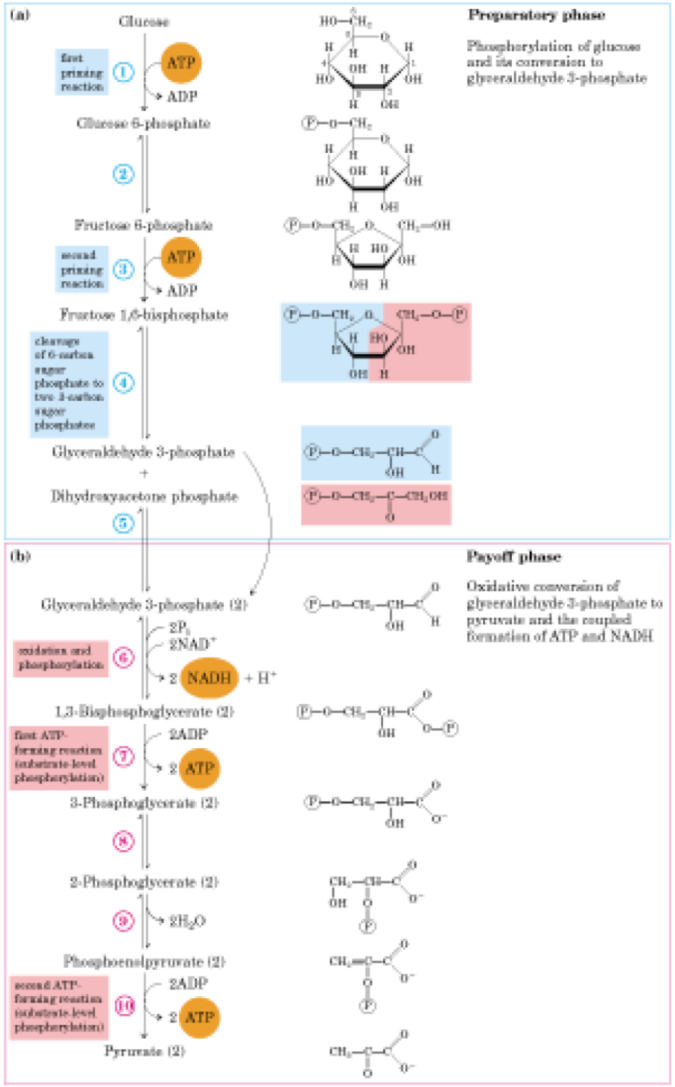

(a)
Glucose
first priming reaction
1
ATP
ADP
Glucose 6-phosphate
2
Fructose 6-phosphate
second priming reaction
3
ATP
ADP
Fructose 1,6-bisphosphate
cleavage of 6-carbon sugar phosphate to two 3-carbon sugar phosphates
4
Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
5
Preparatory phase
Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate
(b)
Glyceraldehyde 3-phosphate (2)
oxidation and phosphorylation
6
2 Pi
2 NAD+
2 NADH + H+
1,3-Bisphosphoglycerate (2)
first ATP-forming reaction (substrate-level phosphorylation)
7
2 ADP
2 ATP
3-Phosphoglycerate (2)
8
2-Phosphoglycerate (2)
9
2 H2O
Phosphoenolpyruvate (2)
second ATP-forming reaction (substrate-level phosphorylation)
10
2 ADP
2 ATP
Pyruvate (2)
Payoff phase
Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate and the coupled formation of ATP and NADH

- O cérebro necessita de cerca de 120 g de glicose/dia, isso é mais que a metade de toda a glicose
- estocada no fígado e músculo.

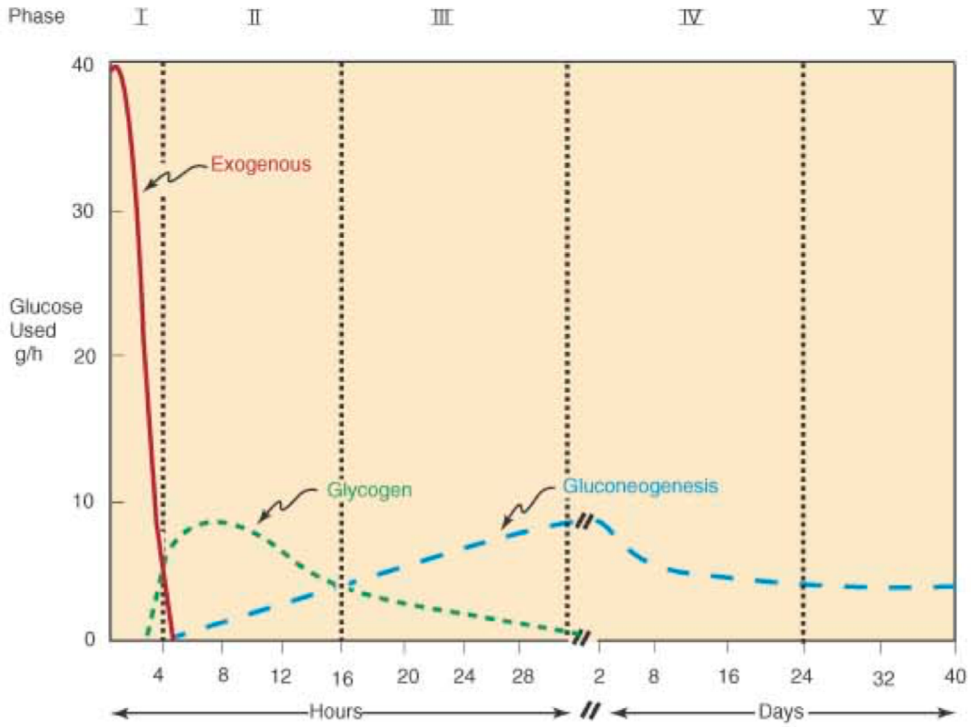
- Entre as refeições, jejuns ou depois de exercícios físicos vigorosos, o glicogênio é depletado

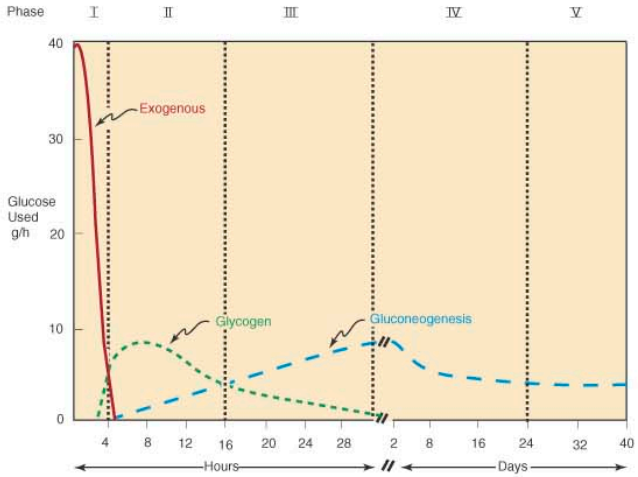
Gliconeogênese

- A capacidade de sintetizar glicose é crucial para a sobrevivência dos animais
- Os níveis de glicose sanguínea devem ser mantidos, para sustentar o metabolismo de tecidos que utilizam glicose como substrato primário.
- Esses tecidos incluem: cérebro, eritrócitos, medula renal, retina, mucosa intestinal, entre outros.

Manutenção da glicemia

- O organismo dispõe de mecanismos para manter a glicemia mesmo em tempos afastados das refeições.
- À medida que vai diminuindo a concentração de glicose circulante derivada da ingestão de alimentos, a degradação do glicogênio hepático incube-se de manter a glicemia.
- Essa reserva é limitada e insuficiente para além de 8 horas de jejum.
- Gliconeogênese se processa no fígado e minoritariamente nos rins.


Phase
I
II
III
IV
V
40
30
20
10
0
Glucose Used g/h
Exogenous
Glycogen
Gluconeogenesis
4
8
12
16
20
24
28
2
8
16
24
32
40
Hours
Days

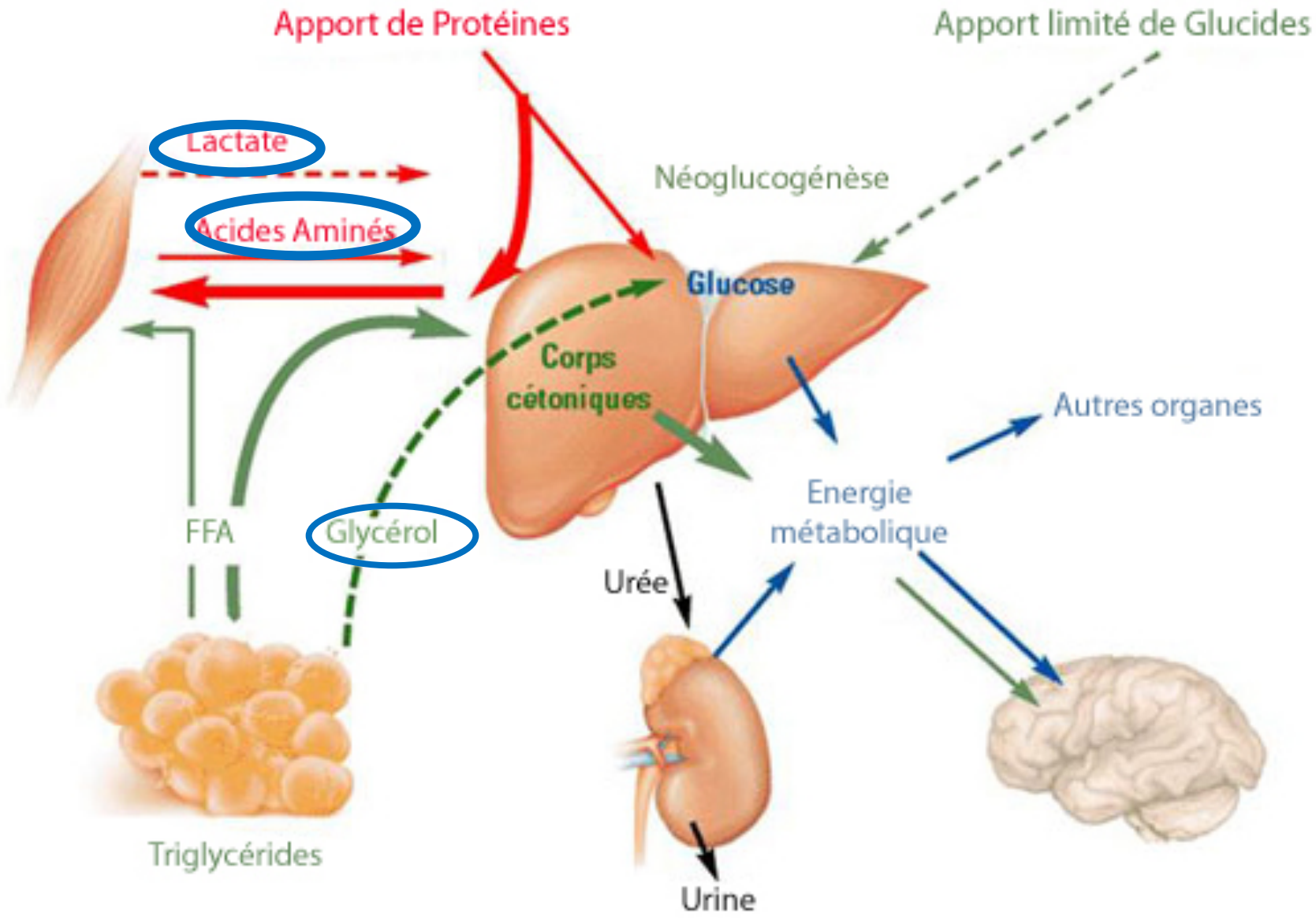


Phase	ORIGIN OF BLOOD GLUCOSE	TISSUES USING GLUCOSE	MAJOR FUEL OF BRAIN
I	Exogenous	All	Glucose
II	Glycogen Hepatic gluco–neogenesis	All except liver. Muscle and adipose tissue at diminished rates	Glucose
III	Hepatic gluconeogenesis Glycogen	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Glucose
IV	Gluconeogenesis, hepatic and renal	Brain, RBCs, renal medulla. Small amount by muscle	Glucose, ketone bodies
V	Gluconeogenesis, hepatic and renal	Brain at a diminished rate, RBCs, renal medulla	Ketone bodies, glucose

Figure 22.9. The five phases of glucose homeostasis. Reprinted with permission from Ruderman, N. B., Aoki,T. T., and Cahill, G. F., Jr. Gluconeogenesis and its disorders in man. In: R. W. Hanson, and M. A. Mehlman (Eds.), *Gluconeogenesis, Its Regulation in Mammalian Species*. New York: Wiley, 1976, p. 515.

Cérebro e hemácias dependem de glicose

Nos mamíferos a gliconeogênese ocorre
ocorre principalmente no fígado. ***Ocorre** em menor extensão também no rim.
Utiliza muitas das enzimas da Glicólise..


Apport de Protéines
Apport limité de Glucides
Lactate
Acides Aminés
Néoglucogénèse
Glucose
Corps cétoniques
Autres organes
Energie métabolique
FFA
Glycérol
Urée
Triglycérides
Urine

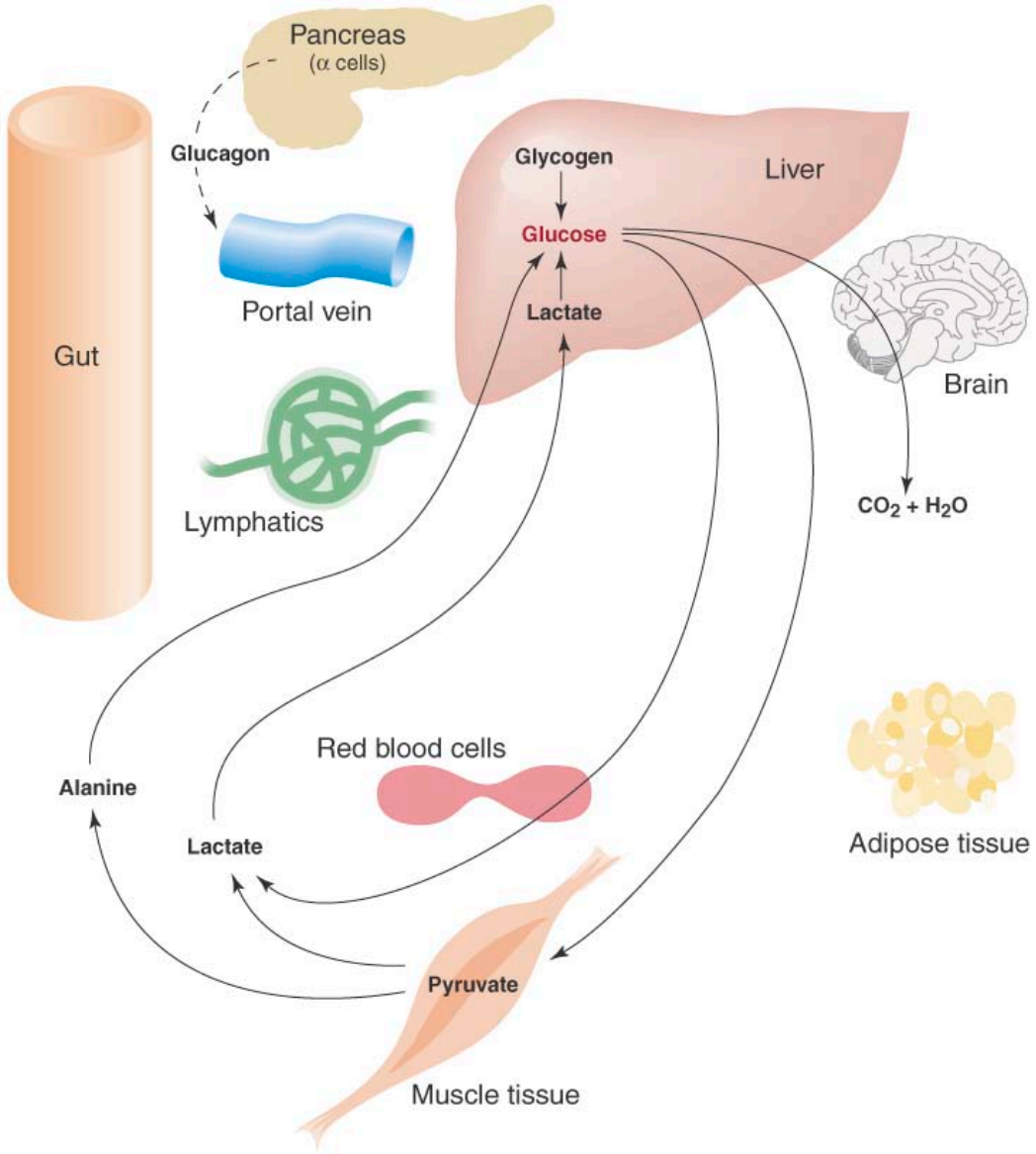
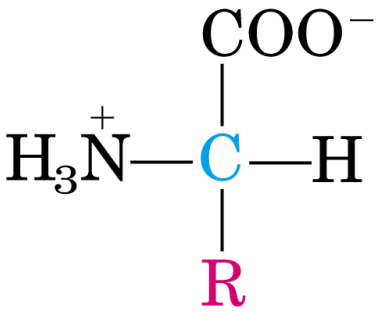


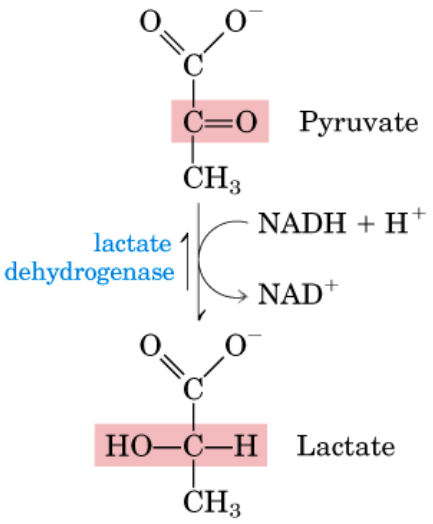
Figure 22.3. Metabolic interrelationships of major tissues in early fasting state.

