III. 탄수화물 생합성(Carbohydrate biosynthesis)

1. Glycolysis (해당작용)의 합성적 역할

1) Dihydroxyacetone phosphate → **Glycerol-3-phosphate**

2) 3-Phosphoglyceric acid → Serine → Glycine → **Cysteine**

3) Pyruvate → **Alanine**

4) Phosphoenolpyruvate + Erythrose-4-phosphate

↓

C7 carboxylic acid : 1st step

↓

Chorismate

↙ ↓ ↘

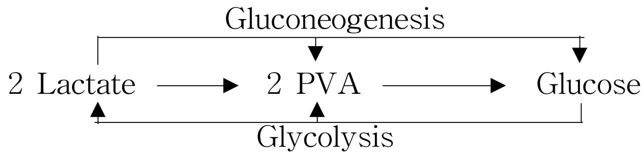
Phe, Tyr Trp

[Shikimate pathway]

＊ Chorismate is a key intermediate in the synthesis of the aromatic amino acids

5) Pyruvate → **oxaloacetate**
(pyruvate carboxylase)

2. 당신형성작용(Gluconeogenesis) : 당신합성작용



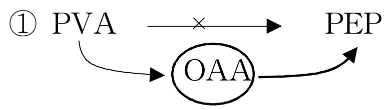
* **Three glycolytic reactions are irreversible (3개의 당분해반응은 비가역적이다)**

1st reaction : **hexokinase** (Glc → Glc-6-ⓟ)

2nd reaction : **PFK-1** (Fru-6-ⓟ → Fru-1, 6-bisphosphate)

3rd reaction : **pyruvate kinase** (PEP → PVA)

1) The by pass reactions of gluconeogenesiss(당신합성작용의 우회반응)



1st step : PVA + CO_2 + H_2O → Oxaloacetate (OAA)
(ATP → ADP)

효소 : **[pyruvate carboxylase]**

위치 : **mitochondria에 존재**

조효소(coenzyme) : **biotin**

* **Oxaloacetate (OAA)는 mitochondria막을 통과하지 못함**

2nd step : OAA ⟶ PEP
GTP   GDP

* 효소 : **[PEP carboxykinase]**

* 위치 : **세포질(cytosol)에 존재**

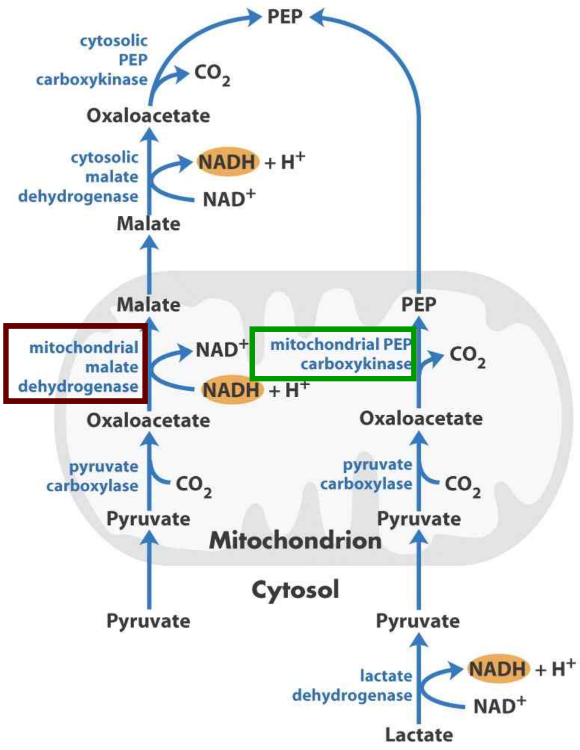


Fig. Alternative paths from pyruvate to phosphoenolpyruvate

2) Fructose-1,6-bisphosphate ⟶ fructose-6-phosphate + Pi

[Fructose-1,6-bisphosphatase]

- allosteric enzyme
- activated by citrate
- inhibited by AMP and fructose-2,6-bisphosphate

3) Glucose-6-phosphate ⟶ Glucose

[Glucose-6-phosphatase]

- found in liver and kidney **(간, 신장에 존재)**
- not ATP product (ATP를 생산하지 않는다)

