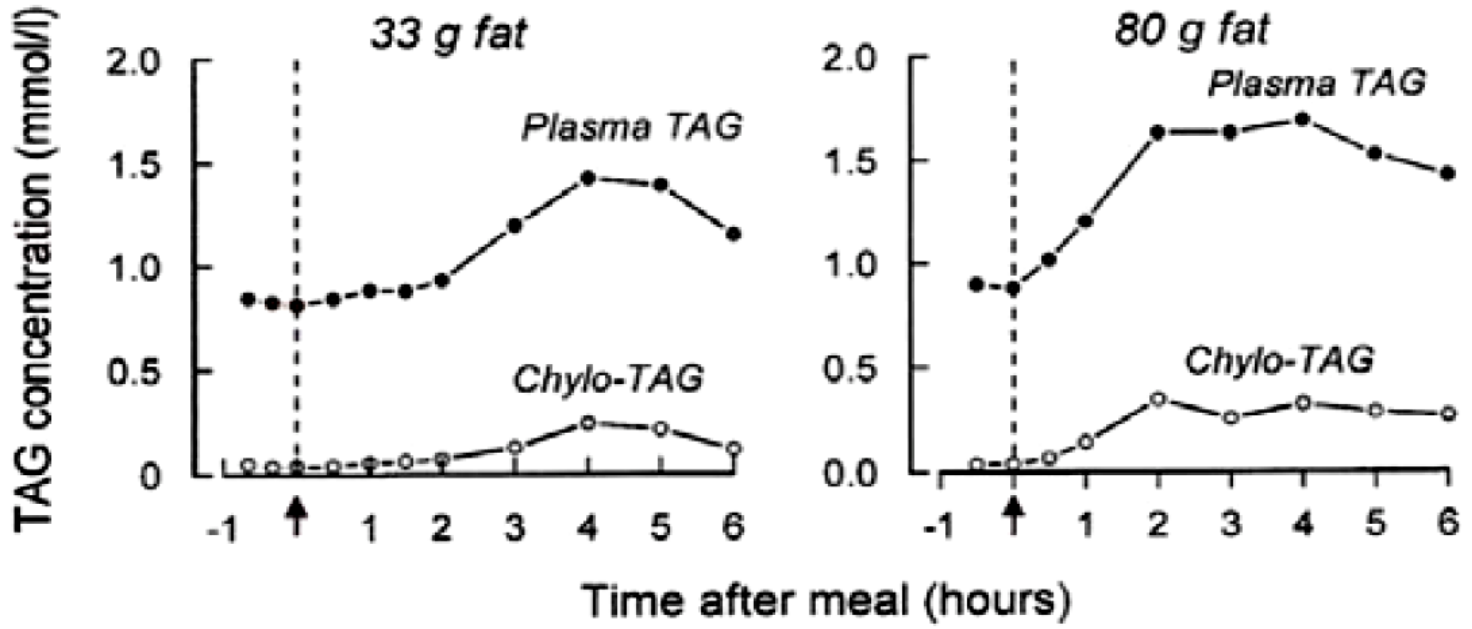
Métabolisme 1 Effets de la prise d'aliments: prise de lipides

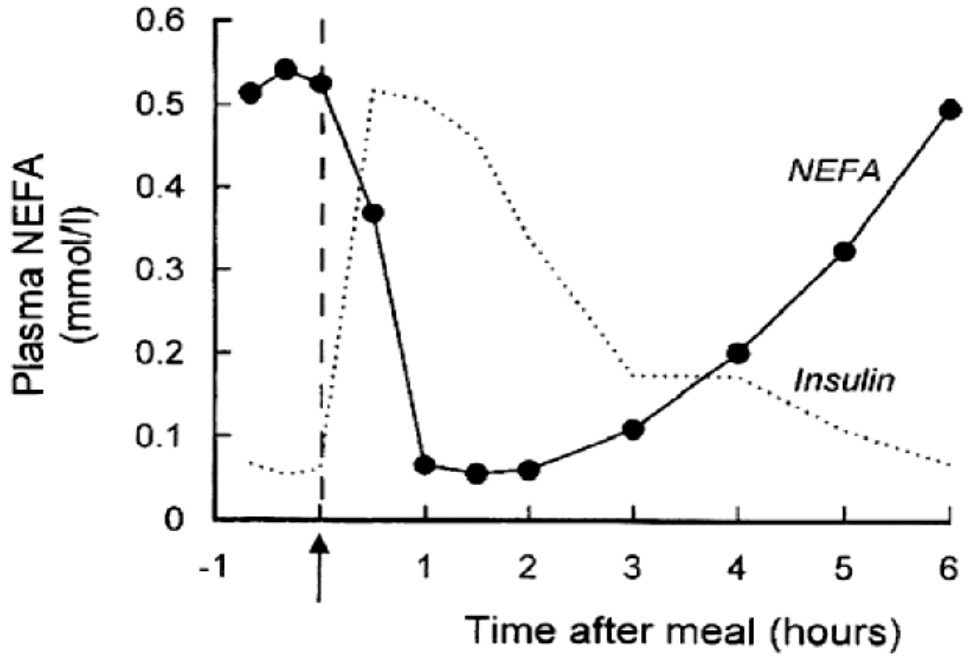
Triacylglycerol concentrations in the plasma after a meal



Concentrations of triacylglycerol (TAG) in whole plasma (solid circles) and in chylomicrons (open circles) after overnight fast and after meals (shown by the arrows) containing either 33 g fat (a typical mixed meal) or 80 g fat (a high-fat meal) in groups of normal subjects. Data from Griffiths *et al.* (1994) and Coppack *et al.* (1990).