Gliconeogênese

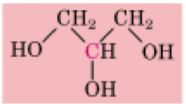
Síntese de glicose a partir de compostos que não são carboidratos:

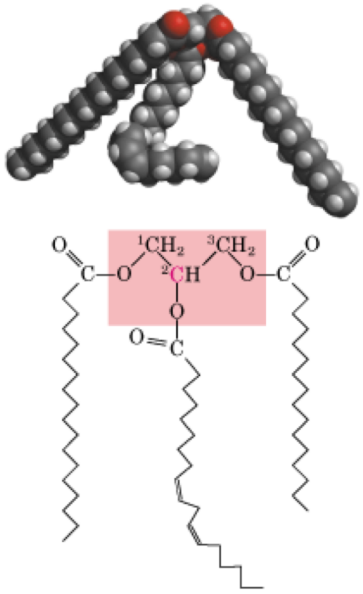
Aminoácidos, lactato e glicerol



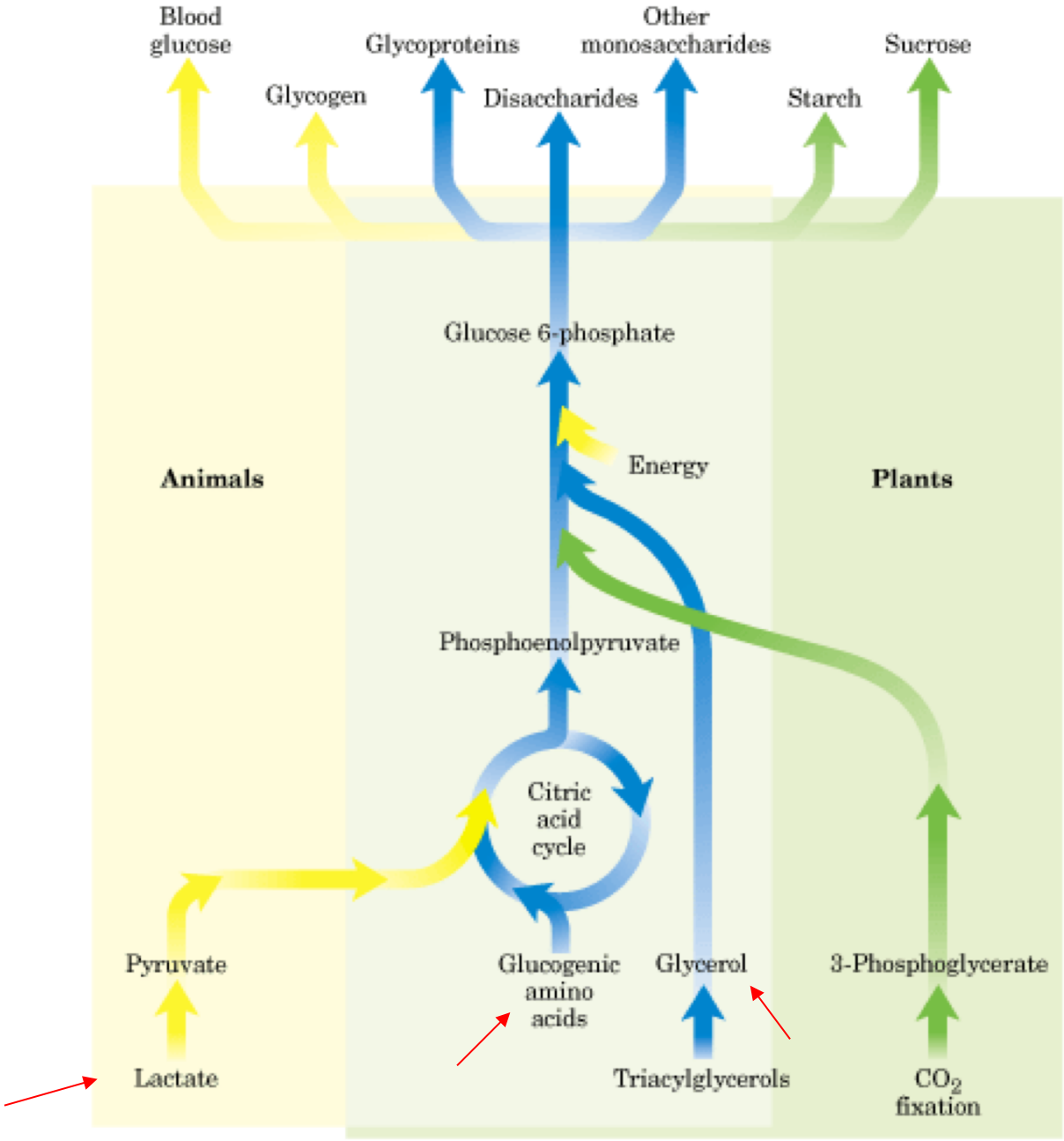


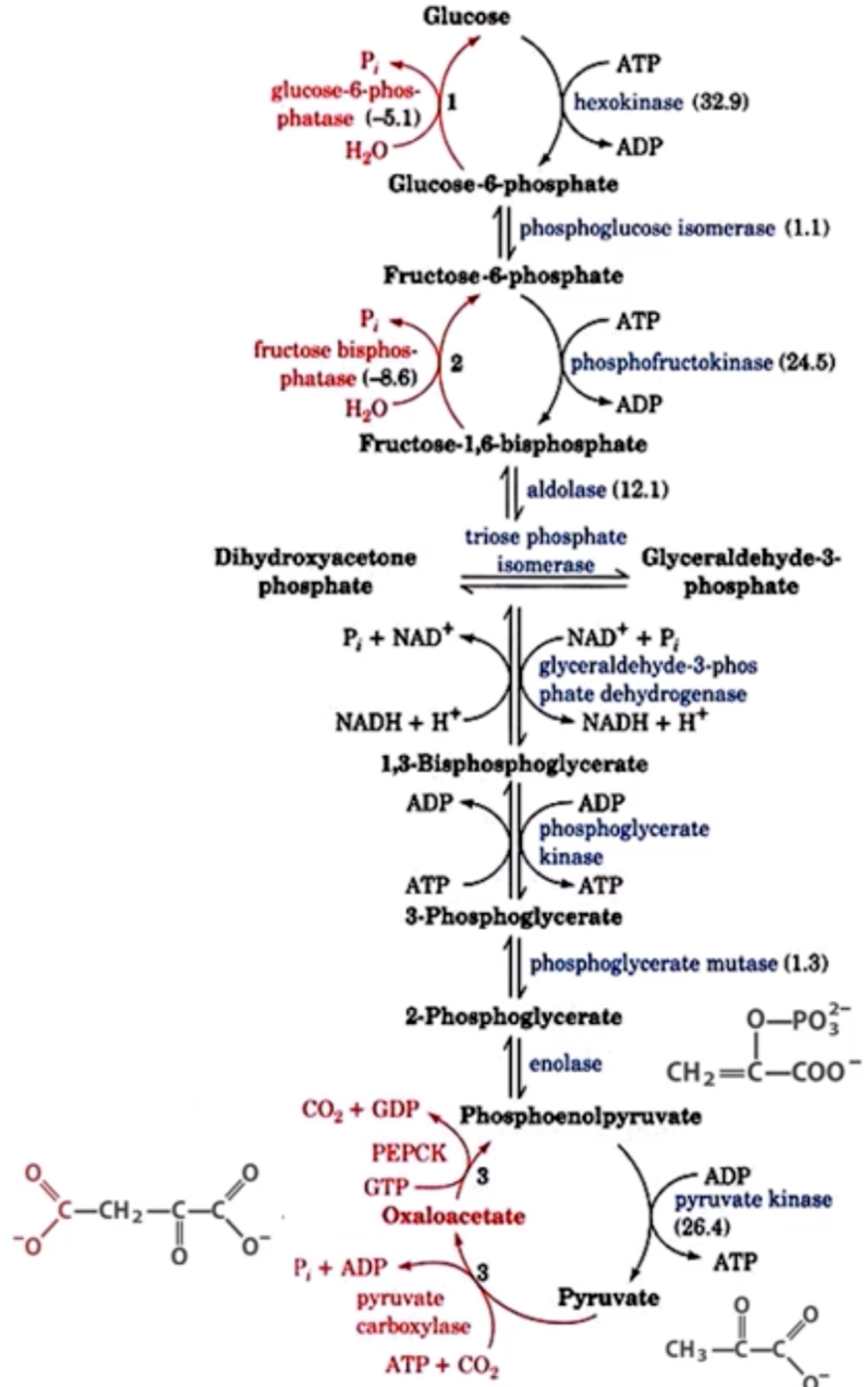
$\Delta G'^{\circ} = -25.1$ kJ/mol



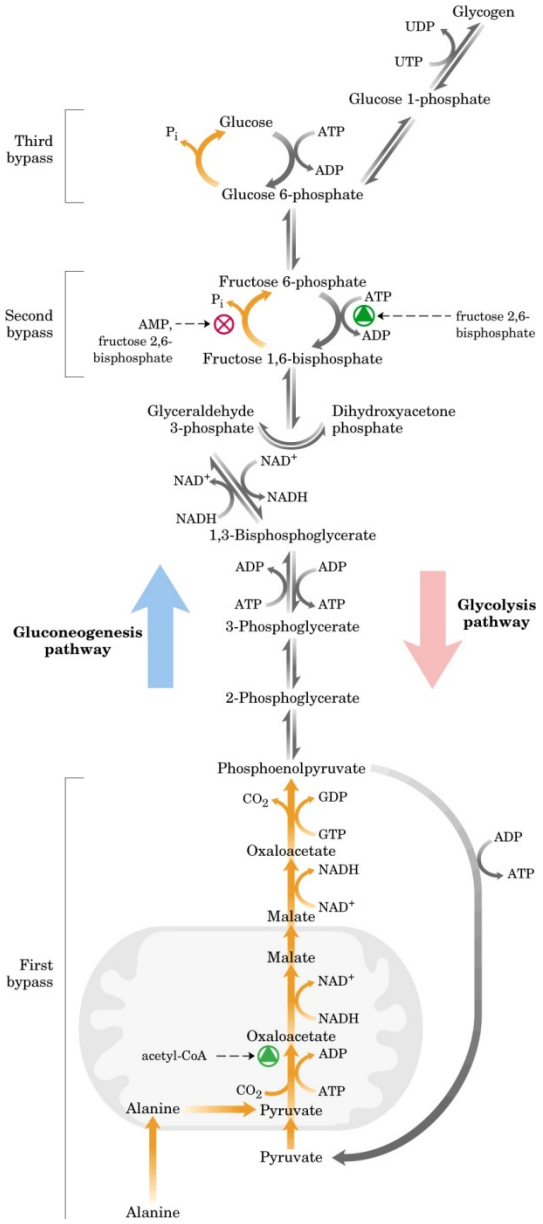


1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol, a mixed triacylglycerol


Blood glucose
Glycogen
Glycoproteins
Disaccharides
Other monosaccharides
Starch
Sucrose
Glucose 6-phosphate
Energy
Animals
Plants
Phosphoenolpyruvate
Citric acid cycle
Pyruvate
Glucogenic amino acids
Glycerol
3-Phosphoglycerate
Lactate
Triacylglycerols
CO_2 fixation


Glucose
P_i
glucose-6-phos-
phatase (–5.1)
H_2O
1
ATP
hexokinase (32.9)
ADP
Glucose-6-phosphate
phosphoglucose isomerase (1.1)
Fructose-6-phosphate
P_i
fructose bisphos-
phatase (–8.6)
H_2O
2
ATP
phosphofructokinase (24.5)
ADP
Fructose-1,6-bisphosphate
aldolase (12.1)
Dihydroxyacetone
phosphate
triose phosphate
isomerase
Glyceraldehyde-3-
phosphate
P_i + NAD^+
$NADH + H^+$
$NAD^+ + P_i$
glyceraldehyde-3-phos
phate dehydrogenase
$NADH + H^+$
1,3-Bisphosphoglycerate
ADP
ATP
ADP
phosphoglycerate
kinase
ATP
3-Phosphoglycerate
phosphoglycerate mutase (1.3)
2-Phosphoglycerate
enolase
$CH_2=C(-O-PO_3^{2-})-COO^-$
CO_2 + GDP
PEPCK
GTP
3
Phosphoenolpyruvate
Oxaloacetate
ADP
pyruvate kinase
(26.4)
ATP
P_i + ADP
pyruvate
carboxylase
ATP + CO_2
3
Pyruvate
$CH_3-C(=O)-COO^-$

3 passos da glicólise são irreversíveis



Reações com energia livre muito negativas têm que ser substituídas na gliconeogênese por reações que tornem essa via termodinamicamente favorável.

table 20–1

Free-Energy Changes of Glycolytic Reactions in Erythrocytes*

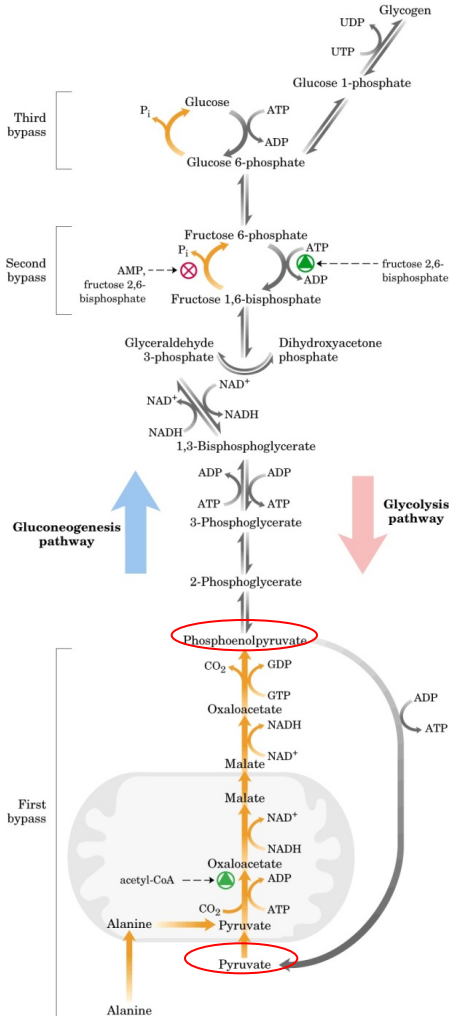
Glycolytic reaction step	$\Delta G'^{\circ}$ (kJ/mol)	ΔG (kJ/mol)
① Glucose + ATP ⟶ glucose 6-phosphate + ADP + H^+	−16.7	−33.4
② Glucose 6-phosphate ⇌ fructose 6-phosphate	1.7	−2.5
③ Fructose 6-phosphate + ATP ⟶ fructose 1,6-bisphosphate + ADP + H^+	−14.2	−22.2
④ Fructose 1,6-bisphosphate ⇌ dihydroxyacetone phosphate + glyceraldehyde 3-phosphate	23.8	−1.25
⑤ Dihydroxyacetone phosphate ⇌ glyceraldehyde 3-phosphate	7.5	2.5
⑥ Glyceraldehyde 3-phosphate + P_i + NAD^+ ⇌ 1,3-bisphosphoglycerate + NADH + H^+	6.3	−1.7
⑦ 1,3-Bisphosphoglycerate + ADP ⇌ 3-phosphoglycerate + ATP	−18.8	1.25
⑧ 3-Phosphoglycerate ⇌ 2-phosphoglycerate	4.4	0.8
⑨ 2-Phosphoglycerate ⇌ phosphoenolpyruvate + H_2O	7.5	−3.3
⑩ Phosphoenolpyruvate + ADP + H^+ ⟶ pyruvate + ATP	−31.4	−16.7

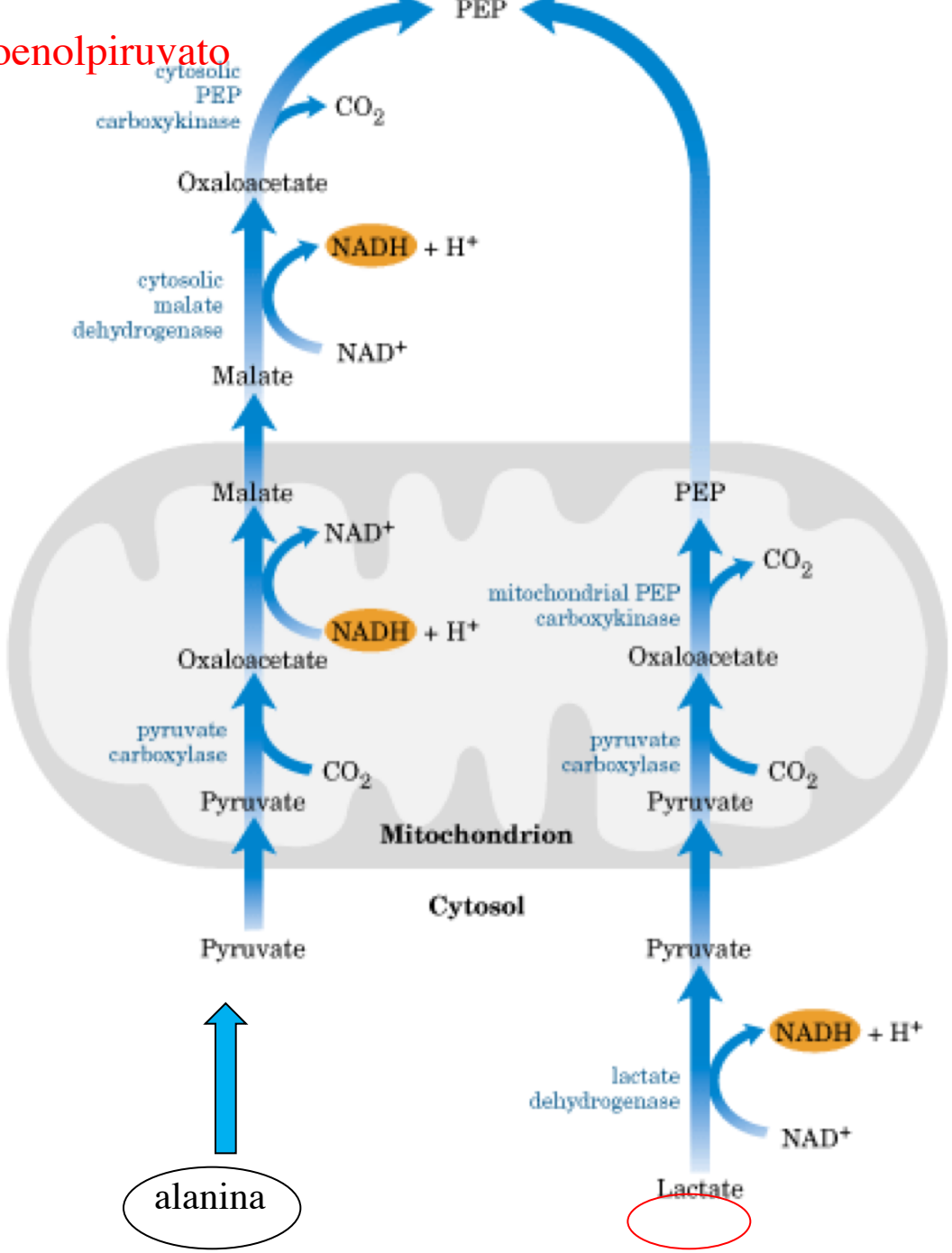
*$\Delta G'^{\circ}$ is the standard free-energy change, as defined in Chapter 14 (see p. 494). At pH 7.0, ΔG is the free-energy change calculated from the actual concentrations of glycolytic intermediates present under physiological conditions in erythrocytes. The glycolytic reactions bypassed in gluconeogenesis are shown in red.

