NATUREZA DA TOXICIDADE

I - DESREGULAÇÃO DA FUNÇÃO CELULAR

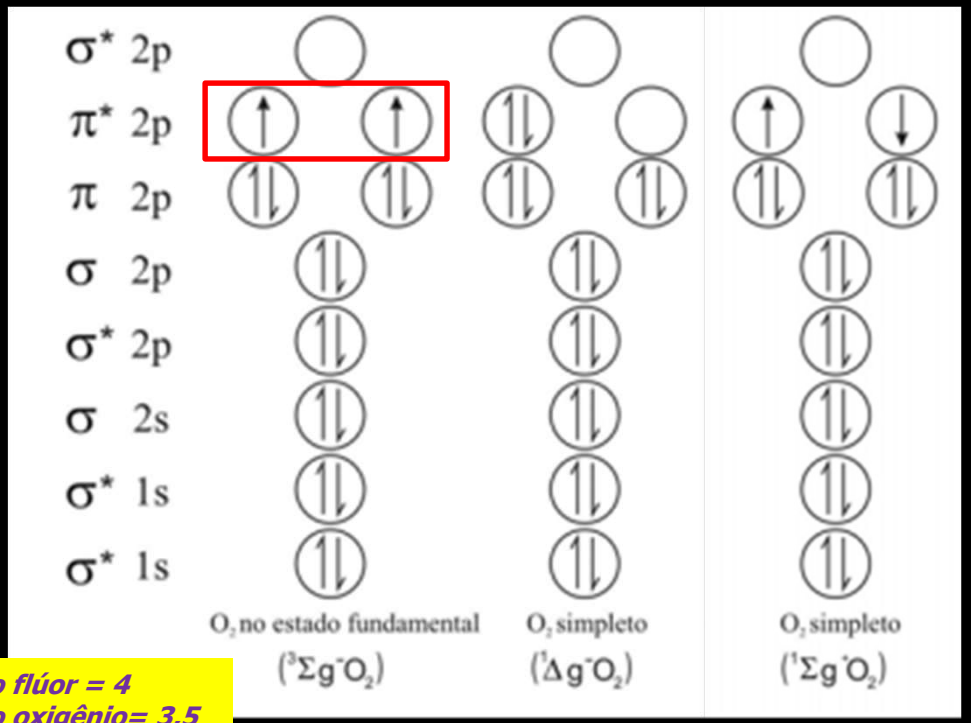
a – desregulação da expressão gênica
b – desregulação de células excitáveis eletricamente

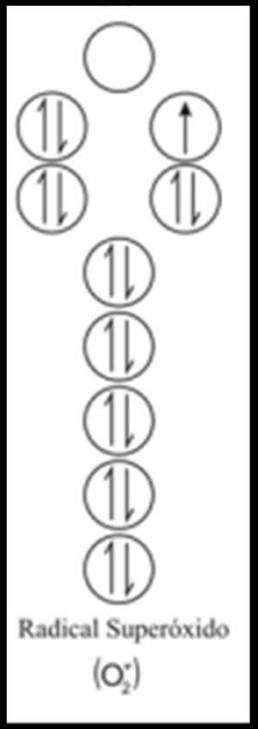
II – DANOS ESTRUTURAIS

a - oxidação de macromoléculas
b - inibição do metabolismo energético
c - reações imunológicas (idiossincrasia)

A –Oxidação de Macromoléculas: Espécies Reativas de Oxigênio e Estresse Oxidativo

I - Espécies Reativas de Oxigênio

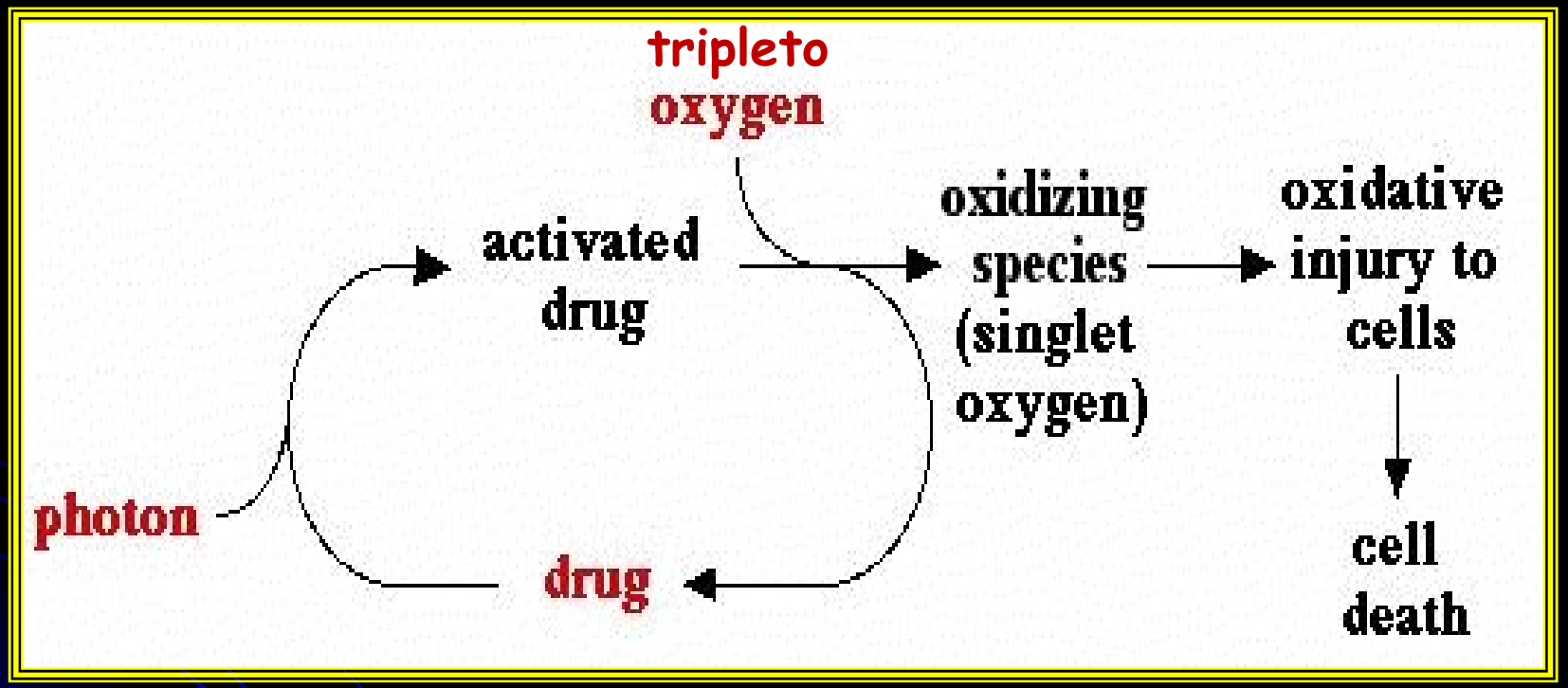




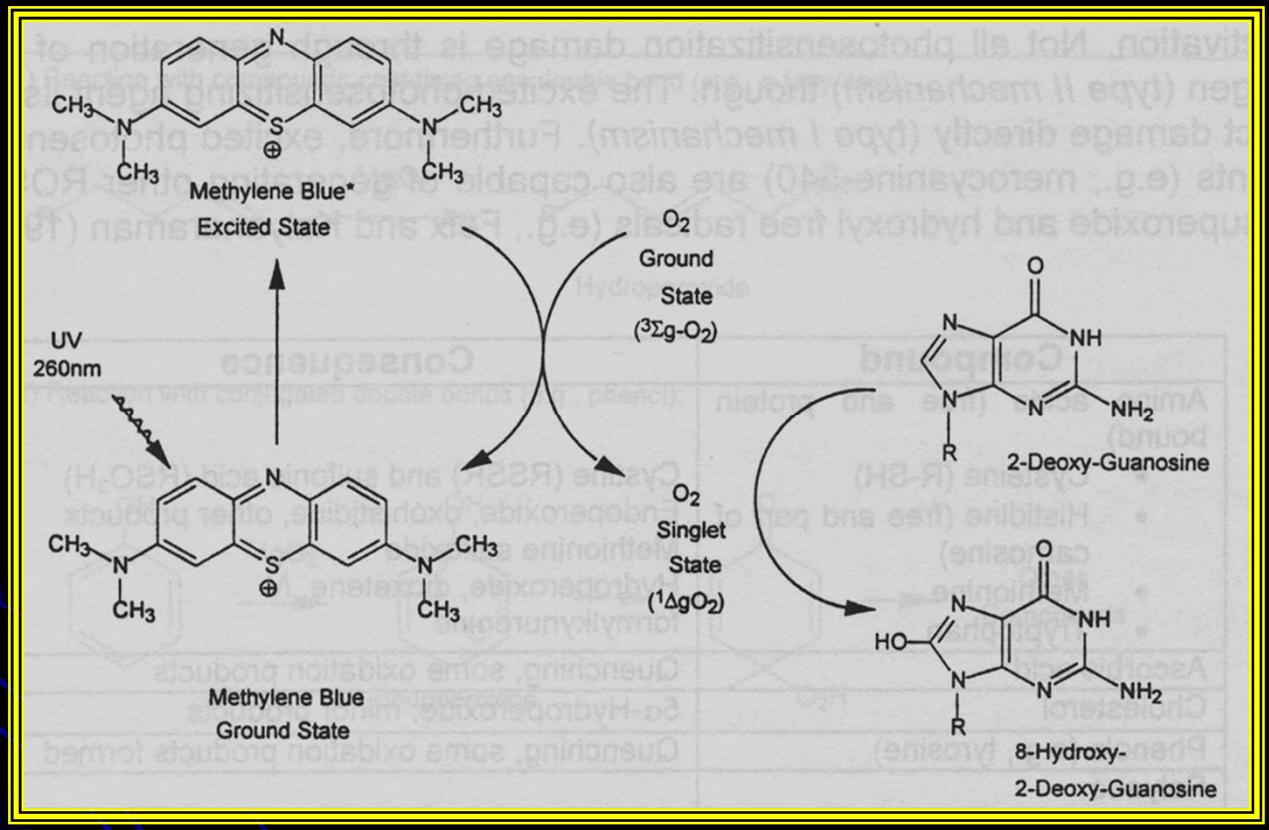
eletronegatividade do flúor = 4
eletronegatividade do oxigênio= 3,5

tripleto singleto singleto radical superóxido

1 – XENOBIÓTICOS INDUZINDO A GERAÇÃO DE OXIGÊNIO SINGLETO



1 – XENOBIÓTICOS INDUZINDO A GERAÇÃO DE OXIGÊNIO SINGLETO



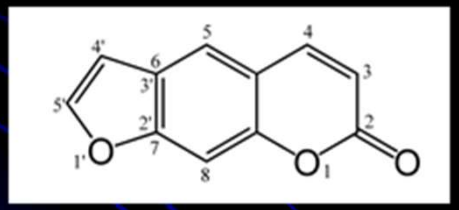
fototoxicidade

Class	Medication
Antibiotics	Tetracyclines (doxycycline, tetracycline)
	Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin)
	Sulfonamides
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen
	Ketoprofen
	Naproxen
	Celecoxib
Diuretics	Furosemide
	Bumetanide
	Hydrochlorothiazide
Retinoid	Isotretinoin
	Acitretin
Hypoglycemics	Sulfonylureas (glipizide, glyburide)

