

UNIVERSIDADE ESTADUAL DE RORAIMA
CURSO DE MEDICINA
Disciplina: Bioquímica
MÓDULO 2: Catabolismo

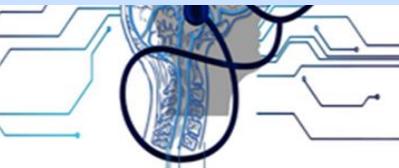
**AULA 7 - VIA GLICOLÍTICA, FERMENTAÇÃO LÁCTICA,
VIA DAS PENTOSES FOSFATO**

Prof. Higo Nasser S. Moreira

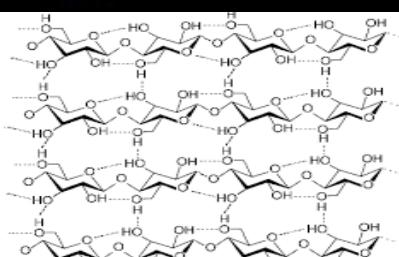
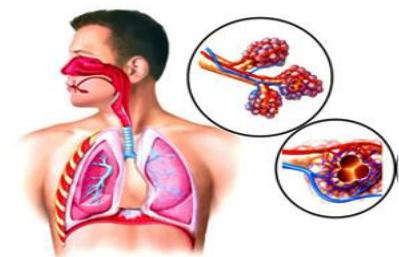
Doctor Scientiae em Bioquímica Aplicada

Universidade Federal de Viçosa – Brasil

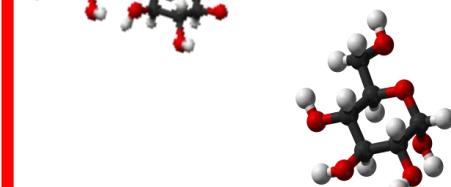
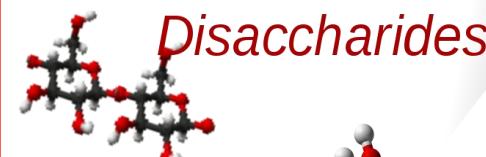
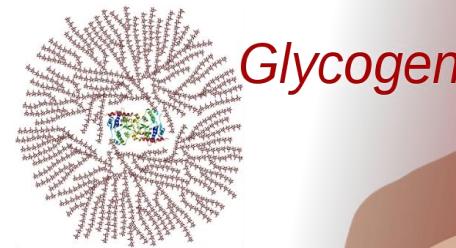
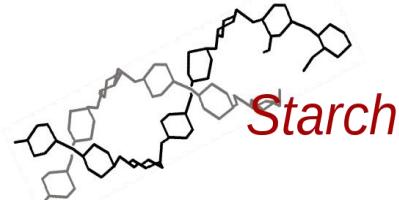
Boa Vista – Roraima



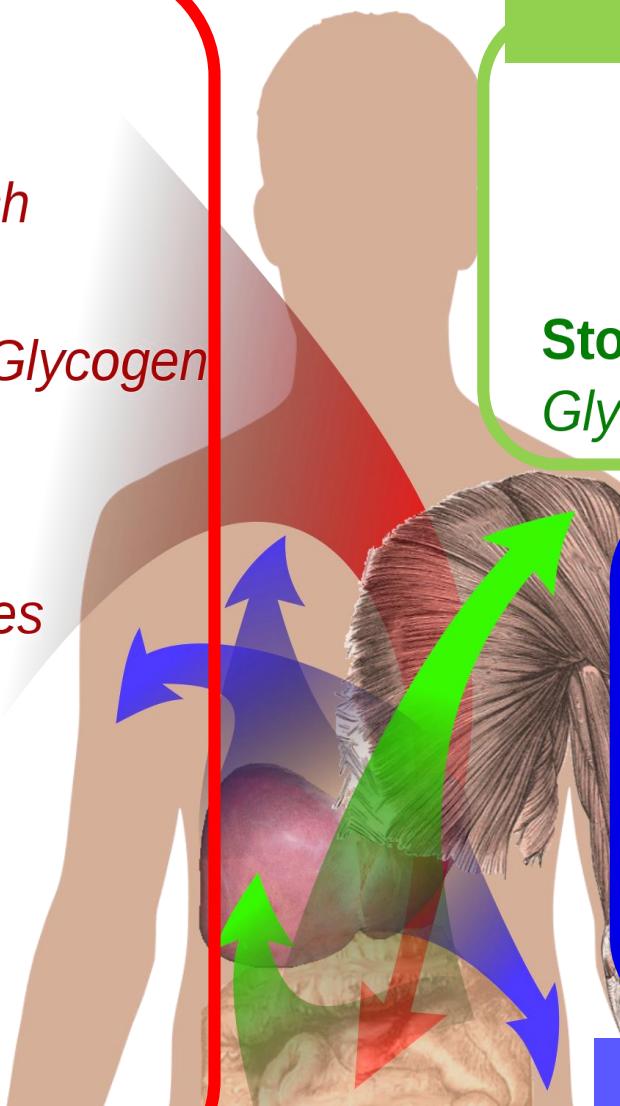
ALIMENTAÇÃO



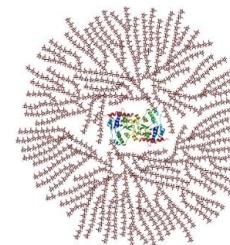
Intake:



Monosaccharides
(glucose, fructose,
galactose)



GLICOGÊNIO



Storage:
Glycogen

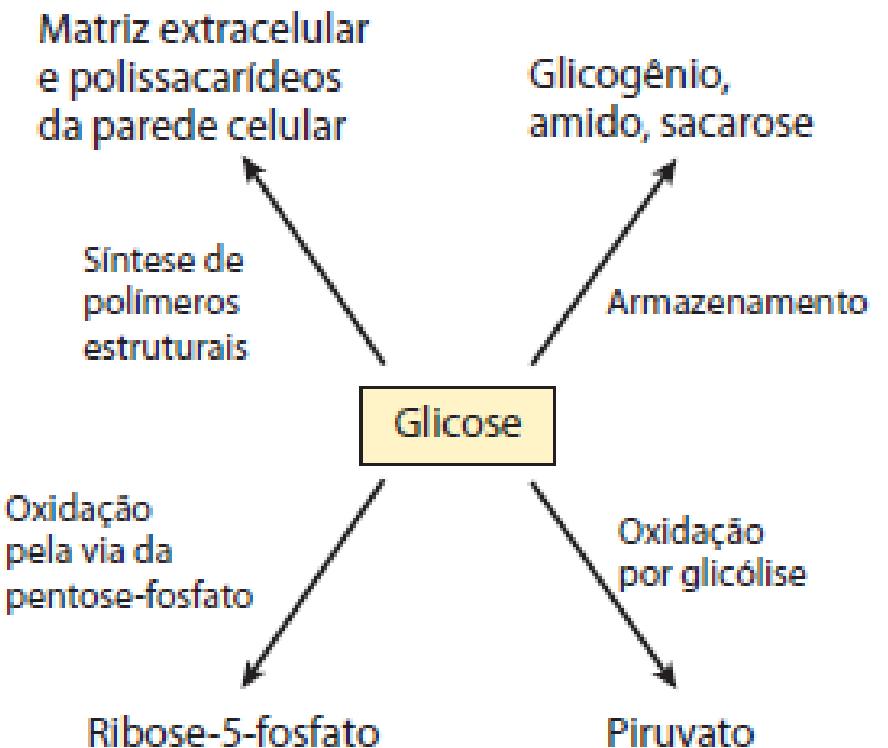
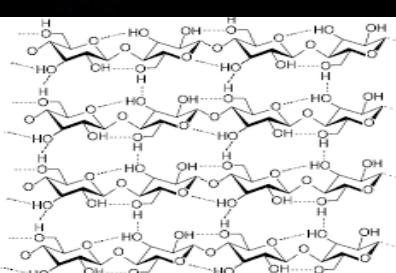
Distribution
and
utilization:
Free glucose



GLICONEOGÊNESE

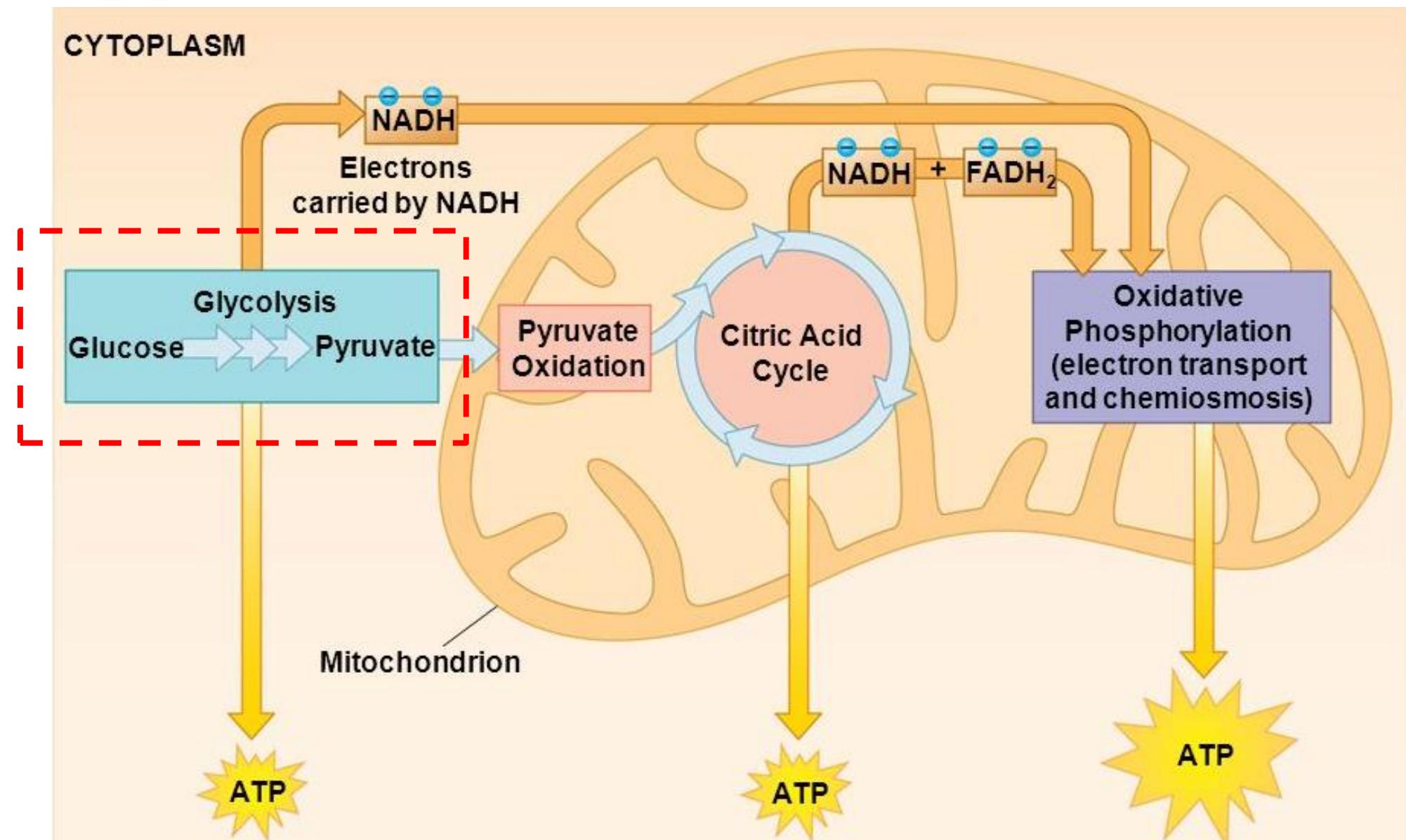
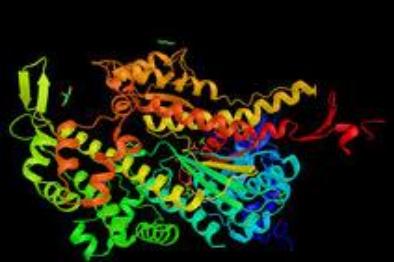
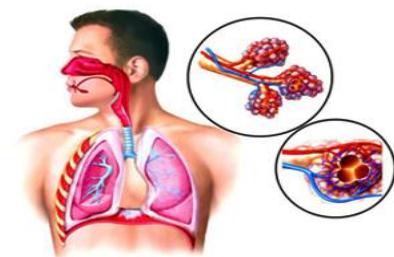
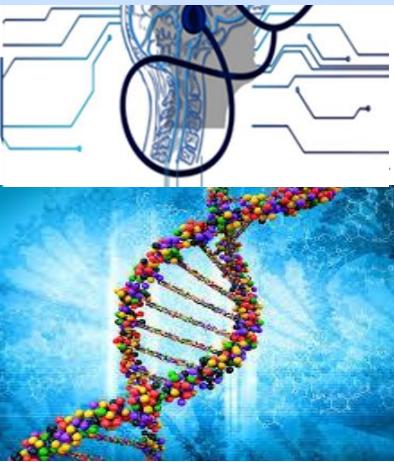
PRINCIPAIS VIAS DO CATABOLISMO DE GLICOSE

1. Via glicolítica (Glicólise)
2. Via das Pentoses fosfato
3. Glicogênese (Síntese de glicogênio)
4. Glicogenólise (Catabolismo do glicogênio)
5. Gliconeogênese (Síntese de glicose no fígado e nos rins)



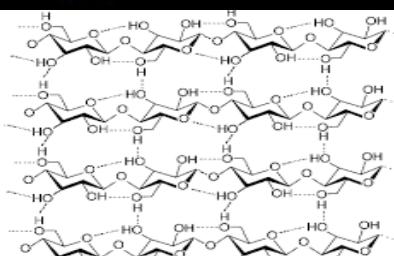
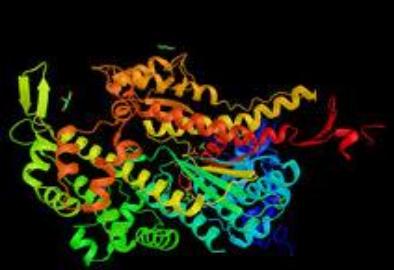
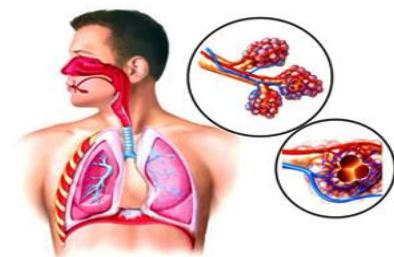
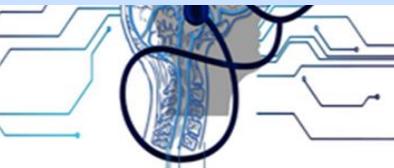
METABOLISMO DE GLICOSE

