Glucose metabolism

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Overview

Starch constitutes the ***main food staples*** in the world, providing the necessary calories to humans.
It is rich in ***carbohydrates*** that fuel cells' activities, mainly the brain cells or neurons, nephrocytes, and rapidly contracting skeletal muscles.
In addition, sperm cells exclusively draw energy from carbohydrates.
It is found in high levels in foods such as potatoes, rice, corn, and wheat.

Figure – source : wikipedia

Carbohydrates at the core of public health concern

- ***Diabetes mellitus*** among **top 10** causes of death in 2021 (WHO, the-top-10-causes-of-death)
- In 2022, 14% of adults aged 18 years and older were living with diabetes, an increase from 7% in 1990 (WHO)
- Predominantly **type 2 diabetes**, though other types do occur(mainly : type 1 and Gestational Diabetes.)

*“ Diabetes is a **chronic disease** that occurs either when the pancreas does not produce enough **insulin** or when the body cannot effectively use the insulin it produces. **Insulin is a hormone that regulates blood glucose**. Hyperglycaemia, also called raised blood glucose or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body’s systems, especially the nerves and blood vessels.”(WHO, diabetes)*

Carbohydrates as 'long chains of simple sugar'

Two main forms :

- **Starch** or **amylum** : found in foods such as potatoes, corn or rice, etc ;
- **Glycogen** is the form in which sugar molecules are stored inside the body(liver.)