Medicamentos com atividade fotossensibilizadora

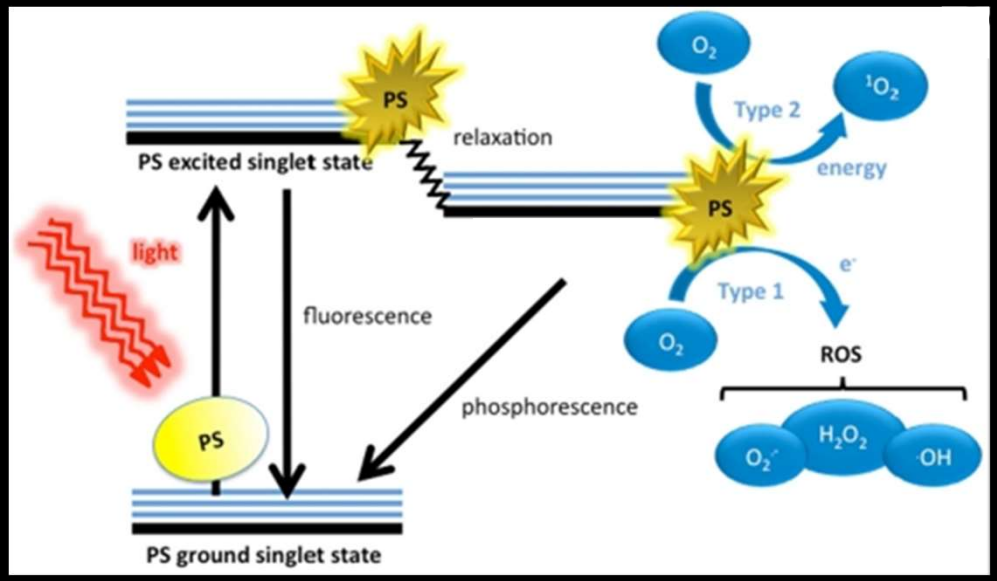
fototoxicidade da tetraciclina

Severe phototoxic reaction on the hands of a bartender who made drinks containing lime juice at an outdoor bar.



psoraleno

Terapia Fotodinâmica



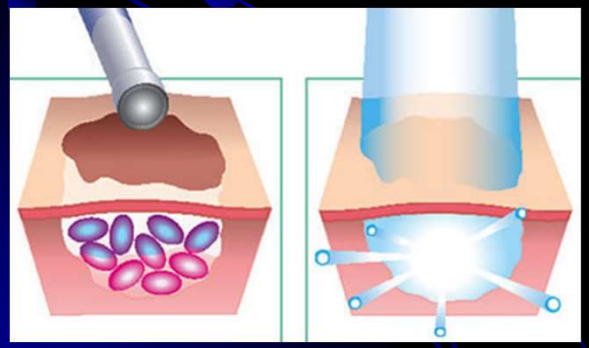
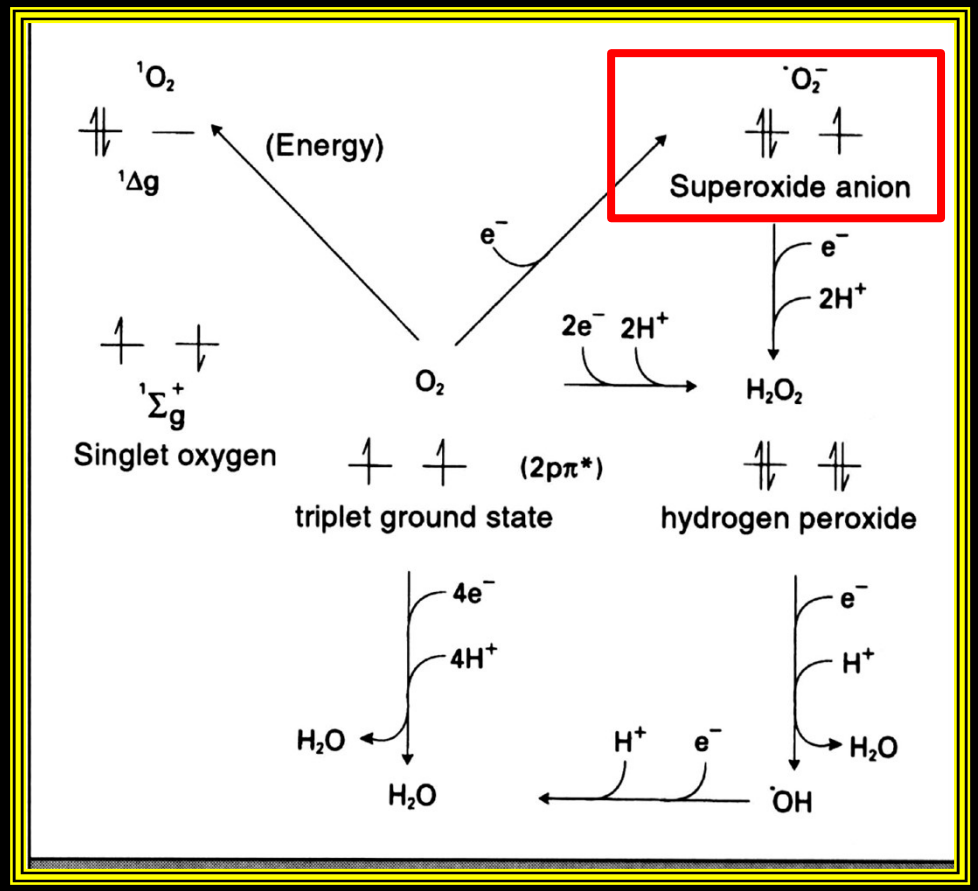


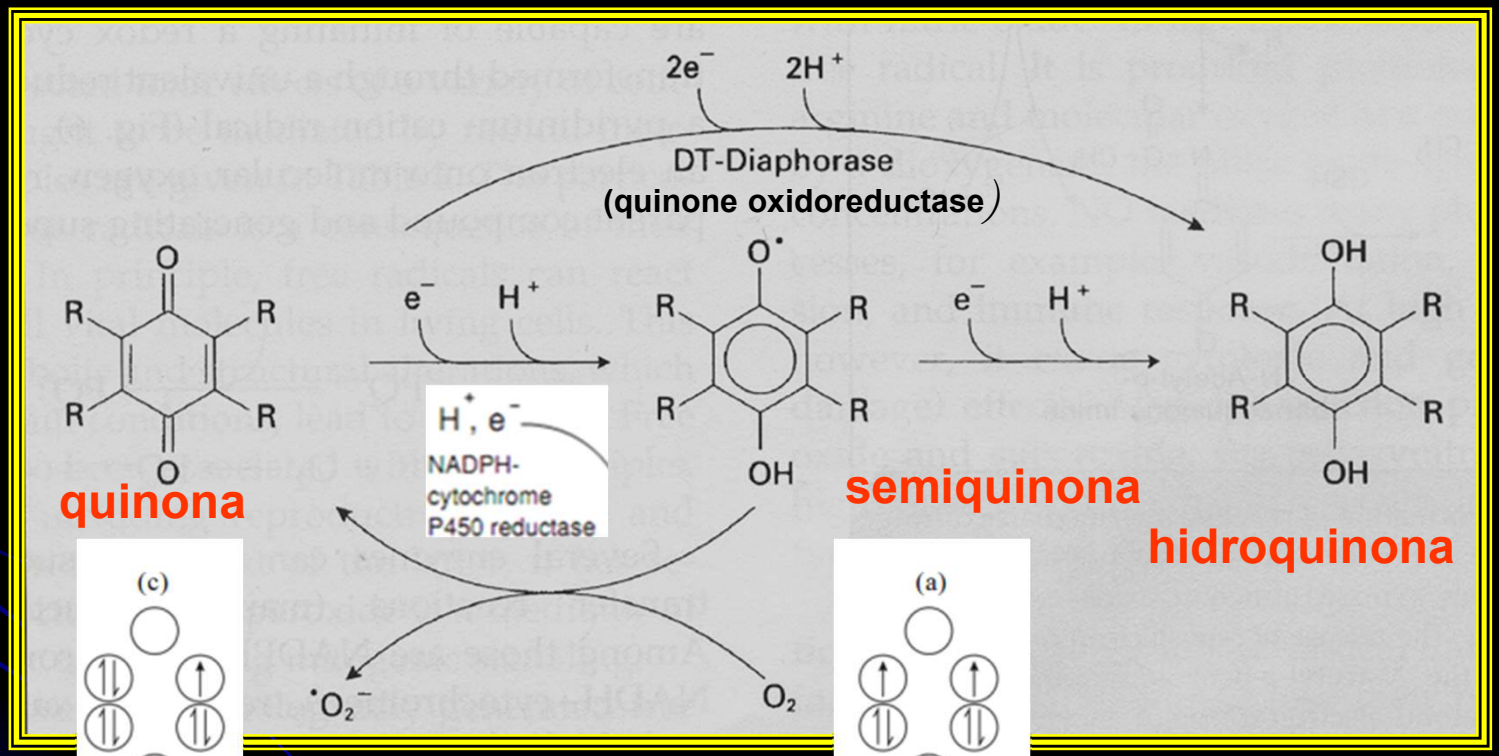
Figure 4: Basal cell carcinoma pre and post-treatment with MAL-PDT (6-month follow-up).

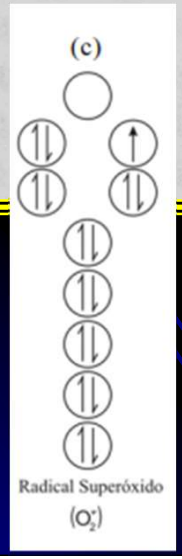


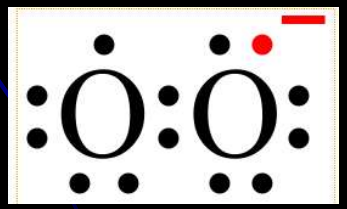
espécies reativas derivadas do oxigênio (EROS)