Métabolisme 1 Effets de la prise d'aliments: prise de lipides

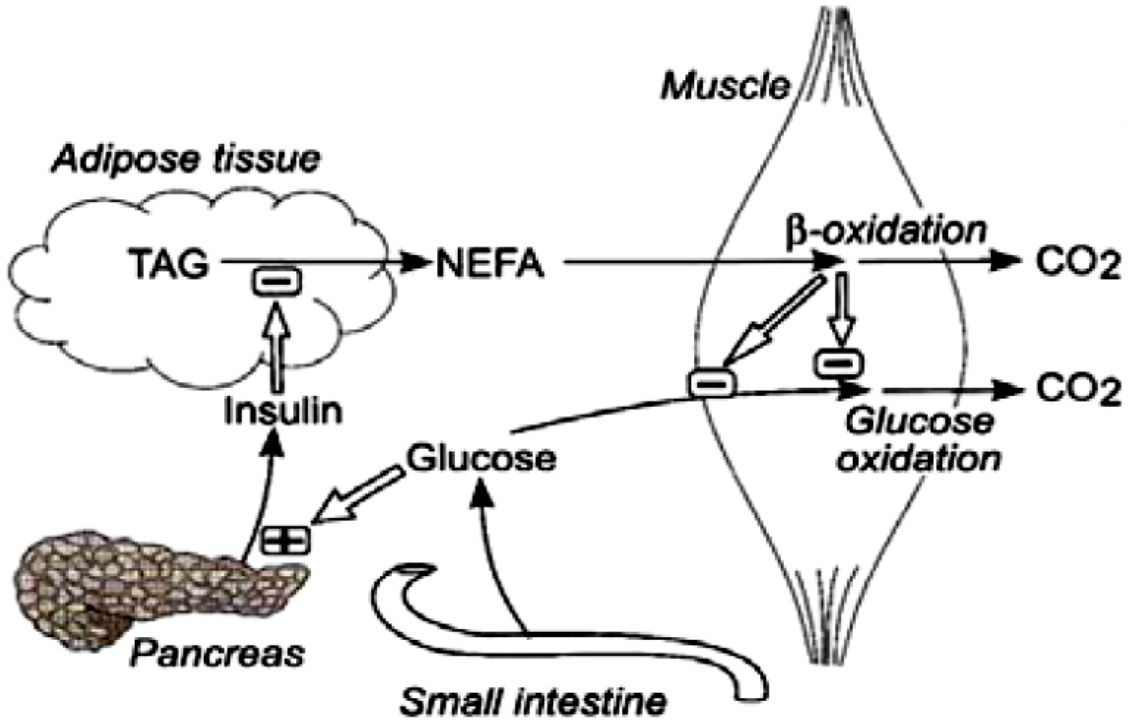
Plasma non-esterified fatty acid (NEFA) concentrations after an overnight fast and following a meal.



The plasma insulin concentration (expressed in nmol/l) is shown as a dotted line. Mean values for eight normal subjects are shown; data taken from Frayn *et al.* (1993).

Métabolisme 1 Métabolisme des graisses et oxidation du glucose

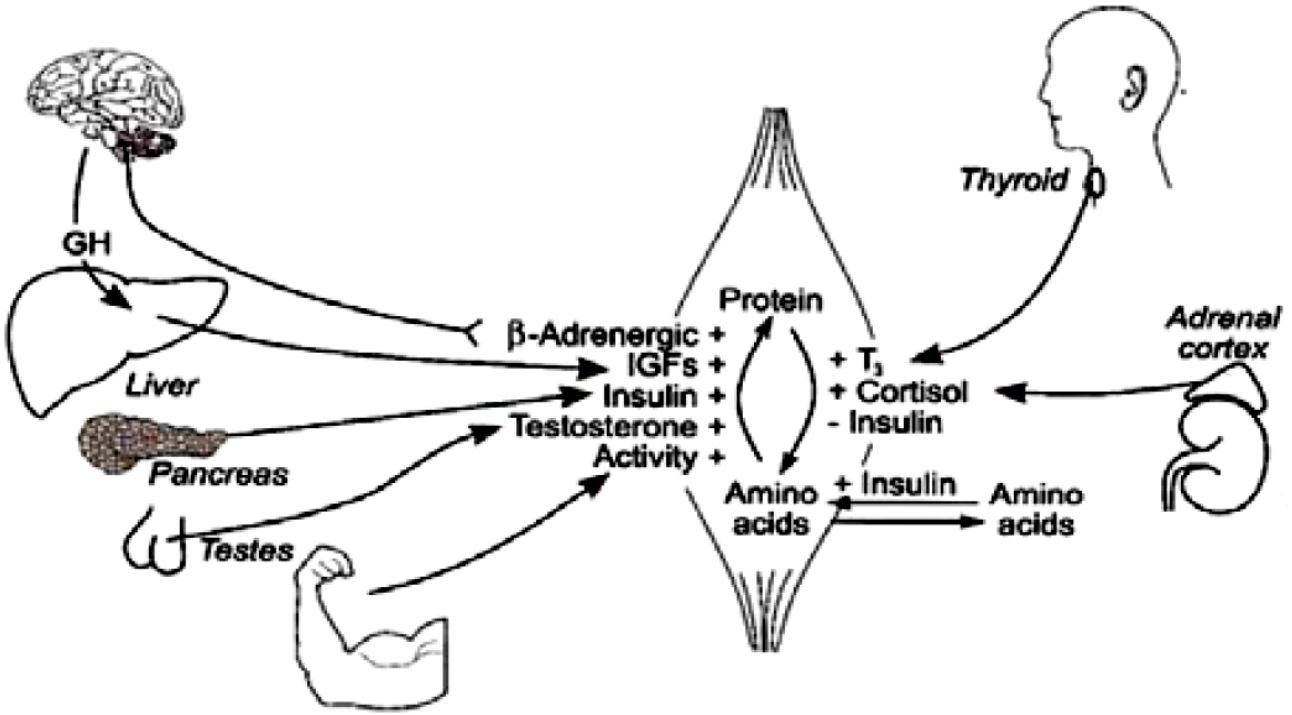
Effect of fat metabolism on glucose oxidation (Randle cycle)