Etapa 1: piruvato a fosfoenolpiruvato

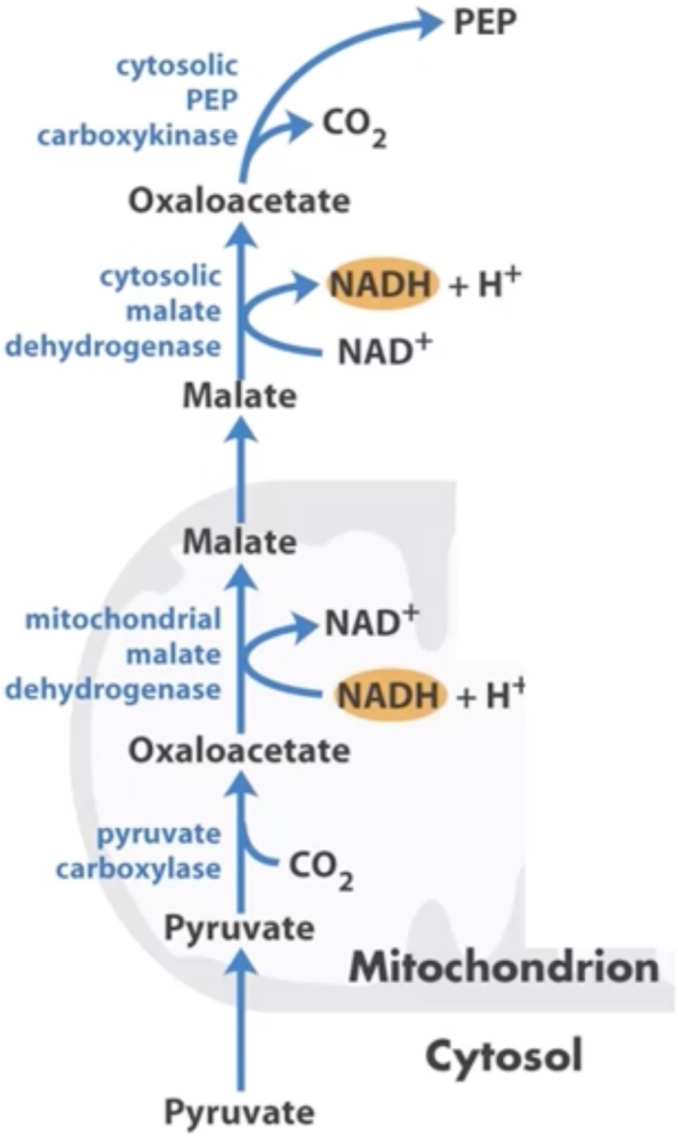
Todas as substâncias
têm que ser convertidas
em oxaloacetato

Os caminhos dependem do precursor





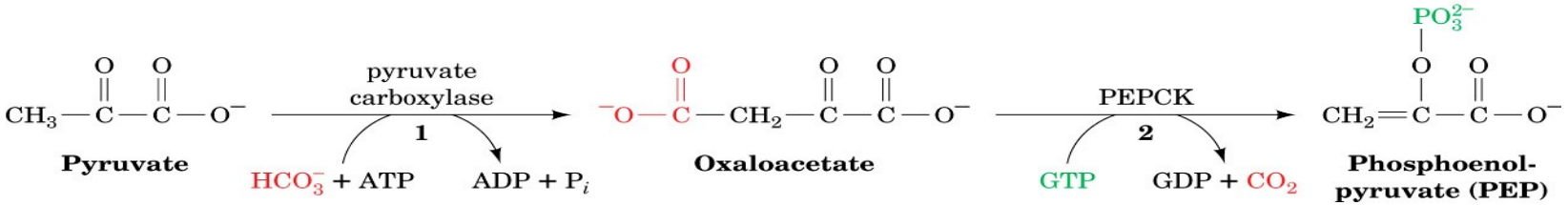
Piruvato - PEP

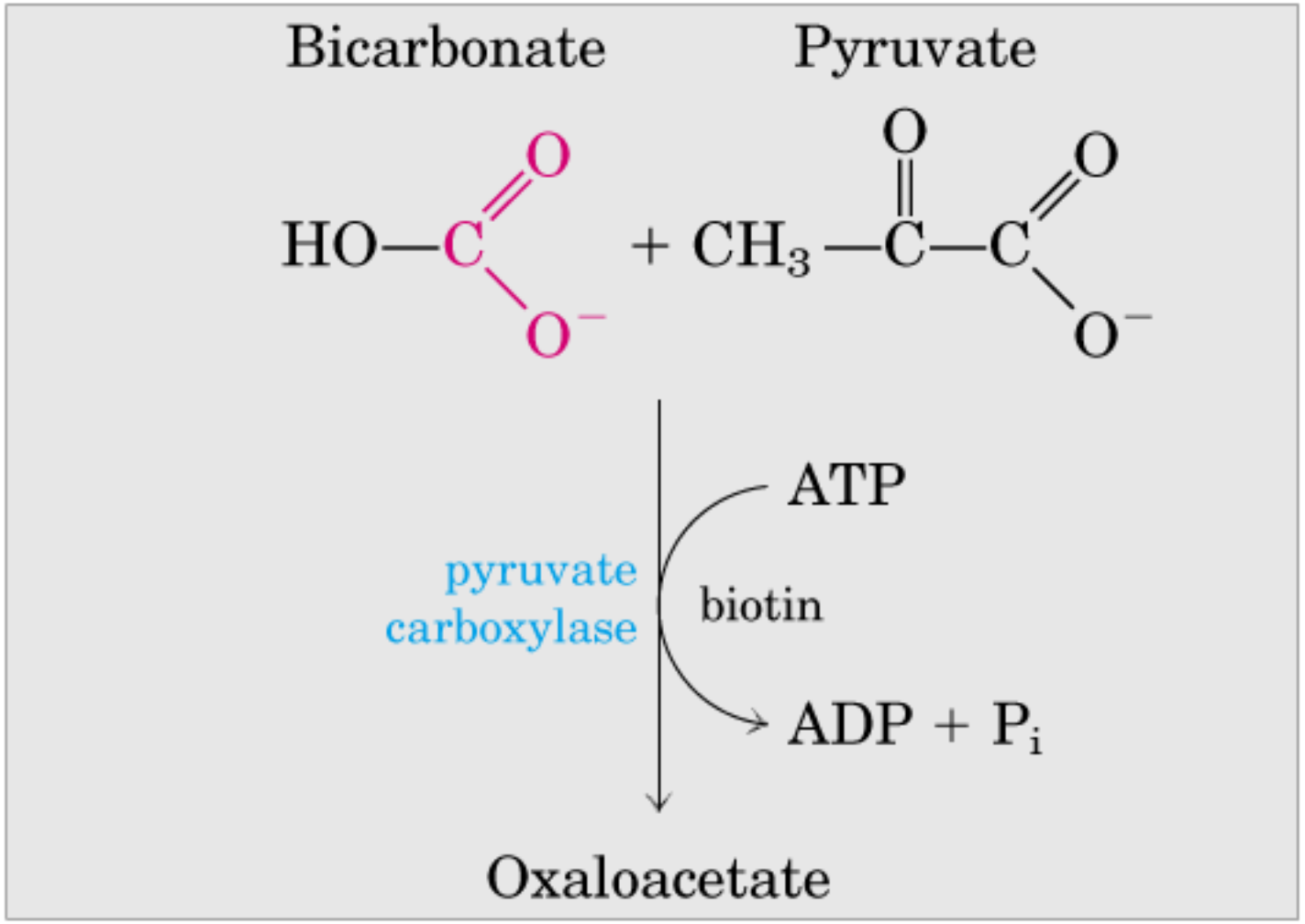


Etapa 1: piruvato a fosfoenolpiruvato

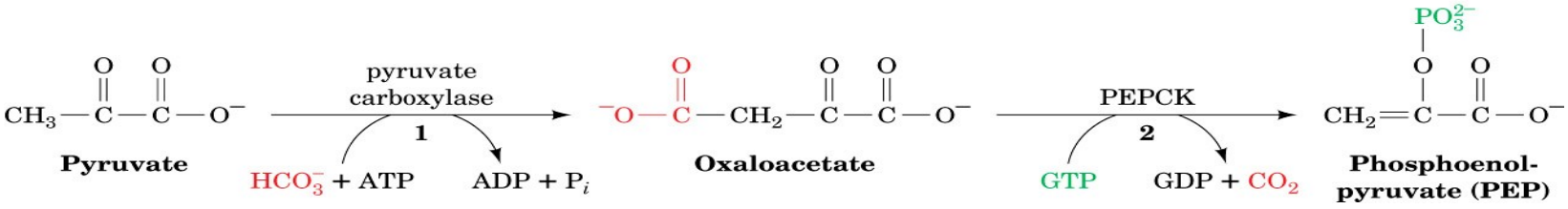
Piruvato carboxilase

Piruvato + CO_2 +H_2O + ATP→Oxaloacetato + ADP +Pi + $2H^+$

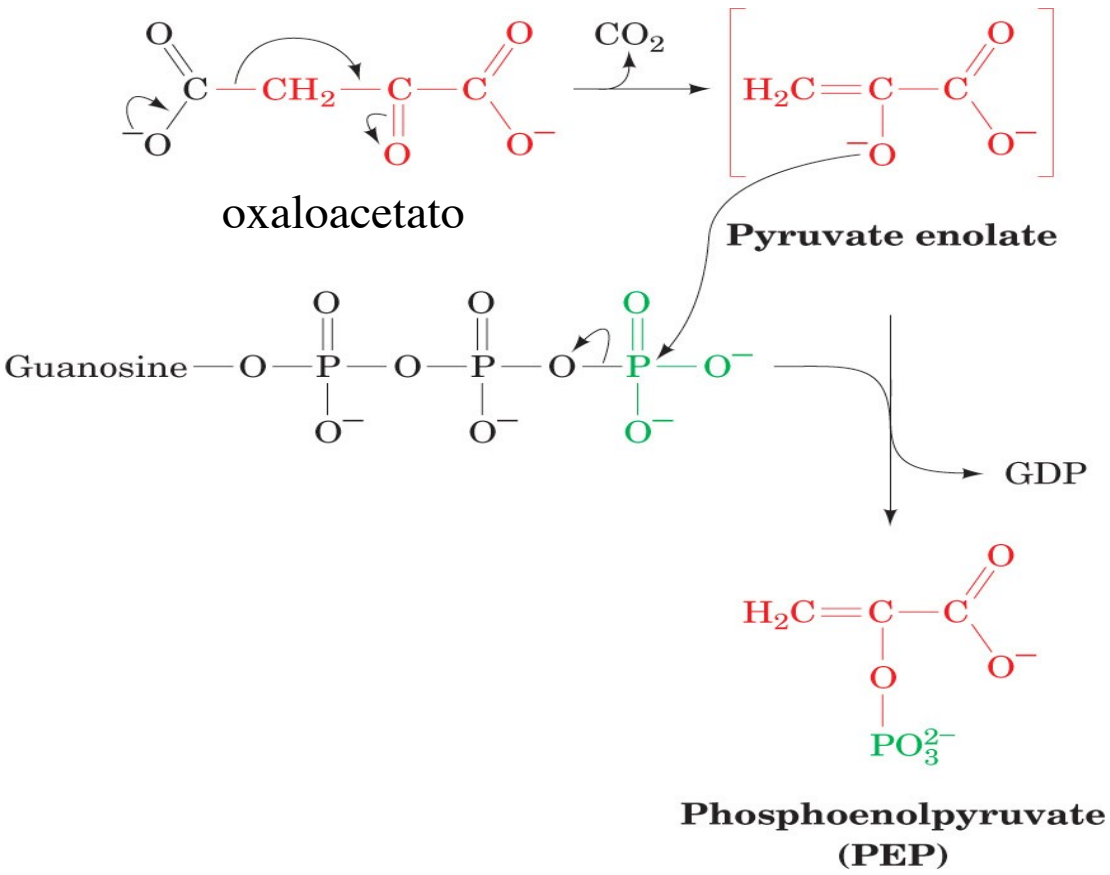



Bicarbonate
Pyruvate
HO—C(=O)—O⁻
+ CH3—C(=O)—C(=O)—O⁻
ATP
pyruvate carboxylase
biotin
ADP + Pi
Oxaloacetate

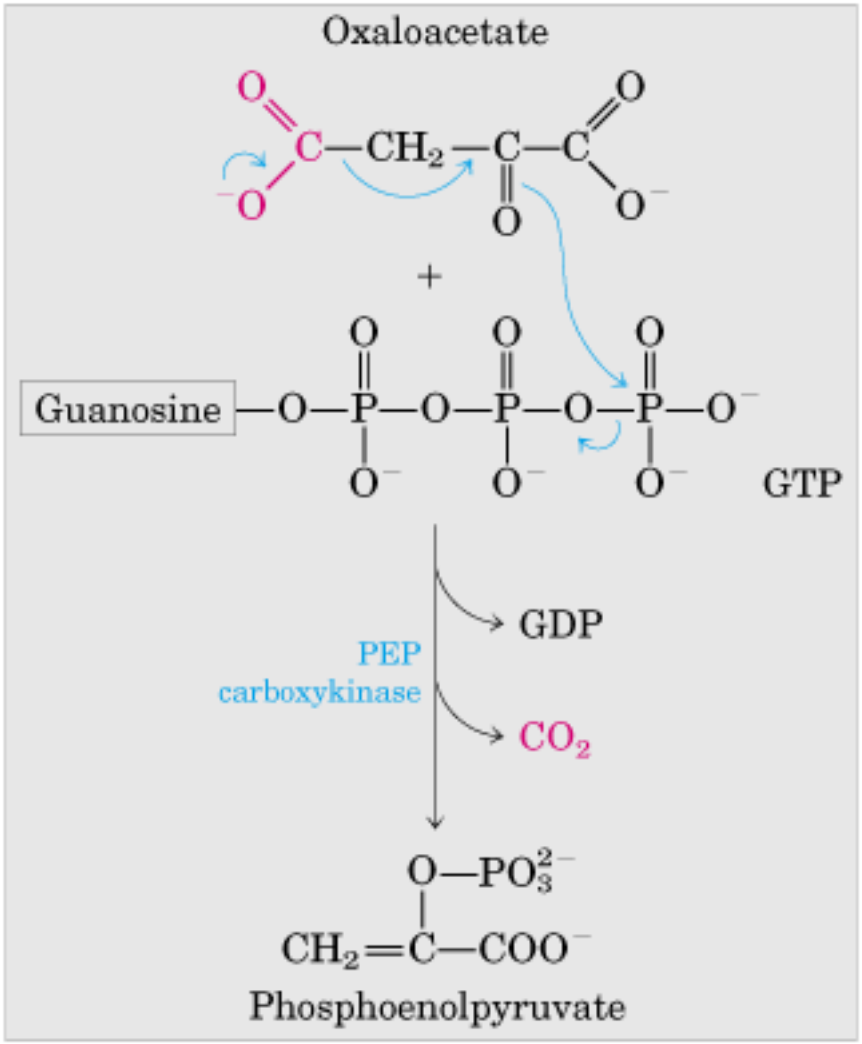
(a)


Pyruvate
pyruvate carboxylase
1
HCO3⁻ + ATP
ADP + Pi
Oxaloacetate
PEPCK
2
GTP
GDP + CO2
PO3 2−
Phosphoenol-pyruvate (PEP)

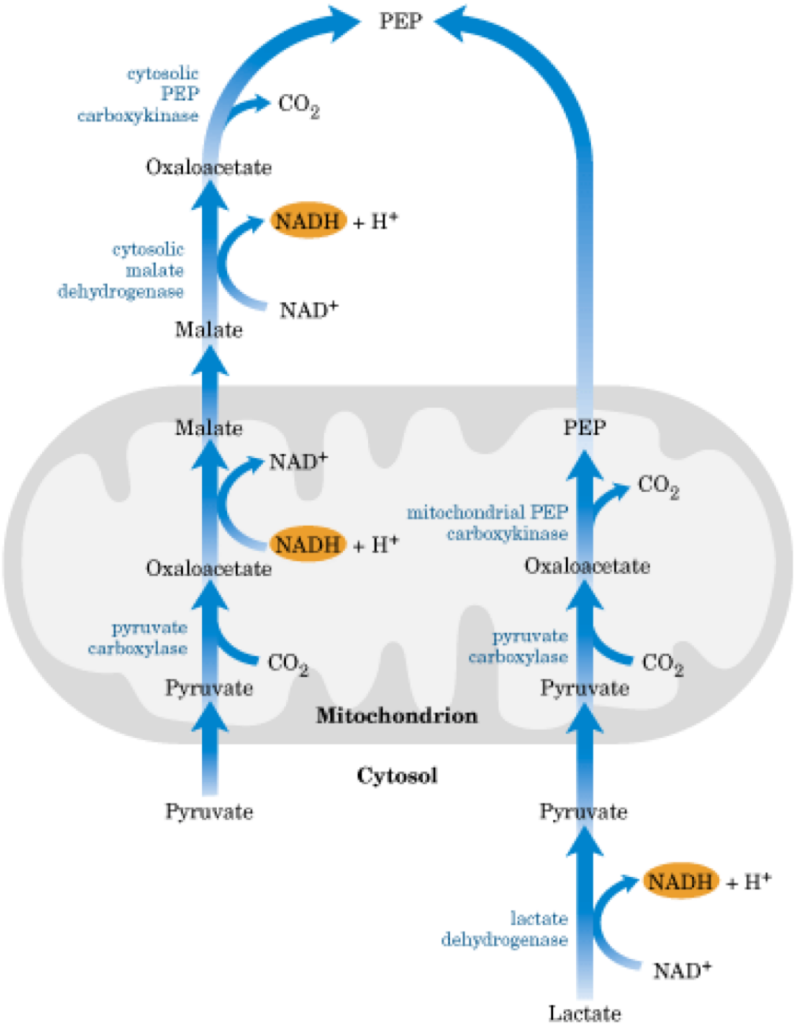
O oxaloacetato é então convertido em fosfoenolpiruvato