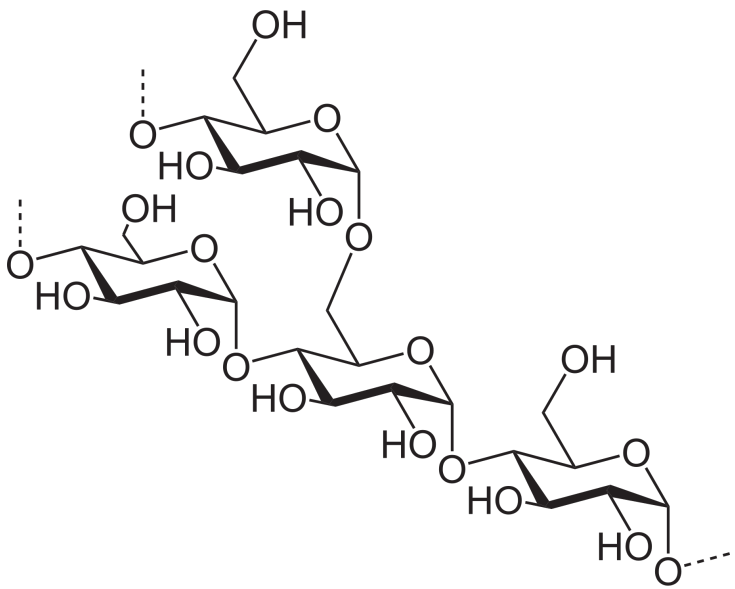


Figure – source :https://en.wikipedia.org/wiki/Starch

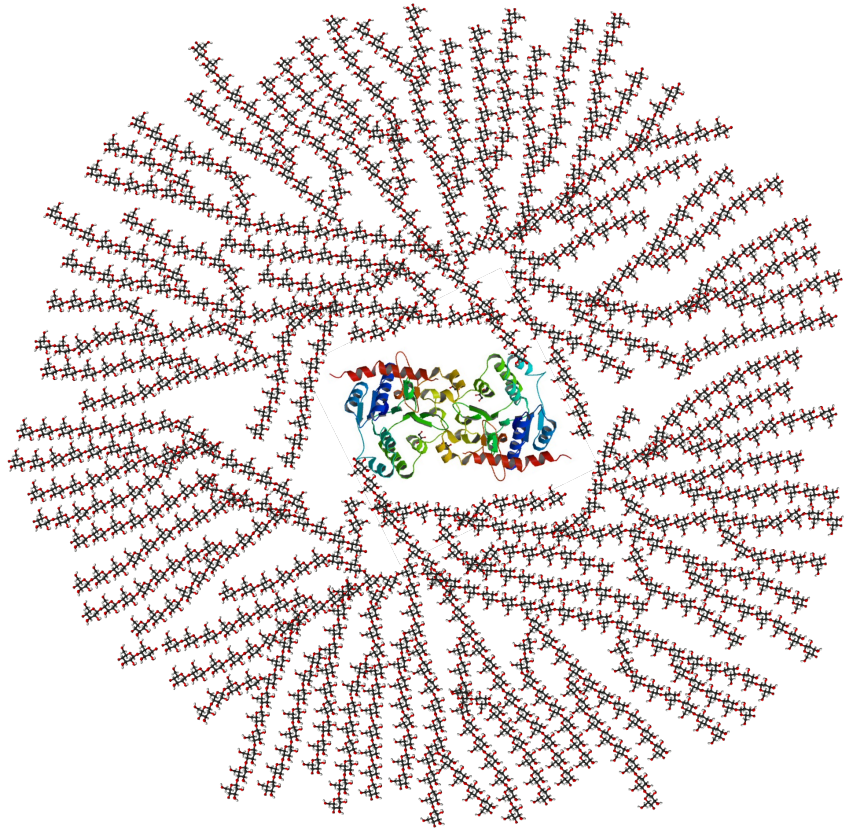


Figure – Glycogen structure : https://en.wikipedia.org/wiki/Glycogen

Digestive physiology of carbohydrates

- Alimentary tract : Carbohydrates are broken down into simple units of sugar molecules, predominantly ***glucoses***. Others include mannose, lactose and fructose.
- These 'simple sugar molecules' are absorbed from the **small intestines** into the bloodstream for further use.

Outlines of major steps in 'food pathway'

I– Ingestion of food such as Starch ; it involves : *mastication*(chewing) and *swallowing*(deglutition). Mastication is favored by jaw muscles and teeth actions in order to break down long chains of molecules while swallowing is divided into three stages : (i) voluntary stage, (ii) pharyngeal stage and (iii) oesophageal stage. The movement of the bolus inside the pharynx stimulates *epithelial swallowing receptor areas'* which send affent signals to brain through *glossopharyngeal* or *trigeminal fibers.* Meanwhile the upward movement of the *larynx*(vocal cord) helps open the *lpper oesophageal sphincter.*

II– Oesophageal movement – Movement is driven by peristaltis which is involuntary.(oesophagus is layered by smooth muscles.) Afferent fibers : vagal fibers ; efferent fibers : glossopharyngeal and vagal nerve fibers. Peristaltis helps open the *lower oesophageal sphincter.*

III– Gastric phase–Stomach functions : (i) storage (1.5 liters) ; (ii) production of chyme ; and (iii) releasing the chyme into the small intestines.

factors promoting stomach emptying	**factors inhibiting stomach emptying**
Food volume and Hormone *Gastrin* (G-cells)	duodenal factors (pyloric sphincter) Hormone *cholecystokinin* (CCK) + and some other hormones, particularly Gastric Inhibitor Peptide.

IV– Small Intestines phase–The control of the peristaltis is mediated by nervous and hormonal signals. Nervous : *gastroenteric reflex* ; hormonal factors : gastrin, CCK, insulin, motilin and serotonin enhance instinal motility, while glucagon and secretin inhibit the intestinal motility. Ileocecal valve prevents backflow from the colon to small intestines.

V– Colic phase–(i) absorption of water and (ii) storage of fecal matter.

VI– Defecation–mediated by two anal sphincters : internal anal sphincter and external anal sphincter. Defecation is initated by defecation reflex involving myenteric plexus + parasympathetic reflexes.

Thus the initial starch which is ingested passes through all these steps while being transformed along the way into **oligosaccharides** trhough
saliva enzyme ptyalin
and pancreatic amylase
and then broken down
into **glucoses** by intestinal
maltase in the small
intestines where absorption
occurs. **Glycemia** is the
concentration of glucose
in the blood. It is a
pivotal clinical parameter.