*** Gluconeogenesis is energetically expensive, but essential**

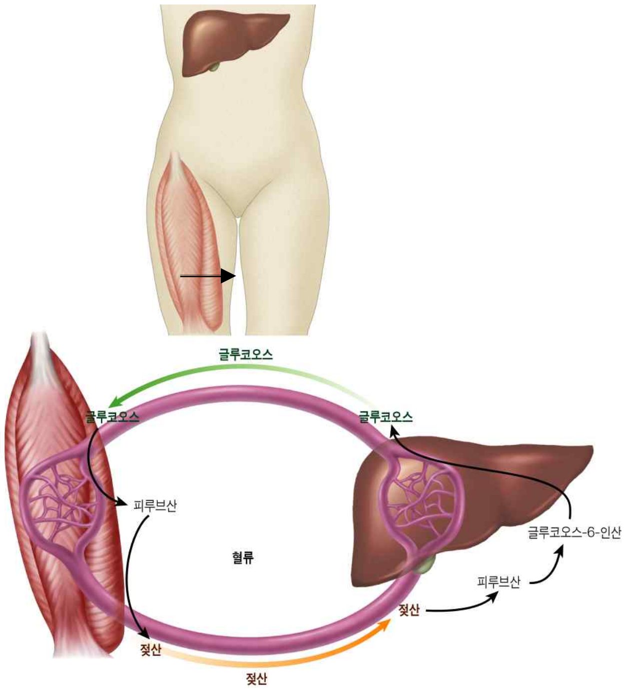
2 Pyruvate + 4ATP + 2GTP + 2NADH + 2H+ + 4H2O →
glucose + 4ADP + 2GDP +6Pi + 2NAD+

3. Gluconeogenesis substrates (당신합성작용기질)

1) Lactate (젖산)

- released in muscle (근육에서 방출)
- transferred to the liver (간으로 전달)
- converted to glucose (글루코스로 전환)

◎ Cori cycle



☞ Cori 회로 :

격렬한 운동을 하는 동안(혐기적조건)에 근육에서 생성된 젖산은 혈액을 통해 간으로 운반되어 gluconeogenesis에 의하여 glucose 로 전환되어 재사용

2) Glycerol

- produce by fat metabolism(지방대사에 의해서 생성된다)
- converted to glycerol-3-phosphate
- glycerol-3-phosphate ⟶ DHAP (해당작용 중간산물)

3) Glucogenic amino acid

Amino acids that can be converted to glycolytic intermediates
(해당작용의 중간산물로 전환될 수 있는 아미노산)

ex) Alanine ⟶ Pyruvate

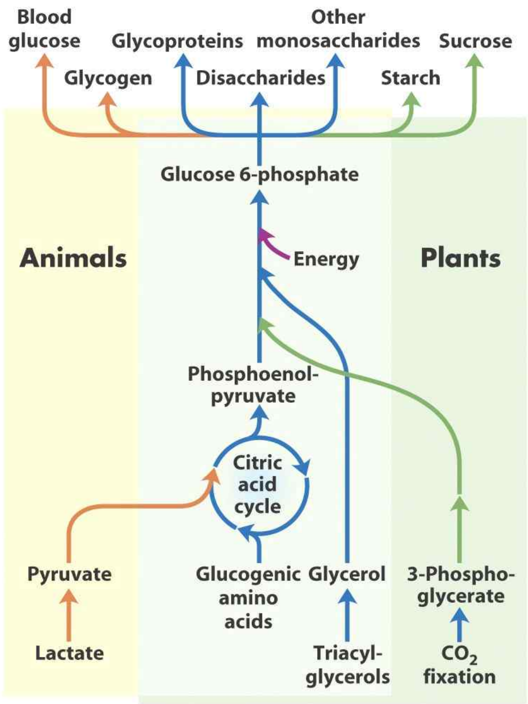


Fig. Carbohydrates synthesis from simple precursors

4. 당신합성작용조절 (Gluconeogenesis regulation)

1) The hormonal regulation in liver is mediated by **fructose-2,6-bisphosphate**

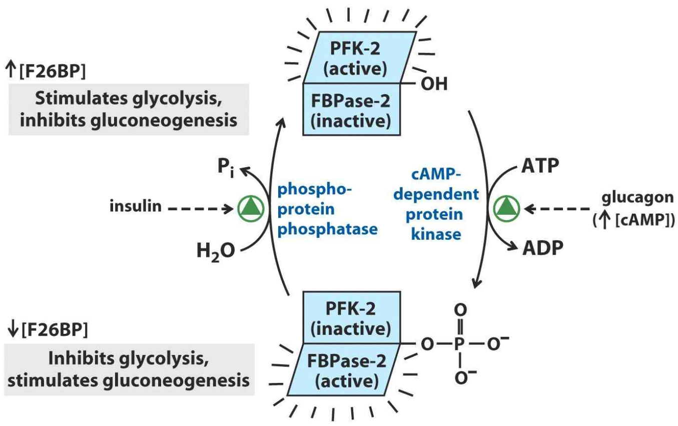
① Fructose-2,6-bisphosphate is an **allosteric effector** for PFK-1 and FBPase-1

☞ Fructose-2,6-bisphosphate (high level)

- 해당작용은 촉진하고 당신합성작용은 억제한다
- PFK-2 (active), FBPase-2 (inactive)

☞ Fructose-2,6-bisphosphate (low level)