A formação de um composto de alta energia é contrabalançada pela Hidrólise do GTP



(b)



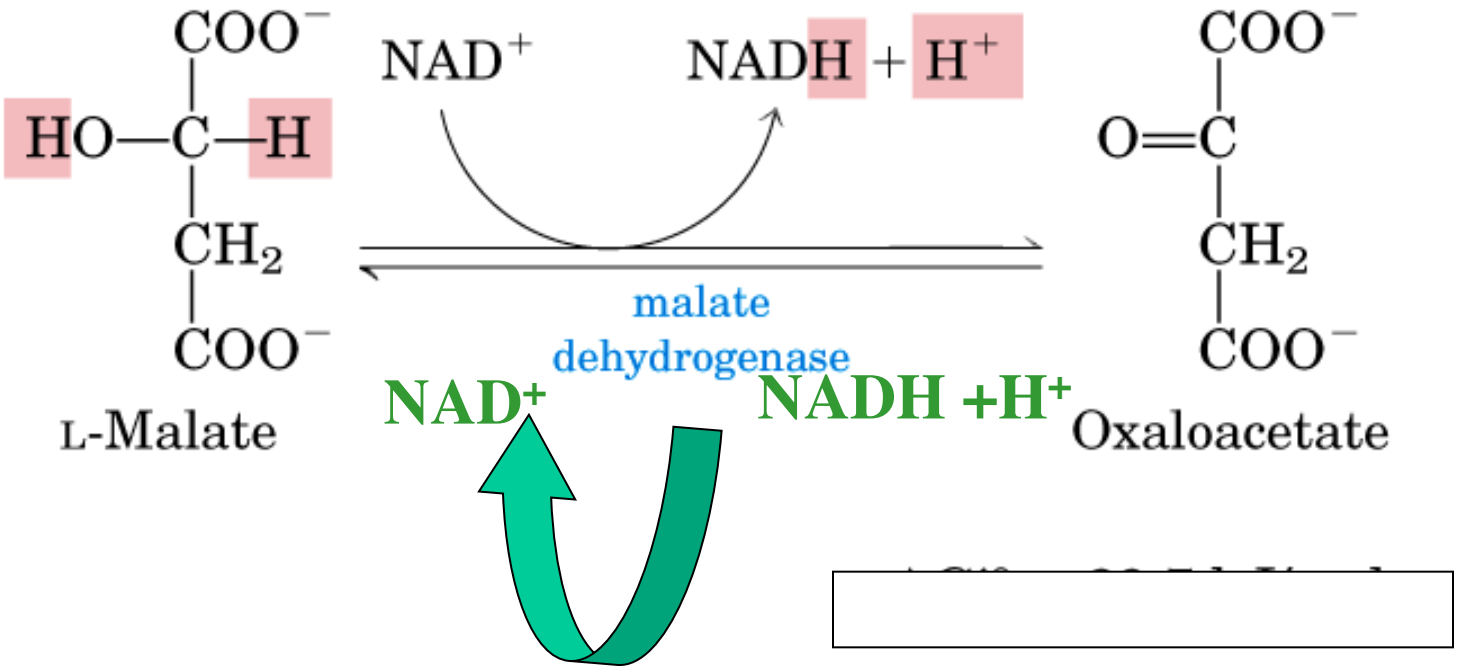
A descarboxilação facilita o ataque do oxigênio da carbonila pelo fosfato do GTP

Alternativamente:

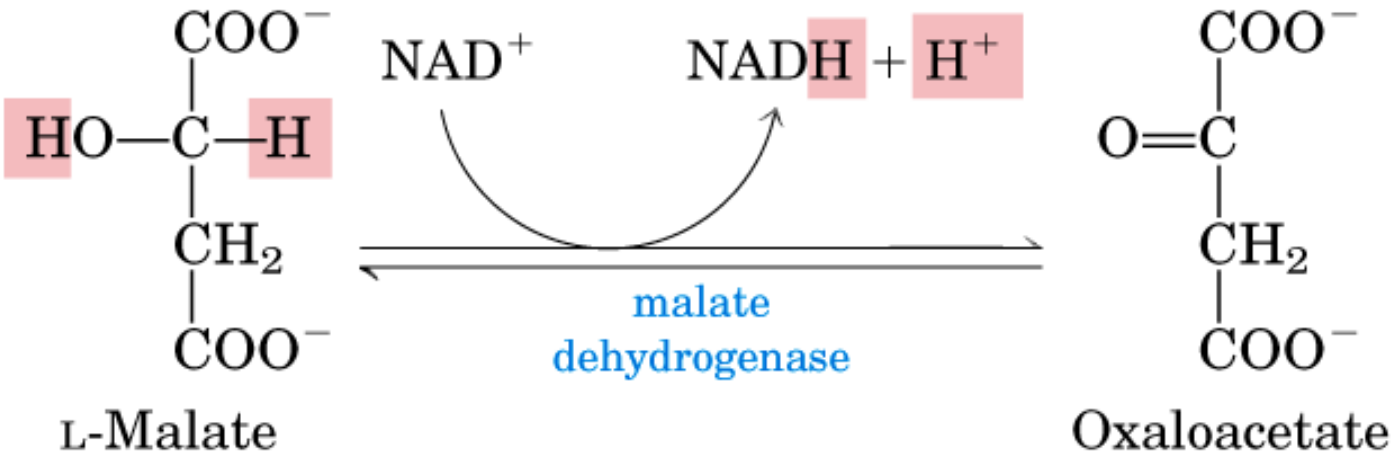
Oxaloacetato + NADH + H^+ $\rightarrow$ L-malato + NAD^+

A reação da malato desidrogenase é reversível ocorre nas duas vias

Ciclio de Krebs e neoglicogênese



No citossol o Malato é reoxidado em oxaloacetato com a produção de NADH citossólico



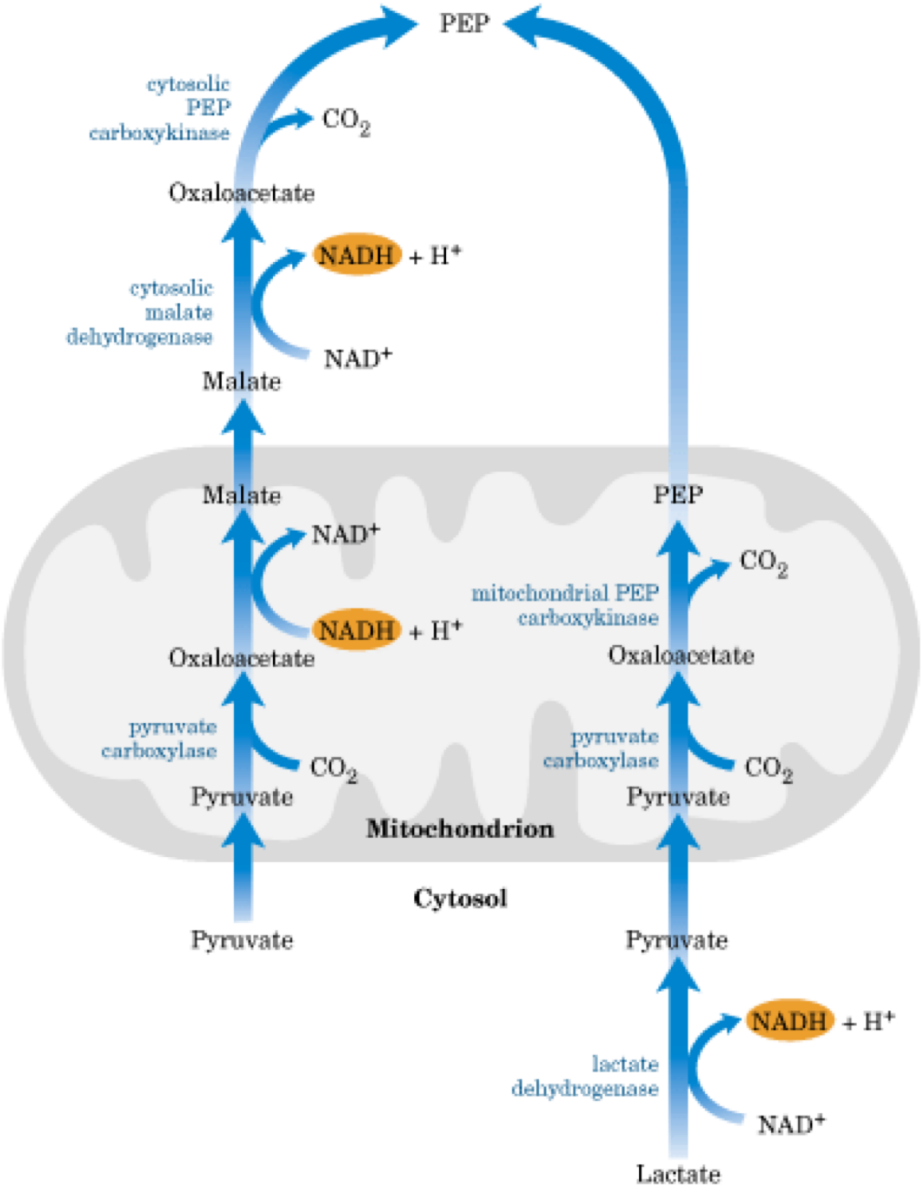
$\Delta G'^{\circ} = 29.7$ kJ/mol

Piruvato + ATP + GTP + HCO_3^- → Fosfoenolpiruvato + ADP+ Pi + CO_2

Lógica para que a reação ocorra na mitocôndria

Citossol:
NADH/NAD+ = 8 x10^{-4}M,

5 vezes menor que na mit.



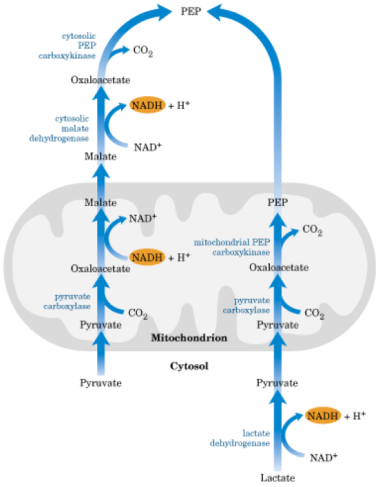
Quando o lactato é o precurssor o caminho é mais curto

Piruvato carboxilase

Piruvato + CO_2 +H_2O + ATP→Oxaloacetato + ADP +Pi + $2H^+$

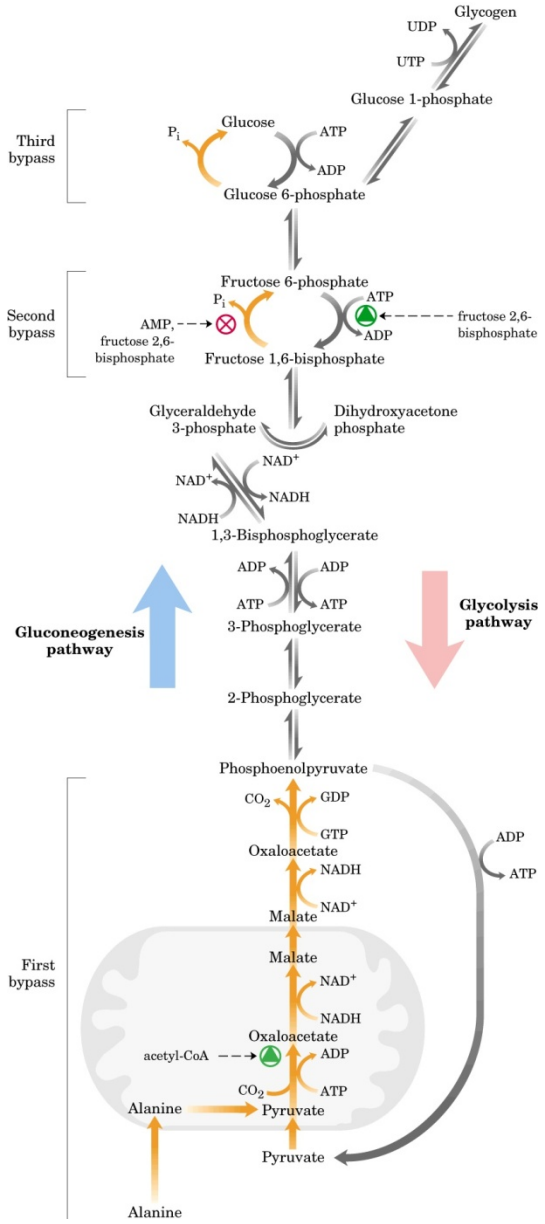
Oxaloacetato + GTP → Fosfoenolpiruvato + CO_2+ GDP

Fosfoenolpiruvato carboxiquinase

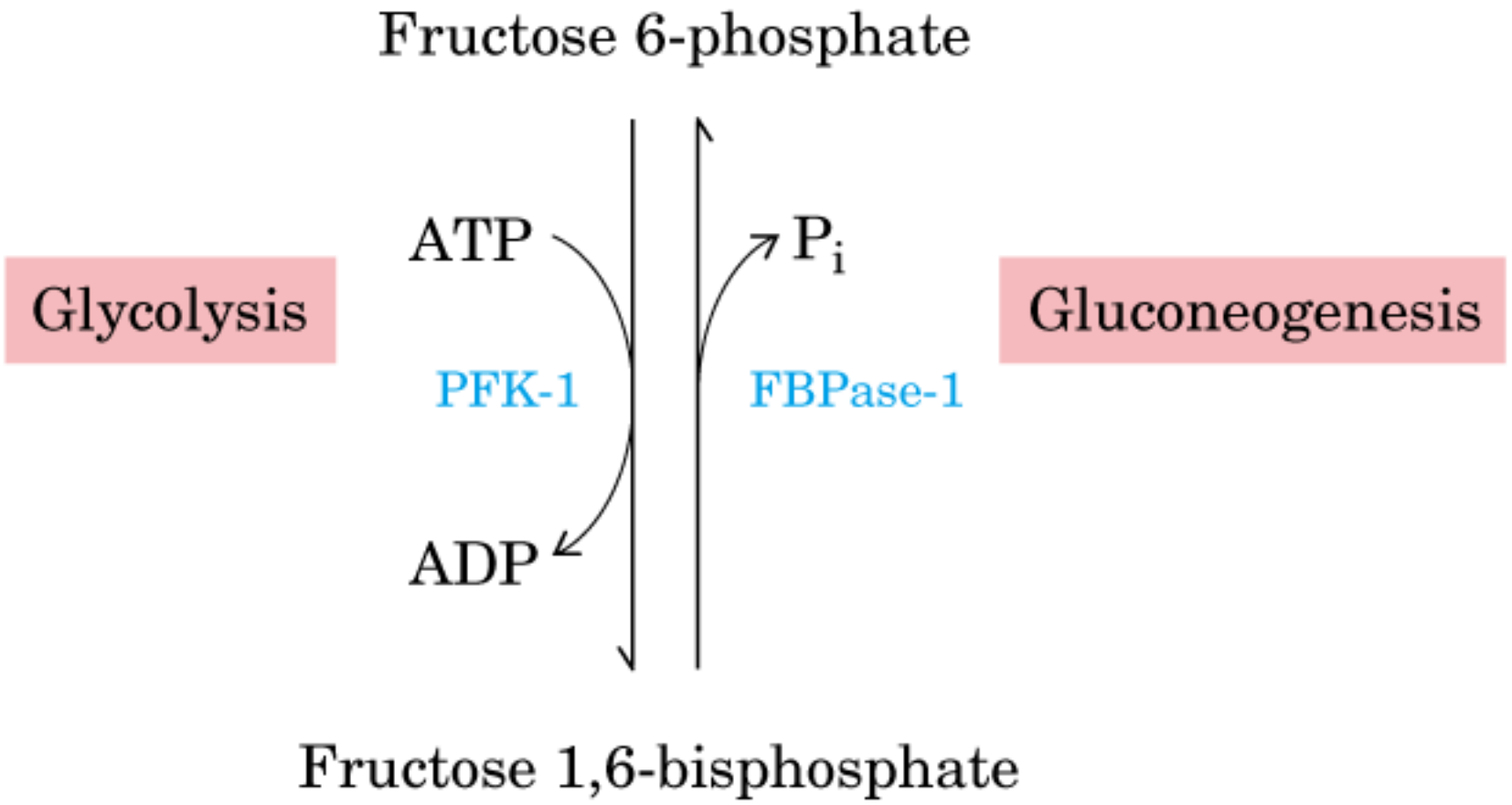


3 passos da glicólise são irreversíveis

Próximo passo irreversível:

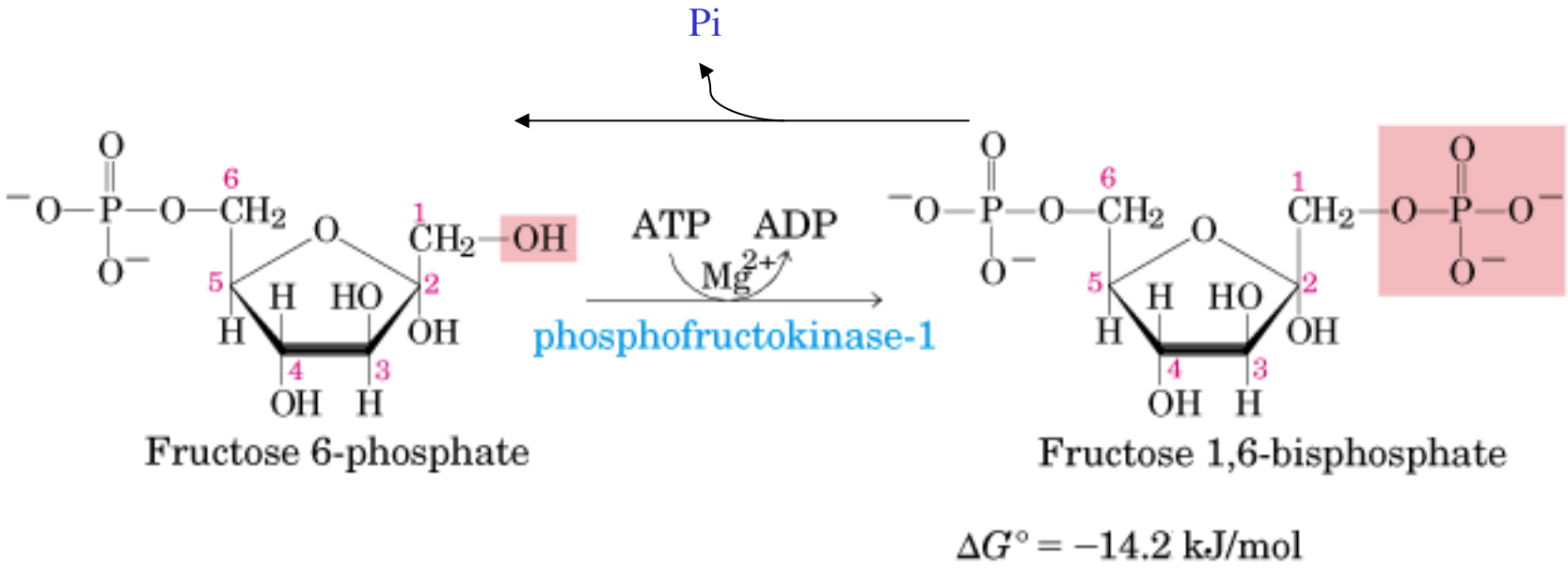


Etapa 2:
Conversão de Frutose 1,6-difosfato a frutose 6 -fosfato



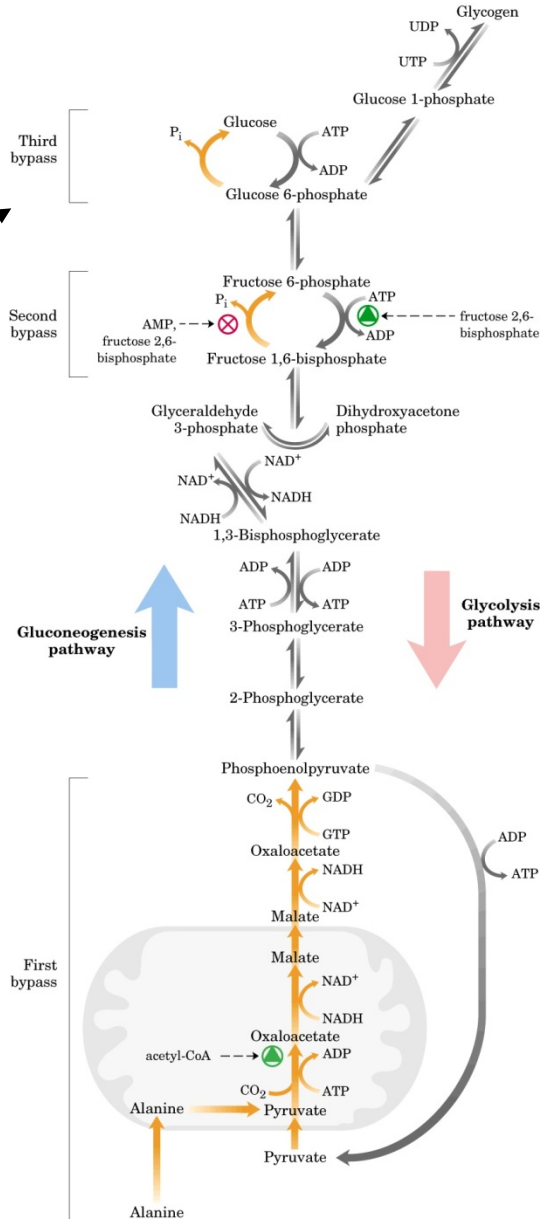
Frutose 1,6-bifosfatase

Frutose-1,6-bifosfatase



3 passos da glicólise são irreversíveis

Próximo passo irreversível:

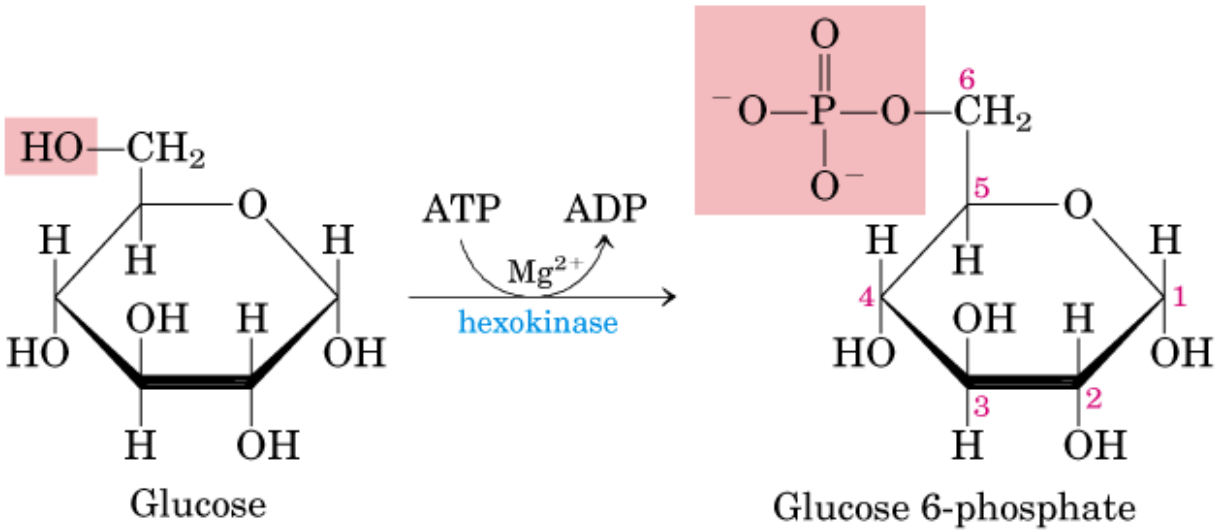


Etapa 3:

No fígado e rins- hidrólise simples de éster fosfórico

Glicose-6-Pi + H_2O → Glicose + Pi

Glicose-6-fosfatase



$\Delta G'^{\circ} = -16.7$ kJ/mol

table 20–2

Sequential Reactions in Gluconeogenesis Starting from Pyruvate*

Pyruvate + HCO_3^- + ATP ⟶ oxaloacetate + ADP + P_i + H^+	×2
Oxaloacetate + GTP ⇌ phosphoenolpyruvate + CO_2 + GDP	×2
Phosphoenolpyruvate + H_2O ⇌ 2-phosphoglycerate	×2
2-Phosphoglycerate ⇌ 3-phosphoglycerate	×2
3-Phosphoglycerate + ATP ⇌ 1,3-bisphosphoglycerate + ADP + H^+	×2
1,3-Bisphosphoglycerate + NADH + H^+ ⇌ glyceraldehyde 3-phosphate + NAD^+ + P_i	×2
Glyceraldehyde 3-phosphate ⇌ dihydroxyacetone phosphate	
Glyceraldehyde 3-phosphate + dihydroxyacetone phosphate ⇌ fructose 1,6-bisphosphate	
Fructose 1,6-bisphosphate + H_2O ⟶ fructose 6-phosphate + P_i	
Fructose 6-phosphate ⇌ glucose 6-phosphate	
Glucose 6-phosphate + H_2O ⟶ glucose + P_i	

Sum: 2 Pyruvate + 4ATP + 2GTP + 2NADH + $4H_2O$ ⟶ glucose + 4ADP + 2GDP + $6P_i$ + $2NAD^+$ + $2H^+$

*The bypass reactions are in red; all other reactions are reversible steps of glycolysis. The figures at the right indicate that the reaction is to be counted twice, because two three-carbon precursors are required to make a molecule of glucose. Note that the reactions required to replace the cytosolic NADH consumed in the glyceraldehyde 3-phosphate dehydrogenase reaction (the conversion of lactate to pyruvate in the cytosol or the transport of reducing equivalents from mitochondria to the cytosol in the form of malate) are not considered in this summary.

table 20–3

Glucogenic Amino Acids, Grouped by Site of Entry*

Pyruvate
Alanine
Cysteine
Glycine
Serine
Tryptophan†

α-Ketoglutarate
Arginine
Glutamate
Glutamine
Histidine
Proline

Succinyl-CoA
Isoleucine†
Methionine
Threonine
Valine

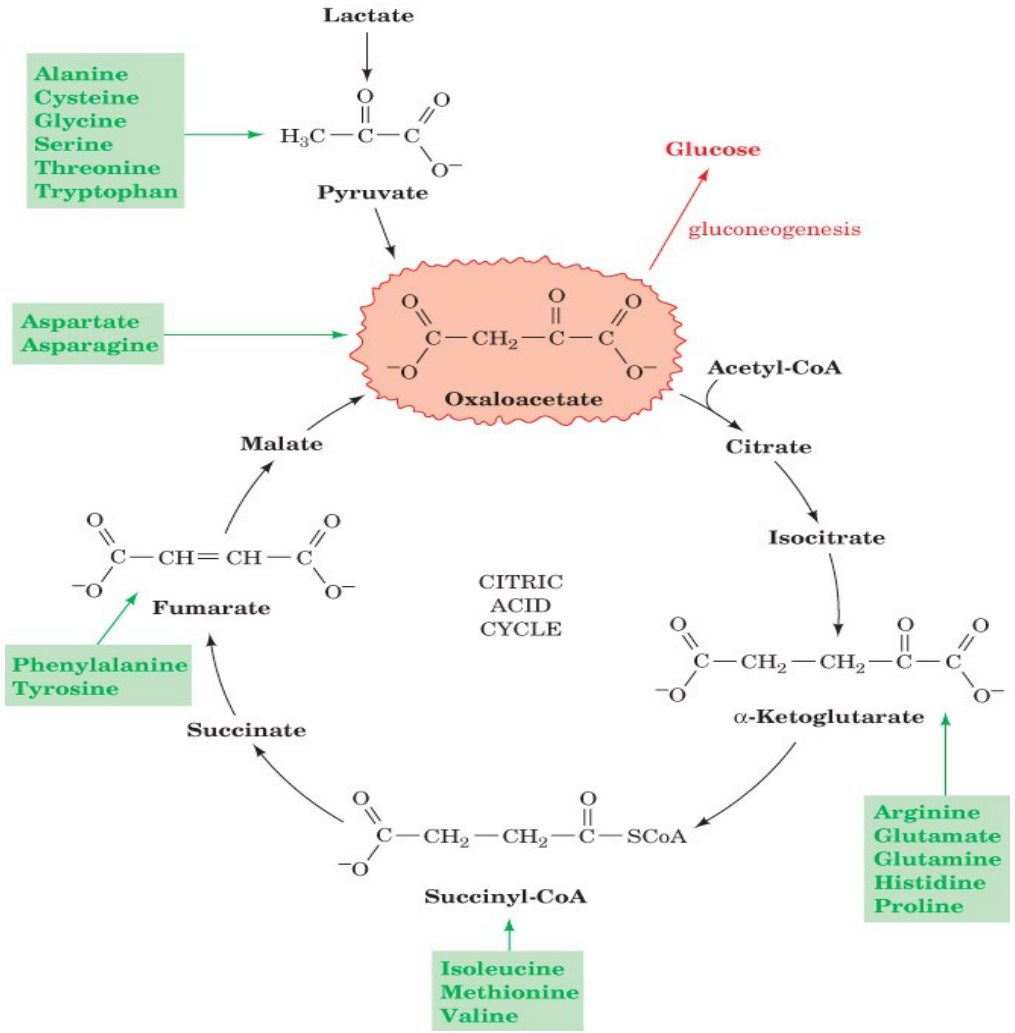
Fumarate
Phenylalanine†
Tyrosine†

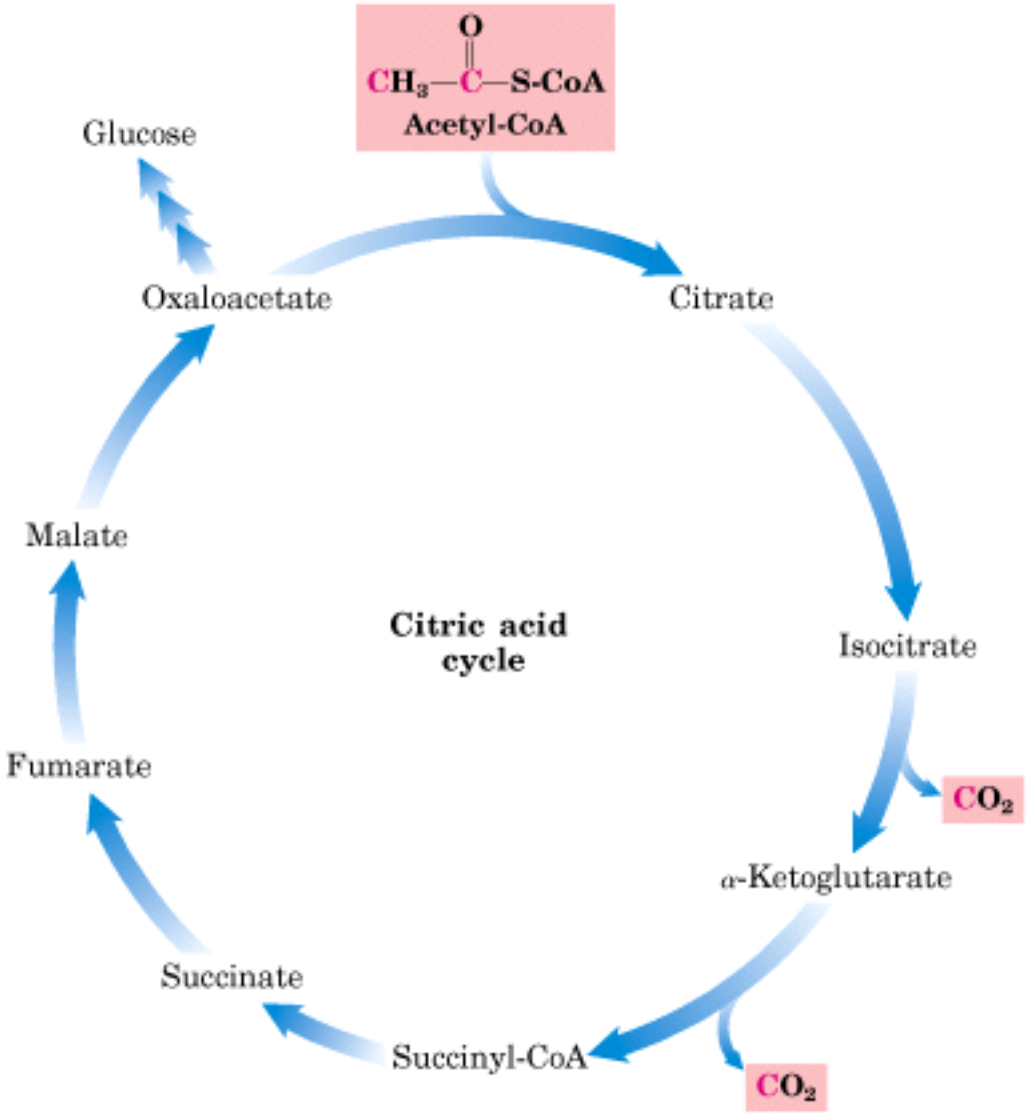
Oxaloacetate
Asparagine
Aspartate

*These amino acids are precursors of blood glucose or liver glycogen because they can be converted to pyruvate or citric acid cycle intermediates. Only leucine and lysine are unable to furnish carbon for net glucose synthesis.

†These amino acids are also ketogenic (see Fig. 18–19).

Pathways converting lactate, pyruvate, and citric acid cycle intermediates to oxaloacetate.