Visão geral da respiração celular

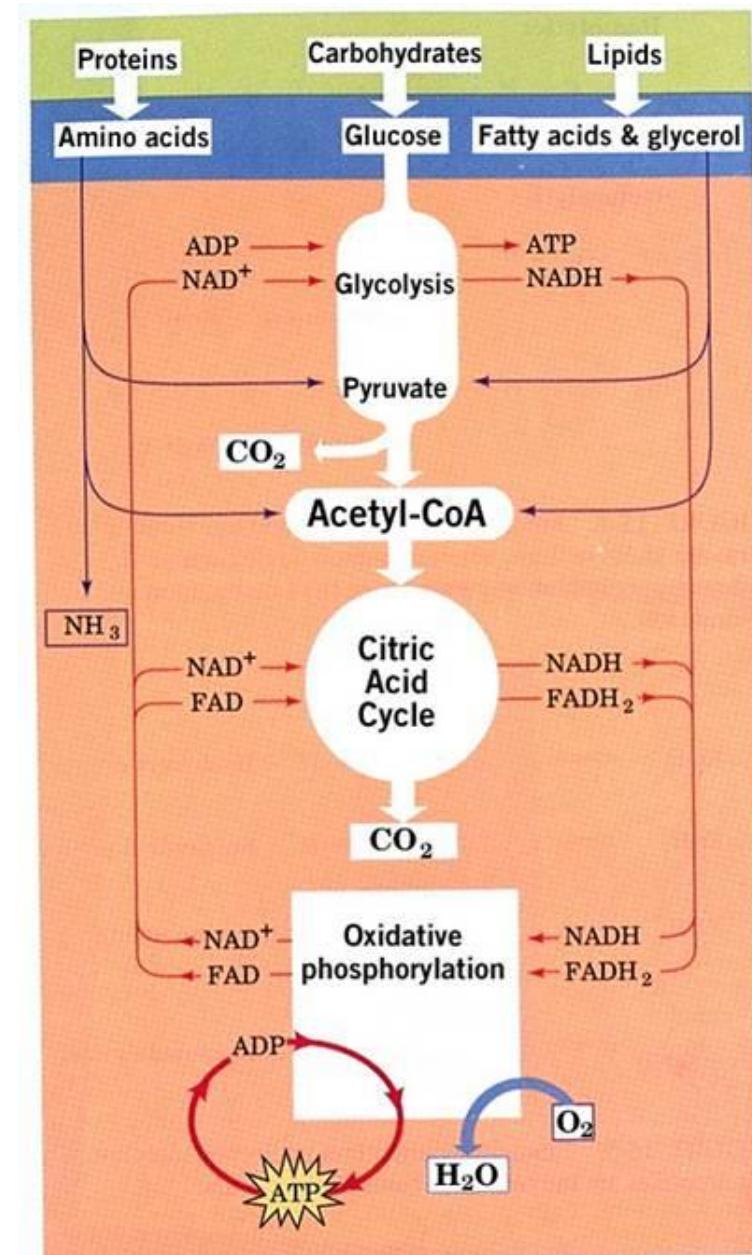


METABOLISMO DE GLICOSE

Visão geral da respiração celular

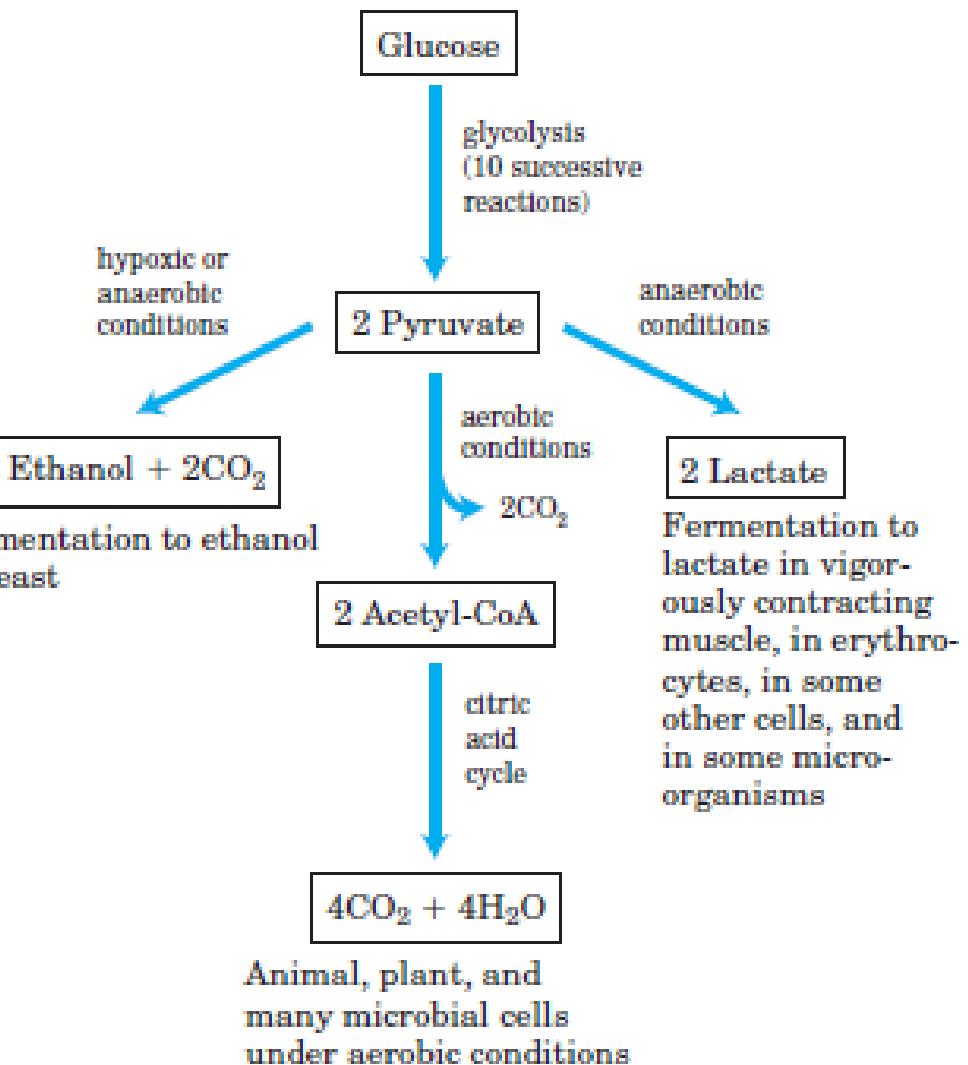


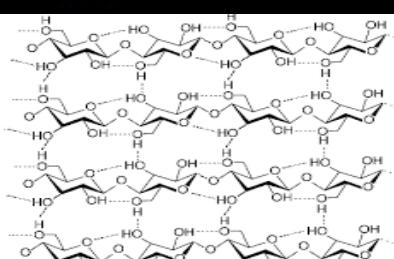
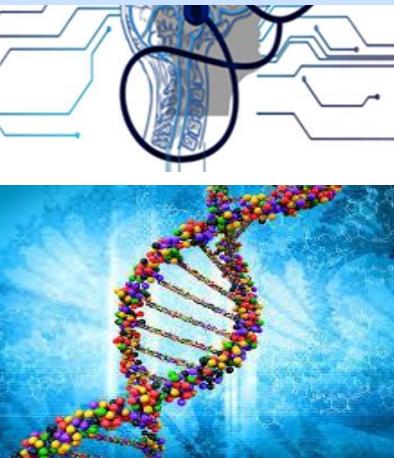
- ✓ **GLICÓLISE** (Greco *glykys*, “doce,” e *lysis*, “quebra”), a molécula de glicose é degradada 2 moléculas de piruvato (3 carbonos)
- ✓ 10 reações: 5 reações na FASE DE PREPARAÇÃO + 5 reações na FASE DE PAGAMENTO.
- ✓ Produção de 4 moléculas de ATP (saldo de 2 ATPs) e 2 NADH + H⁺ POR GLICOSE OXIDADA.



Os 3 principais destinos metabólicos do piruvato

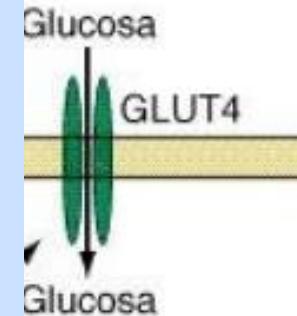
- ✓ Energia remanescente no piruvato: A via glicolítica libera apenas uma pequena fração da energia total disponível na molécula de glicólise.
- ✓ As duas moléculas de piruvato continuarão a serem oxidadas nas etapas seguintes da respiração celular.





Insulina

- ✓ GLUT 1 e GLUT 2: Hepatócitos
- ✓ GLUT3: Neurônios
- ✓ GLUT4 (Dependente de Insulina) – Músculos esquelético e cardíaco. Tecido Adiposo.



Glucosa

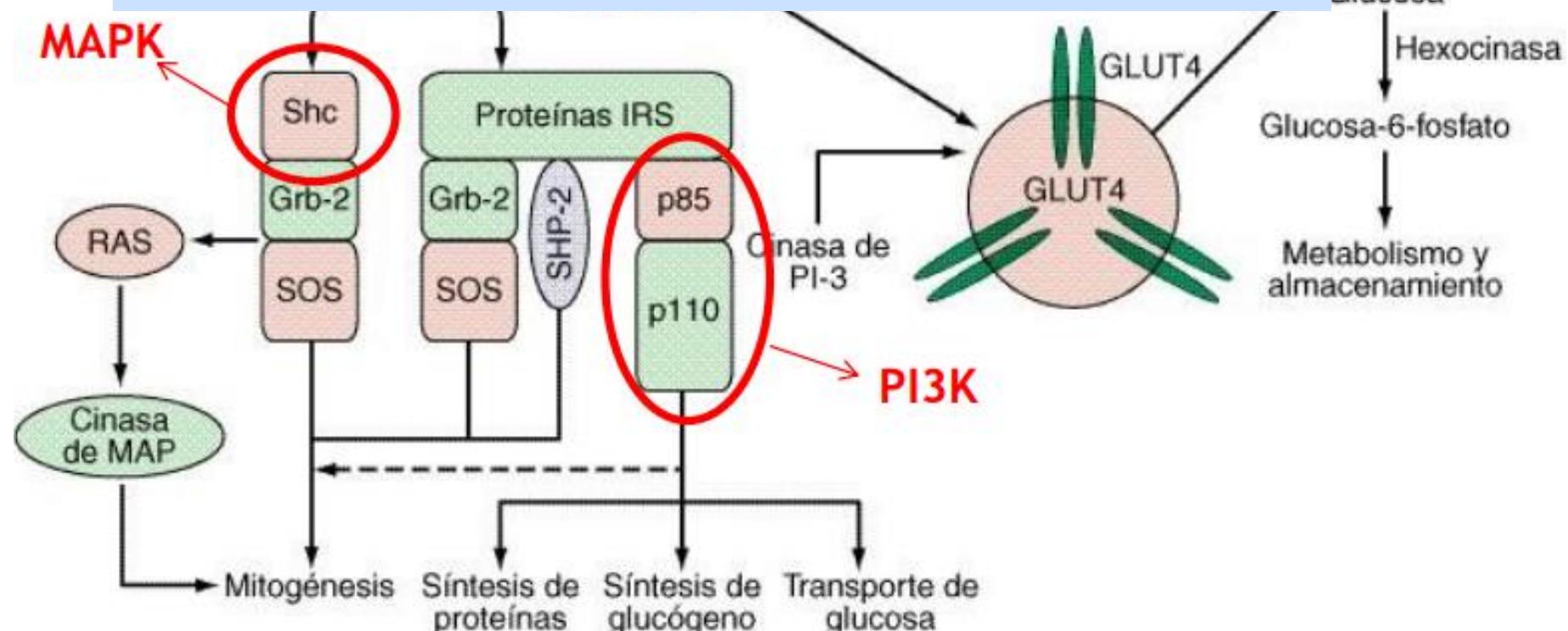
GLUT4

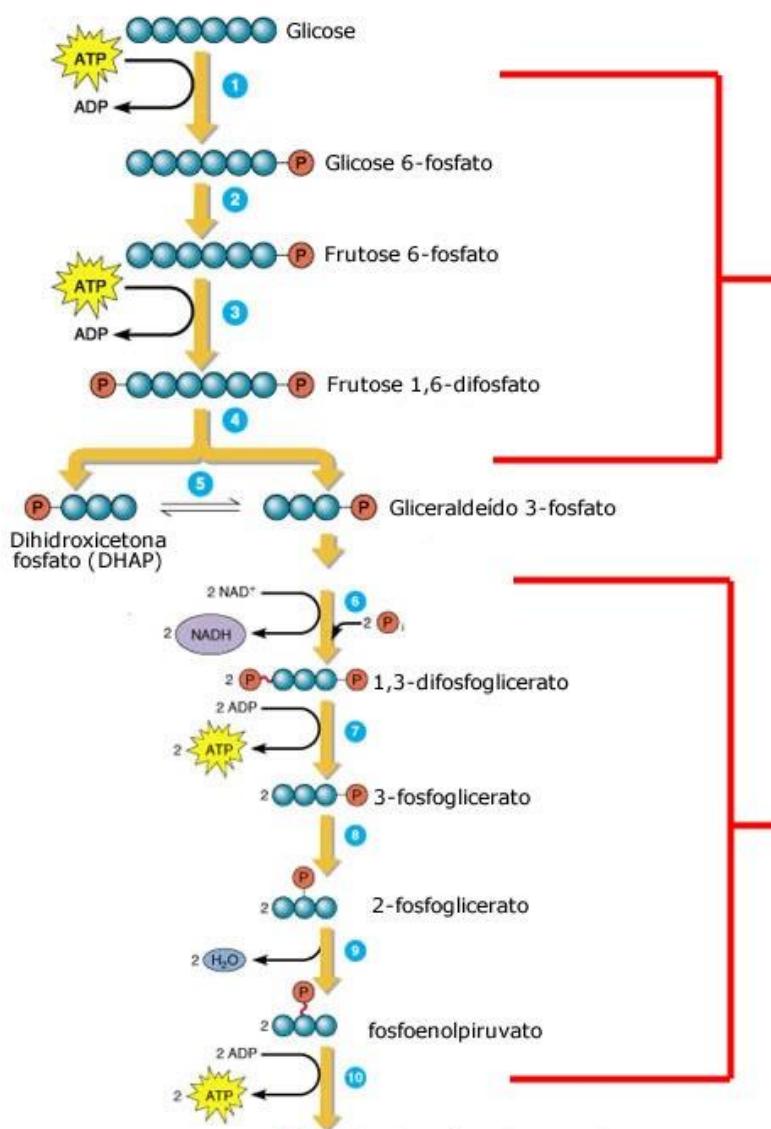
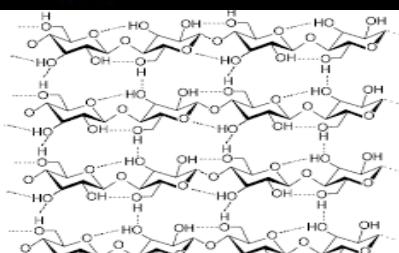
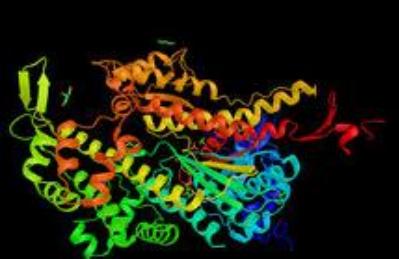
Glucosa

Hexocinasa

Glucosa-6-fosfato

Metabolismo y almacenamiento



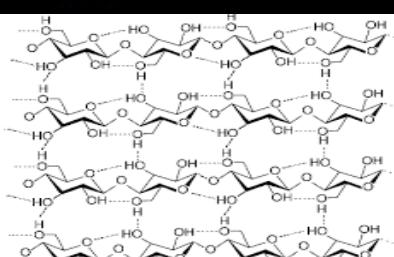


1. FASE PREPARATÓRIA (-2 ATP/Glicose)

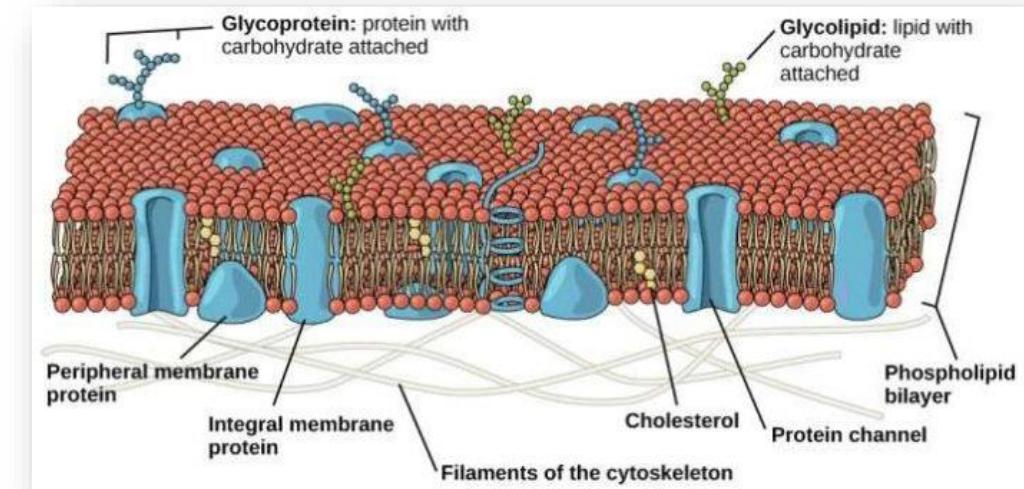
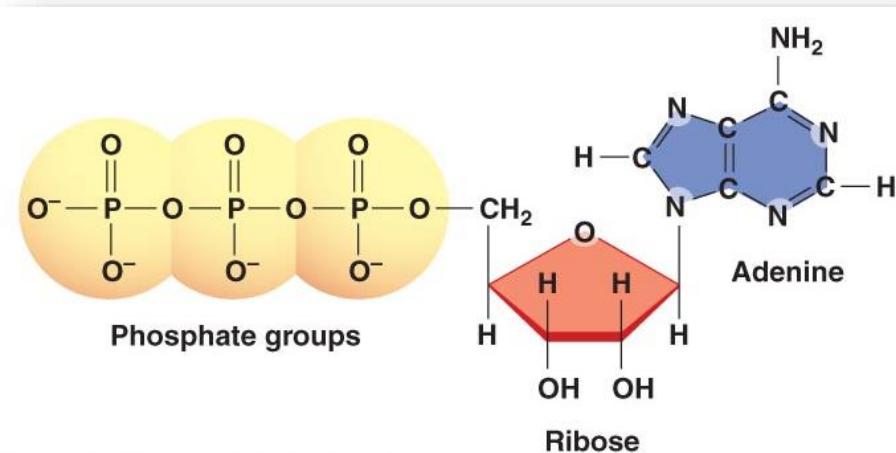
- ✓ Quebra de glicose (6 carbonos) em 2 moléculas de gliceraldeído 3P (3 carbons)
- ✓ A glicose é ativada pelo investimento de 2 moléculas de ATP