- 해당작용을 억제하고 당신합성작용을 촉진한다
- PFK-2 (inactive), FBPase-2 (active)



② The cellular level of fructose-2,6-bisphosphatate is regulated by **glucagon and insulin**

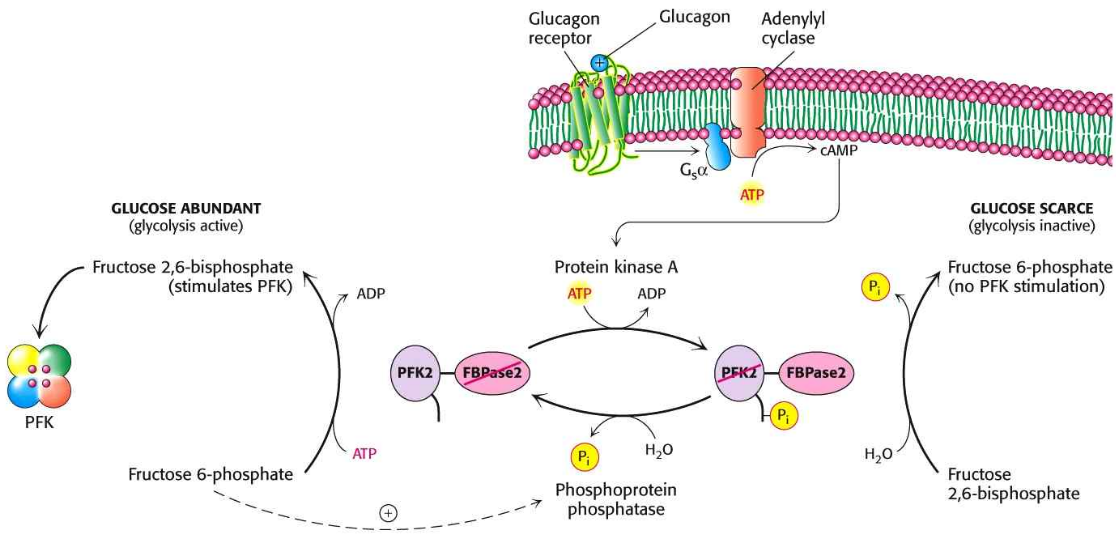


Fig. Control of the synthesis and degradation of fructose 2,6-bisphosphate

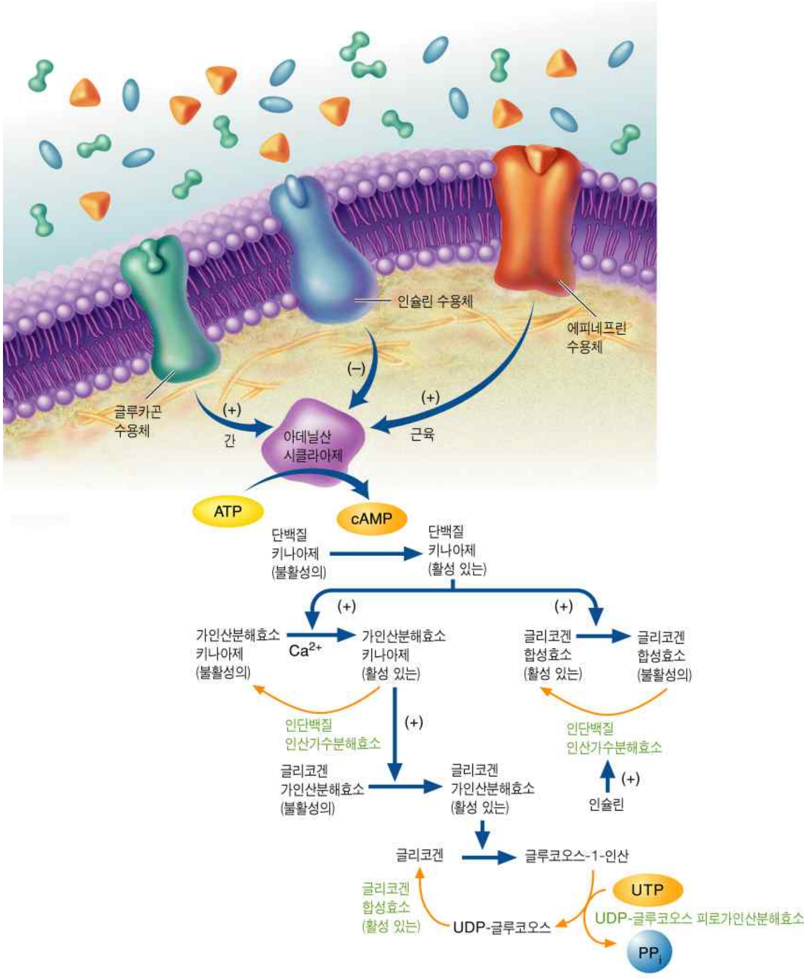


Fig. Glycogen 대사에 영향을 주는 중요한 요인 (Glucagon, epinephrine)