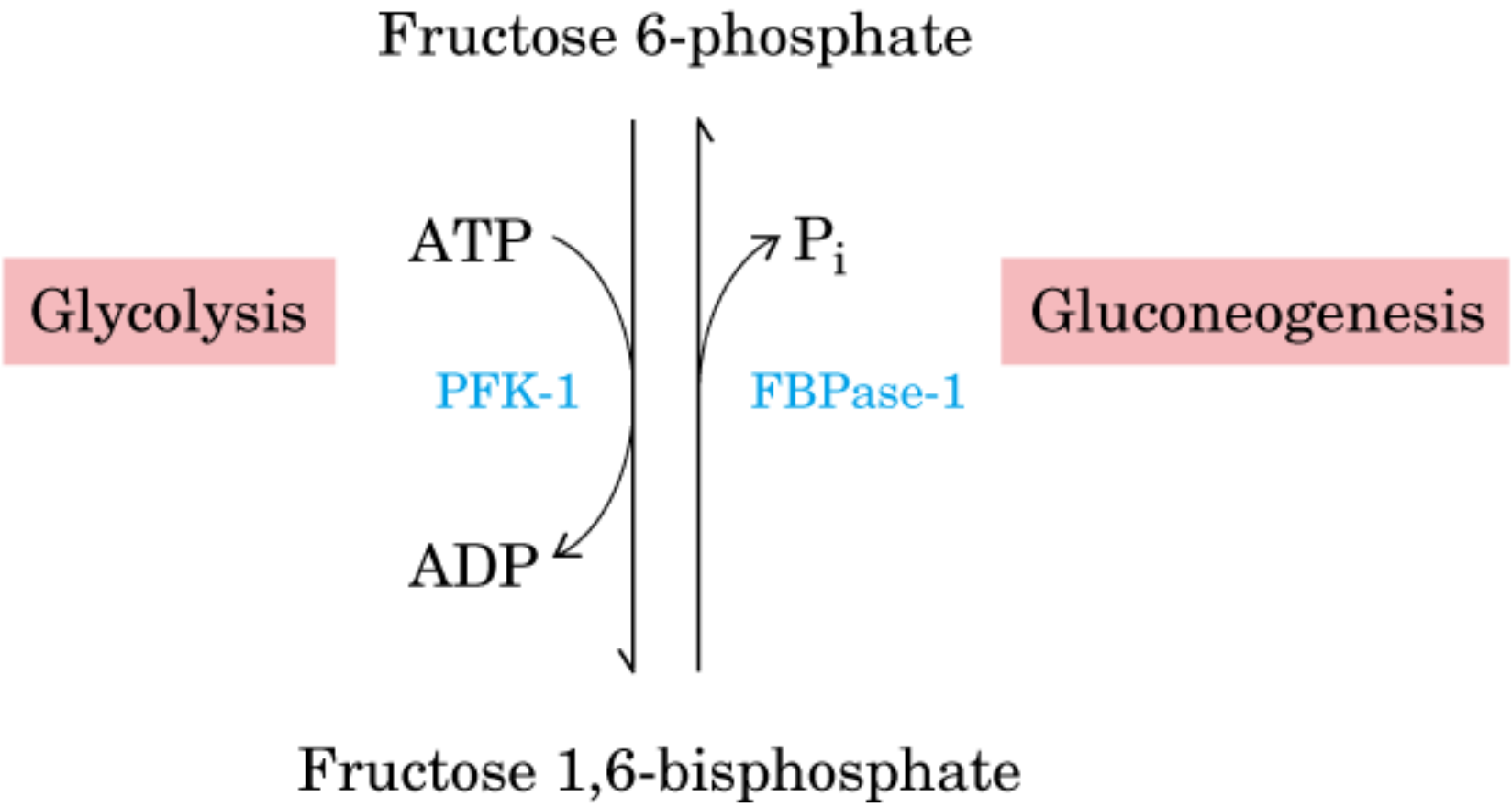

O
CH3—C—S-CoA
Acetyl-CoA
Glucose
Oxaloacetate
Citrate
Isocitrate
CO2
α-Ketoglutarate
CO2
Succinyl-CoA
Succinate
Fumarate
Malate
Citric acid cycle

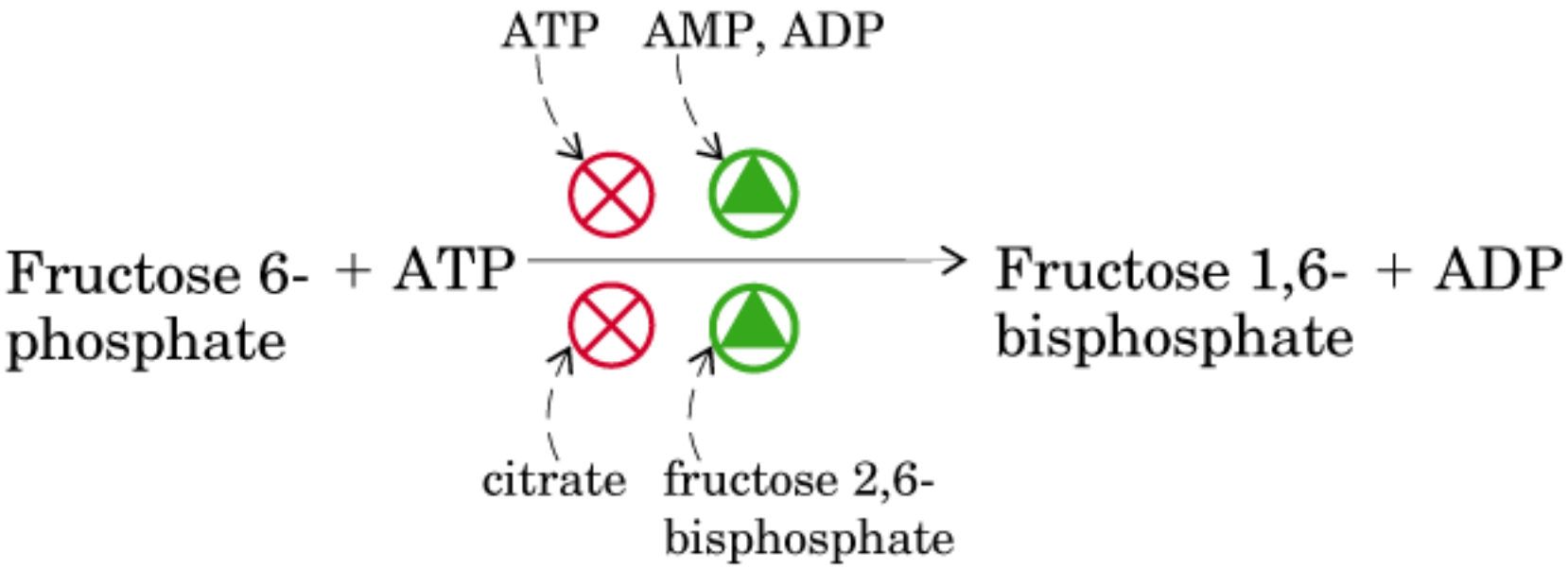
Glicólise e Gliconeogênese são processos espontâneos.
Se as duas vias estiverem ativas simultaneamente em uma célula, isso constituiria
um "ciclo fútil" que gastaria energia.
Portanto, para prevenir o gasto de energia de um ciclo fútil, Glicólise e Gliconeogênese são reciprocamente regulados.

O controle inclui regulação alostérica reciproca por nucleotídeos de adenina.

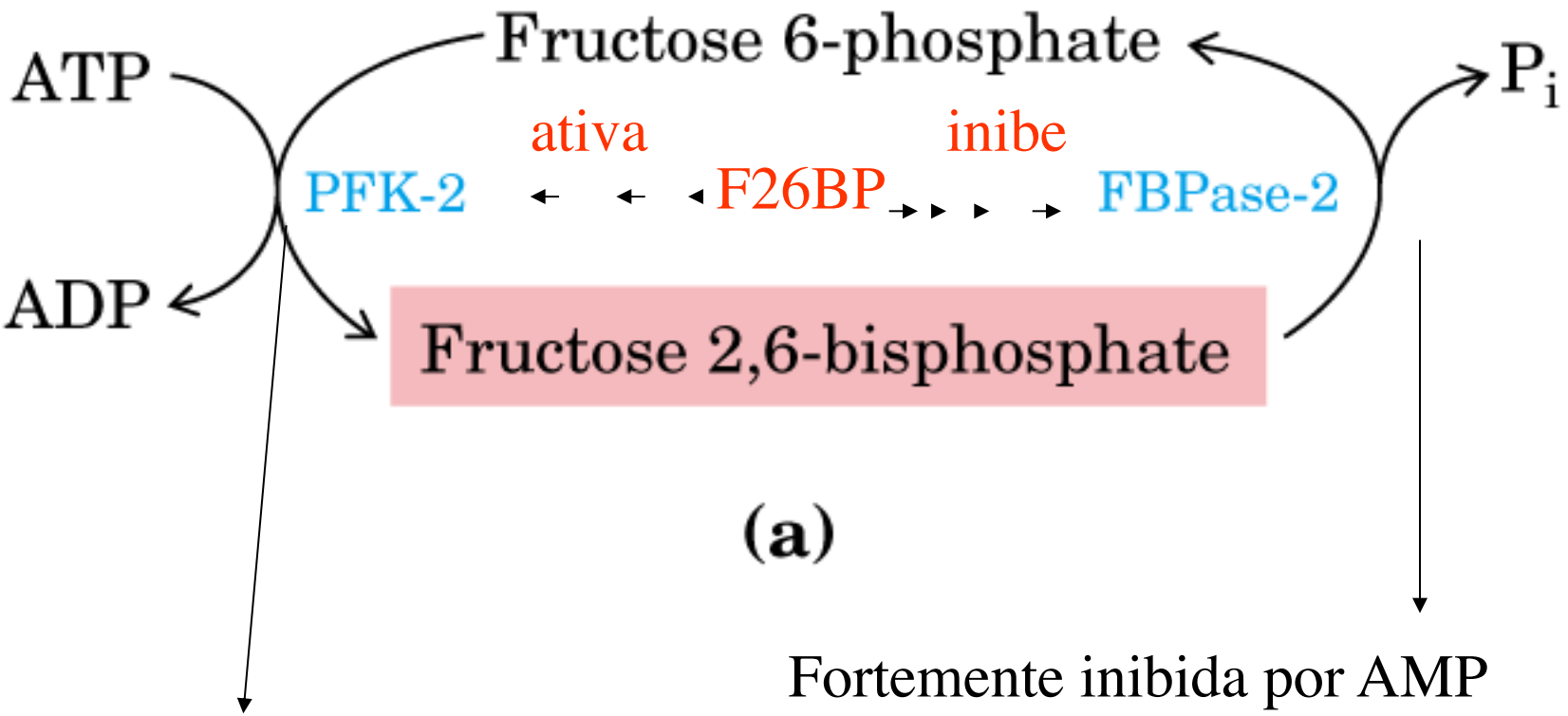
Fosfofrutoquinase (Glicólise) é inibida por ATP e estimulada por AMP.

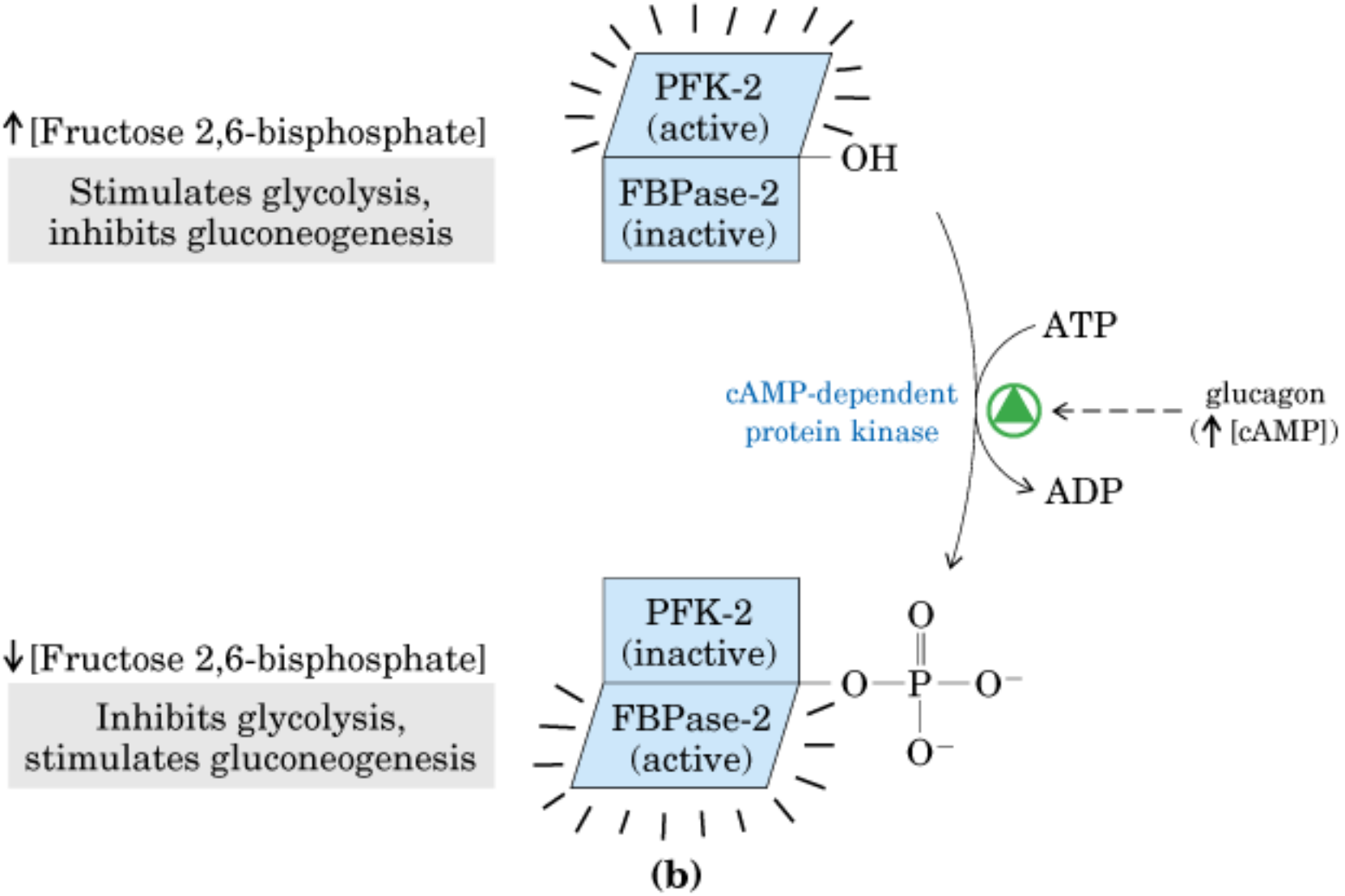
Frutose-1,6-bisfosfatase (Gliconeogênese) é inibida por AMP.


Fructose 6-phosphate
Glycolysis
ATP
P_i
PFK-1
FBPase-1
ADP
Gluconeogenesis
Fructose 1,6-bisphosphate

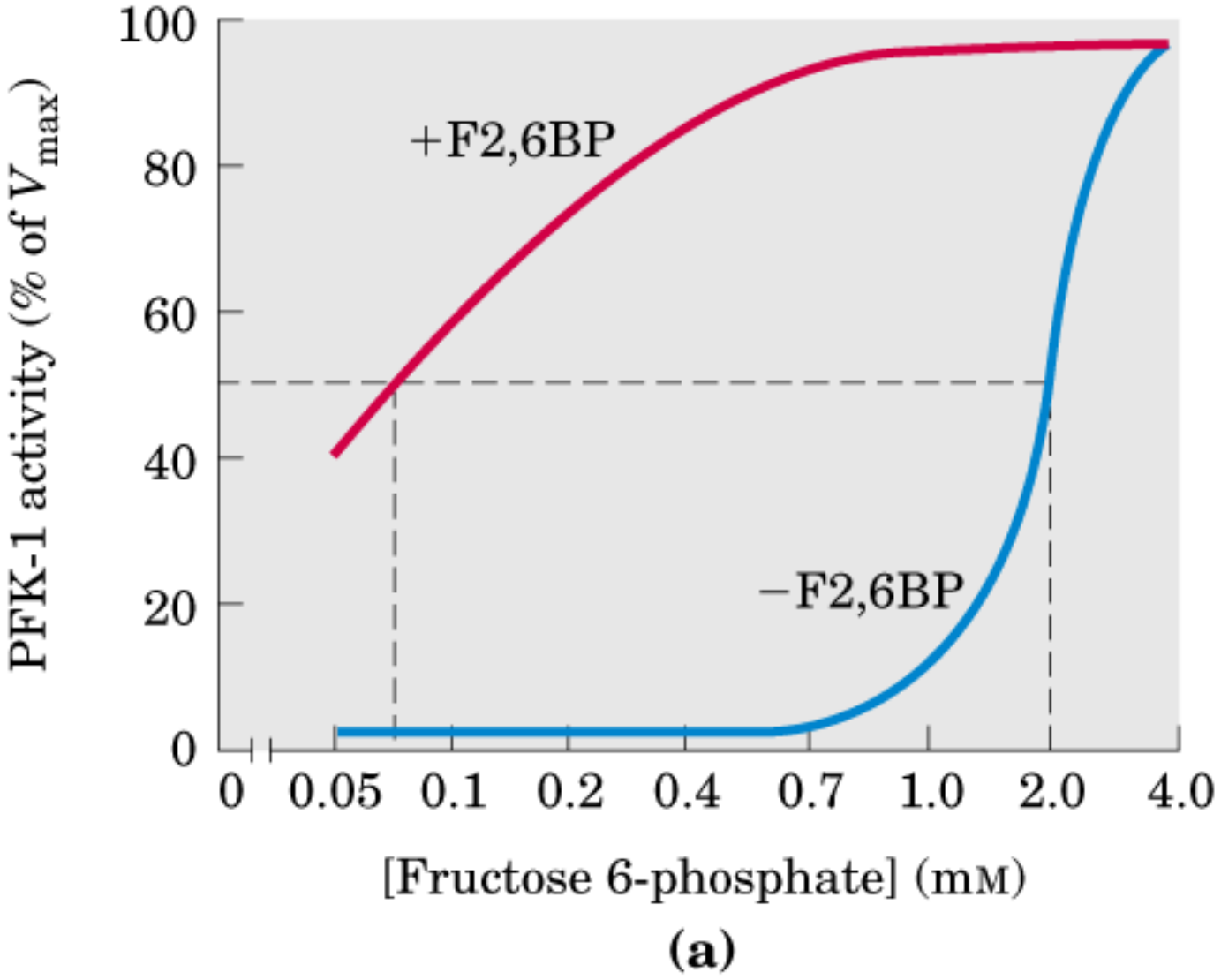

ATP
AMP, ADP
Fructose 6-phosphate
+ ATP
Fructose 1,6-bisphosphate
+ ADP
citrate
fructose 2,6-bisphosphate


AMP
-FRUTOSE 2,6-BISPHOSPHATE
Frutose 1,6 P
Frutose 1,6 bisfosfatase
Frutose 6 P
Pi