Acetyl-CoAs inhibit Pyruvate dehydrogenase by phosphorylation thereby favoring fat oxidation and slowing down markedly glucose oxidation

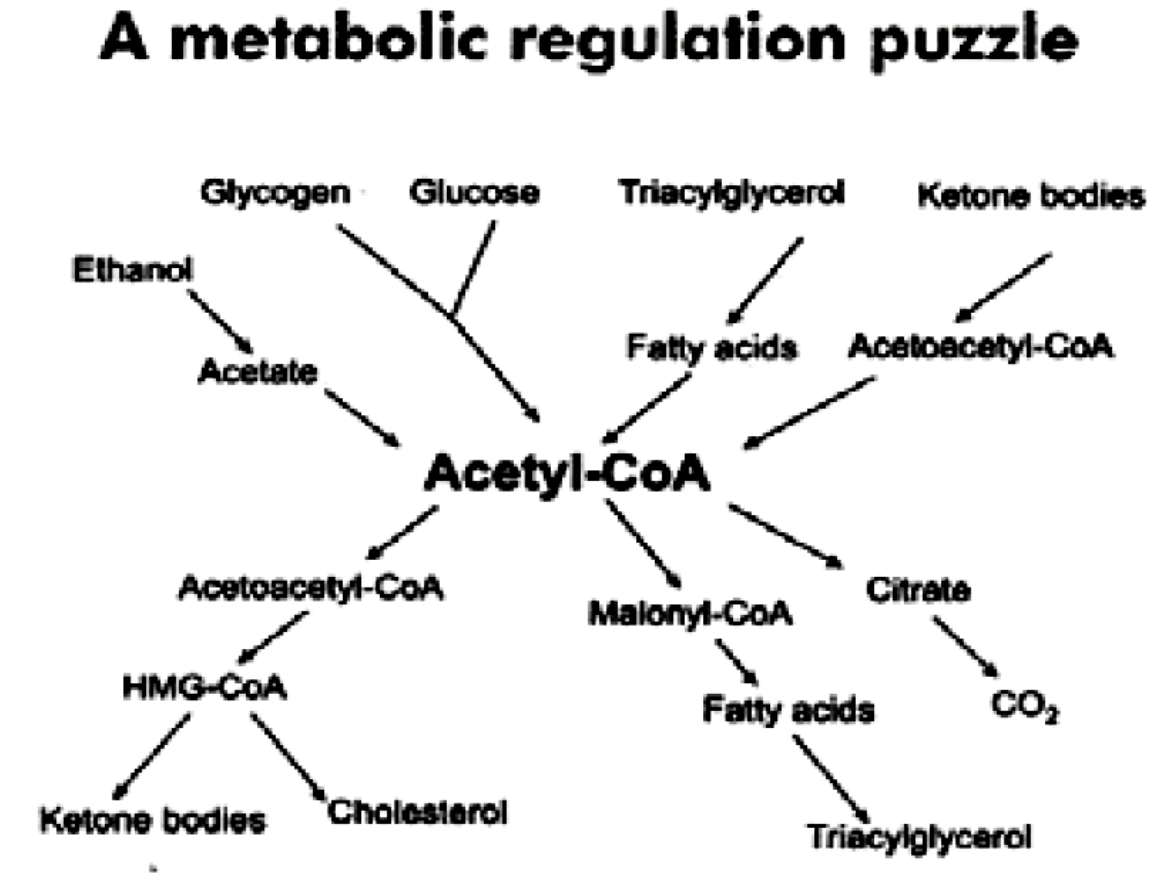
Métabolisme 1 Synthèse et dégradation des protéines dans le muscle

Overall control of protein synthesis and breakdown in muscle



Overall control of protein synthesis and breakdown in muscle (and other tissues). Some of the stimuli here are tissue-specific (especially physical activity, testosterone and β-adrenergic stimulation); more details are given in the text. *IGFs* are the insulin-like growth factors (IGF-1 and -2), generated in the liver in response to growth hormone (GH). β-*adrenergic* represents activation of β-adrenergic receptors, either by noradrenaline released at sympathetic nerve terminals or by adrenaline in the plasma.