③ Glucagon stimulate adenylate cyclase

ATP ⟶ cAMP

* cAMP : second messenger(2차전달자)

cAMP dependent protein kinase 활성화

2) Gluconeogenesis and glycolysis are reciprocally regulated

① **1st control point**

- Pyruvate dehydrogenase complex

Pyruvate ⟶ acetyl-CoA

- Pyruvate carboxylase

Pruvate ⟶ oxaloacetate(OAA)

acetyl-CoA (activator)

② **2nd control point**

- Fructose-1,6-bisphosphatase-1 : inhibited by AMP
- Phosphofructokinase-1 : stimulated by AMP

inhibited by citrate, ATP

③ The hormonal regulation of glycolysis and gluconeogenesis in liver is mediated by fructose-2,6-bisphosphate.

④ Fructose-2,6-bisphosphate is an allosteric effector for the enzyme (PFK-1) and FBPase-1

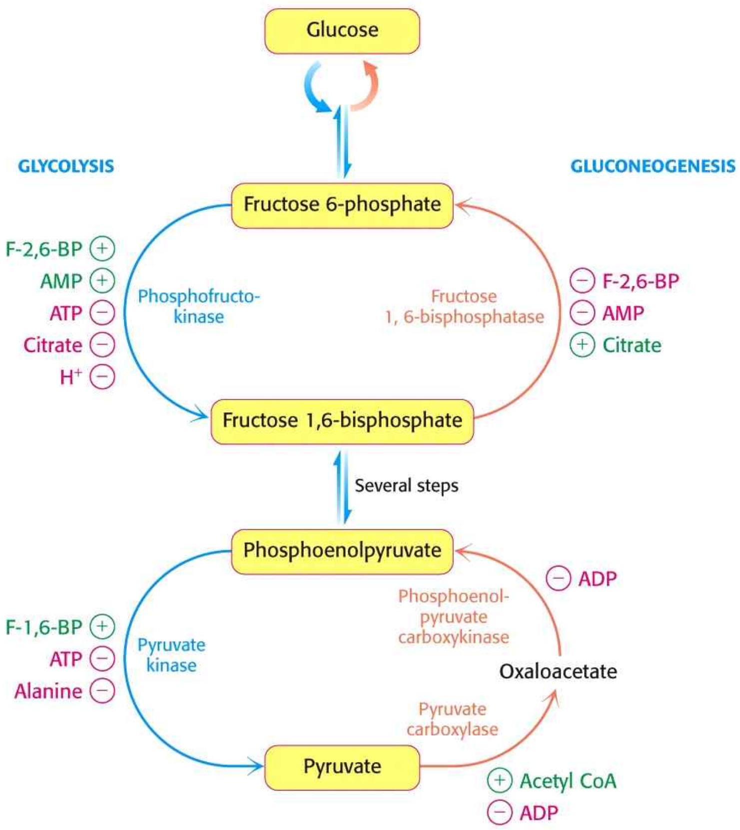


Fig. Reciprocal regulation of gluconeogenesis and glycolysis in the liver

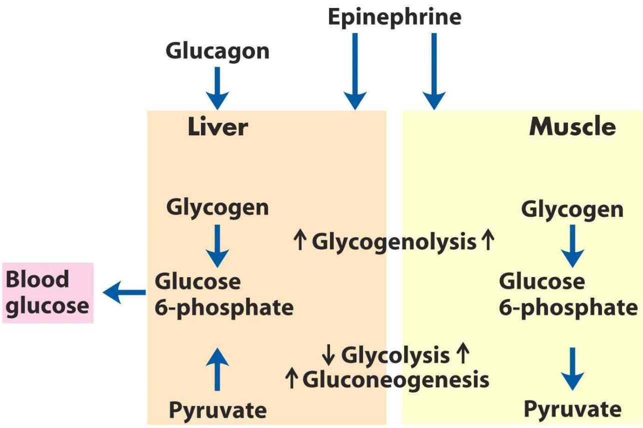


Fig. Difference in the regulation of carbohydrate metabolism in liver and muscle

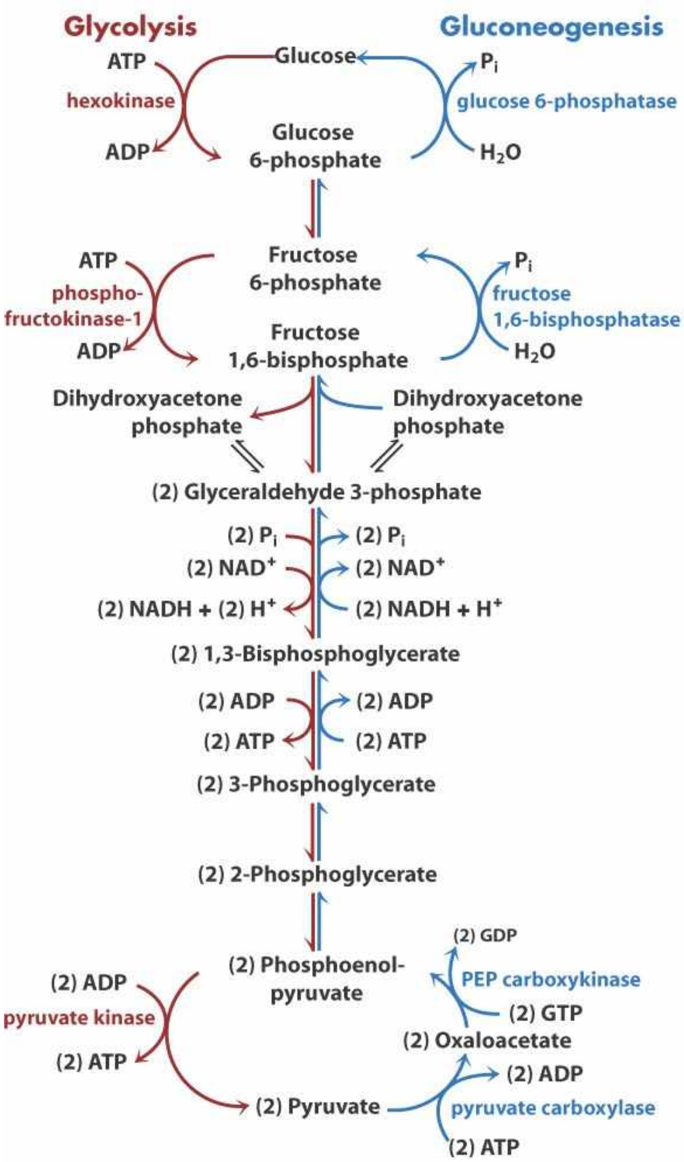


Fig. Opposing pathways of glycolysis and gluconeogenesis in rat liver.

5. Biosynthesis of glycogen, starch and sucrose

* 비환원당말단(nonreducing end)에 단당 단위를 순서적으로 첨가한다.
* **UDP-glucose** is the substrate for glycogen and sucrose synthesis.
  ADP-glucose is the substrate for starch synthesis

1) Sugar nucleotide (UDP-glucose)의 형성

* Sugar phosphate + NTP ⟶ sugar nucleotide (NDP-sugar) + PPi