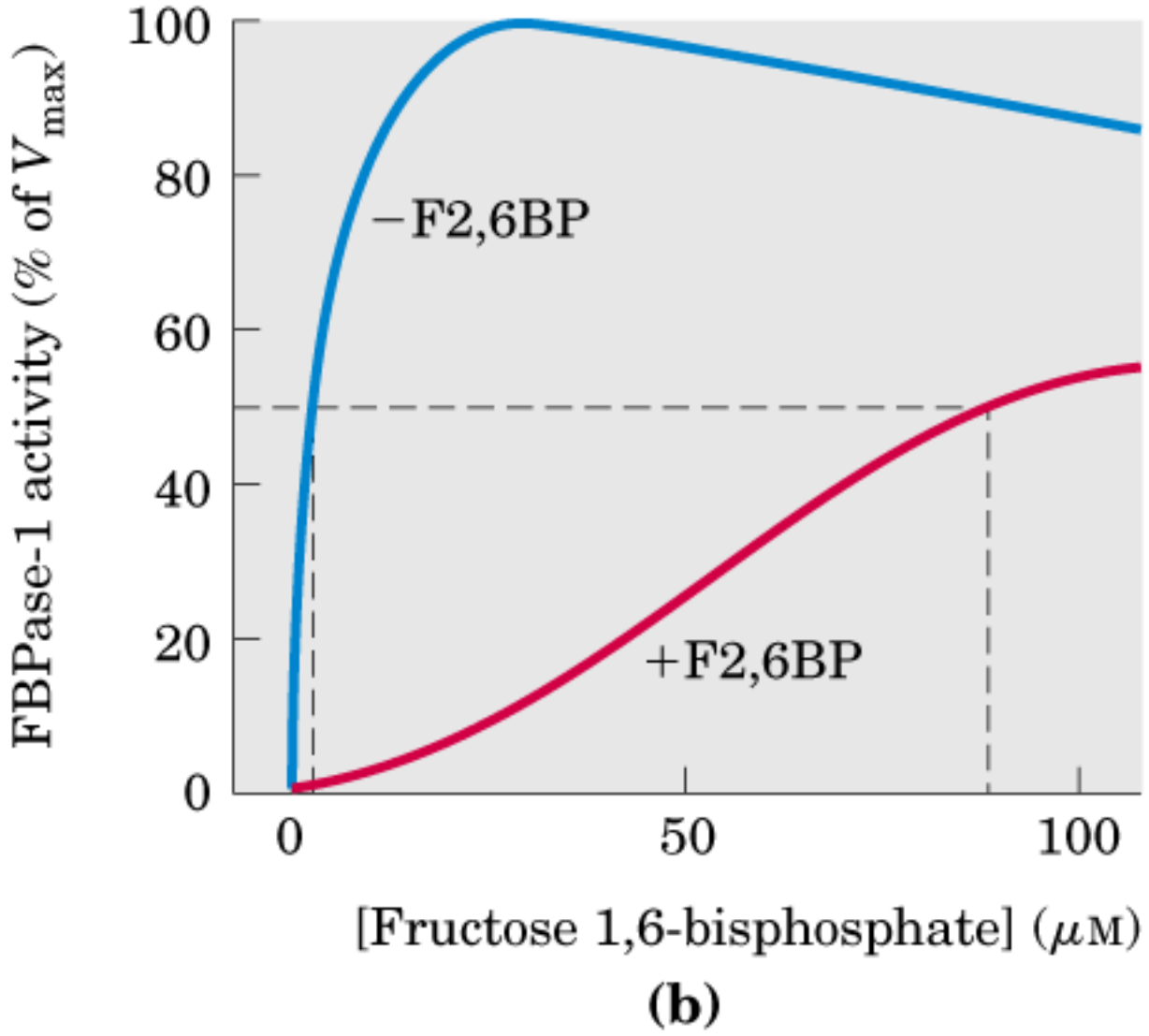

ATP
Fructose 6-phosphate
P_i
ativa
inibe
PFK-2
F26BP
FBPase-2
ADP
Fructose 2,6-bisphosphate
(a)
Fortemente inibida por AMP
Estimulada por AMP e ADP



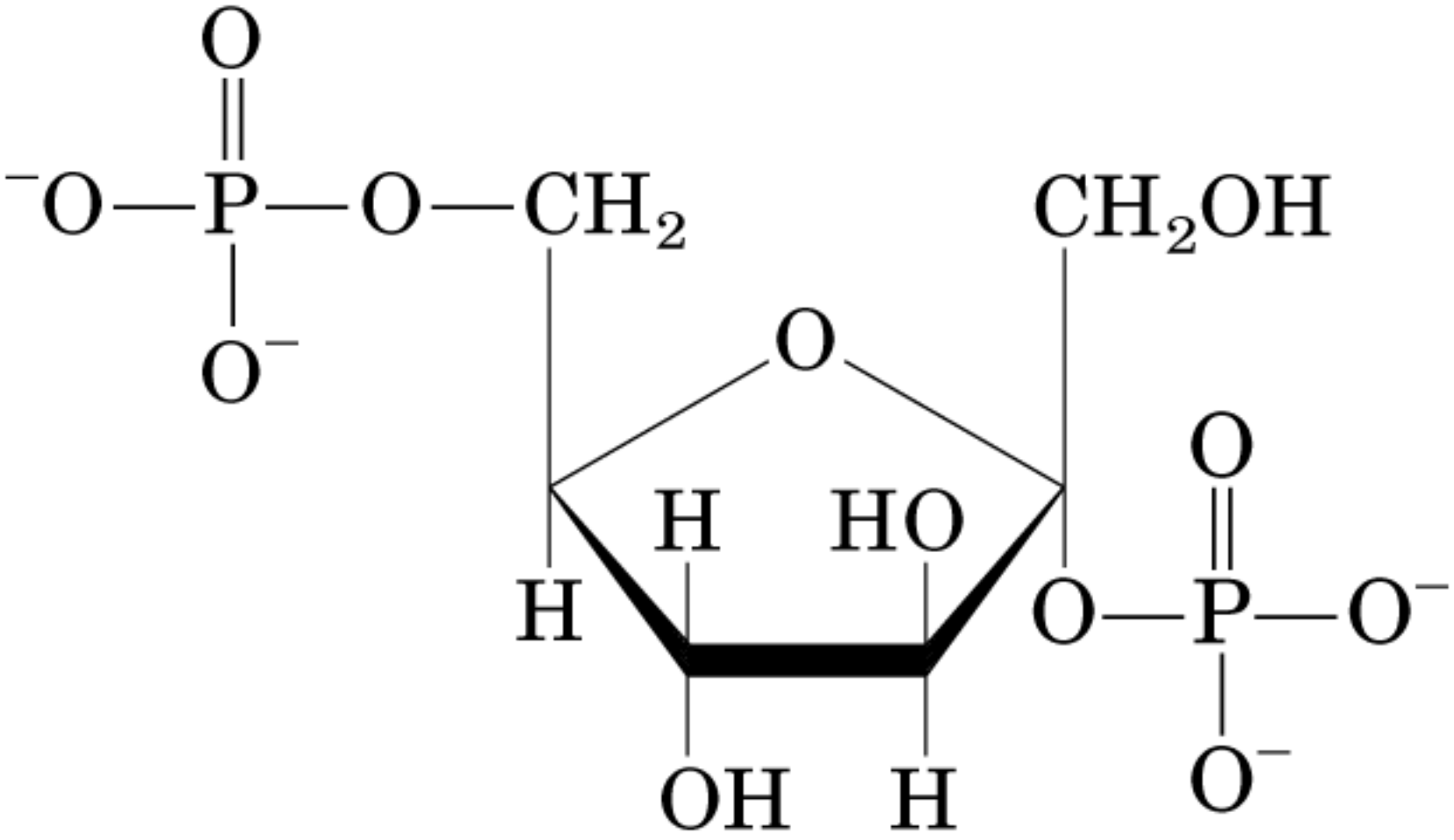
Glucagon aumenta quando a glicemia cai. Neste caso, a produção de cAMP ativa a Proteína quinase com consequente redução nos níveis de frutose 2,6-bifosfato.


PFK-1 activity (% of V_{max})
100
80
60
40
20
0
+F2,6BP
−F2,6BP
0
0.05
0.1
0.2
0.4
0.7
1.0
2.0
4.0
[Fructose 6-phosphate] (mM)

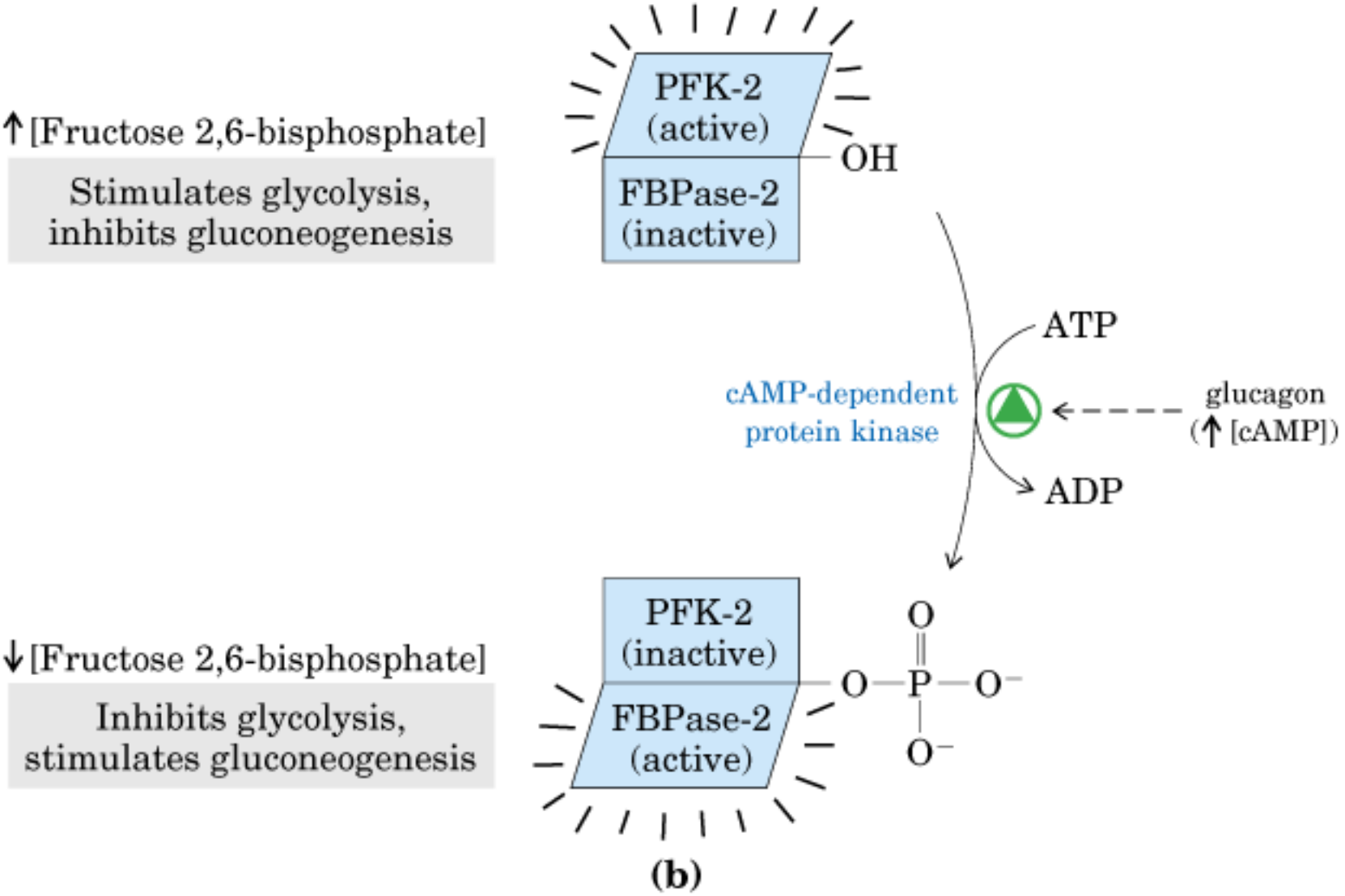
(a)


100
80
60
40
20
0
FBPase-1 activity (% of V_{max})
−F2,6BP
+F2,6BP
0
50
100
[Fructose 1,6-bisphosphate] (μM)

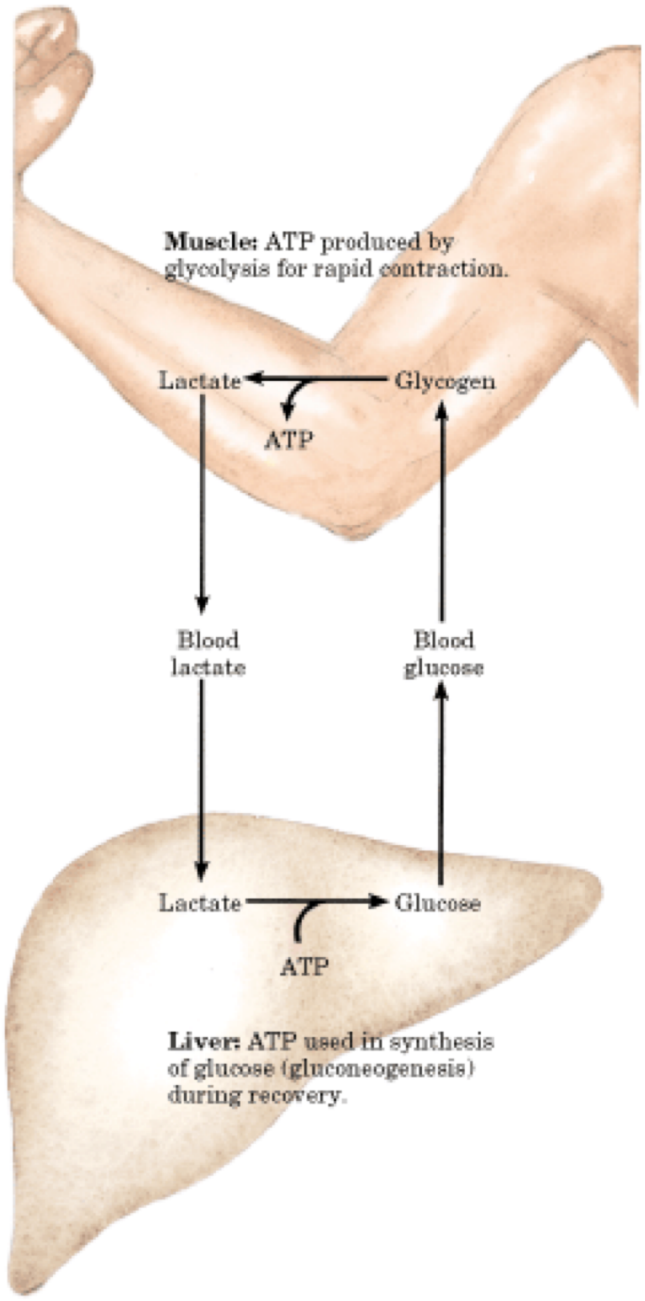
(b)



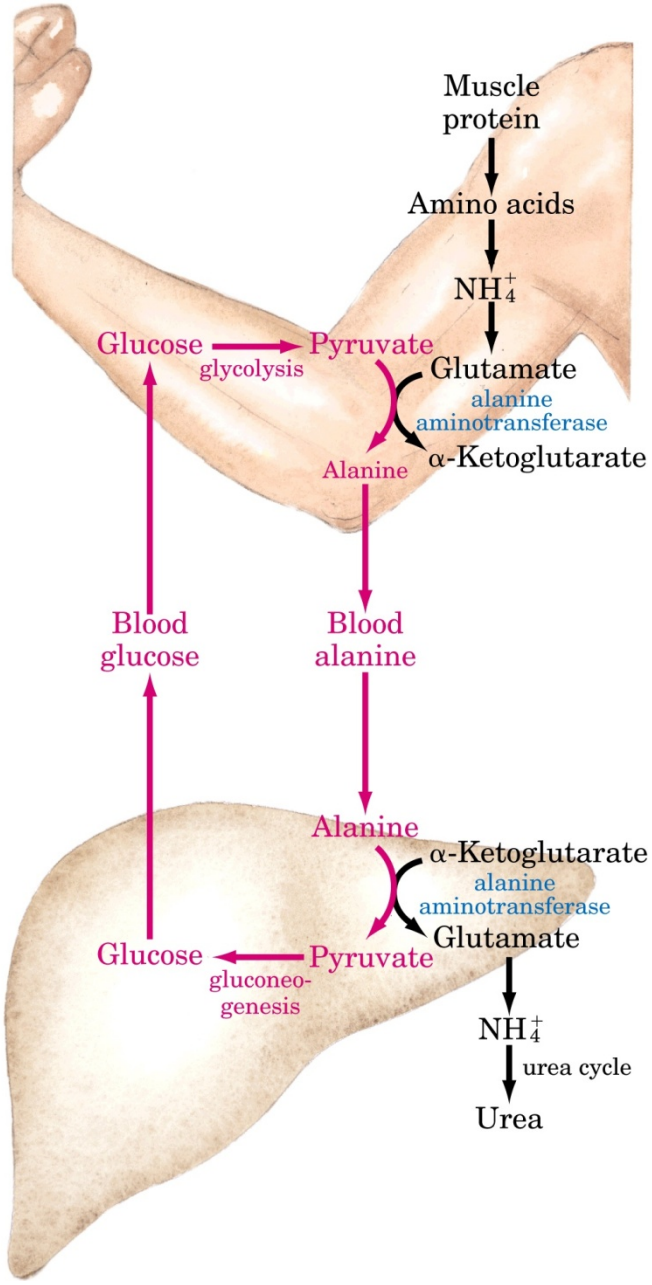
Fructose 2,6 - bisphosphate

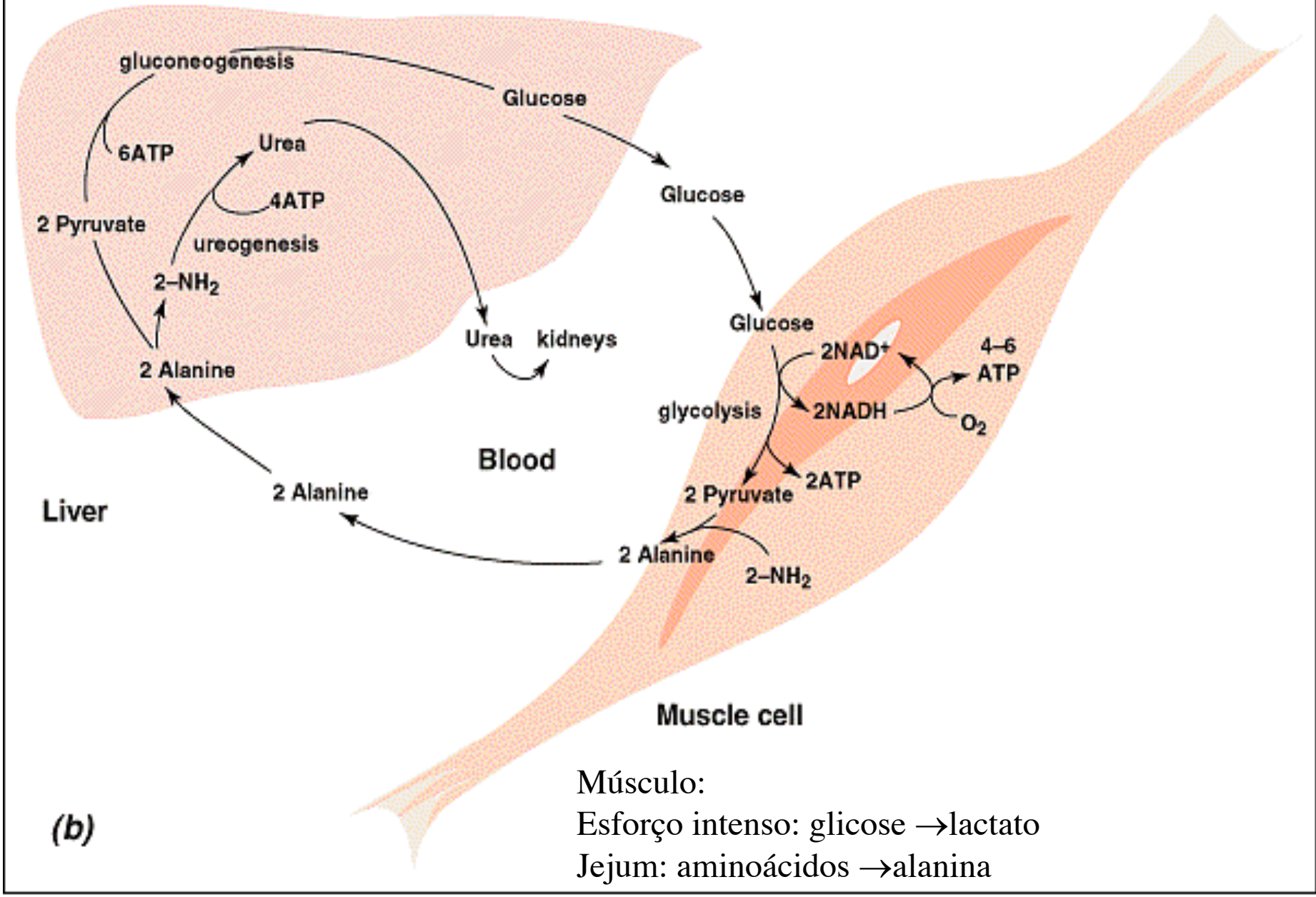


Glucagon aumenta quando a glicemia cai


Muscle: ATP produced by glycolysis for rapid contraction.
Lactate
Glycogen
ATP
Blood lactate
Blood glucose
Lactate
Glucose
ATP
Liver: ATP used in synthesis of glucose (gluconeogenesis) during recovery.