Métabolisme 1 Régulation du métabolisme: multiples voies possibles



Illustrated are some of the pathways by which acetyl-CoA may be generated, and some of the pathways by which it is utilised. Think about this: what determines its fate in any particular cell at any particular time? And what prevents 'futile' metabolic cycling: e.g. fatty acids make acetyl-CoA, acetyl-CoA makes fatty acids; or ketone bodies make acetyl-CoA, acetyl-CoA makes ketone bodies? How can the control of ketone body synthesis (a pathway active in 'catabolic' conditions) be achieved when the initial steps in the pathway seem similar to those for cholesterol synthesis (active in 'anabolic' conditions)?

Métabolisme 1 Régulation du métabolisme en fonction du temps

Court terme

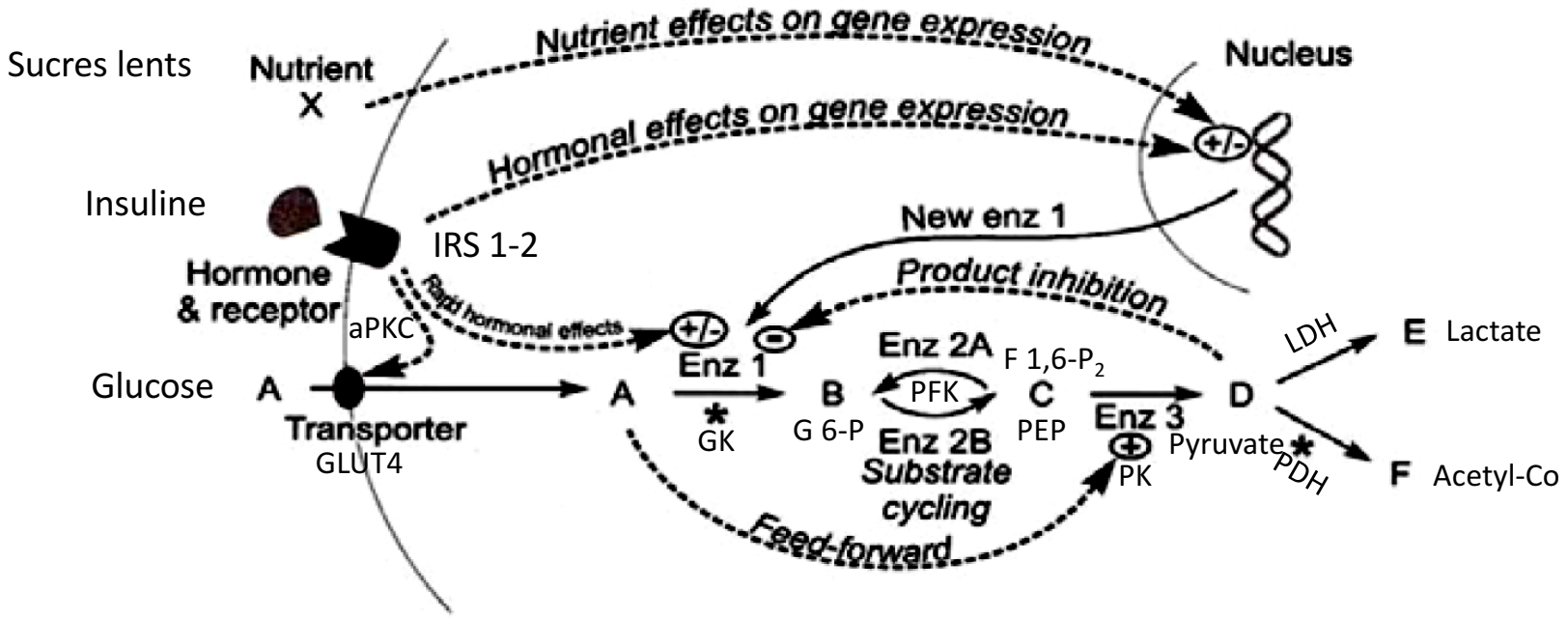
- régulation allostérique par les aliments eux-mêmes
- inhibition compétitive
- interaction avec d'autres protéines
- translocation
- modification covalente *(phosphorylation – déphosphorylation)*

Long terme

- changements dans l'expression des gènes => hormones
  => nutriments

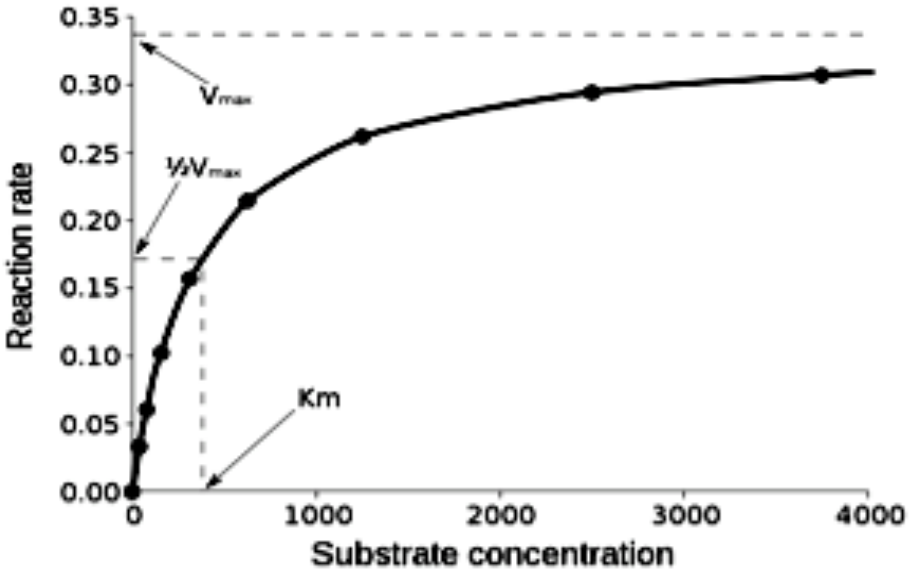
Métabolisme 1 Régulation du métabolisme: exemple du glucose