  (phosphorylase) (pyrophosphate)
* Pyrophosphate ⟶ 2 phosphate
  (pyrophosphatase)

① Glucose + ATP ⟶ glucose-6-ⓟ ⇄ glc-1-ⓟ
(hexokinase) (phosphoglucomutase)

② (Glycogen)n + H_3PO_4 ⟶ (glycogen)n-1 + glc-1-ⓟ
(phosphorylase a)

③ Glucose-1-ⓟ + UTP ⟶ UDP-glucose + PPi
(UDP-glucose pyrophosphorylase)

☞ The formation of UDP-glucose is a key reaction in glycogen biosynthesis.

④ NDP-sugar + acceptor ⟶ NDP + sugar-acceptor

2) Sucrose의 생합성

Fructose-6-ⓟ + UDP-glucose
↓ ← sucrose-6-phosphate synthase
Glucose-Fructose-6-ⓟ + UDP
(sucrose-6-phosphate)
↓ H_2O phosphatase
Sucrose + H_3PO_4

* Sucrose synthetase (in plant)
  Sucrose + UDP ⇄ UDP-glucose + fructose [cellulose biosyhthesis]
  Sucrose + ADP ⇄ ADP-glucose + fructose [starch biosynthesis]

3) 다른 다당류의 합성

① UDP-glucose ⟶ UDP-glucuronate (dehydrogenase; $2NAD^+$ → $2NADH + 3H^+$, $2H_2O$)

UDP-glucuronate ⟶ UDP-xylose + CO_2
(decarboxylase)

* **Glucuronic acid oxidation pathway**

② Amino sugar의 생합성(참조)

Fructose-6-ⓟ + glutamate ⟶ **Glucosamine-6-ⓟ**
amidotransferase

Glucosamine-6-ⓟ + acetyl-CoA ⟶ N-acetylglucosamine-6-ⓟ
acetyltransferase

N-acetylglucosamine-6-ⓟ ⟶ N-acetylglucosamine-1-ⓟ
mutase

N-acetylglucosamine-1-ⓟ + UTP → UDP-N-acetylglucosamine + PPi
pyrophophorylase

UDP-acetylglucosamine ⟶ UDP-N-acetylgalactosamine
epimerase ↘ UDP-N-acetylmannosamine