2 – XENOBIÓTICOS INDUZINDO A ATIVAÇÃO DO OXIGÊNIO MOLECULAR A SUPERÓXIDO

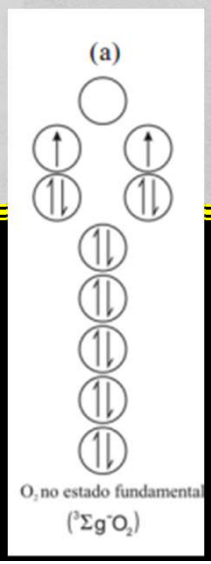
ciclo redox

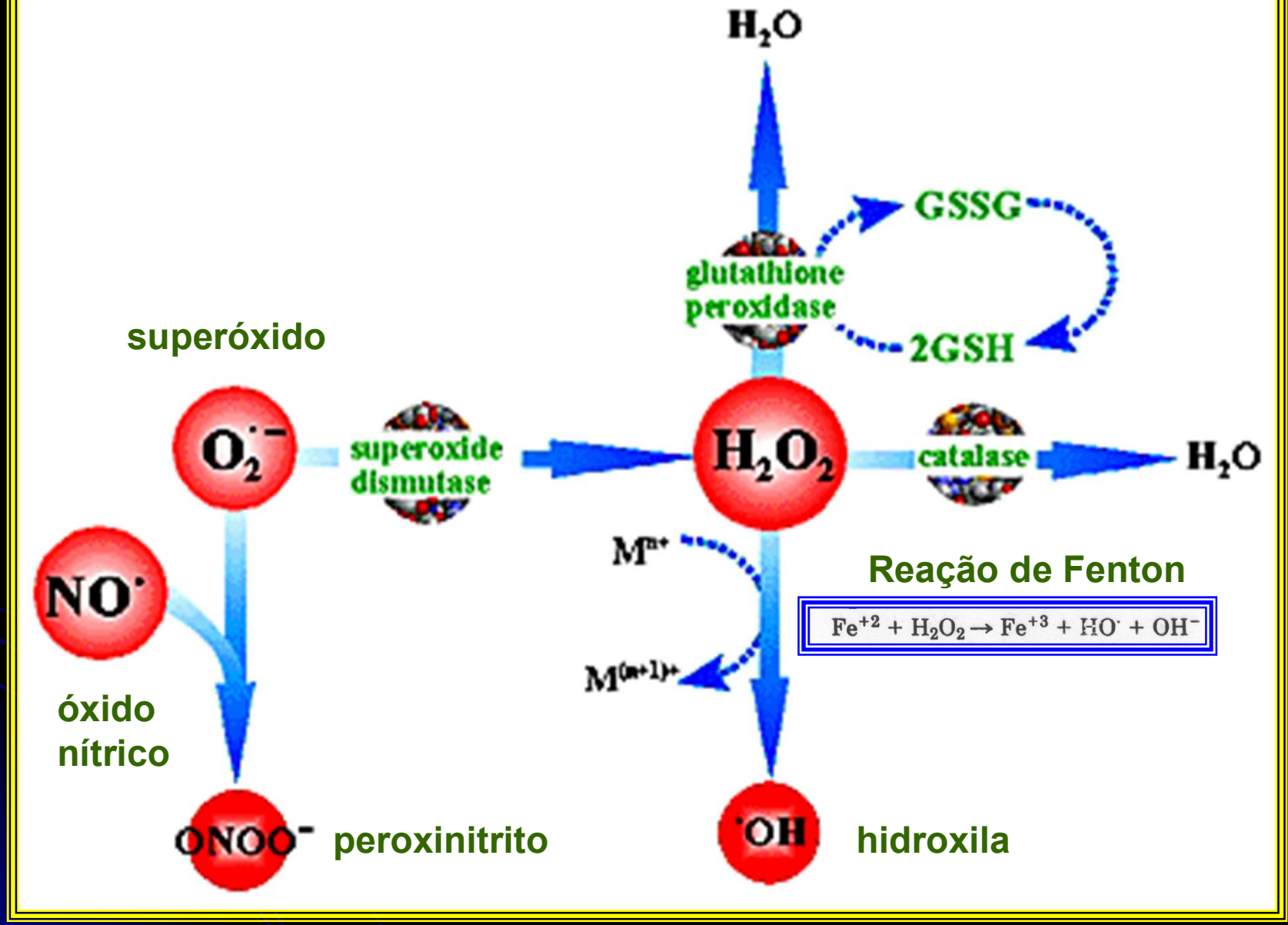




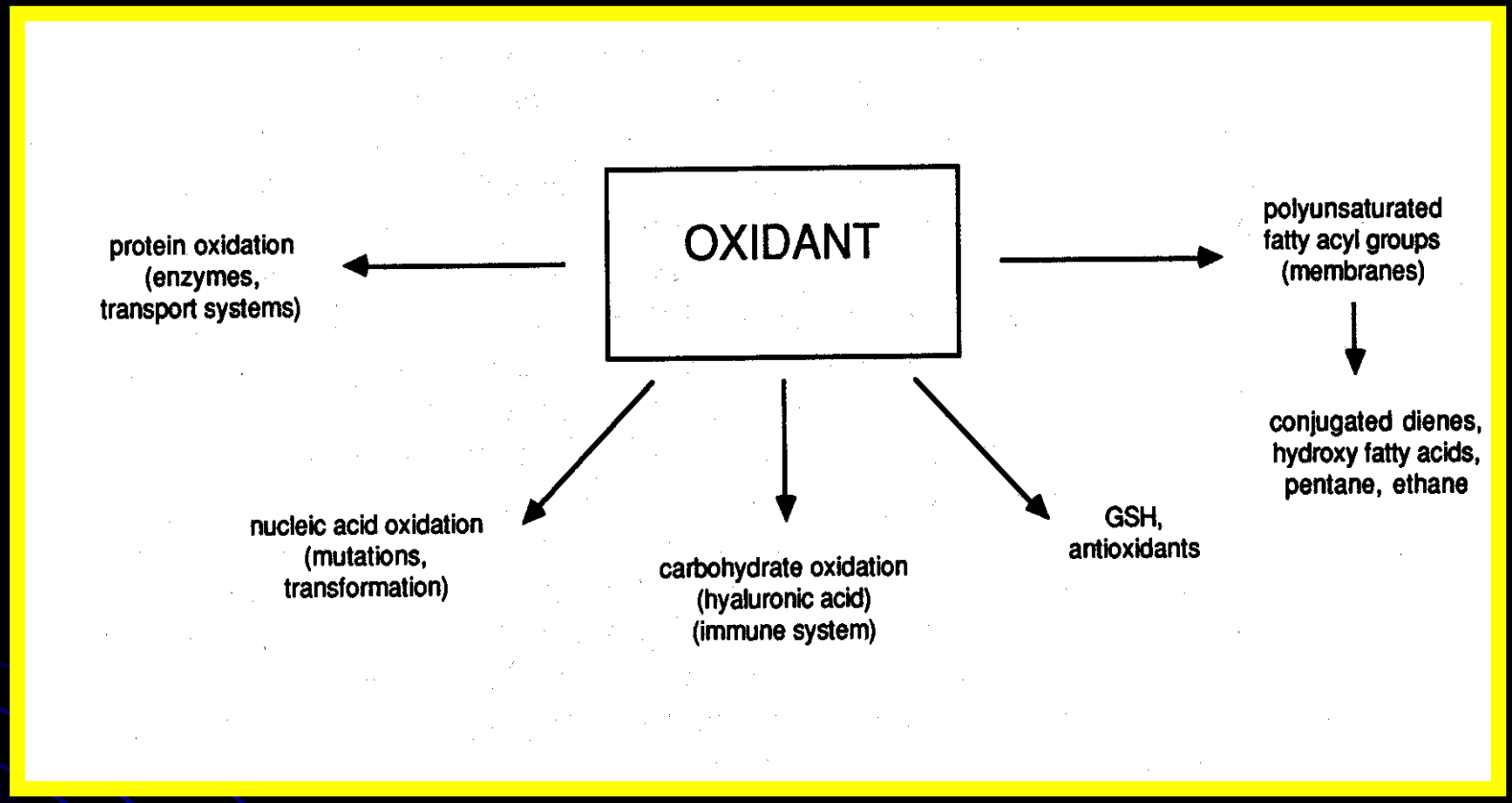


superóxido



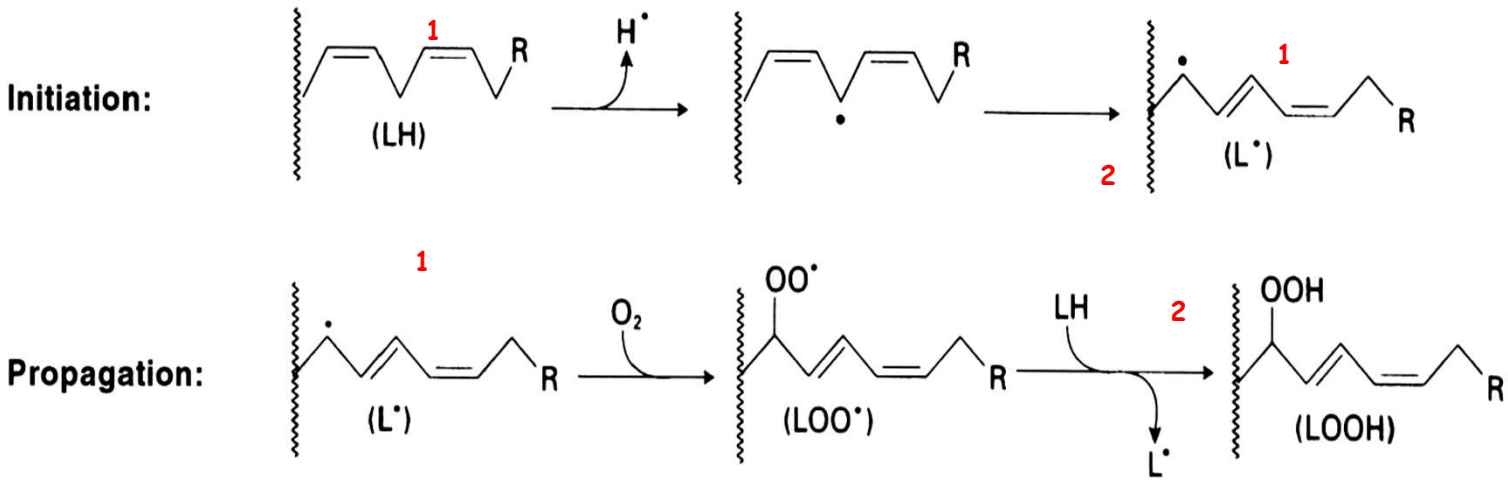


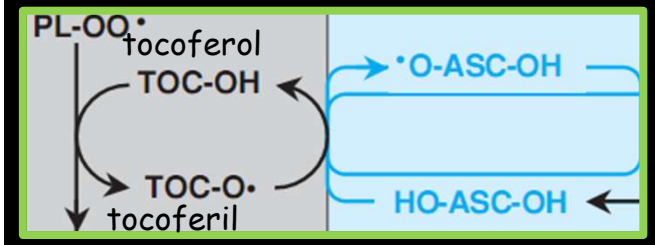
espécies reativas derivadas do oxigênio



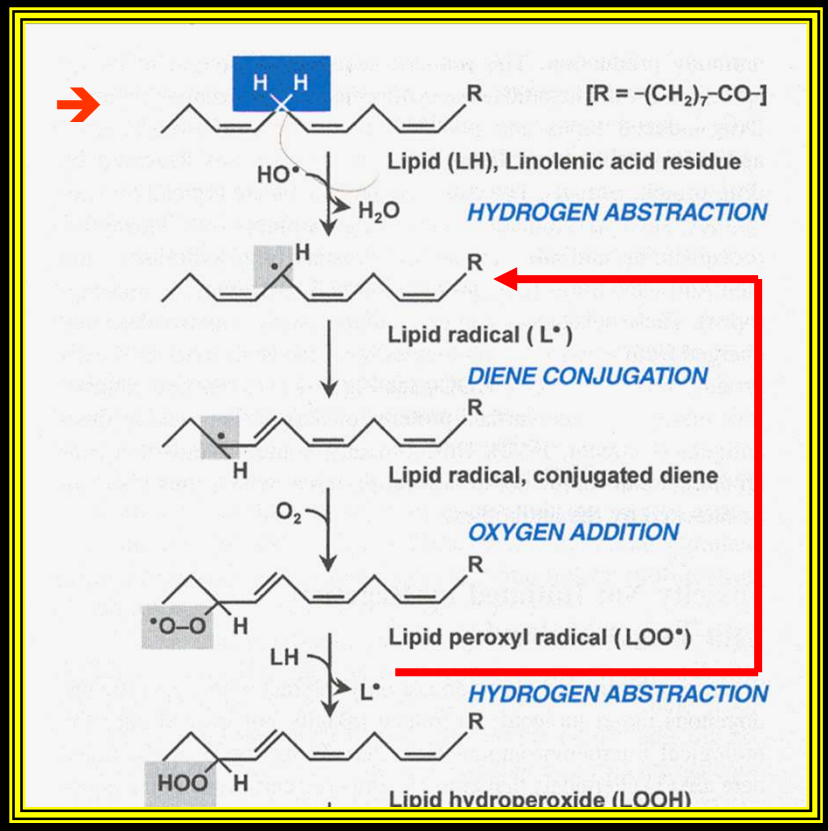
oxidação de macromoléculas

Lipoperoxidação



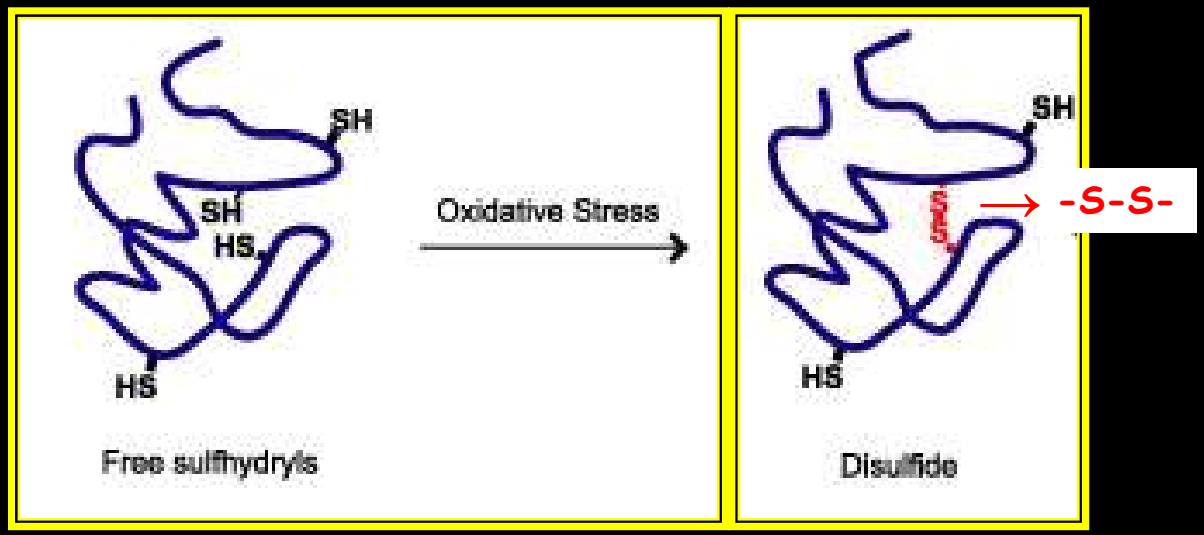


PL-OOH

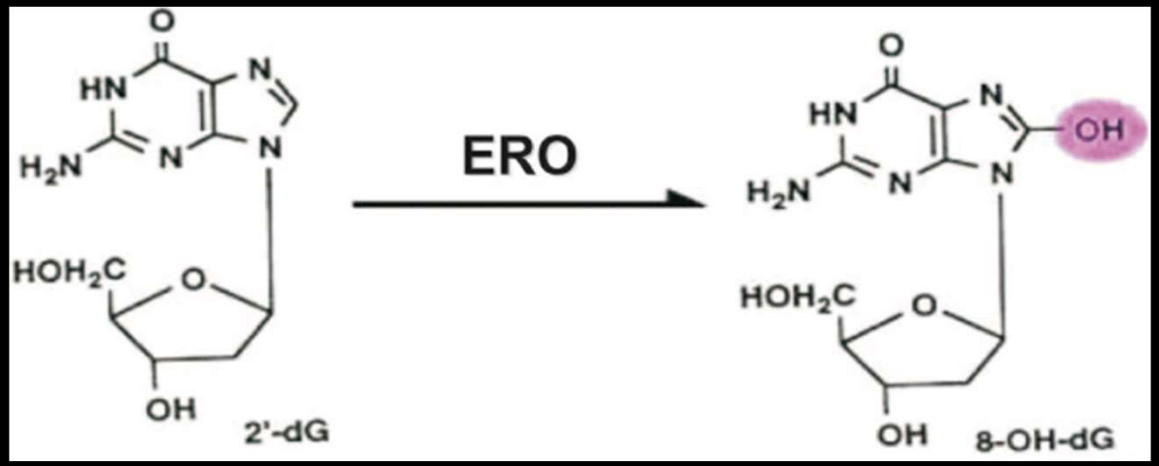


lipoperoxidação iniciada pelo radical hidroxila

oxidação de proteínas
(formação de dissulfetos)

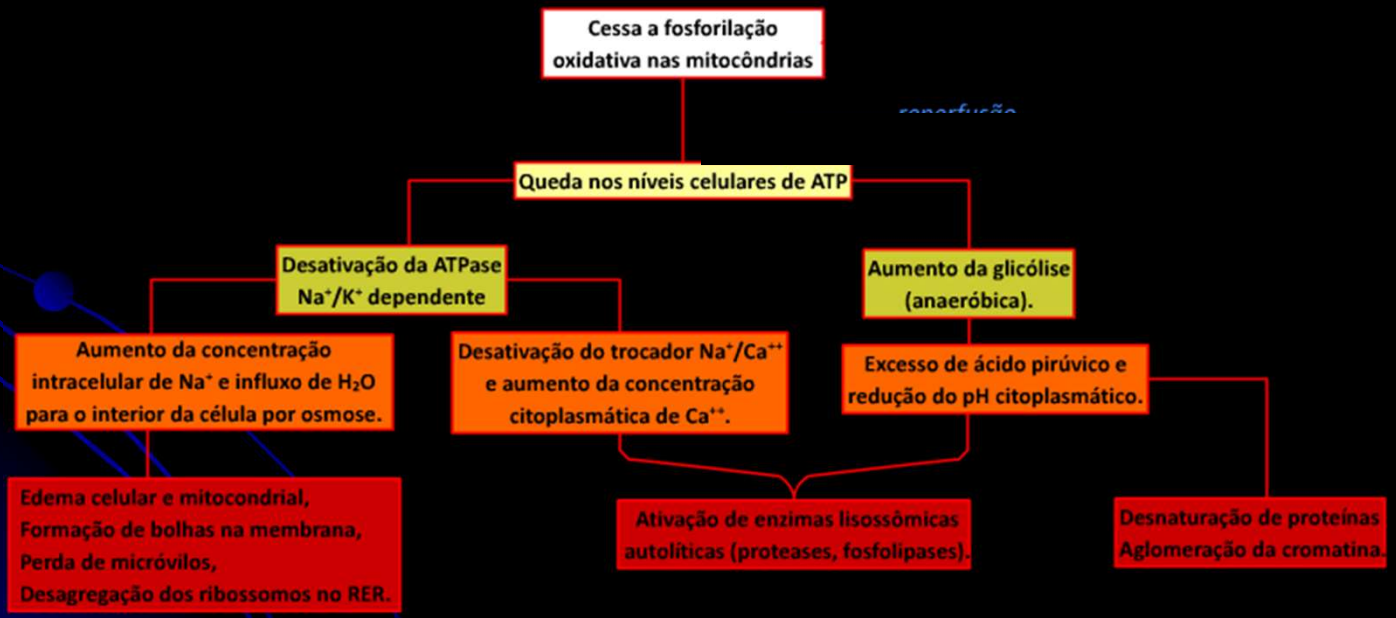


Oxidação do DNA



incorporação de um radical OH^- no carbono 8 da molécula da guanina (2'-dG), formando a 8-hidroxi-guanina (8-OHdG

B - INIBIÇÃO DO METABOLISMO ENERGÉTICO E TOXICIDADE MITOCONDRIAL



https://pt.wikipedia.org/wiki/Hip%C3%B3xia

TABELA 3.2 Agentes comprometendo a síntese de ATP mitocondrial[1]

A. Inibidores da liberação de hidrogênio para ação na cadeia transportadora de elétrons

1. Glicólise (fundamental em neurônios): hipoglicemia, iodoacetato e NO^+ do GAPDH
2. Gluconeogênese (fundamental nas células tubulares renais): depletores da coenzima A (ver abaixo)
3. Oxidação de ácidos graxos (fundamental no músculo cardíaco): hipoglicina, ácido 4-pentenoico
4. Piruvato desidrogenase: arsenito, DCVC, *p*-benzoquinona
5. Ciclo citrato
   (a) Aconitase: fluoroacetato, $ONOO^-$
   (b) Isocitrato desidrogenase: DCVC
   (c) Succinato desidrogenase: malonato, DCVC, PCBD-cys, fungicidas 2-bromohidroquinona, *cis*-crotonaldeído
6. Depletores de TPP (inibe PDH dependente-TPP e α-KGDH): etanol
7. Depletores da coezima A: 4-(dimetilamino)fenol, *p*-benzoquinona
8. Depletores de NADH
   (a) Ver grupo A.V.i na Tabela 3.3
   (b) Ativadores de poli (ADP-ribose) polimerase, MNNG, peróxido de hidrogênio, $ONOO^-$

B. Inibidores do transporte de elétrons

1. Inibidores de complexos de transporte de elétrons
   (a) Coenzima Q redutase-NADH (complexo I): rotenona, amital, MPP^+, paraquat