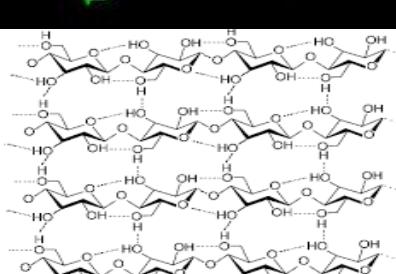
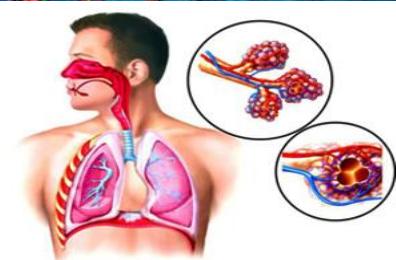
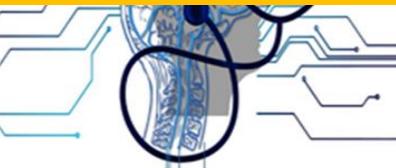
2. FASE DE PAGAMENTO (+4 ATP/Glicose + 2 NADH)

- ✓ 2 moléculas de gliceraldeído 3P (3C) são oxidadas à 2 moléculas de piruvato (3C)
- ✓ Produção de 2 moléculas de NADH
- ✓ Produção de 4 moléculas de ATP

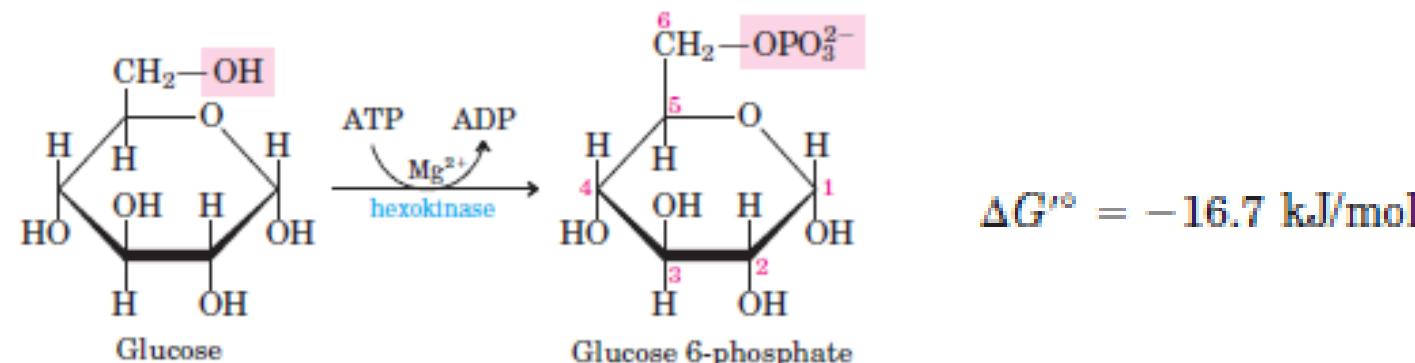
Importância fisiológica dos intermediários fosforilados

- ✓ Membrana plasmática não possui transportadores para açúcares fosforilados, portanto eles não podem deixar a célula.
- ✓ Grupos fosforil ajudam a conservar a energia livre nos metabólitos fosforilados.
- ✓ Energia de ligação resultante da formação dos intermediários fosforilados aumentam a especificidade das reações enzimáticas.

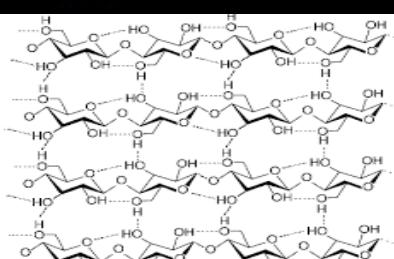
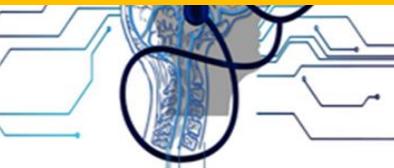




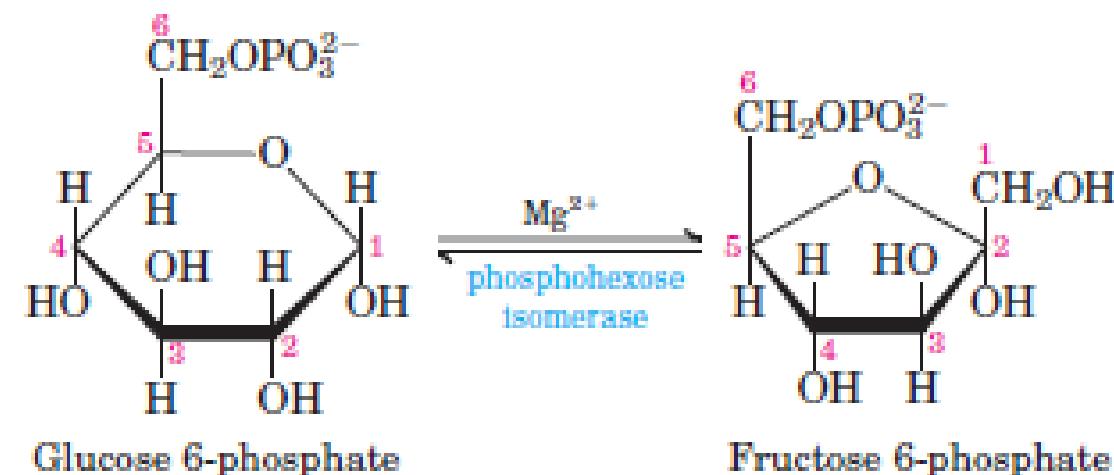
1 – FOSFORILAÇÃO DA GLICOSE: Na primeira reação, glicose é ativada pela fosforilação na hidroxila do carbono 6 com o gasto de 1 ATP.



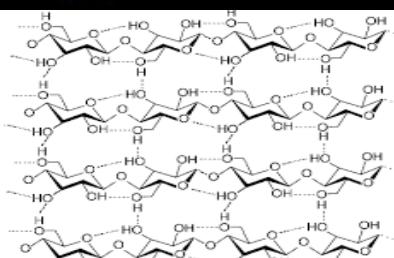
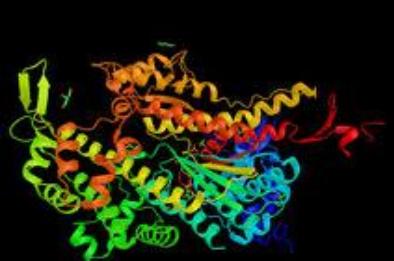
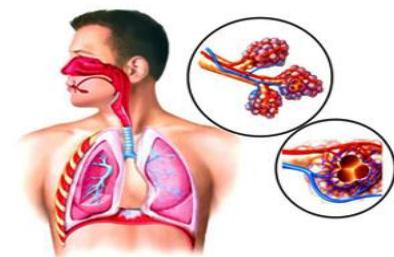
- ✓ Essa reação é irreversível em condições celulares (glicose não sai mais da célula).
- ✓ Enzima requer Mg^{2+} como cofator.
- ✓ HEXOQUINASE está presente em TODAS as células. Hepatócitos possuem uma isoenzima chamada GLICOQUINASE



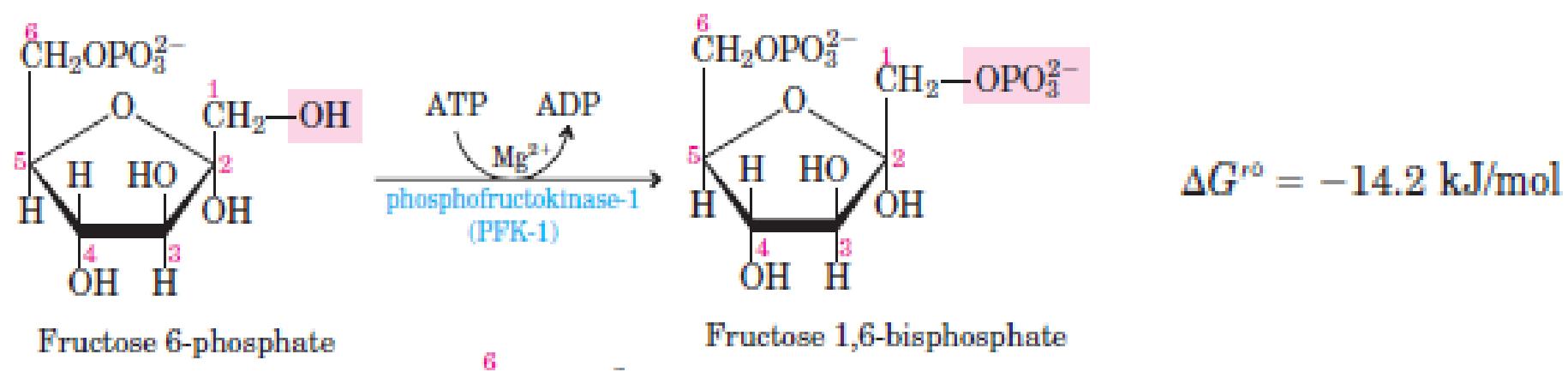
2- CONVERSÃO DA GLICOSE 6-FOSFATO EM FRUTOSE 6-FOSFATO: A enzima fosfoexose isomerase (fosfoglucose isomerase) catalisa a isomerização reversível da glicose 6-fosfato em frutose 6-fosfato.

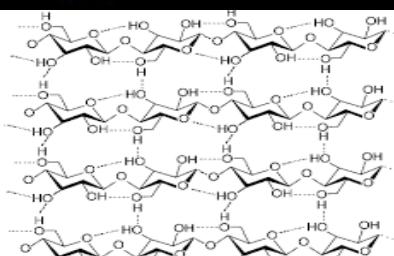
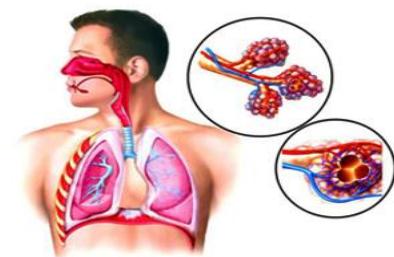


$$\Delta G^{\circ} = 1.7 \text{ kJ/mol}$$

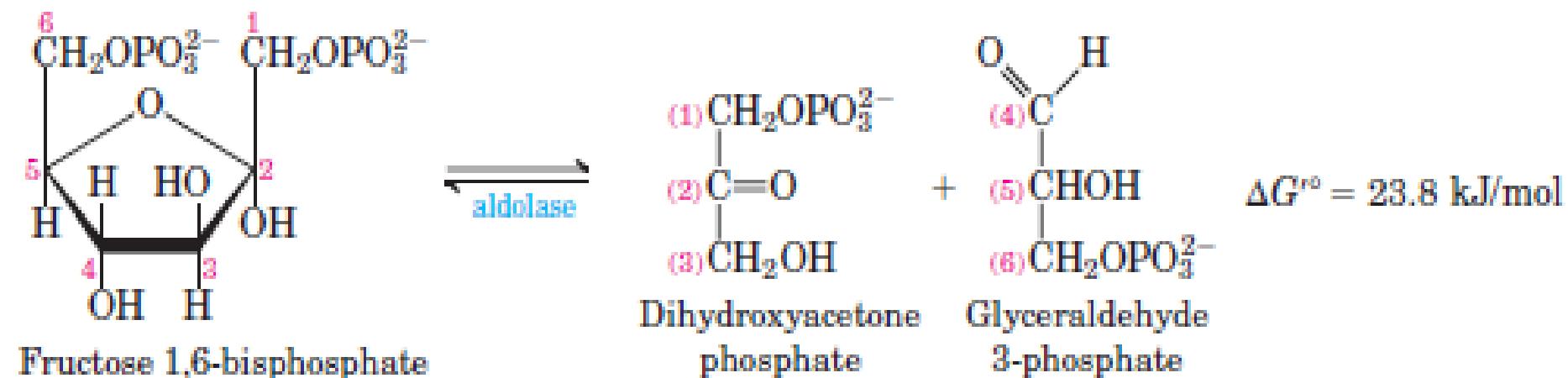


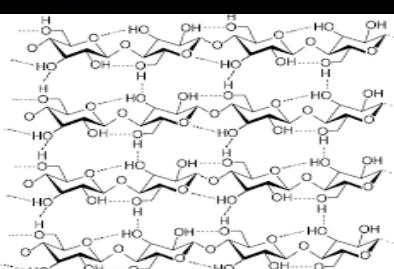
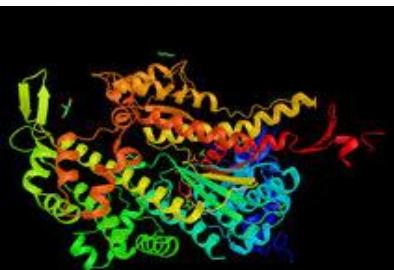
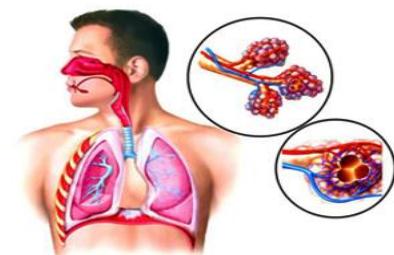
3- FOSFORILAÇÃO DE FRUTOSE 6-FOSFATO EM FRUTOSE 1,6-BIFOSFATO. Na segunda das duas reações de iniciação da glicólise, a FOSFOFRUTOCINASE-1 (PFK-1) catalisa a transferência de um grupo fosforil de ATP para frutose 6-fosfato para produzir frutose 1,6-bifosfato:



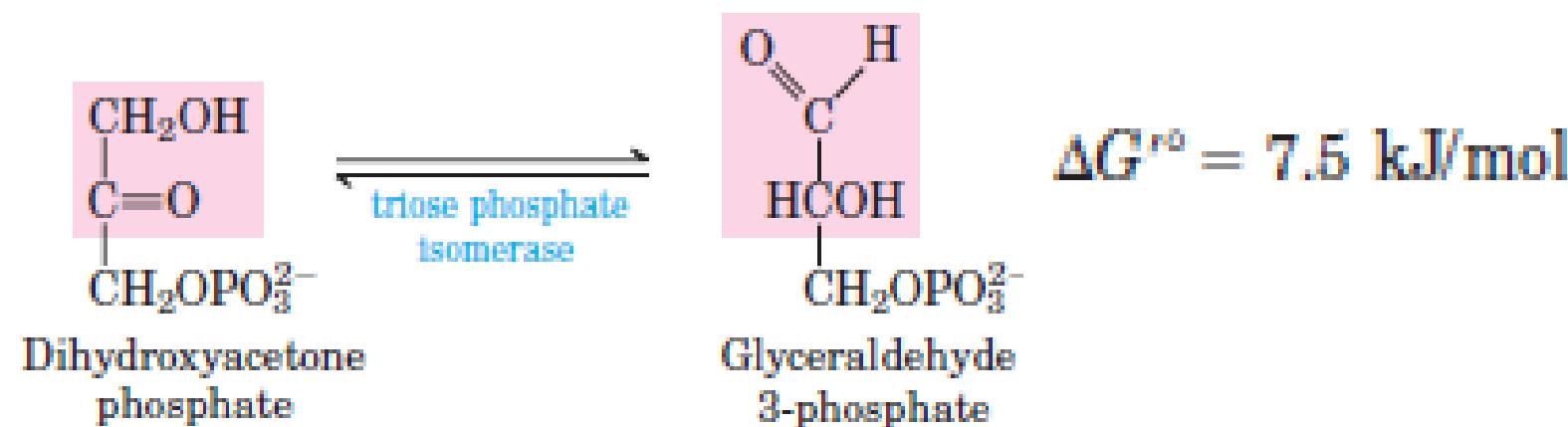


4- CLIVAGEM DE FRUTOSE 1,6-BIFOSFATO a enzima frutose 1,6-bisfosfato aldose, frequentemente chamada simplesmente de aldolase, catalisa uma condensação aldólica reversível. A frutose 1,6-bifosfato é clivada para produzir dois fosfatos triose diferentes, **GLICERALDEÍDO 3-FOSFATO** e **DIIDROXIACETONA-FOSFATO**.