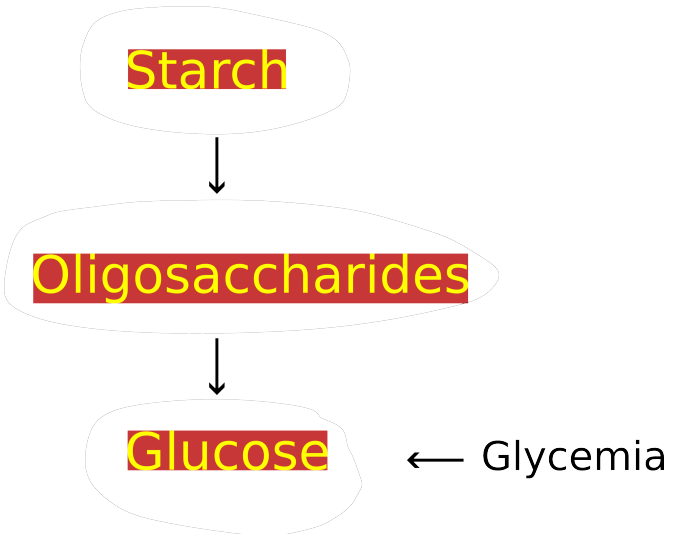


Figure – starch–ologosaccharides–glucose

Glycolysis

How is glucose absorbed ? **Active co-transport** trough Sodium glucose co-transporters(SGLT 1 & 2) followed by glucose transporters(GLUT) :

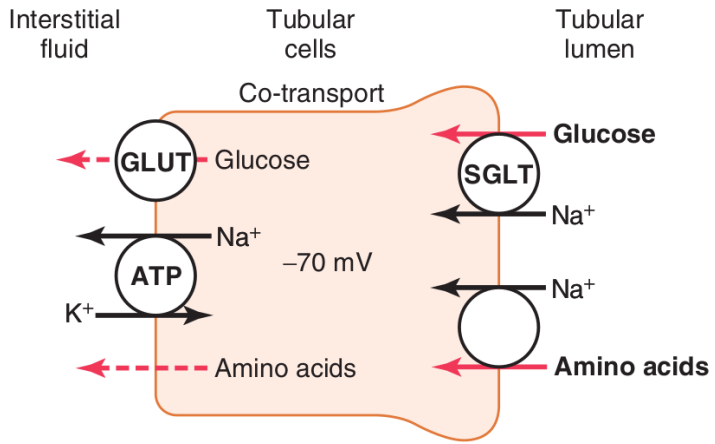


Figure – Active co-transport of glucose(screenshot from [2])

For this section, our reference is [1]. ***Metabolism*** : unity of anabolism and catabolism. Glycolysis is the catabolic process of glucose. Central metabolic process.

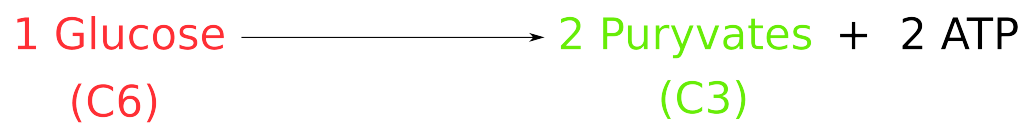


Figure – Degradation of glucose into pyruvate

The absorption of Glucose into the cell is mediated by GLUT and the glycolytic process occurs within the cytosol, which is the 'main interior' of the cell. It is ab **anaerobic** process.

Glycolysis breaks down a 6-carbon glucose into two 3-carbon puryvates :

- Input : 1 molecule of Glucose ;
- Process : Glycolysis with Glycolysis : 10 enzymatic reactions ;
- Output : 2 molecules of pyruvates.

In addition, puryvate can be use in different ways : (i) in **aerobic milieu** : transformed into acetyl-coenzyme A(Acetyl-CoA), a substrate that enters the Kreb's cycle yielding to CO_2 ; (ii) **In anaerobic milieu** : (a) lactic fermentation and (b) alcoholic fermentation.

Importance of glycolysis. Bioenergetics with free energy -183.6 kJ per mol.