   (b) Citocromo Q-citocromo *c* redutase (complexo III): antimicina-A, mixotiazol
   (c) Citocromo oxidase (complexo IV): cianeto, sulfeto de hidrogênio, azida, metanoato, $^•NO$, fosfina (PH_3)
   (d) Inibidores multissítios: dinitroanilina e herbicidas difenileterés, ONOO-
2. Aceptores de elétrons: CCl_4, doxorubicina, menadiona, MPP^+

C. Inibidores da liberação de oxigênio para a cadeia de transporte de elétrons

1. Compostos químicos causando paralisia respiratória: depressores do SNC (p. ex., opioides), convulsivantes
2. Compostos químicos comprometendo a troca de gases pulmonares: CO_2, NO_2, fosgênio, perfluoroisobutano
3. Compostos químicos inibindo a oxigenação de Hb: monóxido de carbono, químicos formadores de metemoglobina
4. Compostos químicos causando isquemia: alcaloides do Ergot, cocaína

D. Inibidores da ação da fosforilação de ADP

1. ATP sintase: oligomicina, cihexatina, DDT, clordecona
2. Translocador de adenina nucleotídeo: atractilosídeo, DDT, ácidos graxos livres, lisofosfolipídeos
3. Transportador de fosfato: *N*-etilmaleimida, mersalila, *p*-benzoquinona
4. Compostos químicos dissipando o potencial de membrana mitocondrial (desacopladores)
   (a) Cationóforos: pentaclorofenol, dinitrofenol-, benzonitrila-, herbicidas tiadiazóis, salicilato, amiodarona, perhexilina, valinomicina, gramidicina, calcimicina (A23187)
   (b) Compostos químicos permeabilizando a membrana interna mitocondrial: PCBD-cys, clordecona

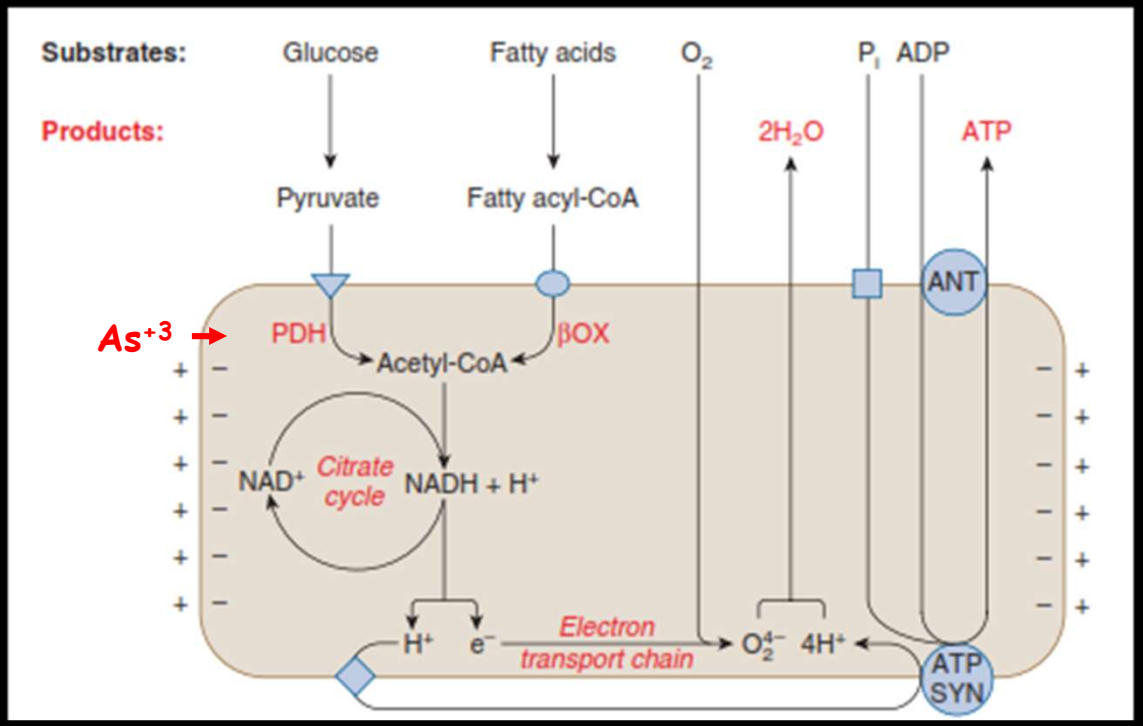
E. Compostos químicos causando lesão do DNA mitocondrial e/ou comprometendo a transcrição de proteínas-chave mitocondriais

1. Fármacos antivirais: zidovudina, zalcitabina, didanosina, fialuridina
2. Cloranfenicol (quando em superdosagem)
3. Etanol (quando consumido cronicamente)

[1] Os sítios finais de ação desses agentes são indicados na Figura 3.8. DCVC = diclorovinil-cisteína; GAPDH = gliceraldeído 3-fosfato desidrogenase; α-KGDH = α-ketoglutarato desidrogenase; MNNG = *N*-metil-*N*-nitro-*N*-nitrosoguanidina; MPP^+ = 1-metil-4-fenilpiridio; PCBD-cys = pentaclorobutadienilcisteína; PDH = piruvato desidrogenase; TPP = tiamina pirofosfato.