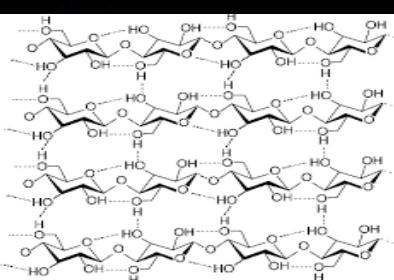
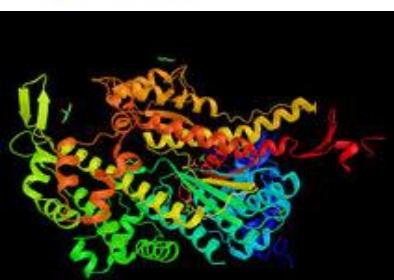
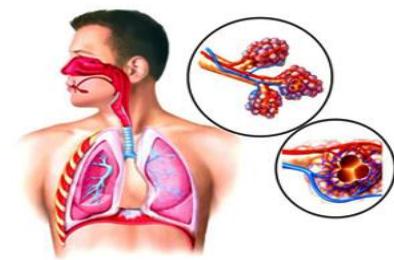
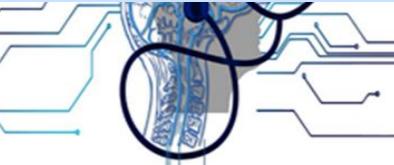




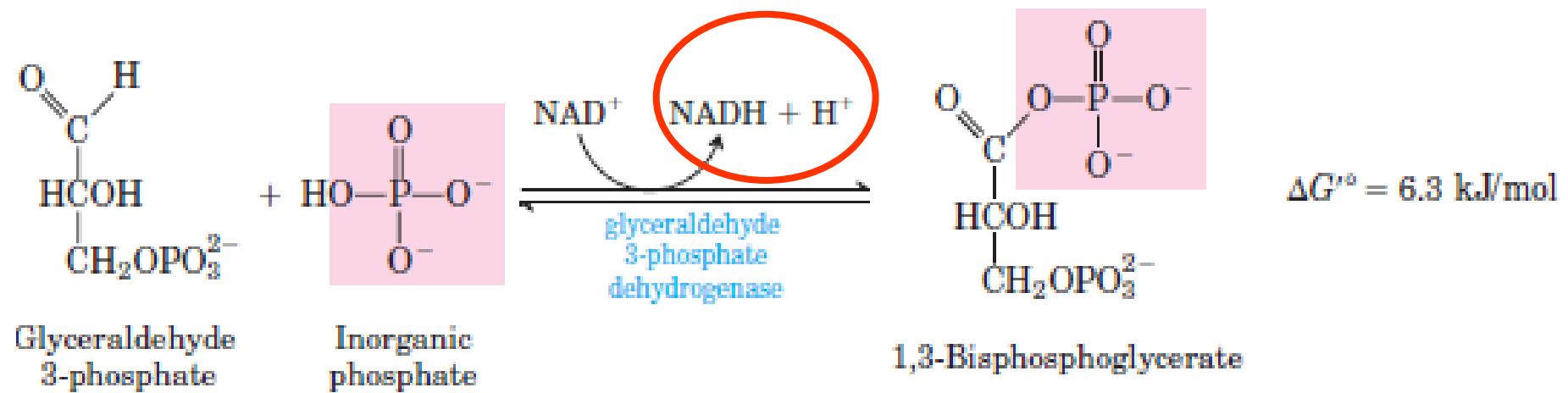
5- INTERCONVERSÃO DAS TRIOSES FOSFATOS. Apenas uma das 2 TRIOSES FOSFATO formadas pela aldolase, o **GLICERALDEÍDO 3-FOSFATO**, pode ser diretamente degradado nas etapas subsequentes da glicólise. O outro produto, DIIDROXIACETONA FOSFATO, é rápida e reversivelmente convertido em **GLICERALDEÍDO 3-FOSFATO** pela quinta enzima da sequência, triose fosfato isomerase:



A fase de pagamento da glicólise produz 4 ATP e 2 NADH por glicose



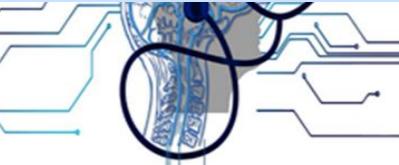
6- OXIDAÇÃO DO GLICERALDEÍDO 3-FOSFATO EM 1,3-BIFOSFOGLICERATO. A primeira etapa na fase de pagamento é a oxidação do GLICERALDEÍDO 3-FOSFATO em 1,3-BIFOSFOGLICERATO, catalisado pela GLICERALDEÍDO 3-FOSFATO DESIDROGENASE:



REAÇÃO DE DESIDROGENAÇÃO

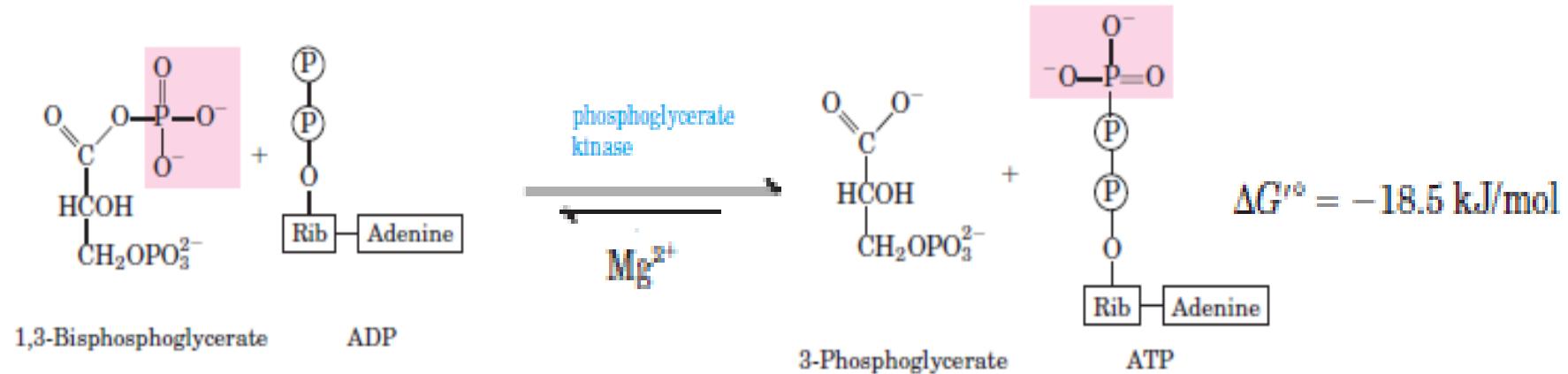
Formação de 2 moléculas de NADH (1 para cada gliceraldeído 3-fosfato). Cada molécula de NADH fornecerá elétrons para a produção de 3 moléculas de ATP na cadeia de transporte de elétrons.

A fase de pagamento da glicólise produz 4 ATP e 2 NADH por glicose



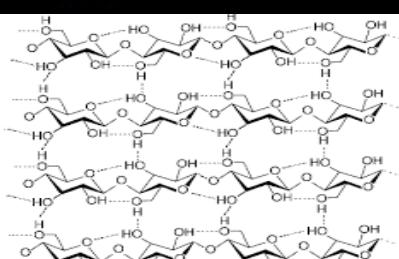
7- TRANSFERÊNCIA DO GRUPO FOSFATO DO 1,3- BIFOSFOGLICERATO PARA O ADP.

A enzima fosfoglicerato quinase transfere o grupo fosforil de alta energia do grupo carboxila do 1,3-bifosfoglycerato para ADP, formando ATP e 3-fosfoglicerato:

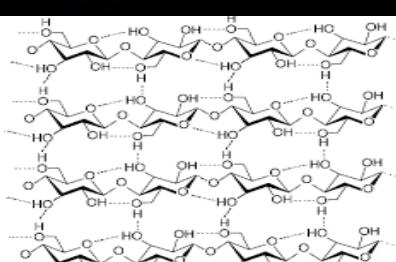
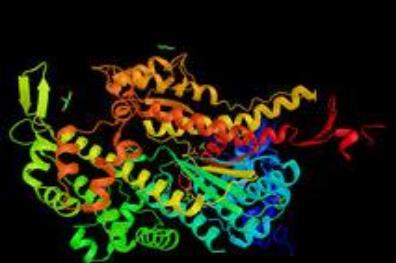
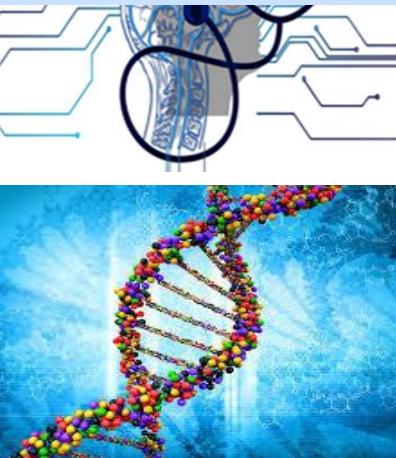


PRIMEIRA FOSFORILAÇÃO À NÍVEL DE SUBSTRATO

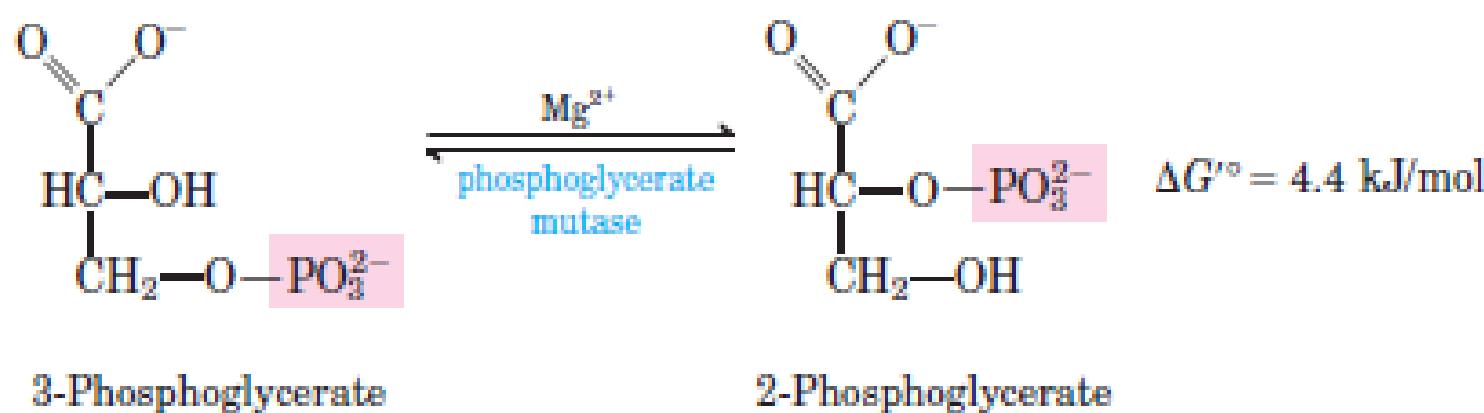
A síntese de ATP pela transferência direta do grupo fosfato de um substrato (intermediário de alta energia) para uma molécula de ADP.



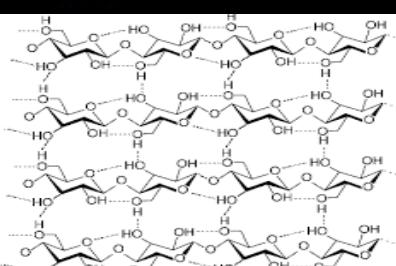
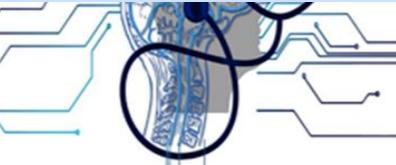
A fase de pagamento da glicólise produz 4 ATP e 2 NADH por glicose



8- CONVERSÃO DE 3-FOSFOGLICERATO EM 2-FOSFOGLICERATO. A enzima fosfoglicerato mutase catalisa uma mudança reversível do grupo fosforil entre C-2 e C-3 do glicerato. Mg^{2+} é essencial para esta reação:

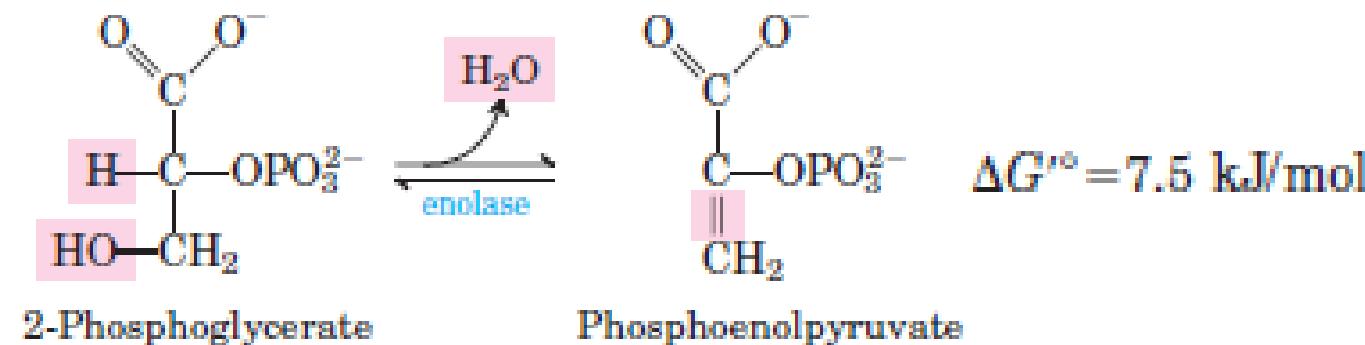


A fase de pagamento da glicólise produz 4 ATP e 2 NADH por glicose



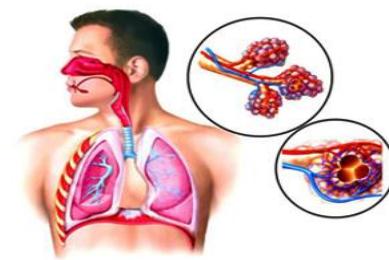
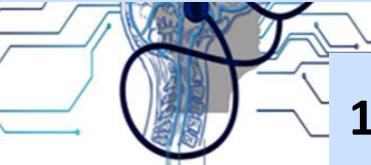
9- DESIDRATAÇÃO DE 2-FOSFOGLICERAÇÃO EM FOSFOENOLPIRUVATO.

Na segunda reação glicolítica que gera um composto com alto potencial de transferência de grupo fosforil, a enolase promove a remoção reversível de uma molécula de água de 2-FOSFOGLICERATO para produzir FOSFOENOLPIRUVATO (PEP).



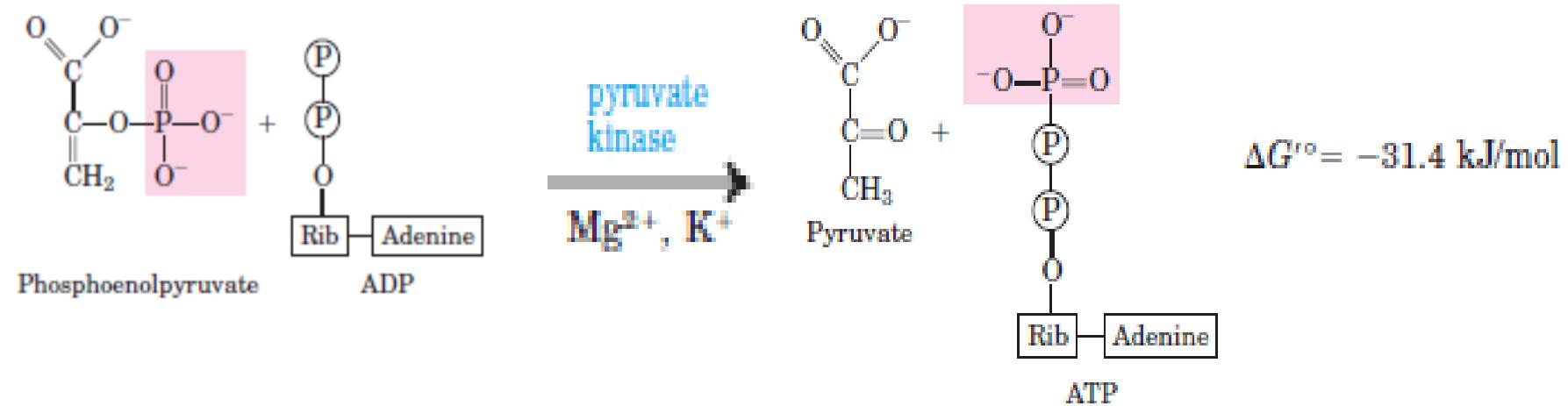
FOSFOENOLPIRUVATO (PEP): Composto mais Rico em Energia da via glicolítica (CRE)

A fase de pagamento da glicólise produz 4 ATP e 2 NADH por glicose



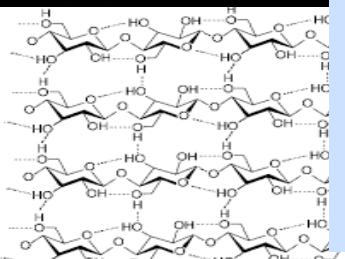
10- TRANSFERÊNCIA DO GRUPO FOSFORIL DO FOSFOENOLPIRUVATO (CRE) PARA ADP.

A última etapa da glicólise é a transferência do grupo fosforil do FOSFOENOLPIRUVATO para o ADP, catalisado pela PIRUVATO QUINASE, que requer K^+ e Mg^{2+} ou Mn^{2+} .