☞ 심화학습

1. Control of the synthesis and degradation of fructose 2,6-bisphosphate
   1) A low blood-glucose level as signaled by glucagon leads to the phosphorylation of the bifunctional enzyme and hence to a low level of fructose 2,6-bisphosphate, slowing glycolysis.
   2) High levels of fructose 6-phosphate accelerate the formation of fructose 2,6-bisphosphate by facilitating the dephosphorylation of the bifunctional enzymes

Table The effects of glucagon, epinephrine, and insulin on carbohydrate metabolism in mammals			
Hormone	**Glucagon**	**Epinephrine**	**Insulin**
Source	Pancreatic α cells	Adrenal medulla	Pancreatic β cells
Primary target	Liver	Muscle>liver	Muscle, liver adipose
Effects on			
[cAMP]	↑	↑	↓
[Fructose-2,6-bisphophate]	↓	↓	↑
[Gluconeogenesis]	↑	↑	↓
[Glycogen breakdown]	↑	↑	↓
(Glycolysis)			

* **인슐린은 탄수화물과 지방대사에 관여하는 많은 유전자의 발현을 변화시킨다.**
  ex) 최대 1500여개의 유전자 발현을 조절
* **탄수화물과 지질대사는 호르몬과 입체다른자리 기전에 의해 통합 조절된다.**
* **간과 근육의 탄수화물대사조절의 차이점은?**