Different methods for achieving changes in metabolic flux within a cell

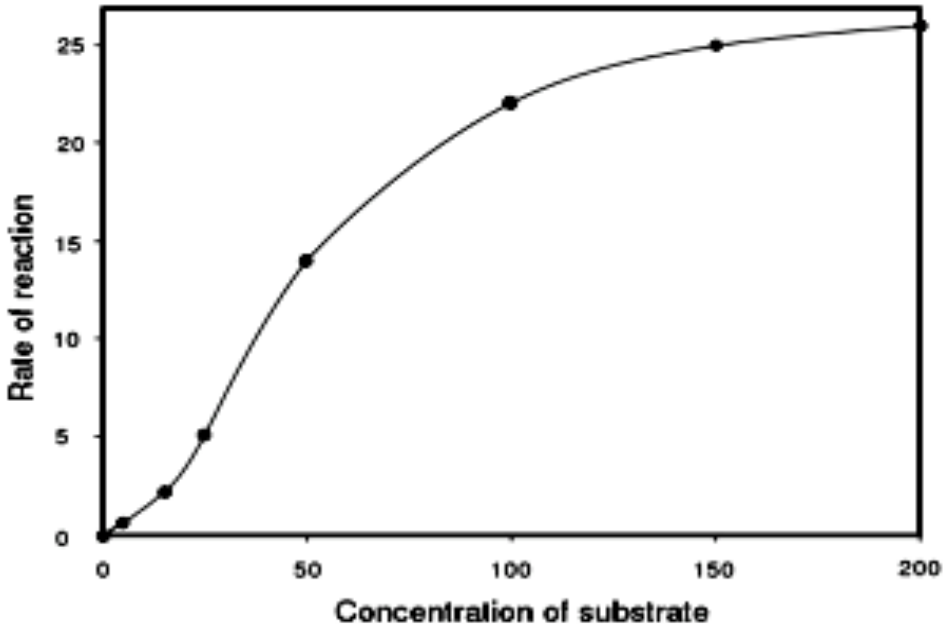


A hypothetical metabolic pathway is shown. Enz 1, Enz 2, etc. are the enzymes converting substrate A to substrate B, B to C, etc. For many pathways, important control points are often the first step, and also the first step after a branch point (marked *).