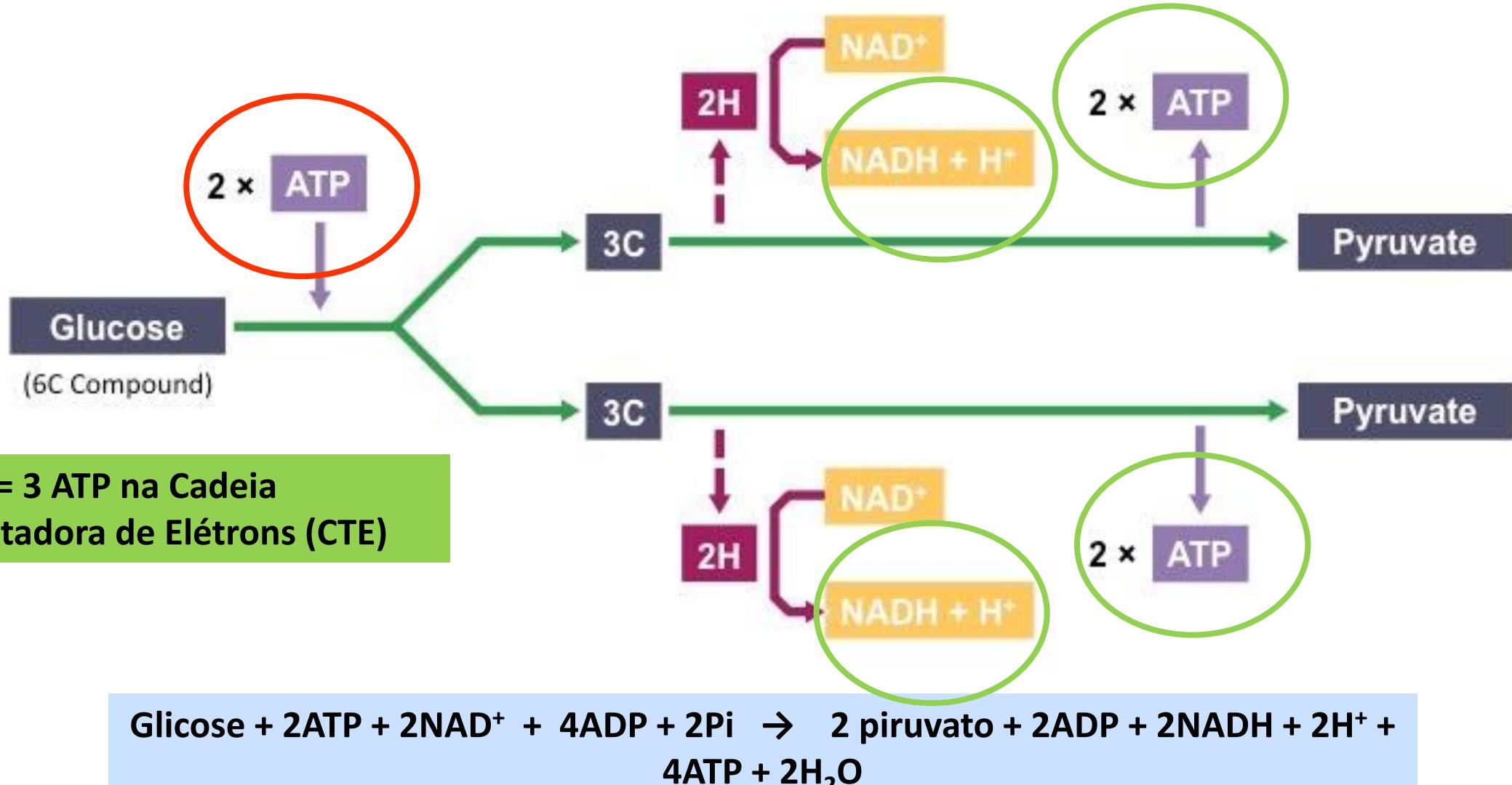
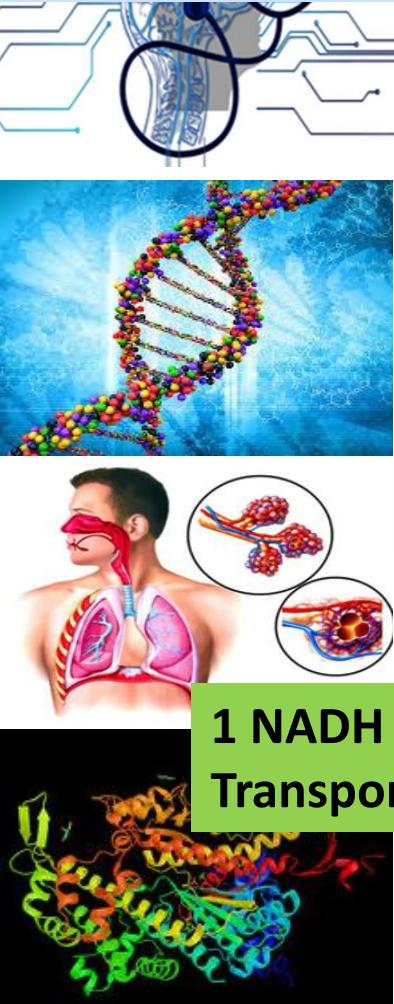


FOSFORILAÇÃO DE SEGUNDO NÍVEL DE SUBSTRATO

A síntese de 2 MOLÉCULAS DE ATP (1 para cada FOSFOENOLPIRUVATO) pela transferência direta do grupo fosfato de um substrato (intermediário de alta energia) para uma molécula de ADP.

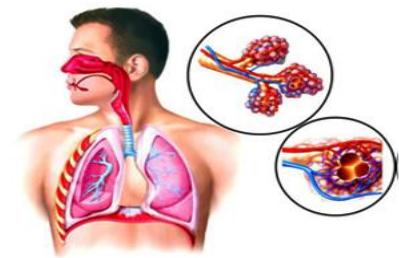
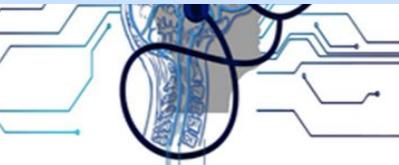


O balanço geral da via glicolítica resulta em um saldo de 2 ATP e 2 NADH



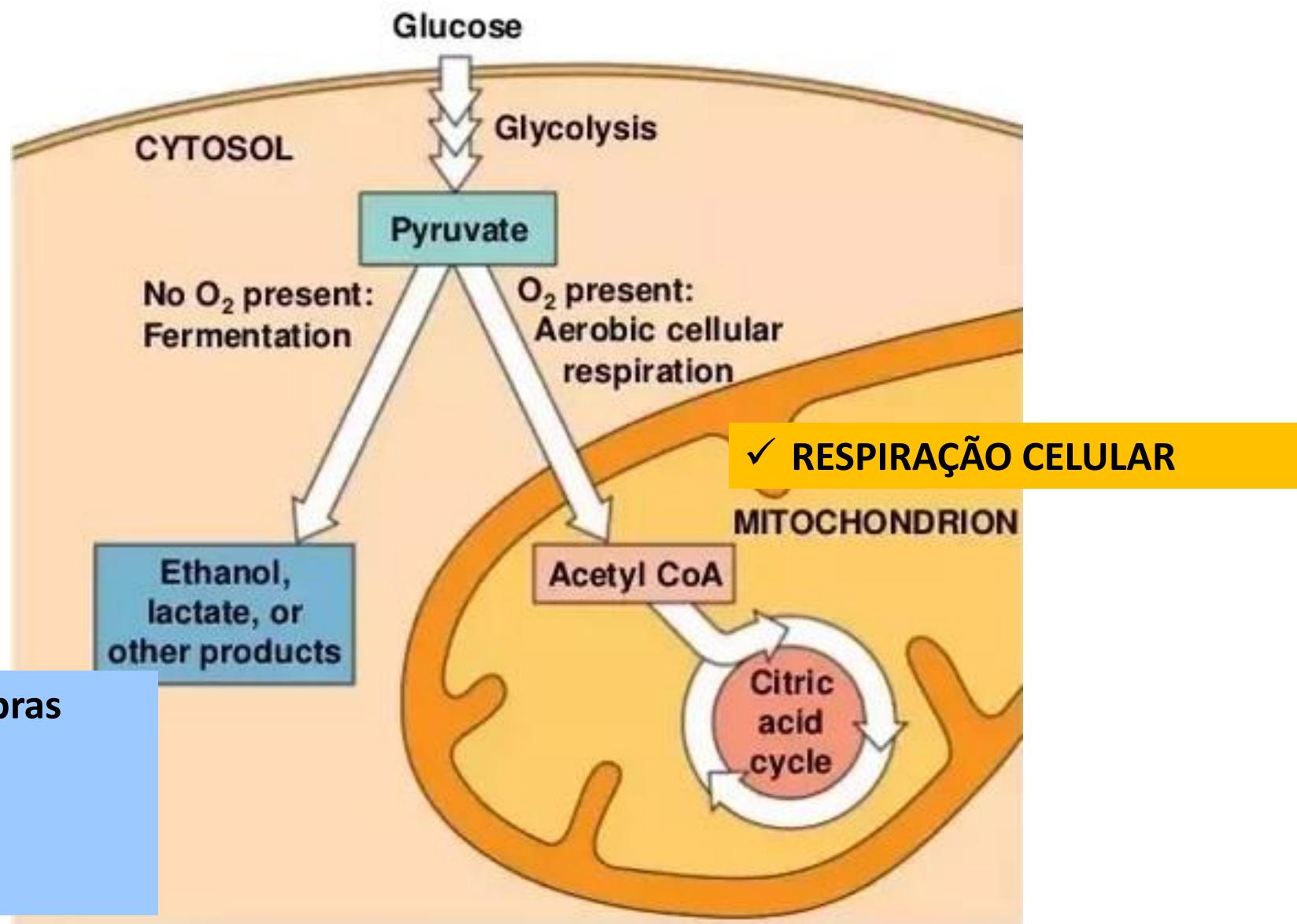
VISÃO GERAL DA VIA GLICOLÍTICA

Os destinos catabólicos do piruvato



✓ **FERMENTAÇÃO LÁCTICA** (Fibras esqueléticas e hemárias)

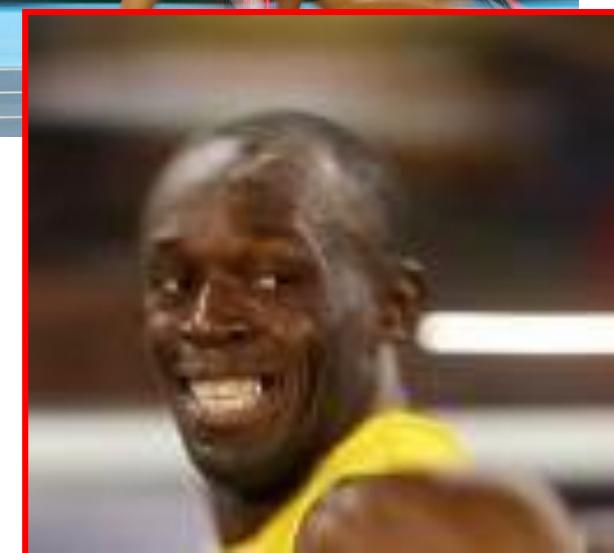
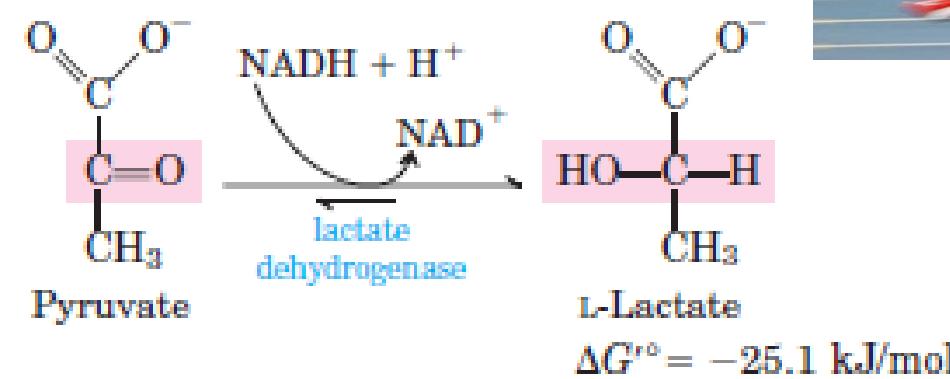
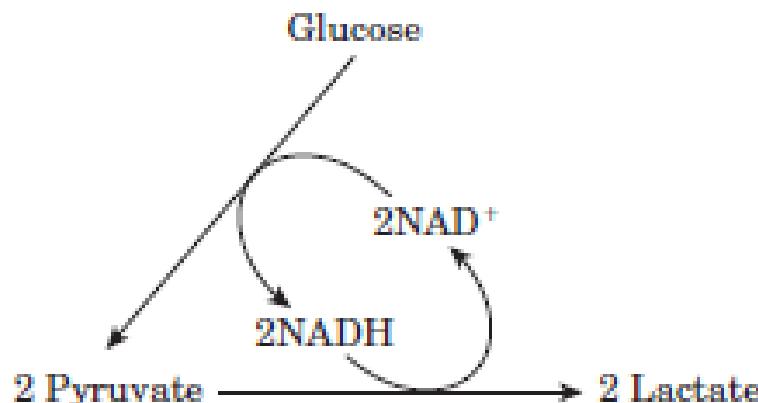
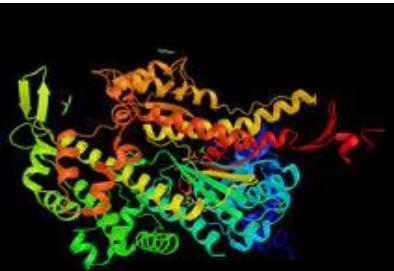
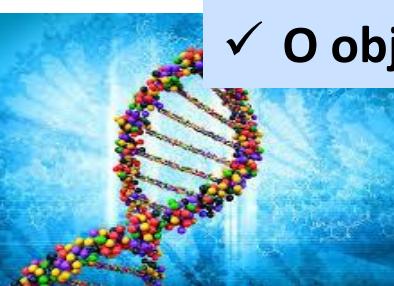
✓ **FERMENTAÇÃO ALCOÓLICA:**
Bactérias e leveduras



O DESTINO DO PIRUVATO EM CONDIÇÕES ANAERÓBICAS

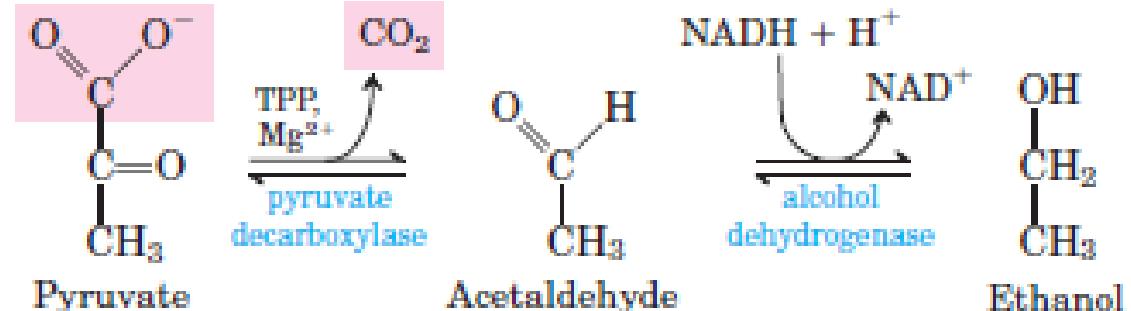
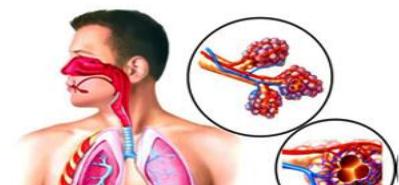
Fermentação láctica

- ✓ O piruvato é o acceptor final de elétrons na fermentação láctica
- ✓ O objetivo da fermentação láctica é a regeneração das concentrações de citosólicas de NAD⁺



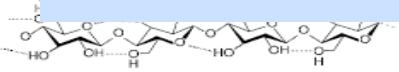


- ✓ O etanol é o produto reduzido na fermentação alcoólica



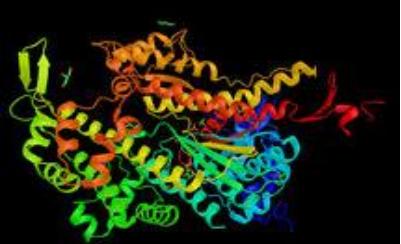
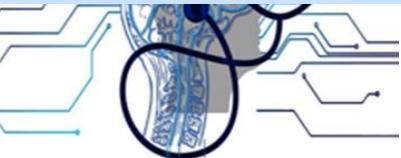
FERMENTAÇÃO EM ESCALA INDUSTRIAL.

- ✓ Os microrganismos são cultivados em um BIORREATOR contendo milhares de litros de MEIO DE CRESCIMENTO - UMA FONTE BARATA DE CARBONO E ENERGIA - sob condições cuidadosamente controladas, incluindo baixa concentração de oxigênio e temperatura constante.
- ✓ Após a separação centrífuga das células do meio de crescimento, os produtos valiosos da fermentação são recuperados das células ou do fluido sobrenadante.



O DESTINO DO PIRUVATO EM CONDIÇÕES ANAERÓBICAS

Fermentação alcoólica vs Fermentação láctica

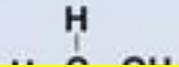


- ✓ Em um processo de fermentação, a célula reduz um **INTERMEDIÁRIO ORGÂNICO** para regenerar as concentrações citosólicas de NAD + (oxidado).
- ✓ O ACEPTOR DE ELÉTRONS FINAL DEFINIRÁ O TIPO ESPECÍFICO DE FERMENTAÇÃO.

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Alcohol Fermentation

Glucose



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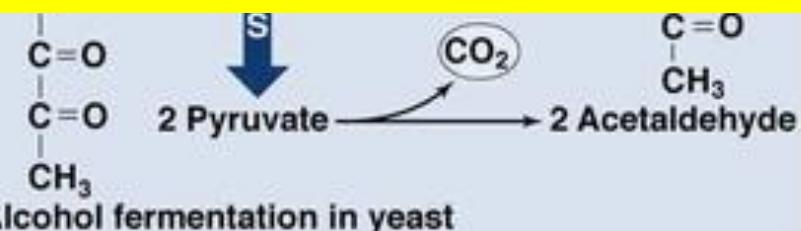
Lactic Acid Fermentation

Glucose



OBSERVAÇÃO IMPORTANTE!