◎ Principles of metabolic regulation : glucose and glycogen

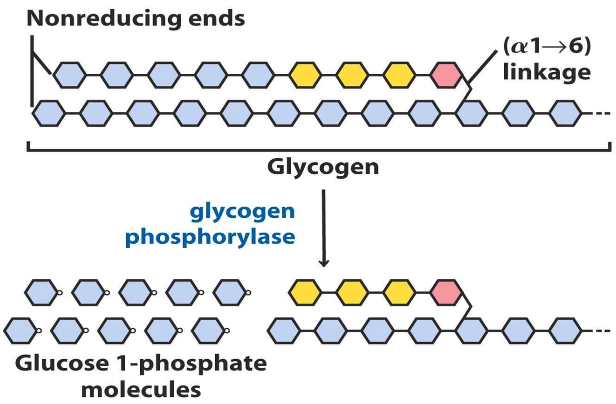


Fig. Glycogen 분해는 glycogen phosphorylase에 의하여 촉매된다

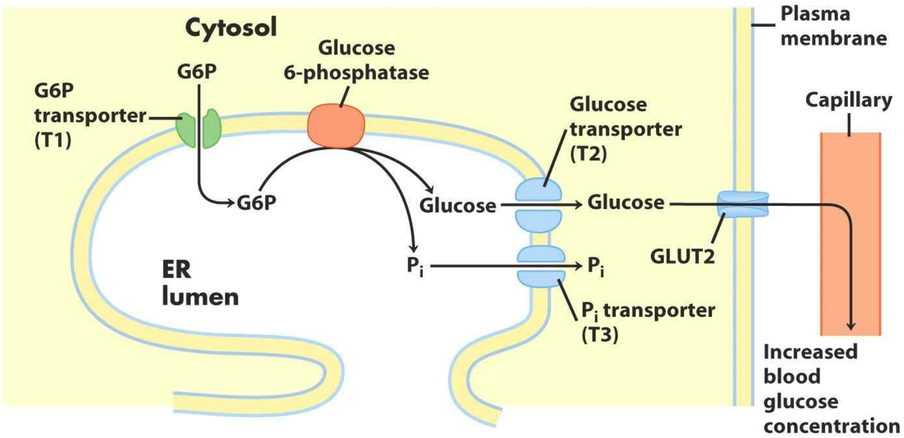


Fig. Hydrolysis of glucose 6-phosphate by glucose 6-phosphatase of the ER

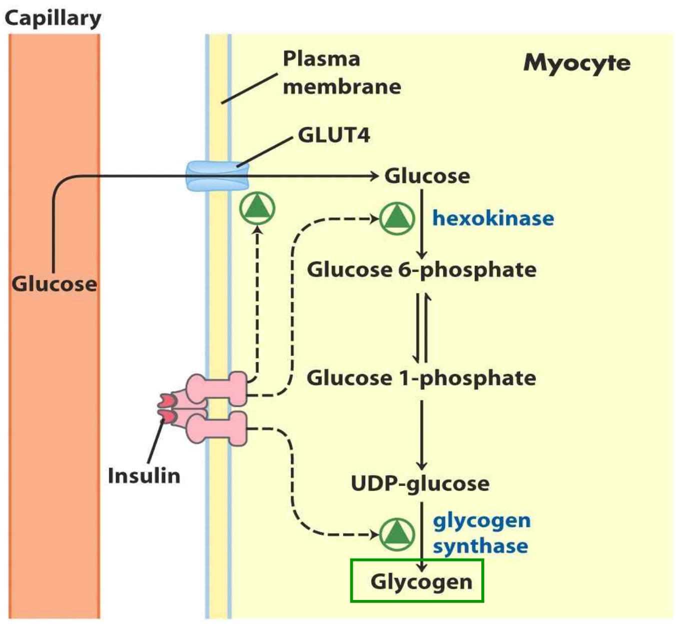


Fig. Control of glycogen synthesis from blood glucose in myocytes

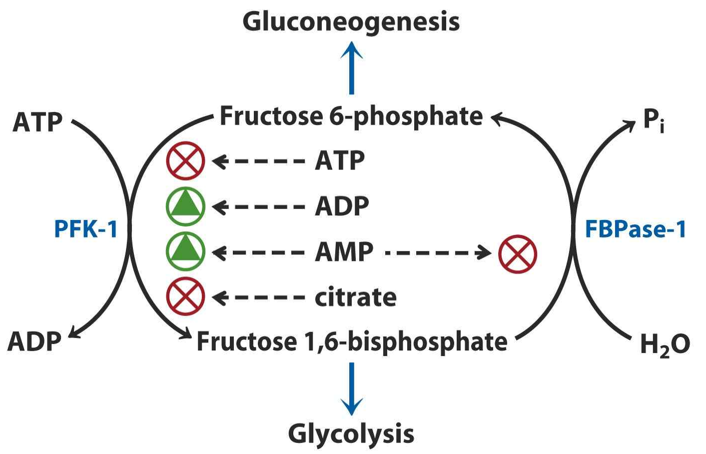


Fig. Regulation of fructose 1,6 bisphosphatase-1(FBPase-1) and phosphofructokinase-1(PFK-1)

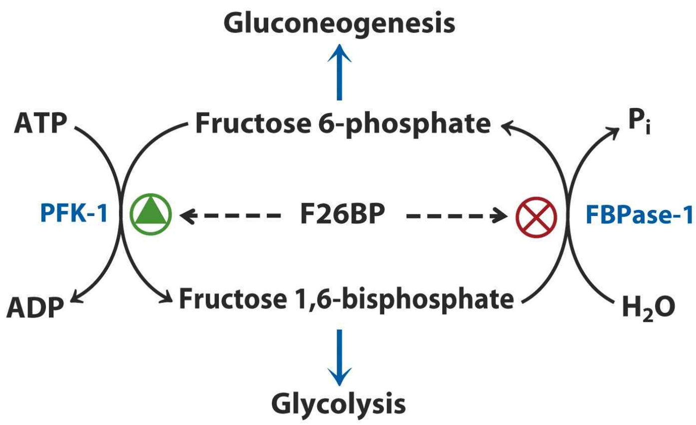


Fig. Role of fructose 2,6 bisphosphate in regulation of glycolysis and gluconeogenesis.