Métabolisme 1 Régulation du métabolisme: cinétiques enzymatiques



Cinétique enzymatique classique

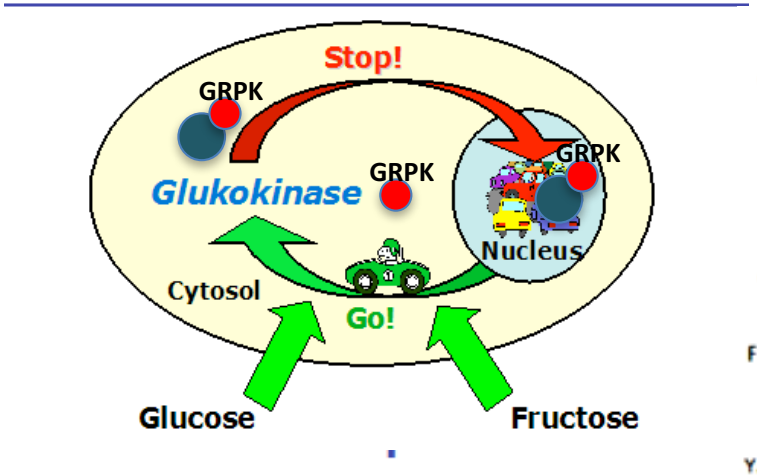


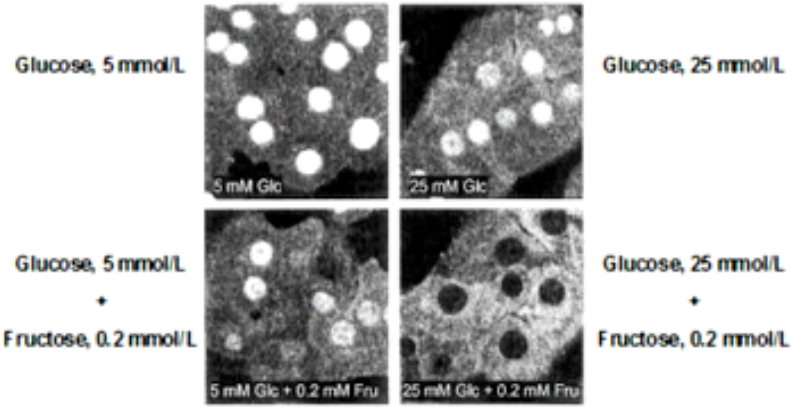
Cinétique enzymatique coopérative

i.e. glucokinase

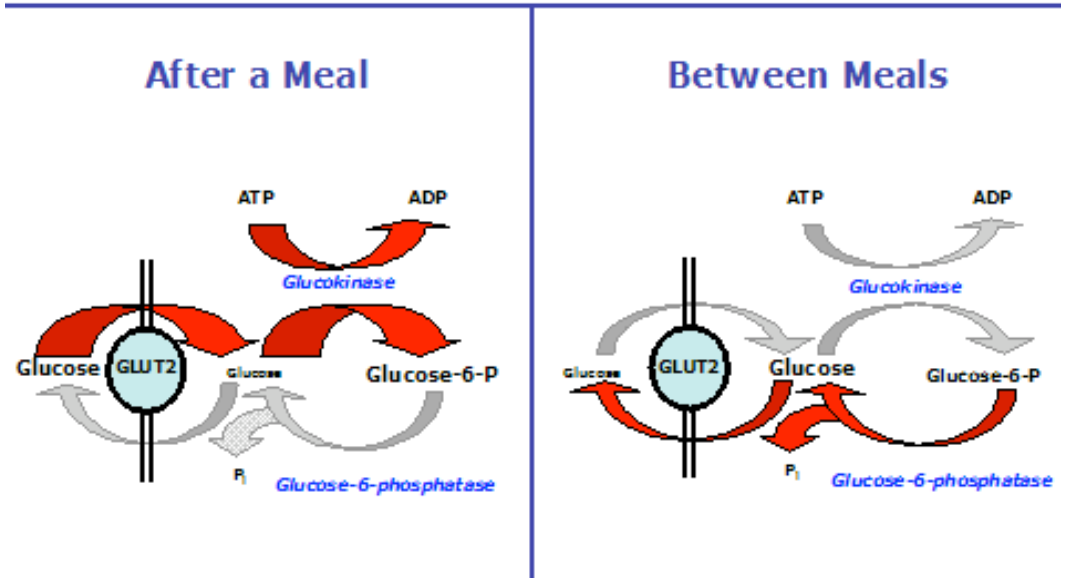
$$v_0 = \frac{V_{\max}[\mathrm{S}]}{K_M + [\mathrm{S}]}$$ ***(équation de Michaelis-Menten)***

Métabolisme 1 Contrôle de l'activité de la glucokinase hépatique: translocation





Y. Toyoda *et. al.*, Horm Metab Res 33, 329-336 (2001).



In hepatocytes of various mammals, GKRP has always been found in molar excess of the amount of GK, but the GKRP:GK ratio varies according to diet, insulin sufficiency, and other factors. Free GKRP shuttles between the nucleus and the cytoplasm. It may be attached to the microfilament cytoskeleton. GKRP competes with glucose to bind with GK, but inactivates it when bound. In conditions of low glucose, GKRP then pulls the GK into the nucleus. Rising amounts of glucose coming into the hepatocyte prompt the GKRP to rapidly release GK to return to the cytoplasm.

GKRP itself is subject to modulation. Fructose and sorbitol can both be converted to fructose-1-phosphate, which inhibits GKRP and frees GK. Fructose 6-phosphate binds to the same site of GKRP, but enhances the ability of GKRP to bind and inactivate GK. In contrast, phosphorylation of GKRP by AMP-activated protein kinase, induced by elevated levels of AMP, reduces its capacity to inactivate GK.

Métabolisme 1 Régulation à long terme du métabolisme: expression de gènes

Par les aliments

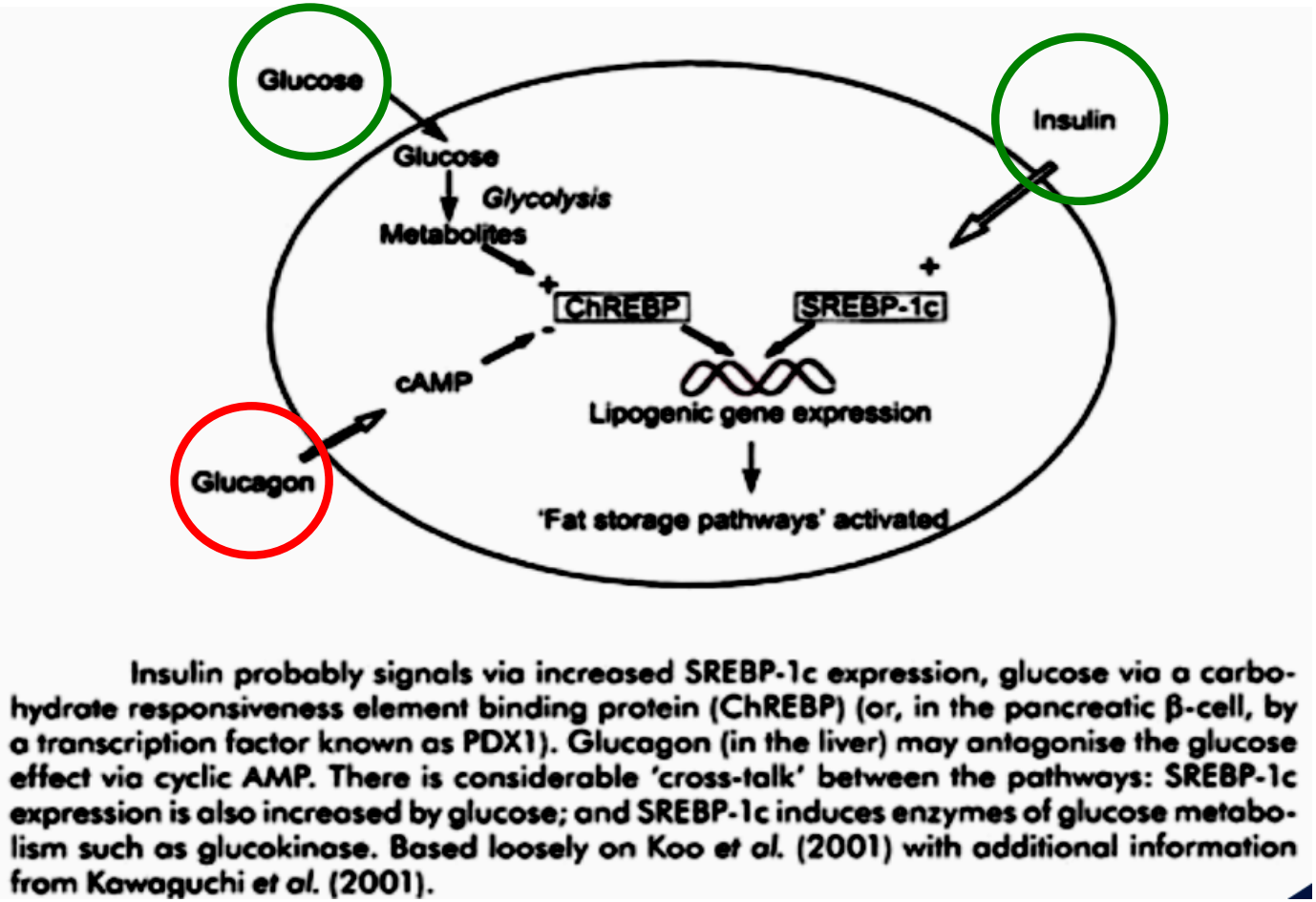
- glucose (*éléments répondant au glucose, autres)*
- acides gras (*Peroxisome proliferator-activated receptors PPARs)*
- acides aminés (*transporteurs, nouveau champ d'investigation)*