A –Inibição da produção de acetil-CoA

Inibição do complexo piruvato desidrogenase (PDH)



Basta uma dose de 15 mg/Kg de arsênio inorgânico trivalente para causar a morte de um ser humano adulto por dano à respiração celular, em poucas horas ou dias.

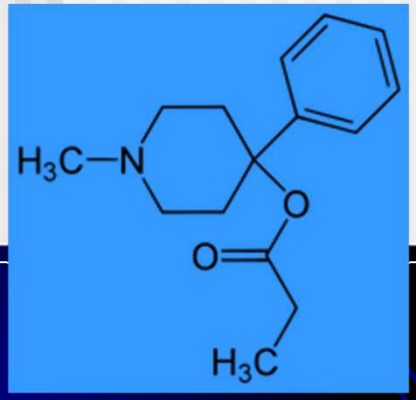
INIBIÇÃO DA CTE E DOÊNÇAS NEURODEGENERATIVAS

Doença de Parkinson Epidemiologia

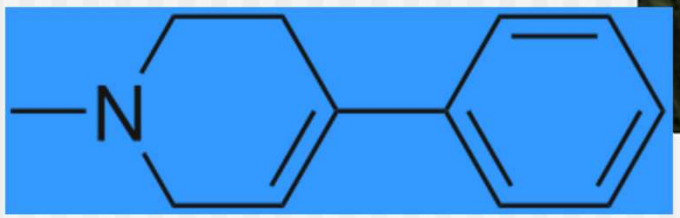
- Geral//, pctes. > 50 anos. Antes de 20 anos é rara (Parkinson Juvenil). Mais comum em homens.
- Prevalência = 1 a 3 % da população > 65anos.
- Incidência = 20 por 100.000 habitantes/ano.
- Risco de desenvolver a doença = 1 em 40.
- Maior prevalência = América do Norte e Europa
- Mais comum em caucasianos (?).
- Associações com vida rural, ingestão de água de poço, cultivo de vegetais, exposição a polpa de madeira e pesticidas (???).

The MPTP Story

- 1976: Barry Kidston in Maryland acute Parkinsonism trying to make MPPP (an analogue of Demerol).
- 1982: 4 patients in Santa Clara with acute Parkinsonism. MPTP discovered to be the cause.



MPPP = Desmethylprodine



MPTP = 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

opióide sintético com efeitos semelhantes aos da morfina e petidina(meperidina)

From: **Elevated Serum Pesticide Levels and Risk of Parkinson Disease**

Arch Neurol. 2009;66(7):870-875. doi:10.1001/archneurol.2009.89

Table 2. Detectable Serum Levels of Organochlorine Pesticides in the 3 Study Groups

	PD Group		Control Group		AD Group	
	Patients, %	Detectable Range, ng/mL	Patients, %	Detectable Range, ng/mL	Patients, %	Detectable Range, ng/mL
β-HCH	76	0.12-1.80	40	0.02-0.43	30	0.05-0.46
p,p′-DDE	72	0.05-18.56	86	0.2-21.85	100	1.29-20.74
Methoxychlor	26	0.14-1.62	23	0.09-0.59	0	NA
α-HCH	8	0.06-0.33	7	0.10-0.11	0	NA
δ-HCH	6	0.11-0.36	2	0.79	0	NA
γ-HCH	6	0.07-0.39	9	0.08-0.25	0	NA
Heptachlor	4	0.15-0.32	2	0.22	0	NA
4,4′-DDD	4	0.12-0.47	5	0.25-0.59	35	0.88-2.39
p,p′-DDT	4	0.17-0.56	0	NA	0	NA
Endrin aldehyde	0	NA	0	NA	0	NA
Endrin	0	NA	0	NA	0	NA
Dieldrin	0	NA	0	NA	0	NA
Heptachlor epoxide	0	NA	0	NA	0	NA
Aldrin	0	NA	0	NA	0	NA
γ-Chlordane	0	NA	0	NA	0	NA
α-Chlordane	0	NA	0	NA	0	NA

Abbreviations: AD, Alzheimer disease; HCH, hexachlorocyclohexane; NA, not applicable; PD, Parkinson disease.

Figure Legend:

Detectable Serum Levels of Organochlorine Pesticides in the 3 Study Groups

From: **Elevated Serum Pesticide Levels and Risk of Parkinson Disease**

Arch Neurol. 2009;66(7):870-875. doi:10.1001/archneurol.2009.89

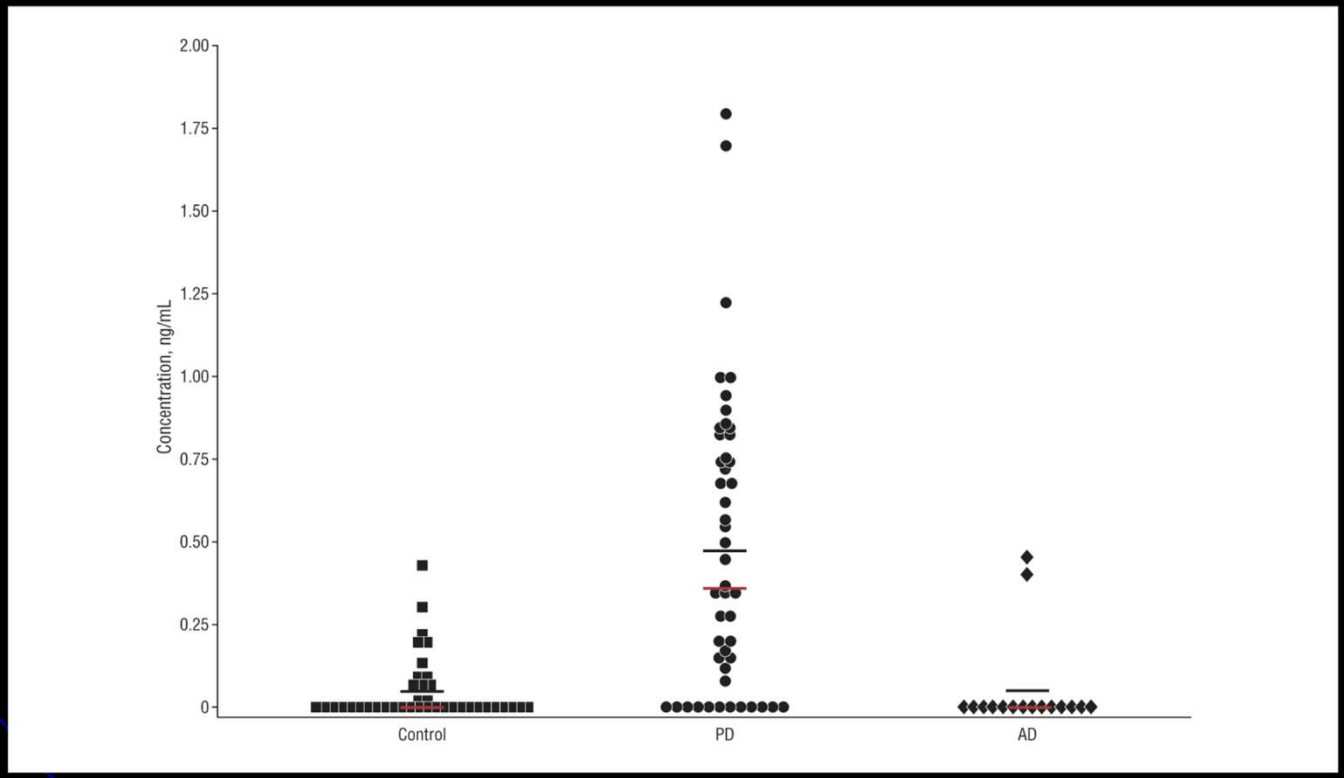
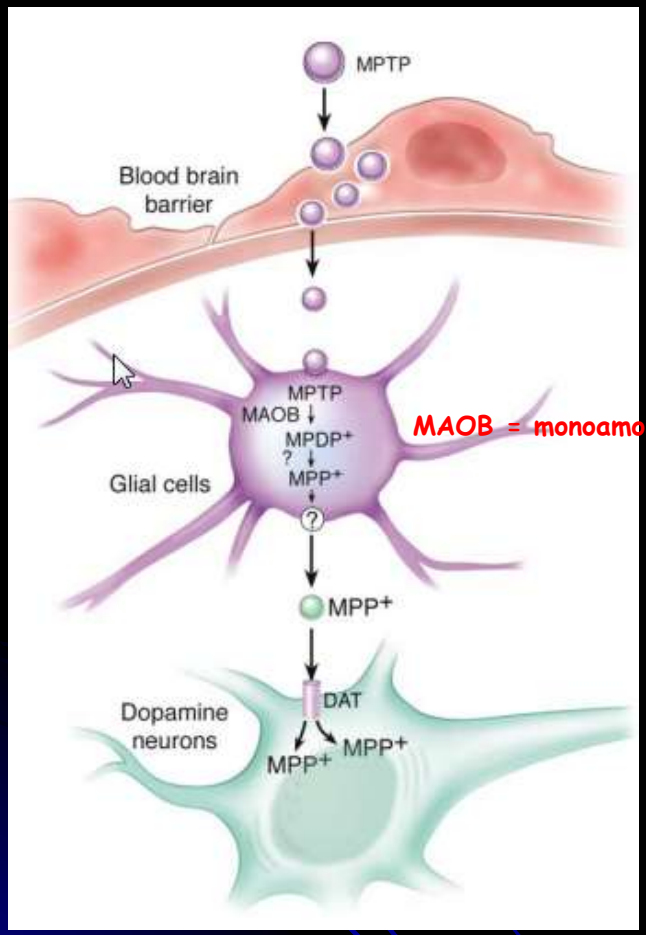


Figure Legend:

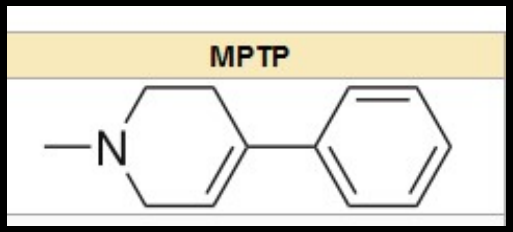
Patients with Parkinson disease (PD) have higher serum β-hexachlorocyclohexane (β-HCH) levels than controls and patients with Alzheimer disease (AD). Levels of β-HCH in patients with AD are not significantly different from those in controls, which indicates that elevated levels of β-HCH are specific to PD in this sample. Black bars indicate the mean values; red bars, median values.