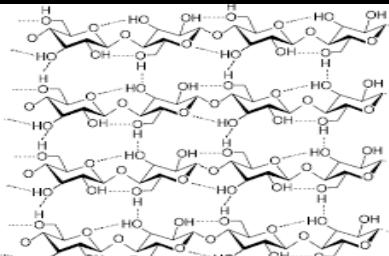
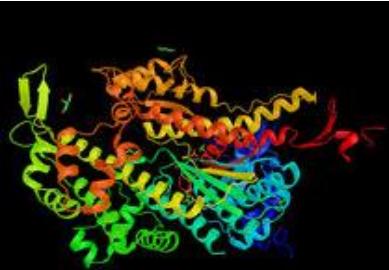
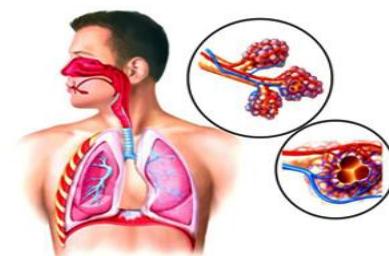
- ✓ PROCESSO DE RESPIRAÇÃO: Molécula inorgânica é o acceptor final de elétrons
- ✓ PROCESSOS FERMENTATIVOS: Um intermediário orgânico é o acceptor final de elétrons



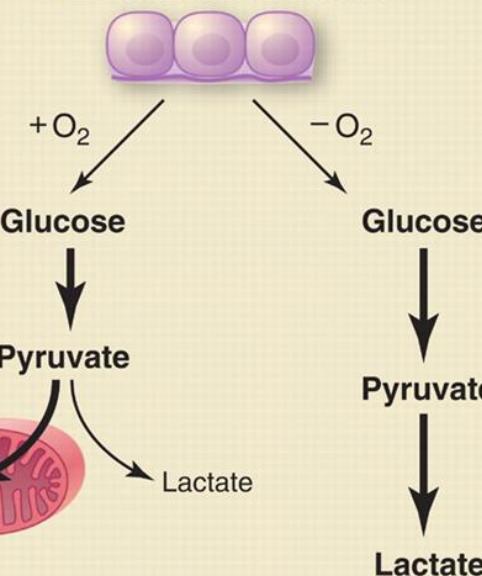
O EFEITO WARBURG: As células cancerosas fermentam a glicose mesmo quando há oxigênio suficiente.

Como a fermentação da glicose é muito menos eficiente do que a respiração, as células cancerosas consomem muito mais glicose (19X mais em média) para obter a mesma quantidade de energia.

EFEITO PASTEUR, 1857



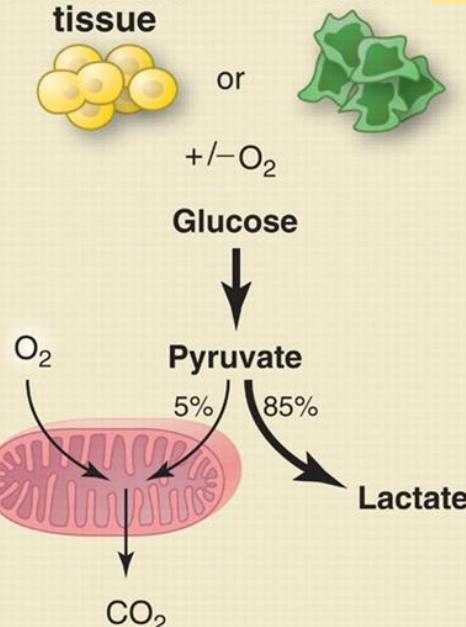
Differentiated tissue



Oxidative phosphorylation
~36 mol ATP/
mol glucose

Anaerobic glycolysis
2 mol ATP/
mol glucose

Proliferative tissue



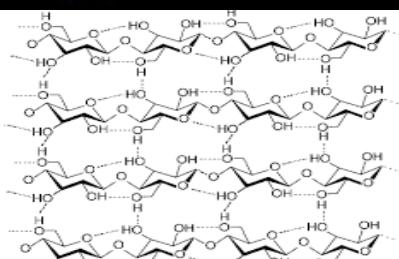
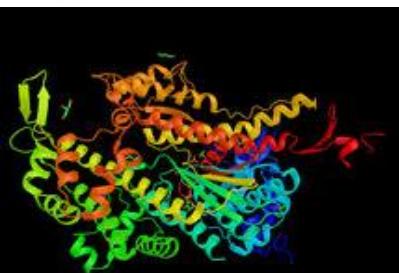
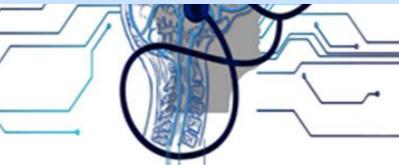
Aerobic glycolysis
(Warburg effect)
~4 mol ATP/mol glucose

EFEITO WARBURG, 1920

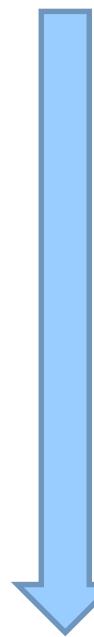
Otto Warburg
(1883-1970):
Awarded the 1931 Nobel Prize
in Physiology and Medicine



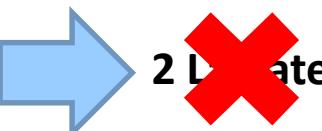
Otto Warburg,
1883-1970



Glucose

**RESPIRAÇÃO AERÓBICA EM UMA CÉLULA NORMAL**

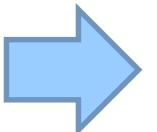
2 Pyruvate



2 Lactate

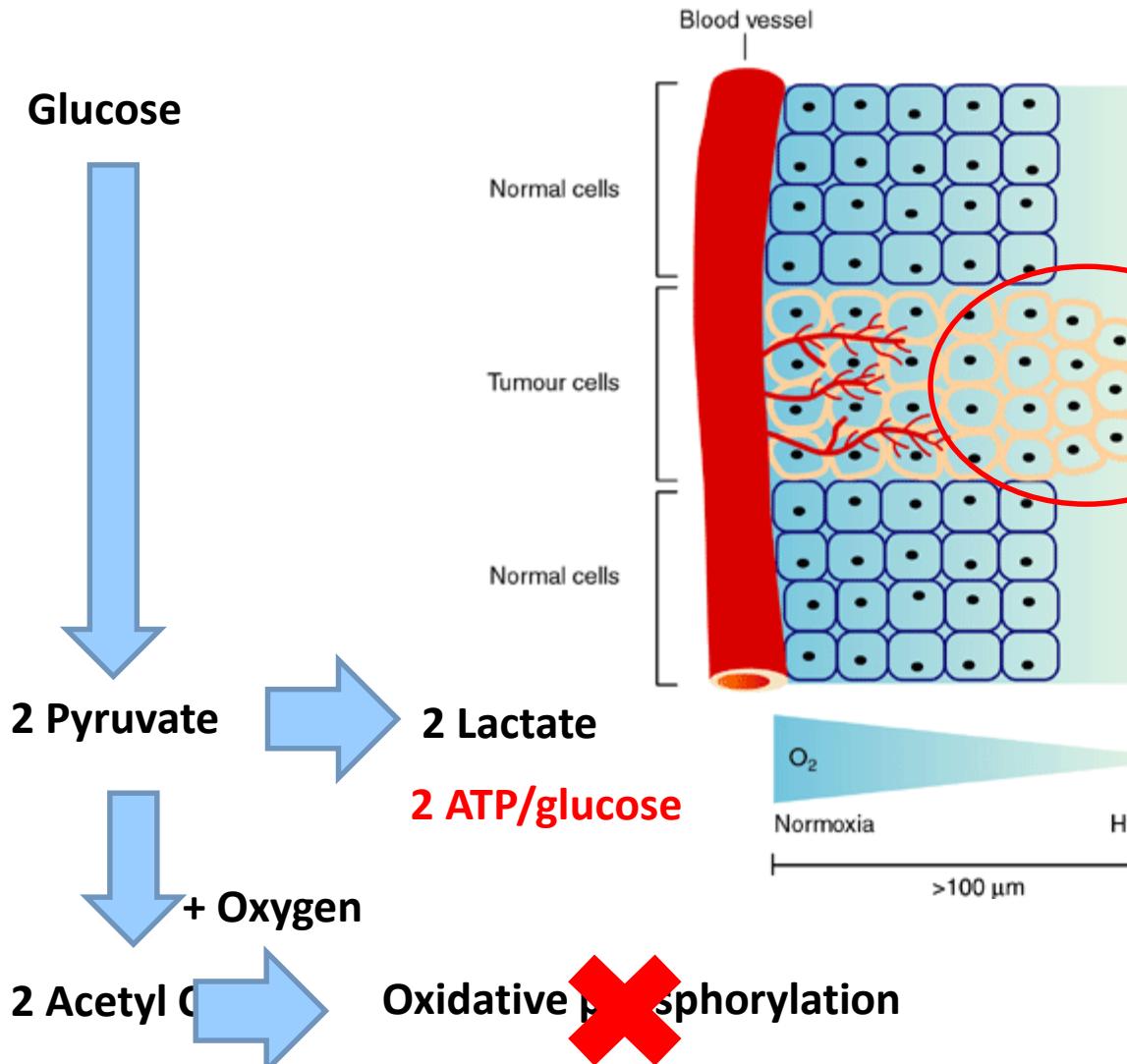
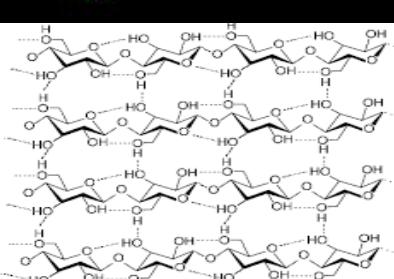
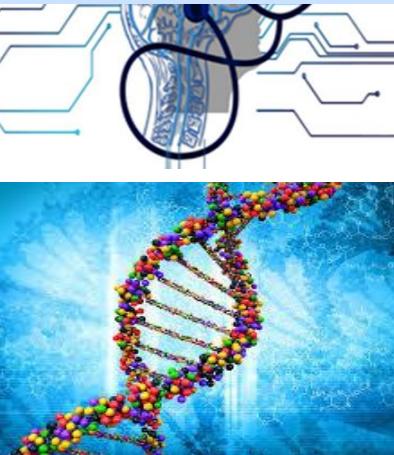


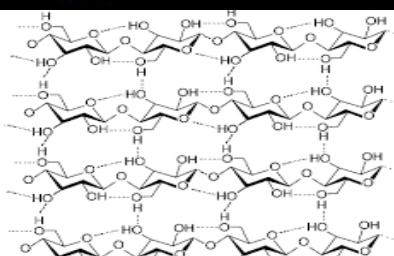
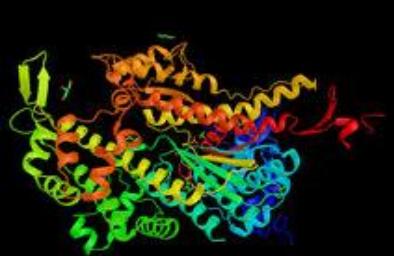
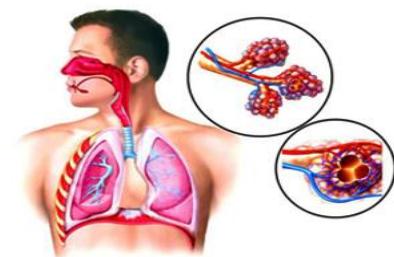
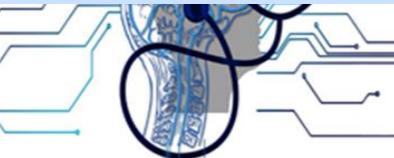
2 Acetyl CoA



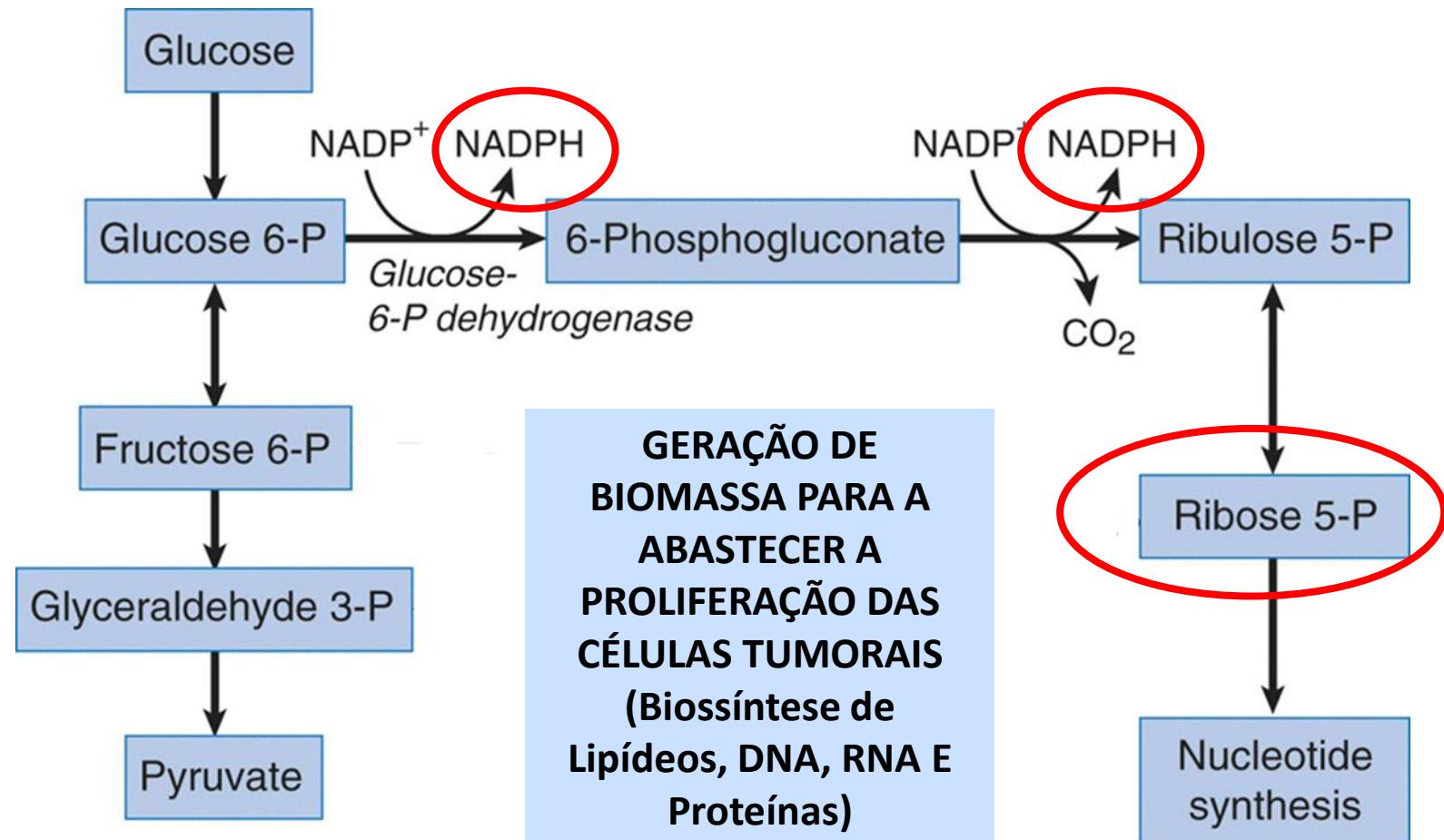
Oxidative phosphorylation ~38 ATP/glucose

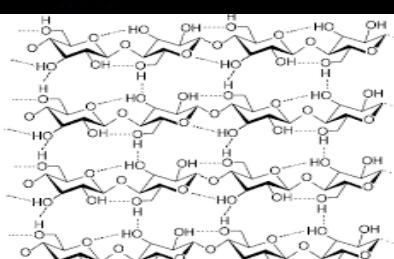
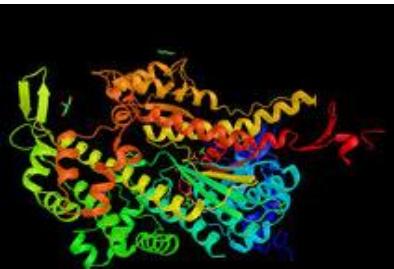
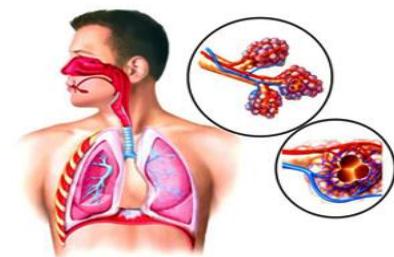
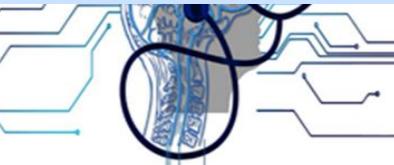
+ Oxygen