Ciclo Glicose-alanina
Transporte de amônia para o fígado





Músculo:
Esforço intenso: glicose →lactato
Jejum: aminoácidos →alanina

Transformação de alanina e lactato em glicose inicia-se por sua conversão a piruvato

Alanina + α-cetoglutarato → Piruvato + Glutamato

alanina aminotransferase

gliconeogênese

Piruvato → Glicose

Metabolismo do etanol

O fígado é responsável pelas duas primeiras etapas no catabolismo do etanol

álcool desidrogenase citosólica

$$\text{Etanol} + NAD^+ \rightarrow \text{acetaldeído} + NADH + H^+$$

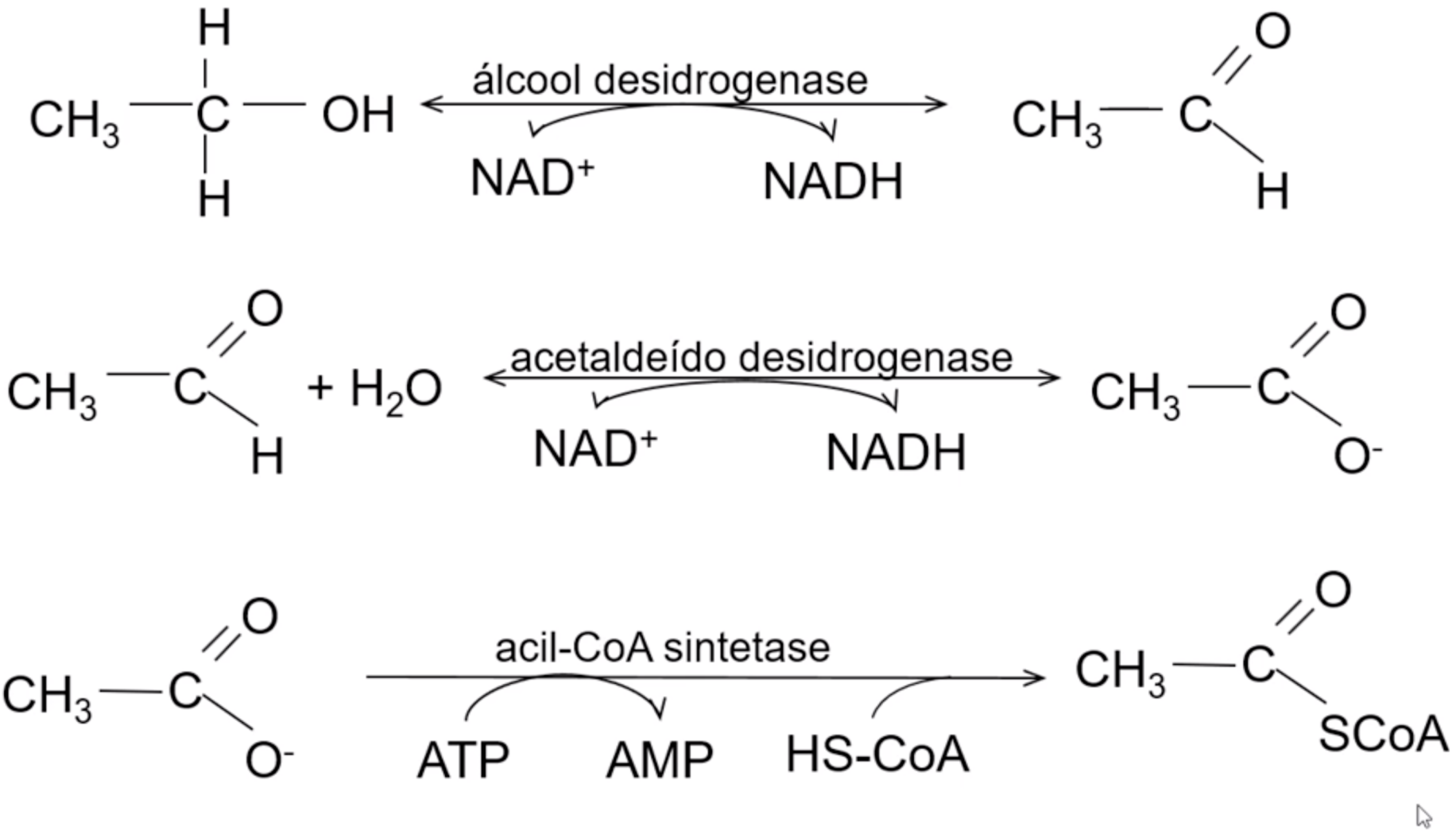
álcool desidrogenase mitocondrial

$$CH_3CHO + NAD^+ + H_2O \rightarrow CH_3COO^- + NADH + H^+$$

acetaldeído

acetato

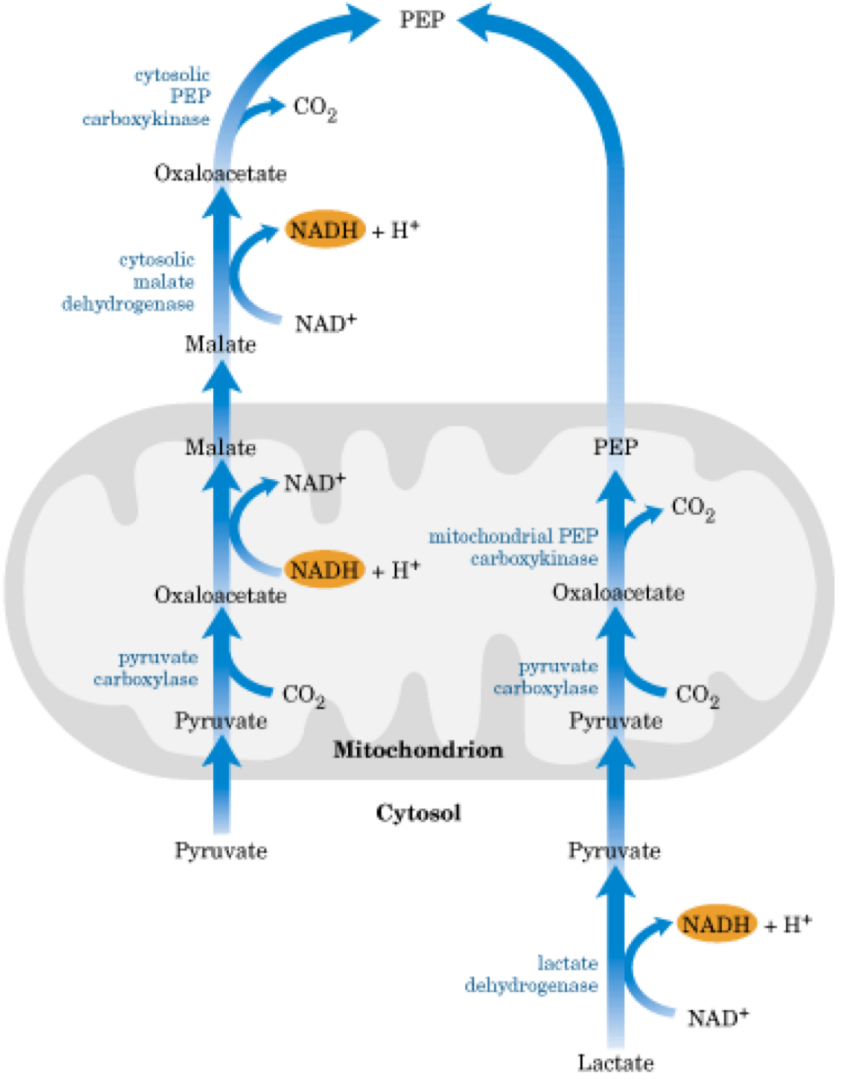
Ingestão mesmo moderada de álcool gera muito NADH


álcool desidrogenase
NAD+
NADH
acetaldeído desidrogenase
NAD+
NADH
acil-CoA sintetase
ATP
AMP
HS-CoA
SCoA

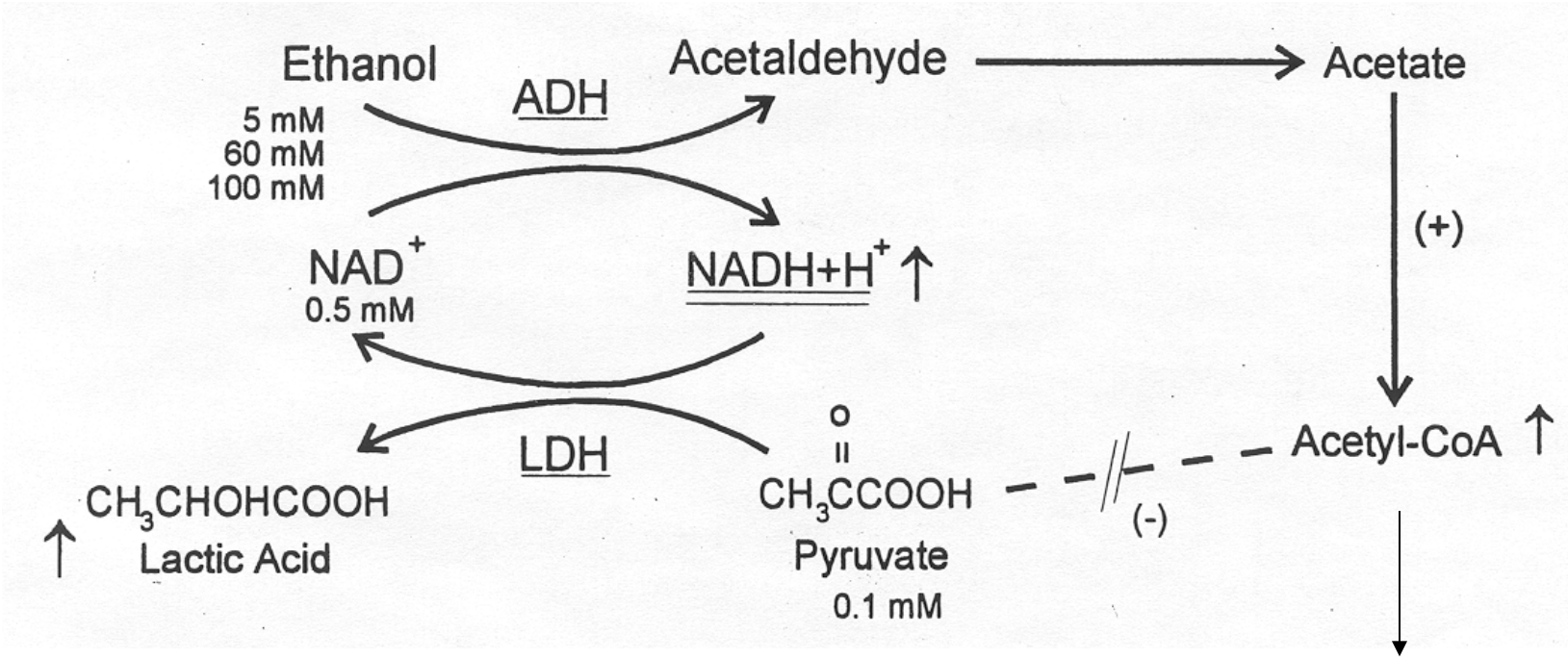
Ingestão mesmo moderada de álcool gera muito NADH

Enzimas da gliconeogênese (lactato desidrogenase e malato desidrogenase requerem NAD^+

Inibição da gliconeogênese
Inibe oxidação de ácido graxo e
Pode ocorrer cetogênese,
Pode levar a acidose lática



Conditions in the cytoplasm 1



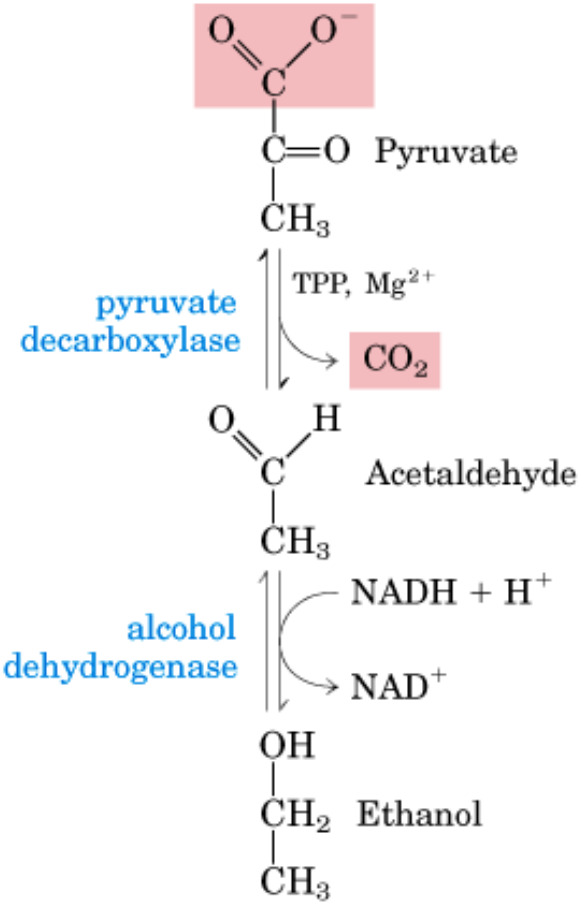
Acúmulo de lactato

Escapa acetato para
O sangue (krebs inibido por NADH

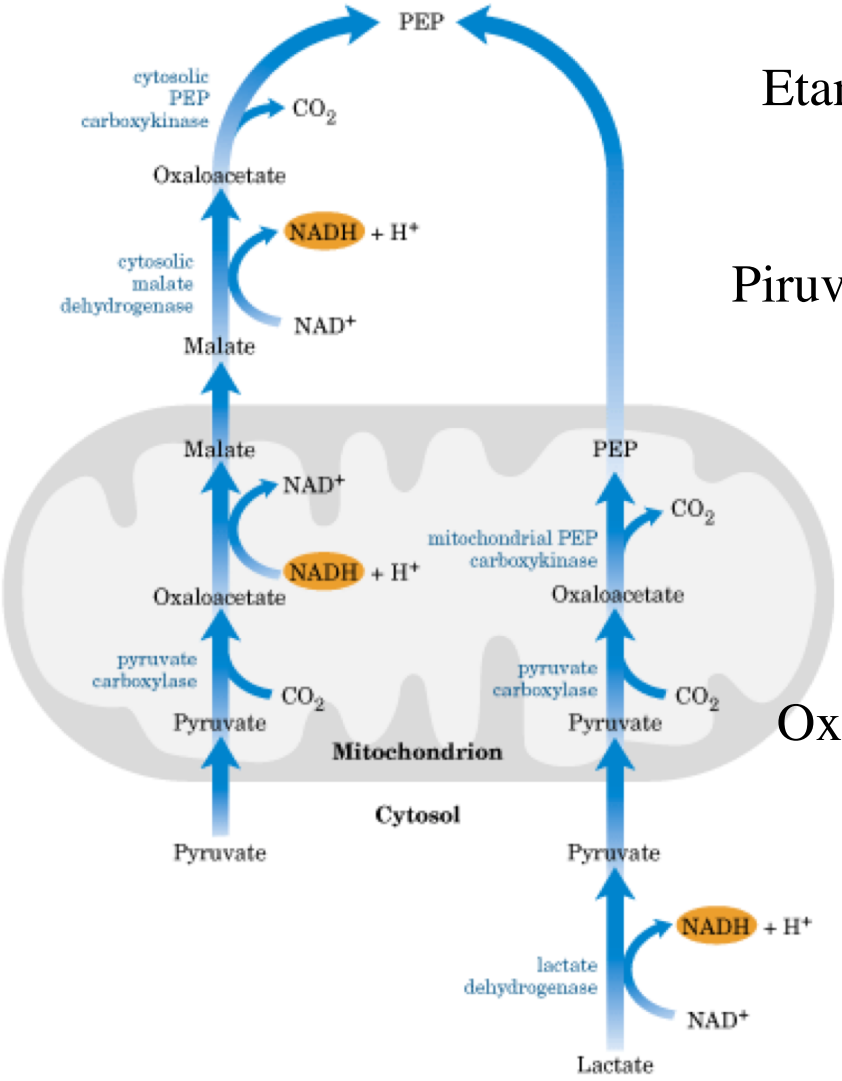
Etanol + $NAD^+ \rightarrow$ acetaldeído + NADH + H^+

Piruvato + NADH + H+ $\rightarrow$ Lactato + NAD^+

Oxaloacetato + NADH+ H+ $\rightarrow$malato + NAD+



A síntese da glicose é limitada pelas quantidades de piruvato e oxaloacetato disponíveis para reações catalisadas pela piruvato carboxilase e PEP carboxiquinase



Etanol + NAD^+ → acetaldeído + NADH + H^+

Piruvato + NADH + H+ → Lactato + NAD^+

Oxaloacetato + NADH+ H+ →malato + NAD+