INIBIÇÃO DA CTE E DOÊNÇAS NEURODEGENERATIVAS

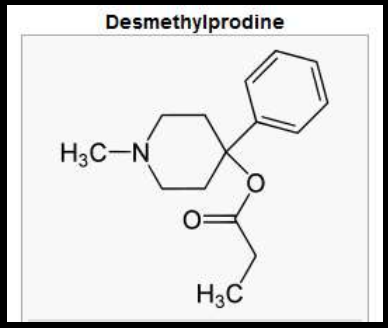


MAOB = monoamonioxidase B

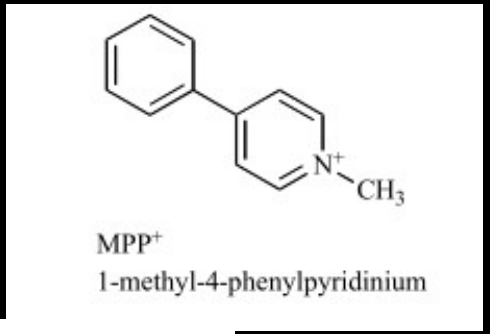
DAT = transportador de dopamina

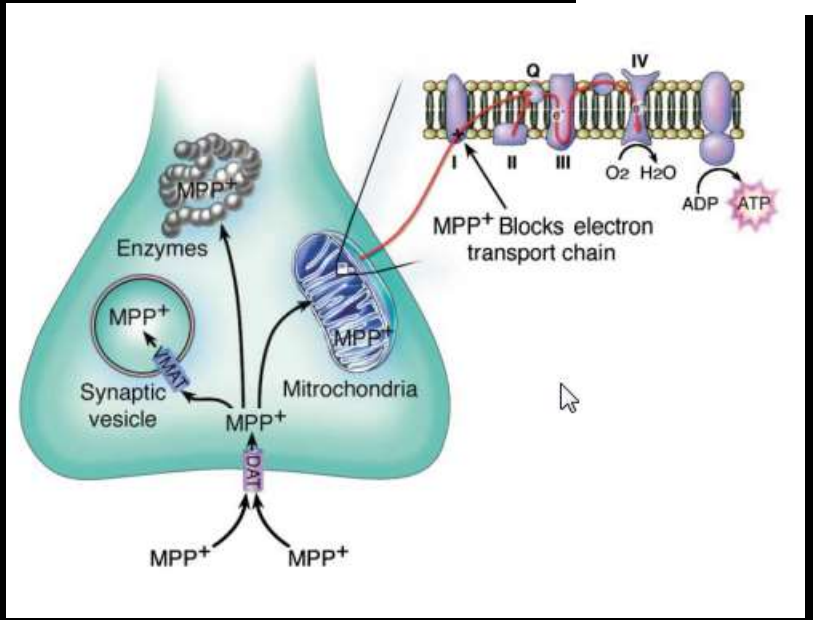


1-metil-4-fenil-1,2,3,6-tetraidropiridina

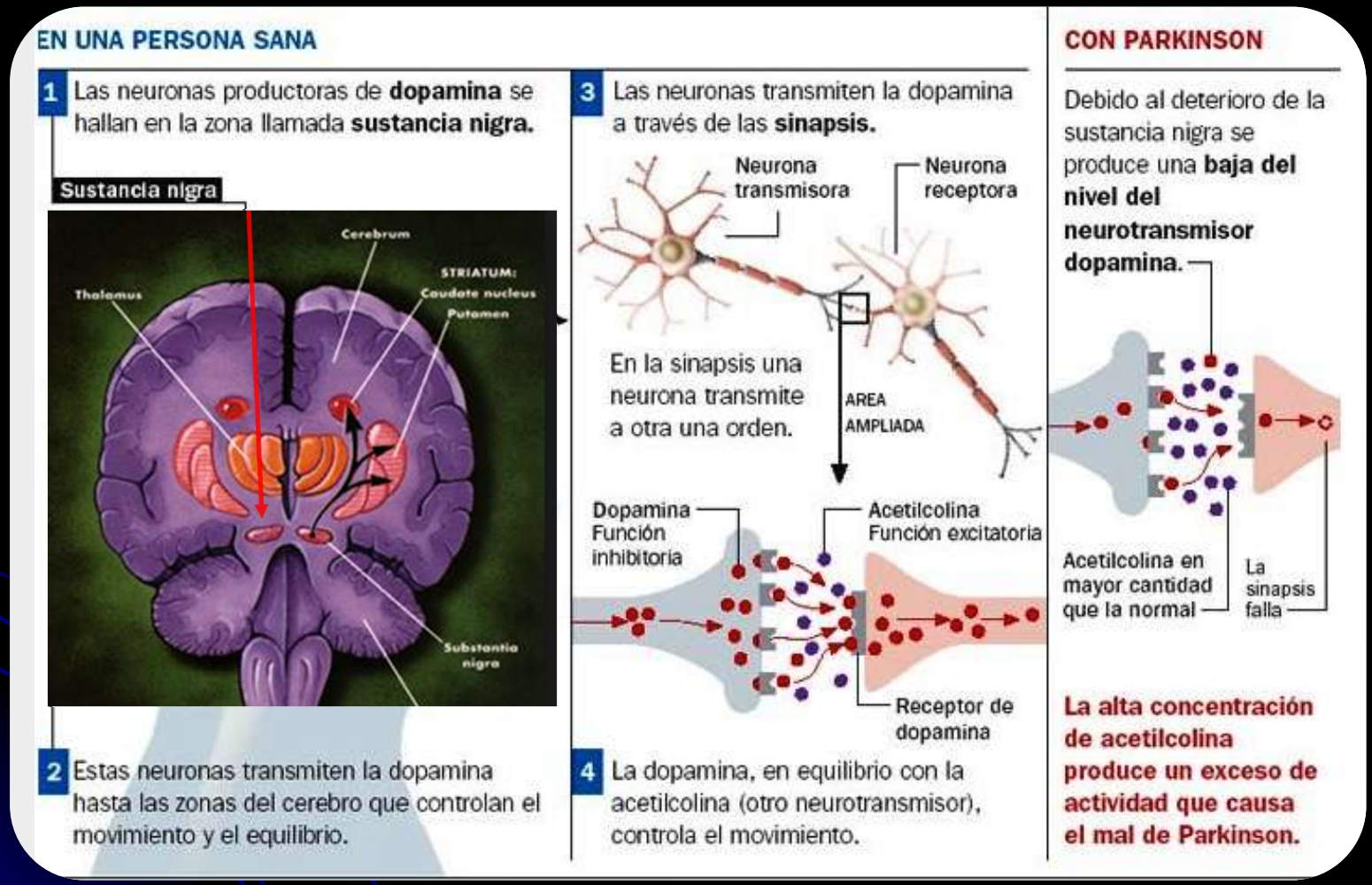


1-Methyl-4-phenyl-4-propionoxypiperidine (MPPP)



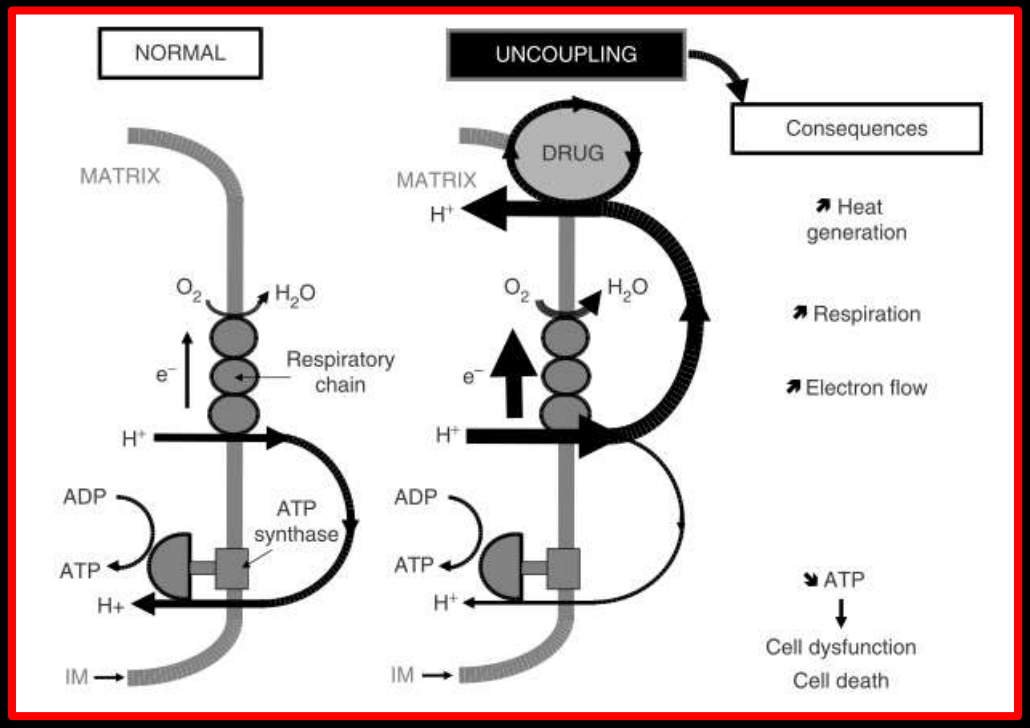


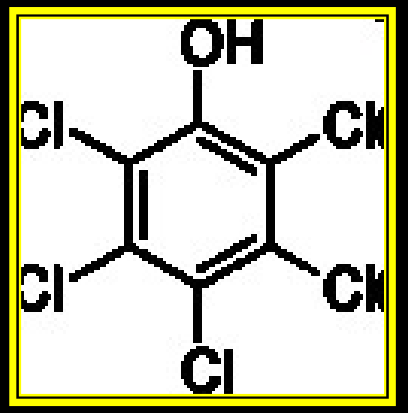
INIBIÇÃO DA CTE E DOÊNÇAS NEURODEGENERATIVAS



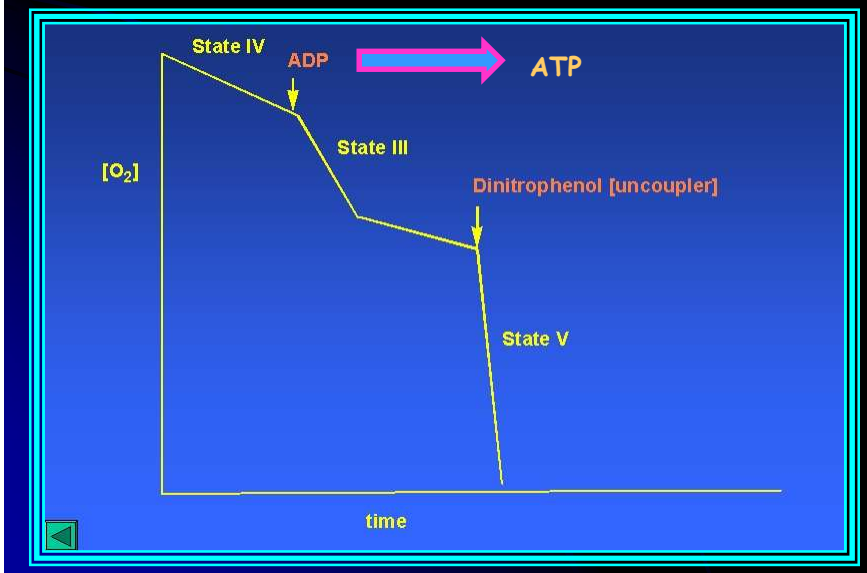
fisiopatologia do mal de Parkinson

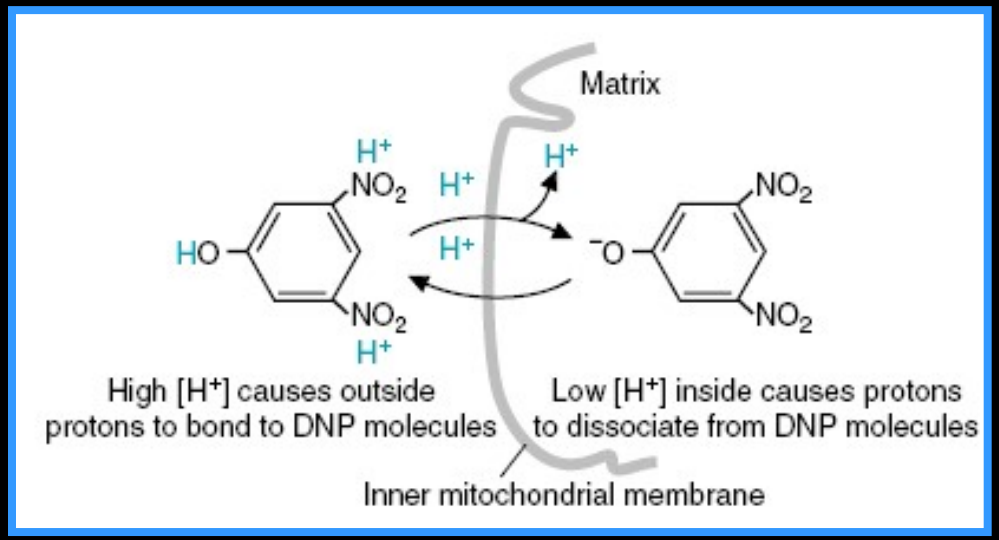
D - Desaclopadores da Fosforilação Oxidativa