Células tumorais consomem muita glicose



**POR QUÊ A CÉLULA TUMORAL FAVORECERIA UM PROCESSO
ENERGETICAMENTE INEFICIENTE?**



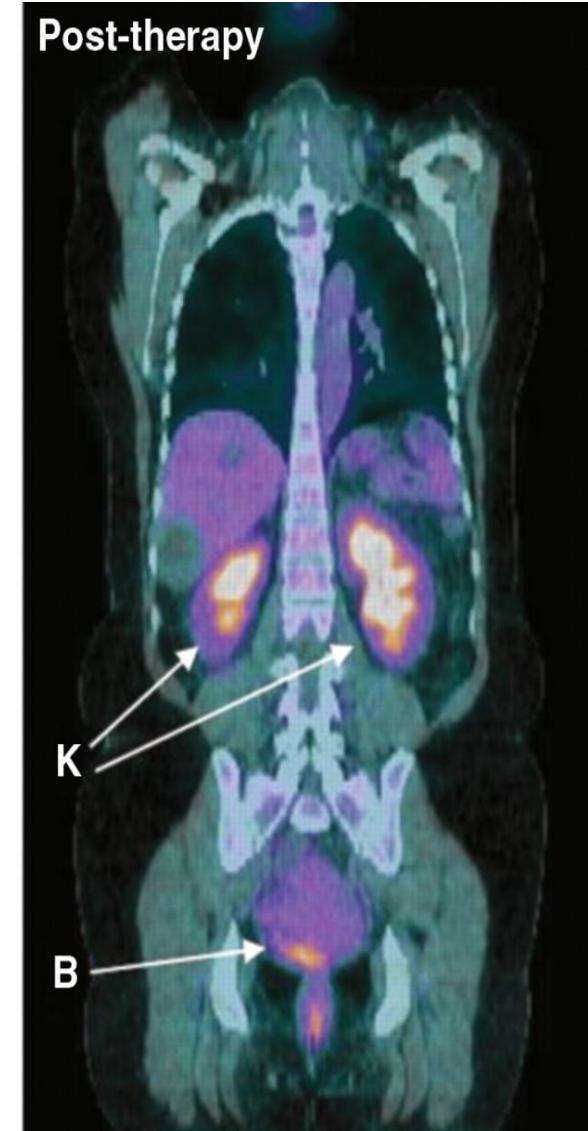
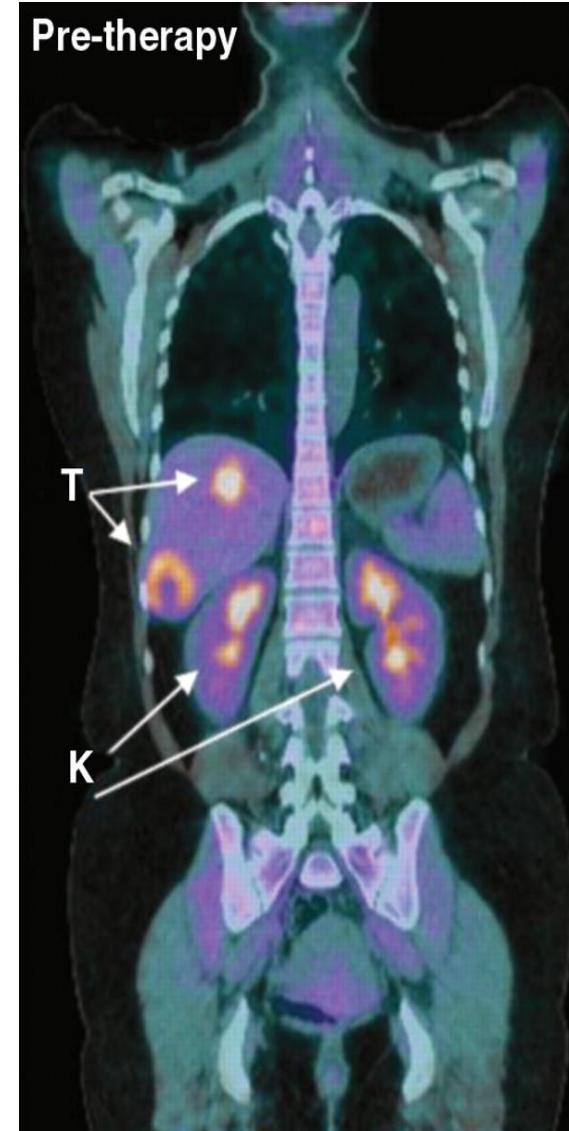
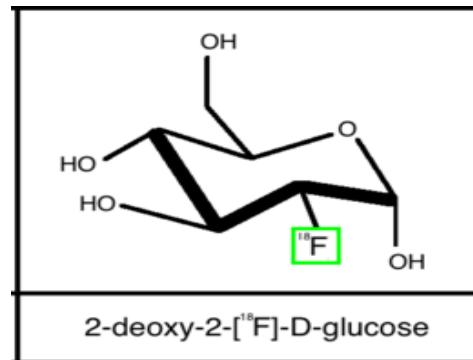
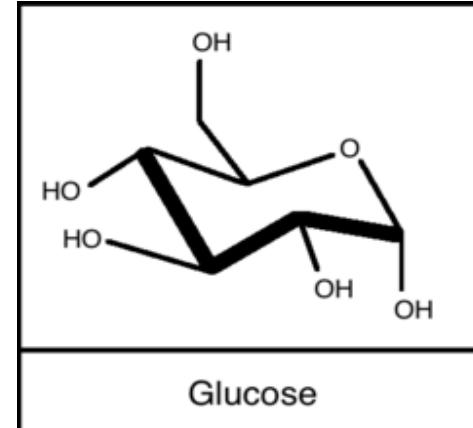
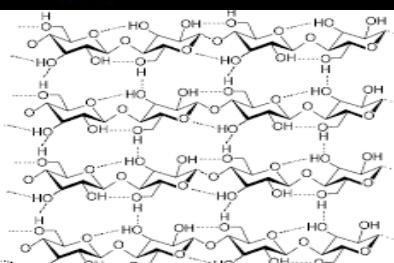
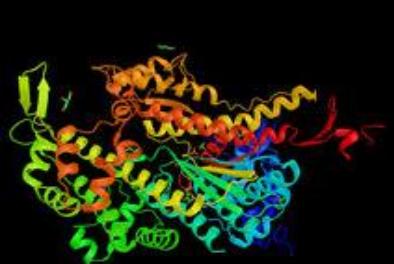
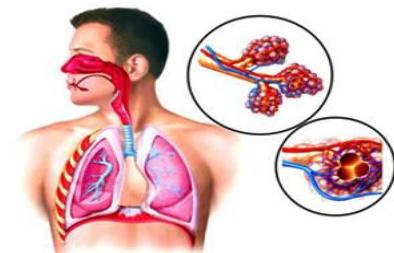
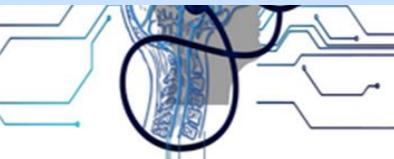


INIBIDORES DA HEXOQUINASE

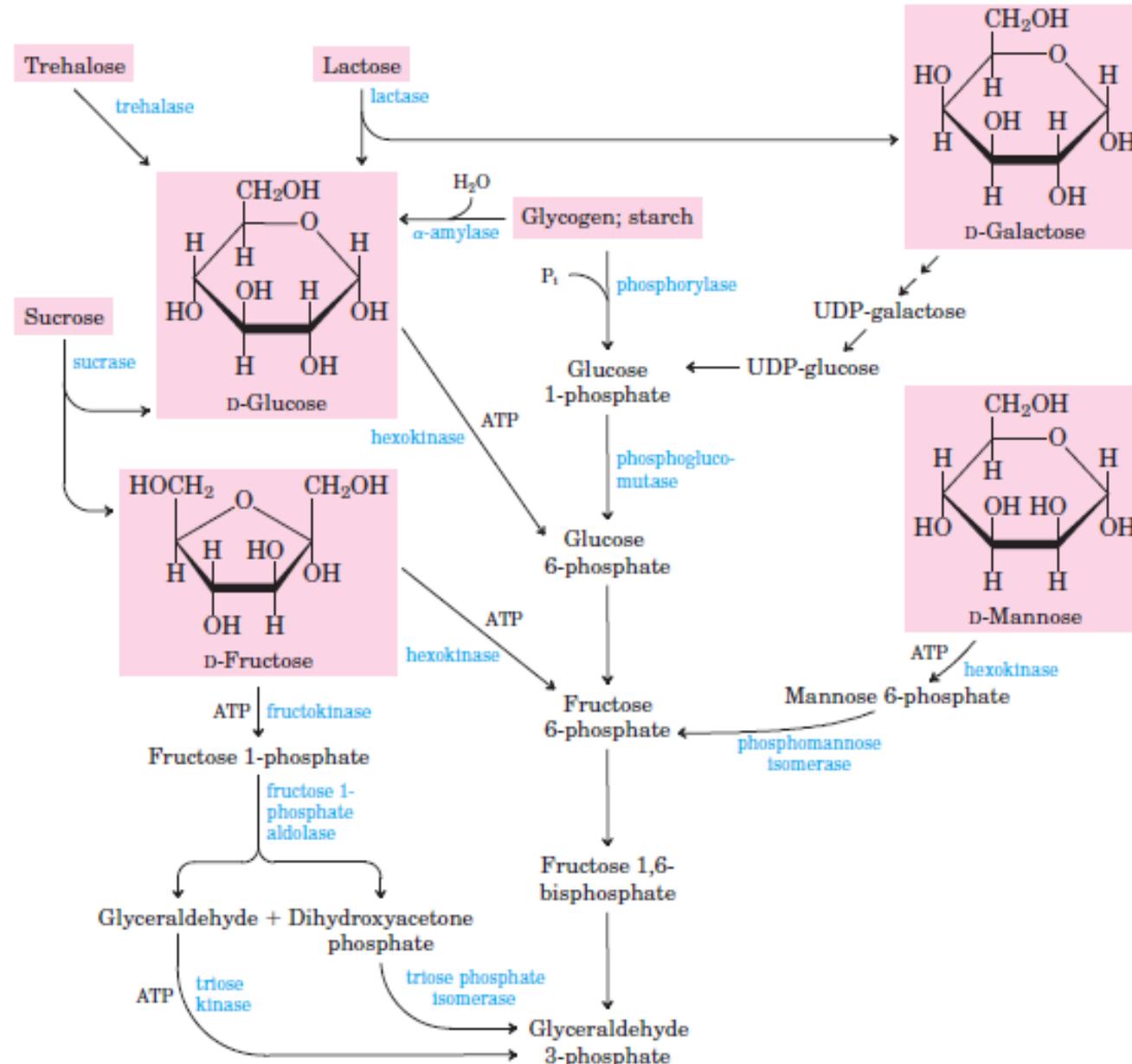
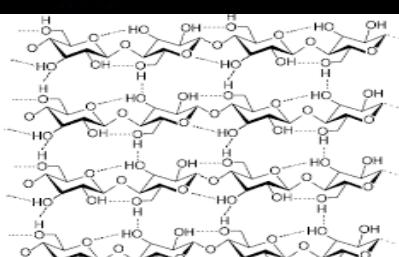
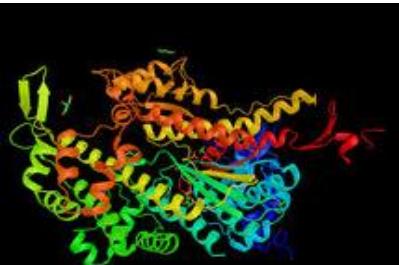
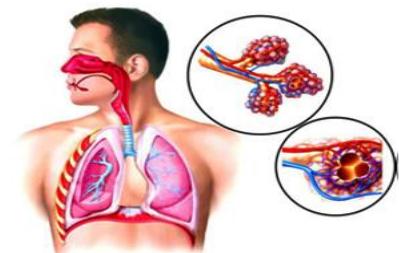
- ✓ 2-desoxiglicose
- ✓ Lonidamina
- ✓ 3-bromopiruvato

- ✓ Previnem a formação de glicose 6-fosfato, inibindo simultaneamente a via glicolítica e a via das pentoses-fosfato
- ✓ Na ausência da via das pentoses fosfato, a célula não pode sintetizar nuleotídeos.

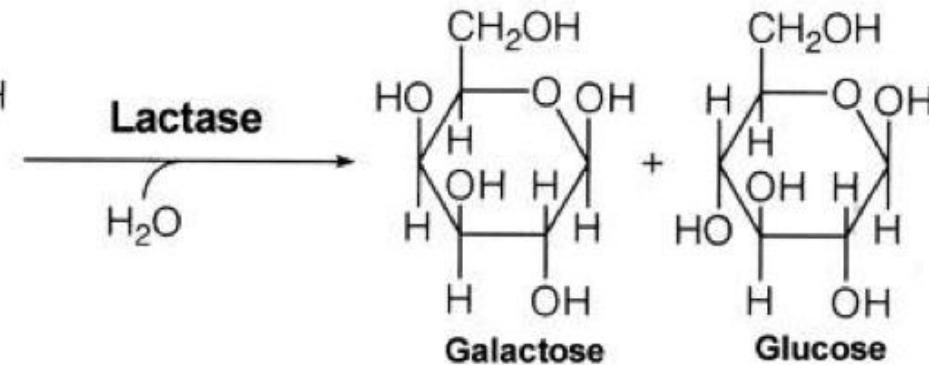
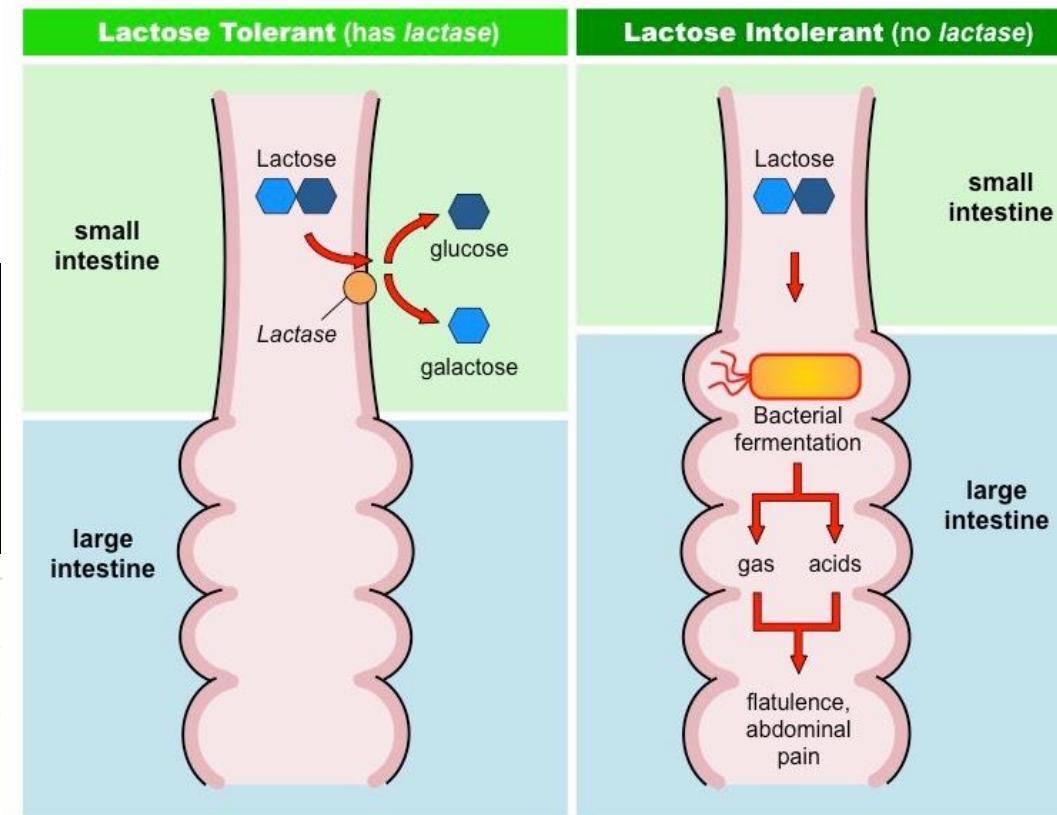
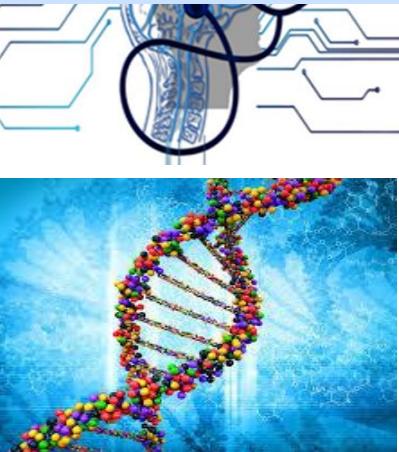
METABOLISMO DO CÂNCER POR TOMOGRAFIA POR EMISSÃO DE PÓSITRONS (PET-SCAN) E 2-DEOXI-2-GLICOSE (FDG)