Step 1 : Phosphorylation of Glucose by Hexokinase

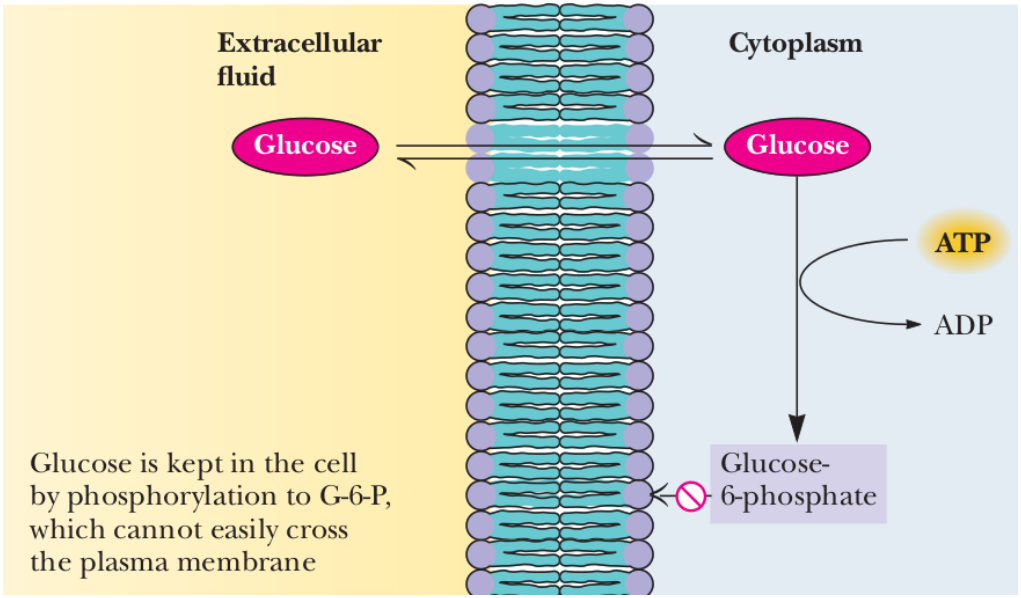


Figure – Screenshot from [1]

This is a priming step : it is non reversible. Enzyme : Hexokinase. In brain : Hexokinase I. Other isoenzymes exist : HK I, II and III.

The concentration of Glucose-6-Phosphate provides a feedback negative on HK actions :

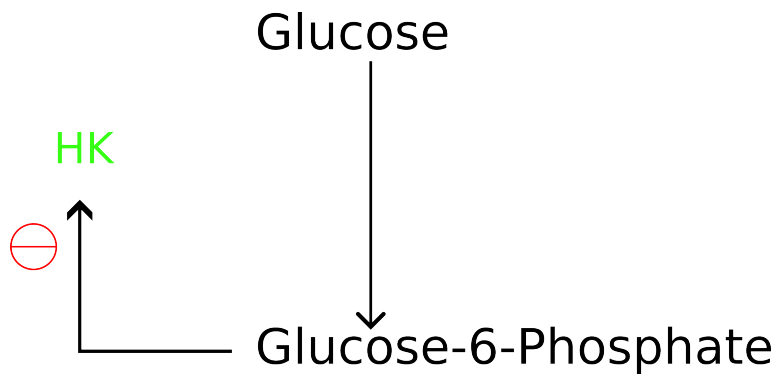


Figure – Glucose-6-Phosphate concentration regulates HK

Step 2 :Isomerase modifies Glucose-6-Phosphate A mere change of conformation/isomere(left vs right hand). Enzyme : phosphoglucoisomerase. It requires Mg^{2+} and it's highly specific to Glucose-6-Phosphate.

Step3 : Second phosphorylation through ATP –Enzyme : phosphofructokinase (PFK). Output : **Fructose–1,6–Bisphospahte(FBP)**

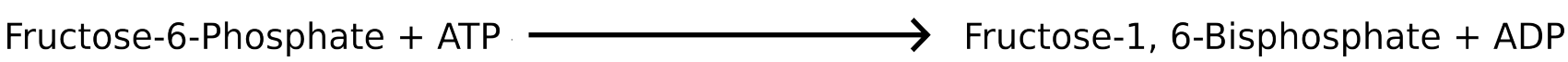


Figure – Frucotose–1,6–Bisphosphate

As mentioned in [1], Fructokinase is a potent factor which accelerates the reaction. Moreover, ATP is an allosteric inhibitor of this enzyme.

Allosteric regulation of PFK : high ATP concentration inhibits PFK, decreasing the enzyme's affinity for fructose-6-phosphate.