pentaclorofenol

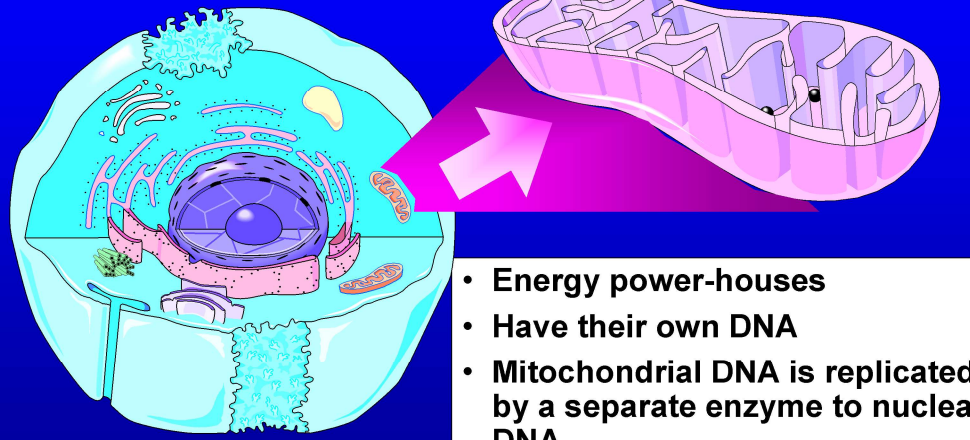




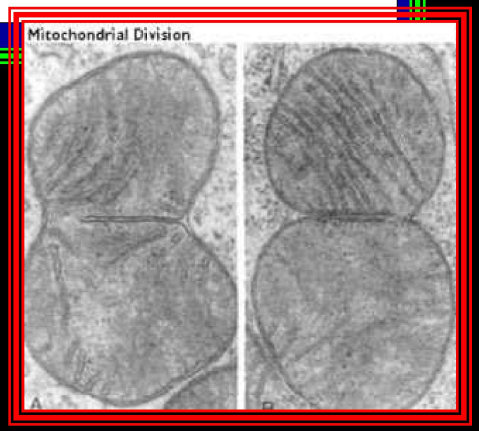
INIBIÇÃO DA BIOGÊNESE MITOCONDRIAL

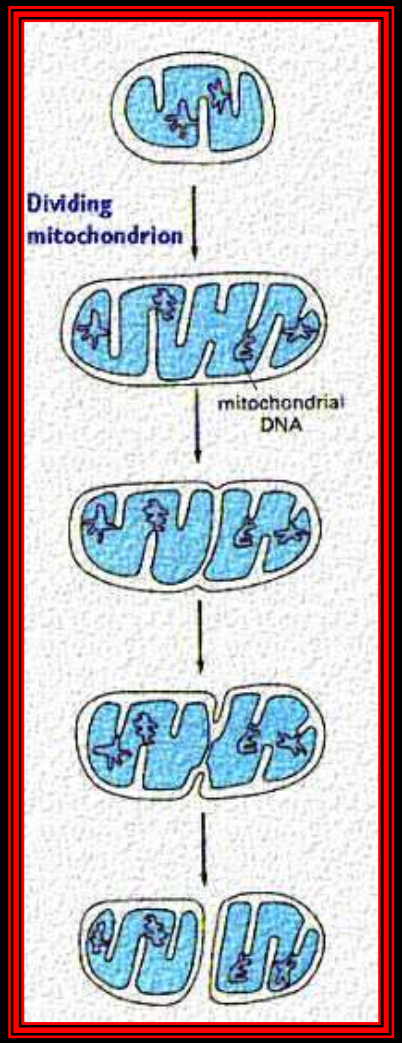
INIBIDORES DA BIOGÊNESE MITOCONDRIAL

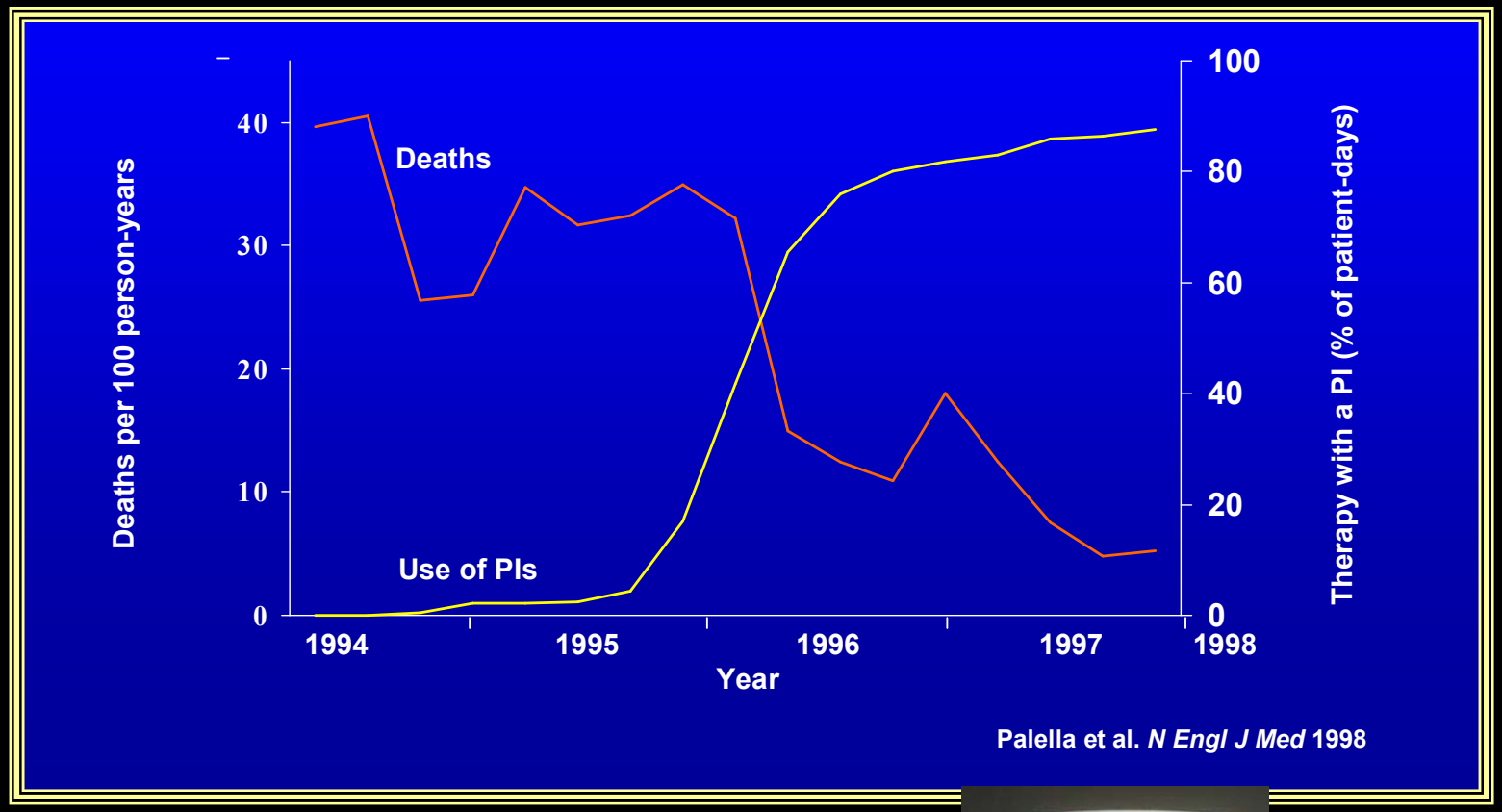
Mitochondria



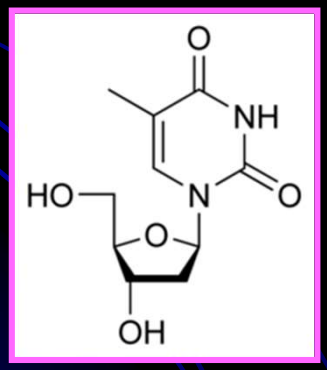
- Energy power-houses
- Have their own DNA
- Mitochondrial DNA is replicated by a separate enzyme to nuclear DNA