OUTROS MONOSSACARÍDEOS SÃO CATABOLIZADOS NA VIA GLICOLÍTICA

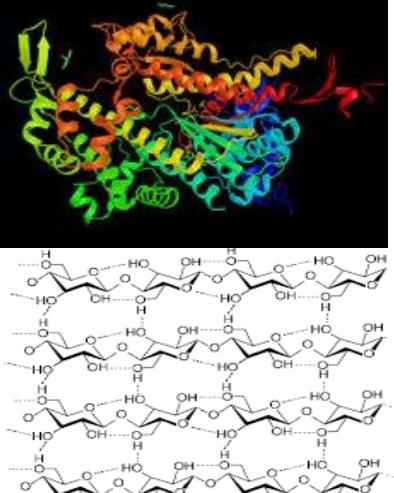
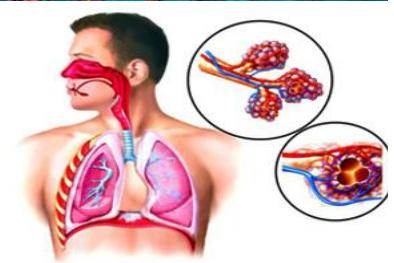
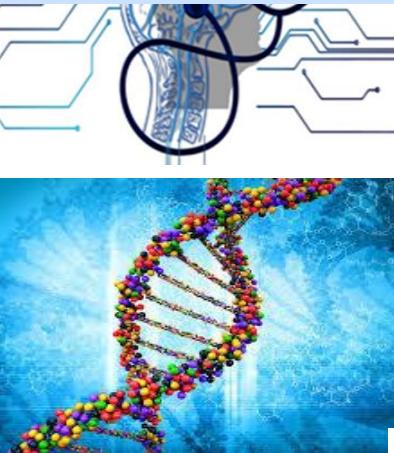


ASSIMILAÇÃO DE LACTOSE E INTOLERÂNCIA À LACTOSE



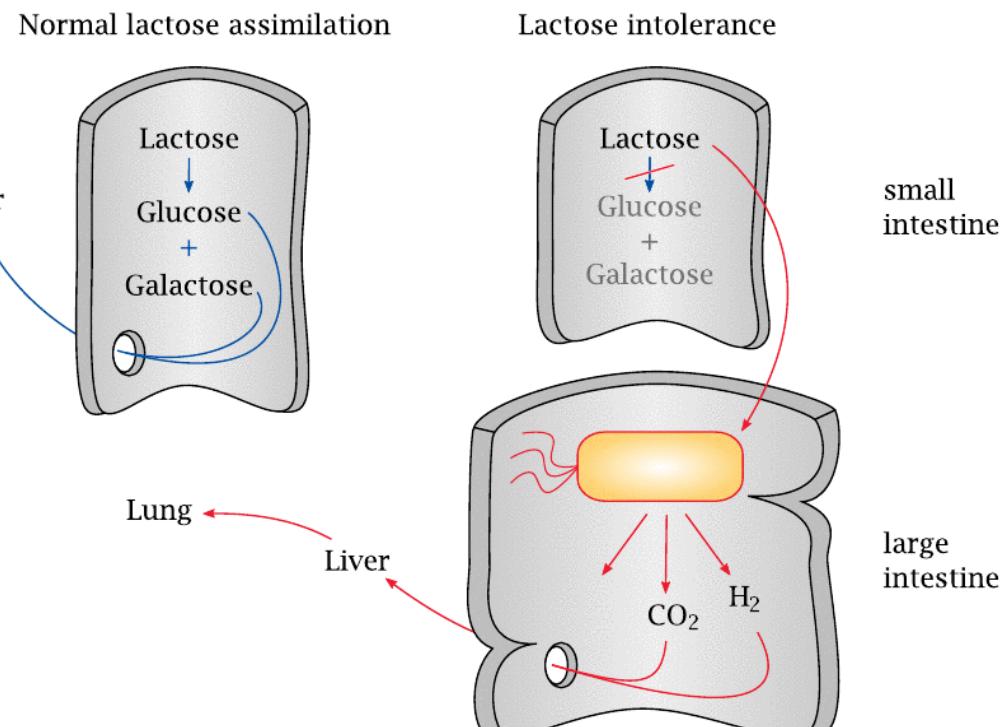
- ✓ Incapacidade de digerir quantidades significativas de lactose
- ✓ Resultado da insuficiência da lactase, enzima essencial para a conversão da lactose em glicose e galactose.

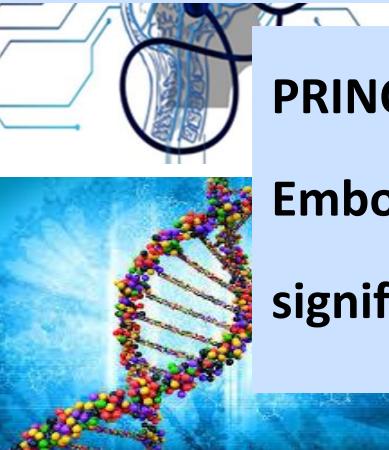
ASSIMILAÇÃO DE LACTOSE E INTOLERÂNCIA À LACTOSE



SINTOMAS DA INTOLERÂNCIA À LACTOSE

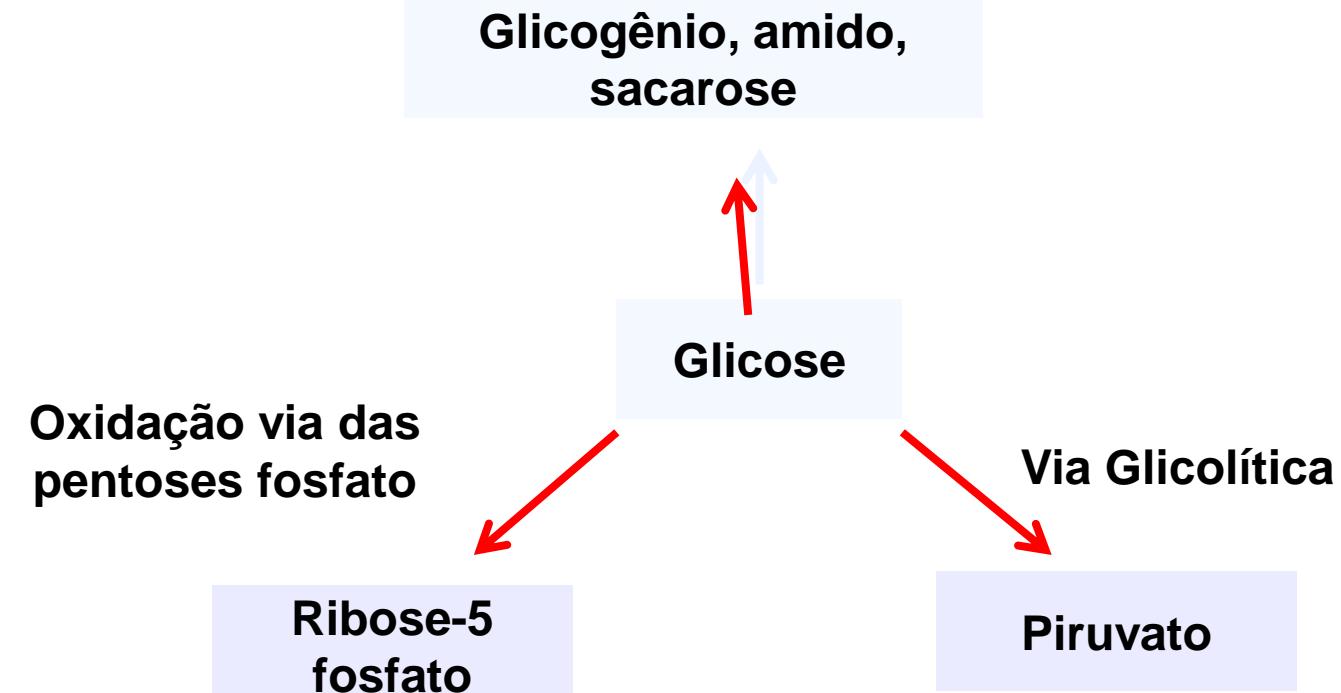
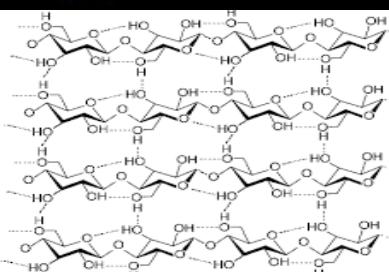
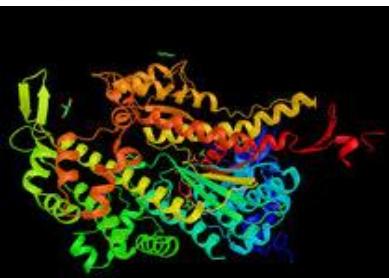
- ✓ A intolerância não envolve o sistema imunológico
 - ✓ Náusea, cólicas, distensão abdominal, dor abdominal, gases, diarréia

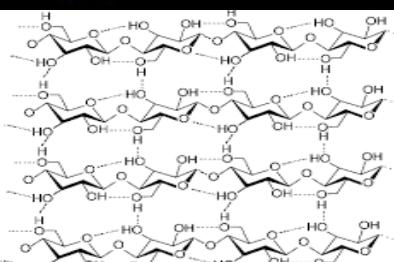
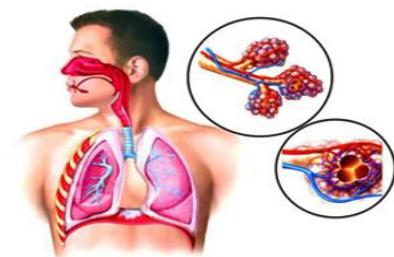




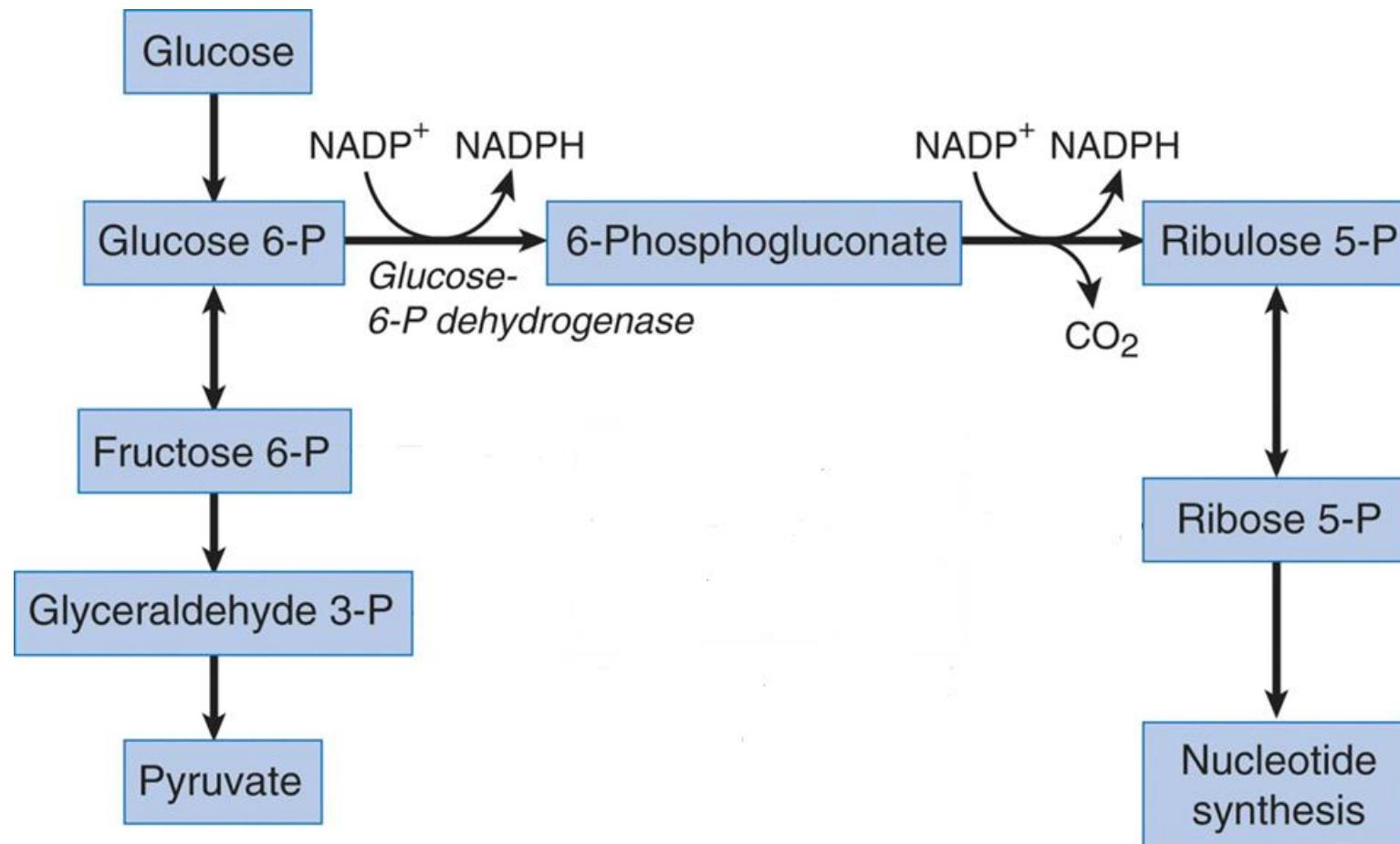
PRINCIPAIS VIAS DE UTILIZAÇÃO DE GLICOSE

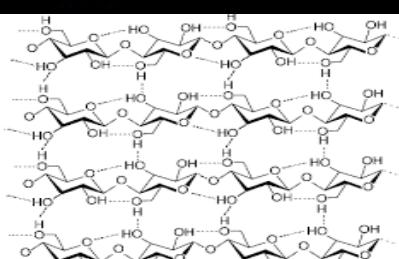
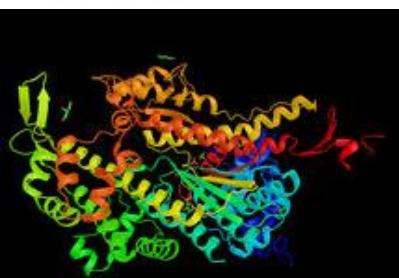
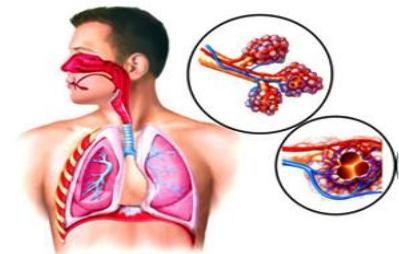
Embora não sejam os únicos destinos possíveis para a glicose, essas 3 vias são as mais significativas em termos de quantidade de glicose que flui através delas na maioria das células.





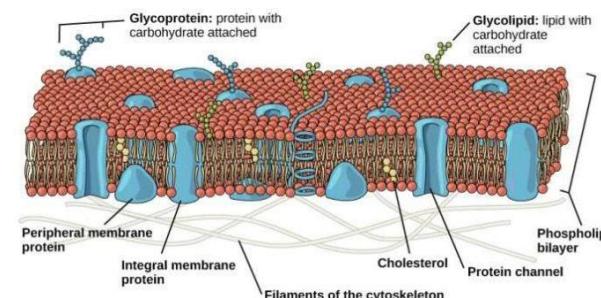
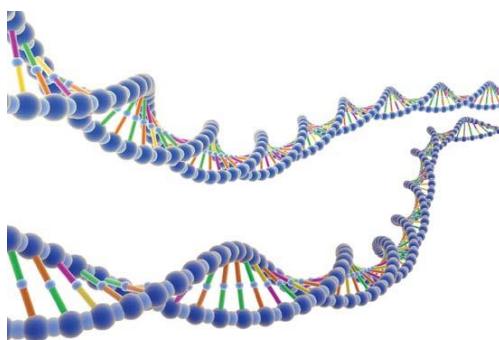
- ✓ A fase oxidativa produz PENTOSE fosfatos e NADPH
- ✓ A glicose 6-fosfato é particionada entre a glicólise e a via da pentose fosfato





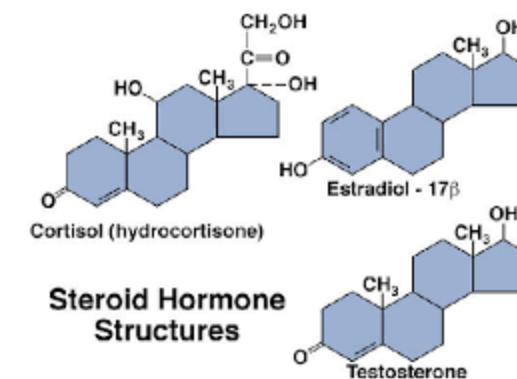
O PAPEL DA VIA DA PENTOSE FOSFATO

- ✓ Síntese de NADPH (para reações redutivas na biossíntese de ácidos graxos e esteróides);
- ✓ Síntese de Ribose 5-fosfato (para a biossíntese de ribonucleotídeos - RNA e DNA - e vários cofatores).



Biossíntese de Ácidos Nucléicos

Biossíntese de lipídeos



Biossíntese de hormônios