Par les hormones

- insuline
- glucagon
- hormones stéroidiennes
- hormones thyroidiennes

Métabolisme 1 Régulation à long terme du métabolisme: expression de gènes

Insulin and glucose control expression of lipogenic genes by independent routes



Insulin probably signals via increased SREBP-1c expression, glucose via a carbohydrate responsiveness element binding protein (ChREBP) (or, in the pancreatic β-cell, by a transcription factor known as PDX1). Glucagon (in the liver) may antagonise the glucose effect via cyclic AMP. There is considerable 'cross-talk' between the pathways: SREBP-1c expression is also increased by glucose; and SREBP-1c induces enzymes of glucose metabolism such as glucokinase. Based loosely on Koo *et al.* (2001) with additional information from Kawaguchi *et al.* (2001).

The transcription factor sterol regulatory-element-binding protein-1c (SREBP-1c) also plays a major role in the effect of insulin on the transcription of hepatic genes such as glucokinase and fatty acid synthase.

Métabolisme 1 Régulation à long terme du métabolisme: expression de gènes

Regulation of gene expression by glucose

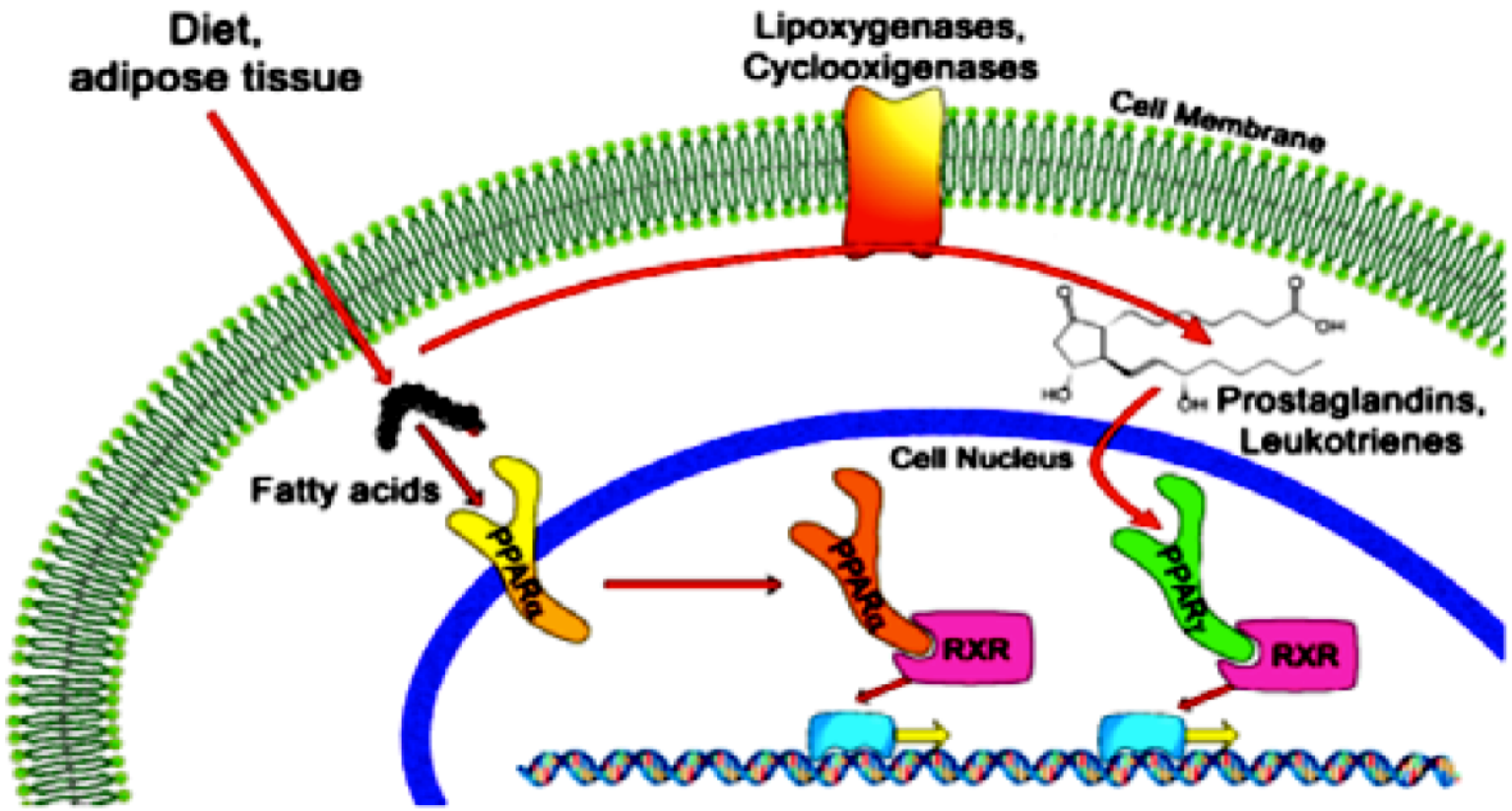
Some genes whose expression is increased by glucose (at a cellular level) or by carbohydrate availability.