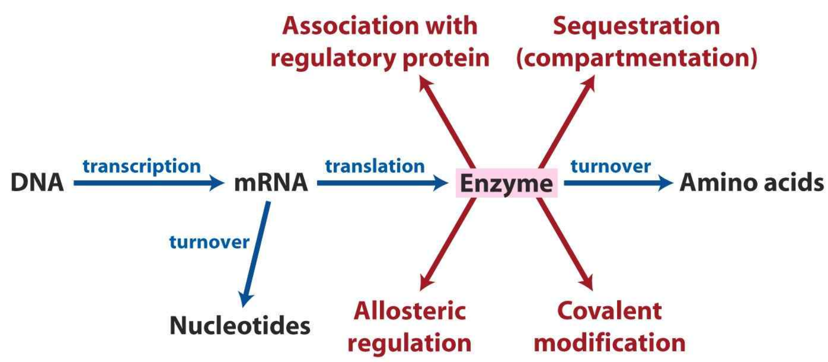
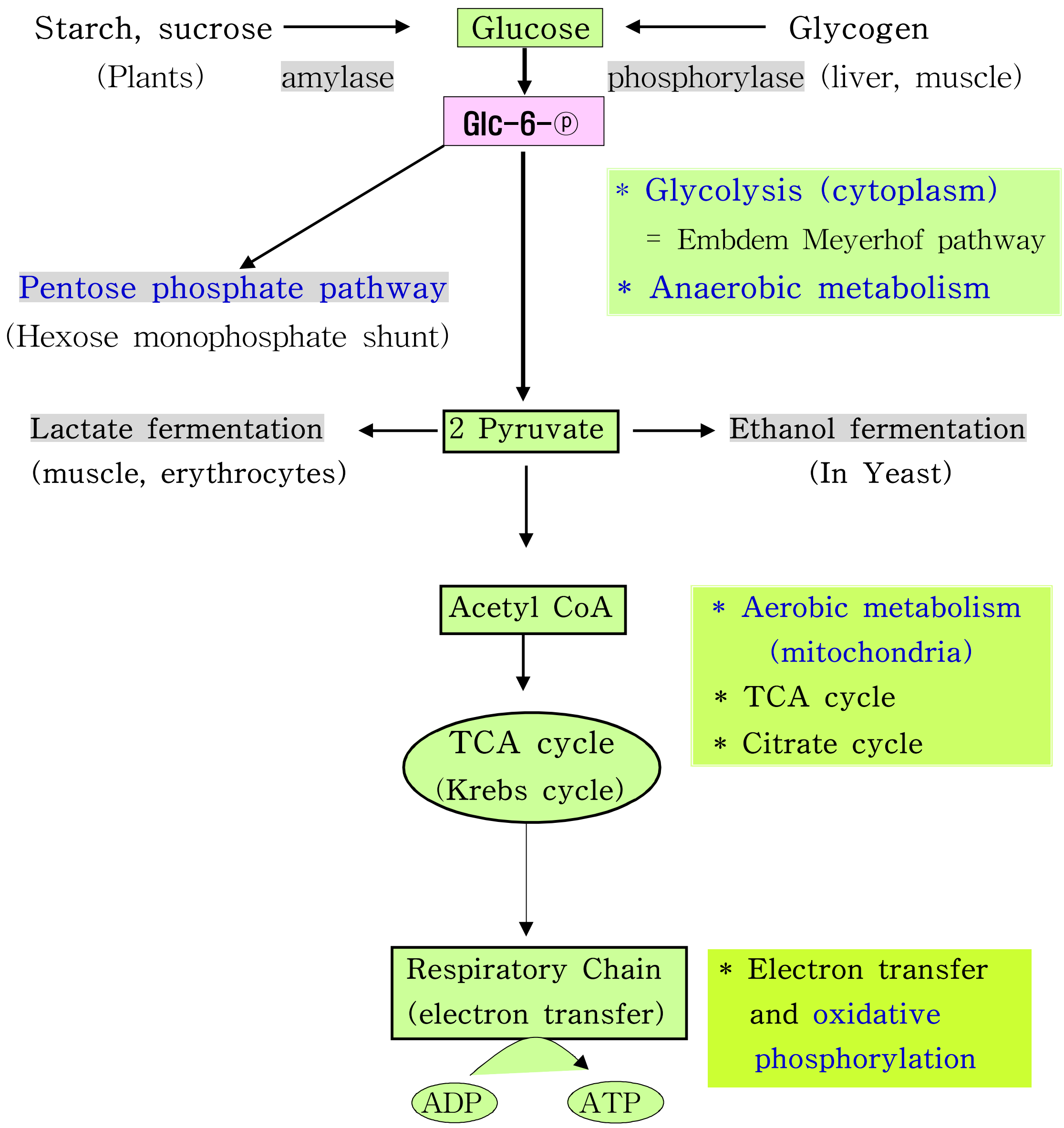


Fig. Factors that determine the activity of an enzyme

◎ Carbohydrate catabolism



◎ Catabolism of carbohydrate

- Glycolysis (해당작용)
- Pentose phosphate Pathway (5탄당 대사)
- TCA cycle = Citrate cycle
- Cori cycle
- Gluconeogenesis

◎ Oxidative phosphorylation

핵심용어

Glycogenolysis - 글리코겐분해
Gluconeogenesis - 글루코스 신합성
Debranching enzyme - 가지제거 효소
Sugar nucleotide - 당 뉴클레오타이드
Adenylase kinase - 아데닐산 카이네이스
Futile cycle - 낭비회로
Glucagon - 글루카곤
Priming - 시발
Glycolysis - 당분해
Glycogenesis - 글리코겐합성
Glycogenin - 글리코게닌
Homeostasis - 항상성
Metabolic regulation - 대사조절
Substrate cycle - 기질회로
Enzyme cascade - 효소연쇄증폭

문제풀이 : 당분해속도에서 산소공급의 효과

건강한 세포에서 당분해의 조절단계는 아무 조직이나 기관에서 글루코스의 이화를 연구함으로써 확인할 수 있다. 예를 들면, 심근에 의한 글루코스의 소비는 분리된 건강한 심장을 통하여 인공적으로 순환되는 혈액에 의해 측정될 수 있으며, 심장을 통한 혈액의 순환 전후의 혈당의 농도를 측정함으로써 가능하다. **만약 순환되는 혈액에서 산소가 제거된다면 심장근육은 일정한 속도로 글루코스를 소비하게 된다. 이때 산소를 혈액에 공급하게 되면 글루코스 소비 속도는 현저하게 떨어지며 새롭게 낮은 속도로 유지된다. 그 이유를 설명하라.**