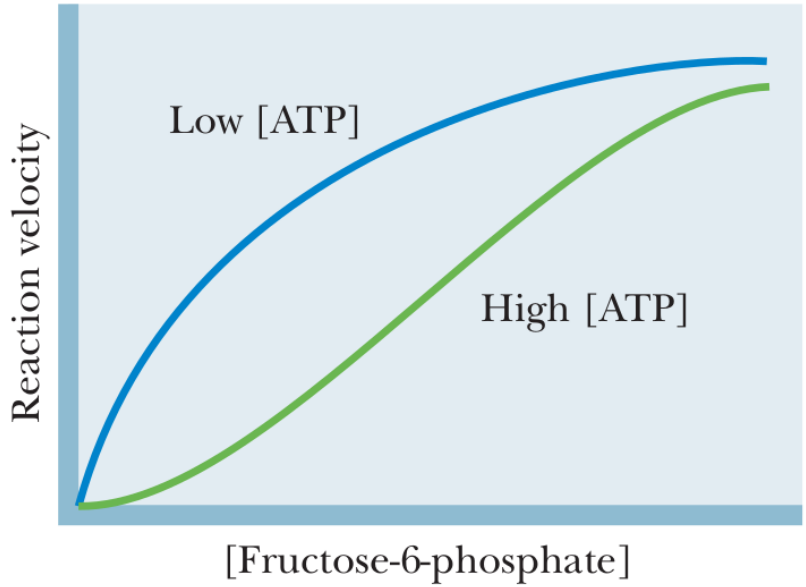
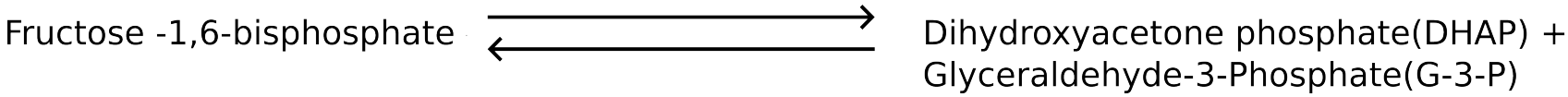


Figure – allosteric regulation of PFK(screenshot from [1])

Step 4 : FBP splits into two 3-carbon derivatives



Step 5 : Isomerase reaction —DHAP must be transformed into G3P :

> *"The other triose phosphate, dihydroxyacetone phosphate, must be converted to glyceraldehyde-3-phosphate by the enzyme* ***triose phosphate isomerase.****"(cf., op.cit., p.621)*

Step 6 : Dehydorgenase converts G3P into 1,3-bisphosphoglycerate

It's an **axidation** occuring together with a reduction of NADH.

Glyceraldehyde-3-Phosphate(G-3-P) + HPO_4^{2-} $\rightleftharpoons$ 1,3-bisphosphoglycerate + NADH + H^+

Figure – ez : G3P dehydrogenase

Step 7 : obtention of 3-phosphoglycerate

1,3-BPG + ADP $\rightleftharpoons$ 3-Phosphoglycerate(3-PG) + ATP

Step 8 : phosphoryl transfer by phosphoglycerate mutase–Change of position of the phosphate : $3-PG \longleftrightarrow 2-PG$. The reaction is catalyzed by phosphoglycerate mutase.

Step 9 : obtention of phosphoenolpuryvate(PEP)

$$\text{2-PG} \xrightleftharpoons{Mg^{2+}} \text{PEP} + H_2O$$

Figure – enzyme : enolase

Step 10 : PEP gives pyruvate

$$\text{PEP} + H^+ \xrightarrow[K^+]{Mg^{2+}} \text{Pyruvate} + ATP^{4-}$$

enzyme : Pyruvate kinase

Fate of pyruvate ?

- In aerobic conditions : transformed into Acetyl-CoA which enters Kreb's cycle (mito) ;
- In anaerobic conditions : **lactic fermentation** or **alcoholic fermentation**. The enzymes catalyzing these reactions are lactate dehydrogenase(LDH) and alcohol dehydrogenase.

Conclusion

Carbohydrates constitute one big class of molecules with major importance to human life. They manifest as the exclusive source of energy fueling the functioning of our brain among others. The breakdown of carbohydrates through digestion yields glucose molecules which are the primary substrates that enter the cell and undergoes the glycolysis. A glycolysis consists of 10 reactions involving two priming reactions which will be the target for regulatory processes. Finally, the final products, two pyruvates, are substrates for either Kreb's cycle(mitochondria) or fermentations according to whether the milieu is aerobic or anaerobic.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