Gene	Comments
Liver isoform of pyruvate kinase	Glycolysis
Acetyl-CoA carboxylase	Synthesis of fatty acids from cytosolic acetyl-CoA (see later, Box 4.3)
Fatty acid synthase	
S_{14} (or Spot 14)	Lipogenesis*
SREBP-1c	Transcriptional regulation
Insulin	(In the pancreatic β-cell)
SGLT-1	Increased by presence of glucose in the intestinal lumen
PDX1	Transcription factor in pancreatic β-cell increasing insulin gene expression

*S_{14} is believed to be involved in lipogenesis in liver and adipose tissue.
Note that the expression of several genes is increased by insulin and glucose acting in concert, and the definition of a 'glucose-regulated' gene is not always clear.

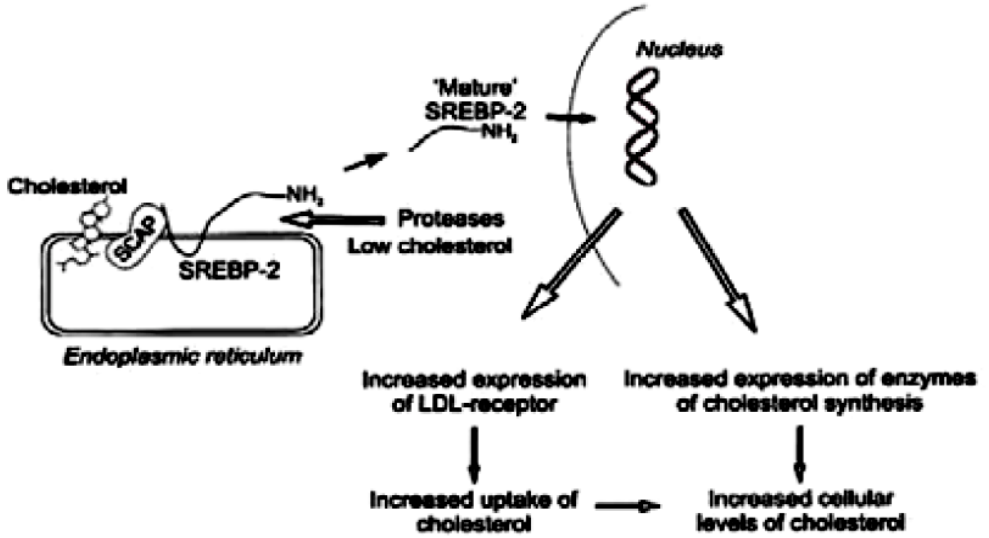
Métabolisme 1 Régulation à long terme du métabolisme: expression de gènes

Regulation of gene expression by fatty acids



Métabolisme 1 Régulation à long terme du métabolisme: expression de gènes

Regulation of specific gene expression by cholesterol, the SREBP system



SREBP=
Sterol Regulatory Element Binding Protein

ACAT (cf. p. 431)

The SREBP system. The full-length SREBP protein is located in the endoplasmic reticulum (a system of membranous cavities within the cytoplasm). It is associated with the SREBP cleavage activating protein (SCAP), which 'senses' the level of cholesterol, or related sterols, within the cell. When the cellular cholesterol content is low, specific proteases cleave SREBP to release the N-terminal portion, known as 'mature' SREBP. (Note that cholesterol does not float around in the cytosol: in fact it is associated with membranes in the cell.) Mature SREBP moves to the nucleus where it binds to sterol response elements in the promoter regions of many genes. If SREBP-2 is concerned (as shown in the figure), these are mainly genes concerned with cholesterol metabolism (LDL receptor, enzymes of cholesterol synthesis). SREBP-1 appears to be regulated more by expression of the full-length protein (which is increased by insulin in the case of SREBP-1c); proteolytic cleavage then seems to be constitutive, so the more SREBP-1 protein that is produced, the more the relevant genes are activated. These are mainly genes concerned with fat storage (including acetyl-CoA carboxylase and fatty acid synthase).