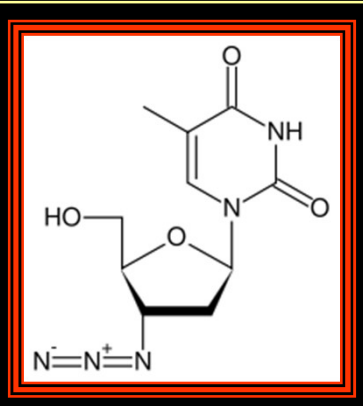




Palella et al. *N Engl J Med* 1998

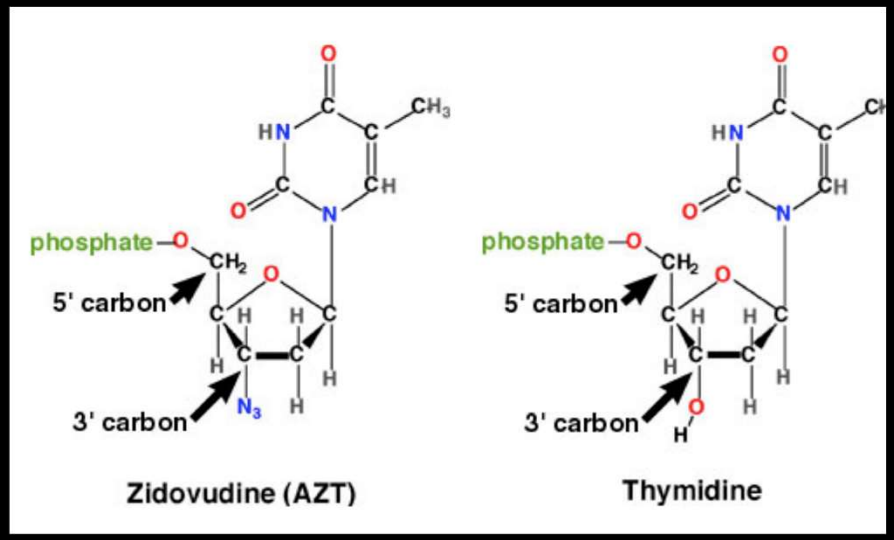


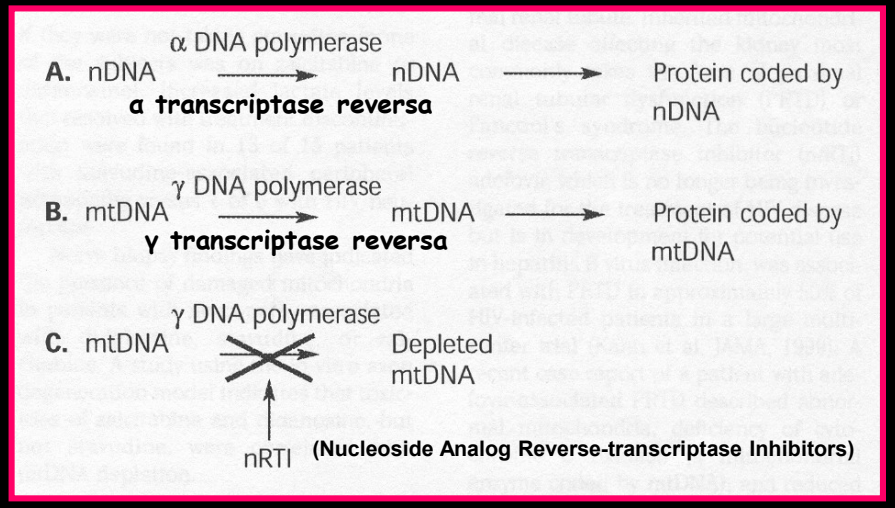
Timidina

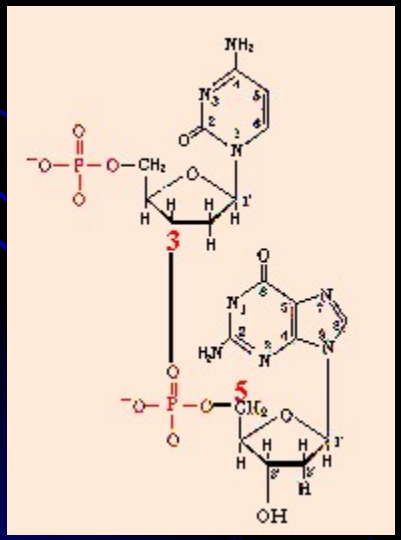


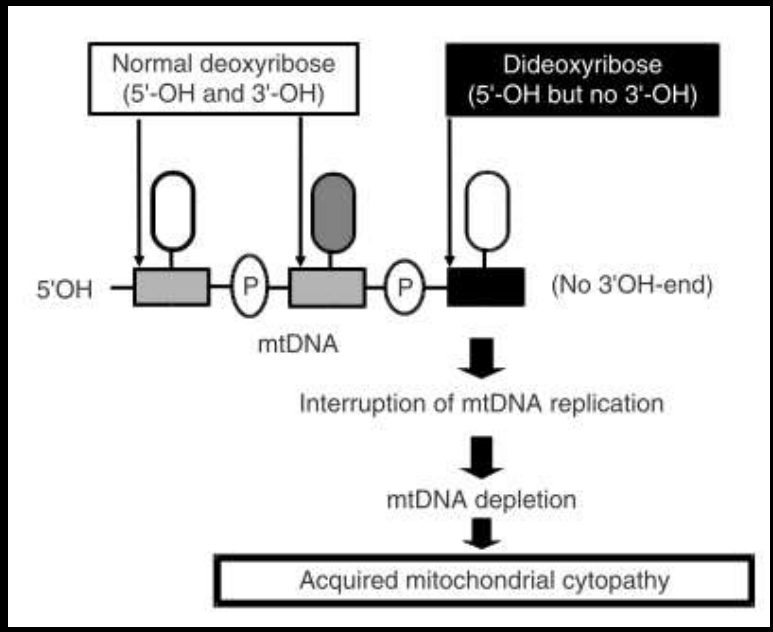
AZT; Azidotimidina
zidovudine

Inibição da Replicação do DNA

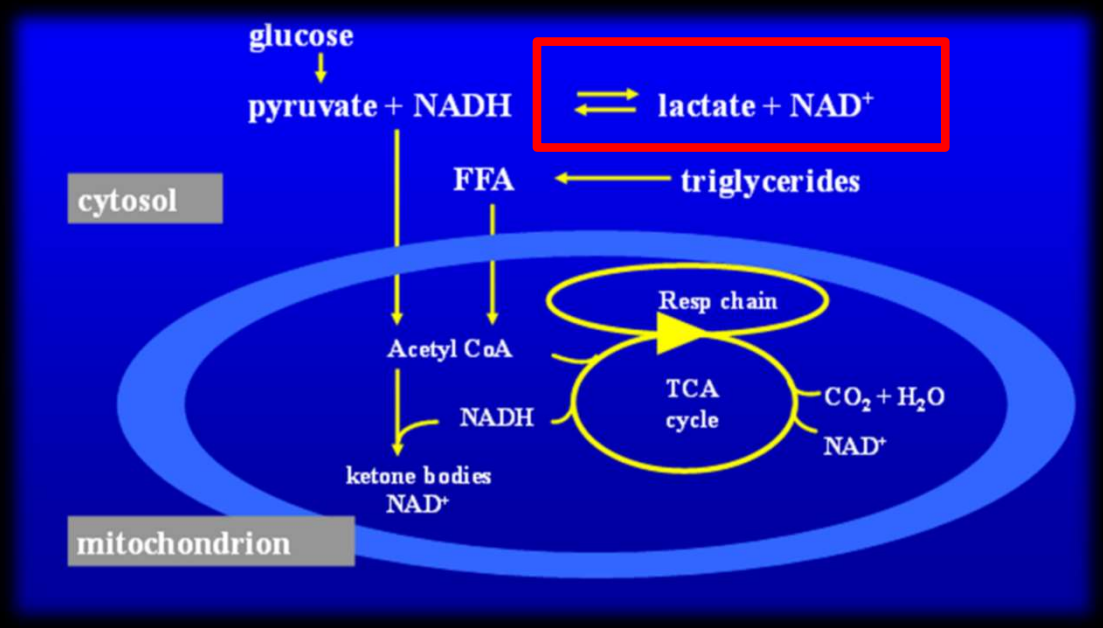








ACIDOSE METABÓLICA



LACTATE LEVEL		
2.1-5 mmol/L	5-10 mmol/L	>10 mmol/L
Asymptomatic, mild elevation	Mild-moderate symptoms (abdominal pain, nausea, distension, increase in ALT)	Fatal lactic acidosis/steatosis

Sinais e Sintomas

- **Anemia**
- **Astenia (fraqueza)**
- **Cansaço**
- **Confusão mental**
- **Constipações**
- **Diarreia**
- **Dor de cabeça**
- **Estomatite (feridas na boca)**
- **Granulopenia (diminuição dos leucócitos)**
- **Mal estar**
- **Manchas na pele**
- **Náusea**
- **Perda de apetite**
- **Ulcerações**
- **Vômito**

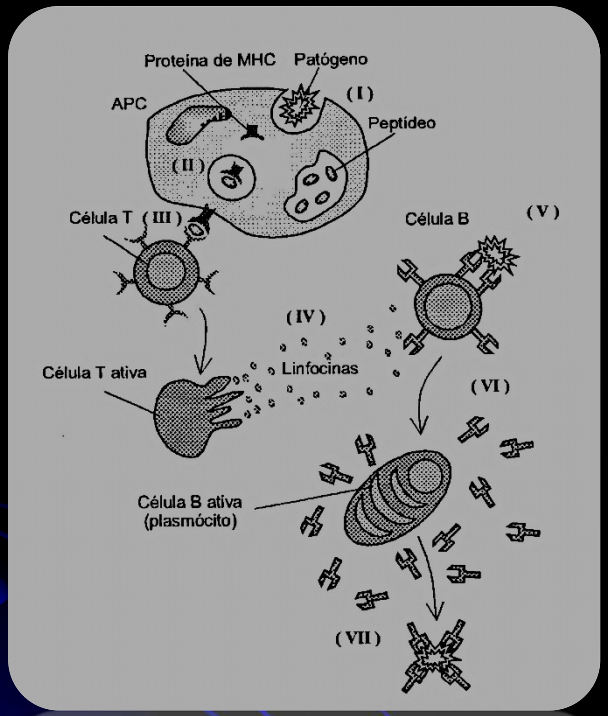
TOXICIDADE IDIOSSINCRÁTICA

gr. idiosugkrasía,'temperamento particular'

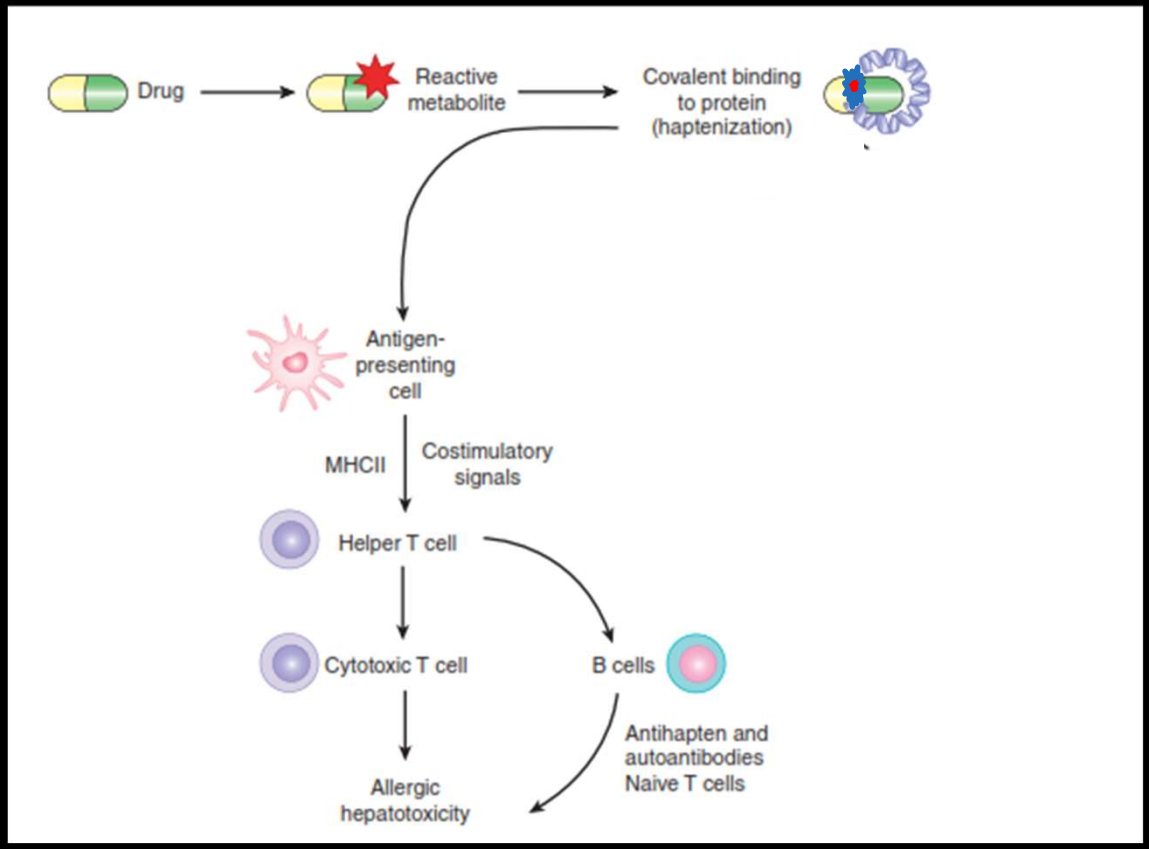
Esquema simplificado dos mecanismos de reconhecimento e ativação do sistema imunológico

APC = célula apresentadora de antígeno (macrófago)

MHC = complexo de histocompatibilidade principal (major histocompatibility complex)



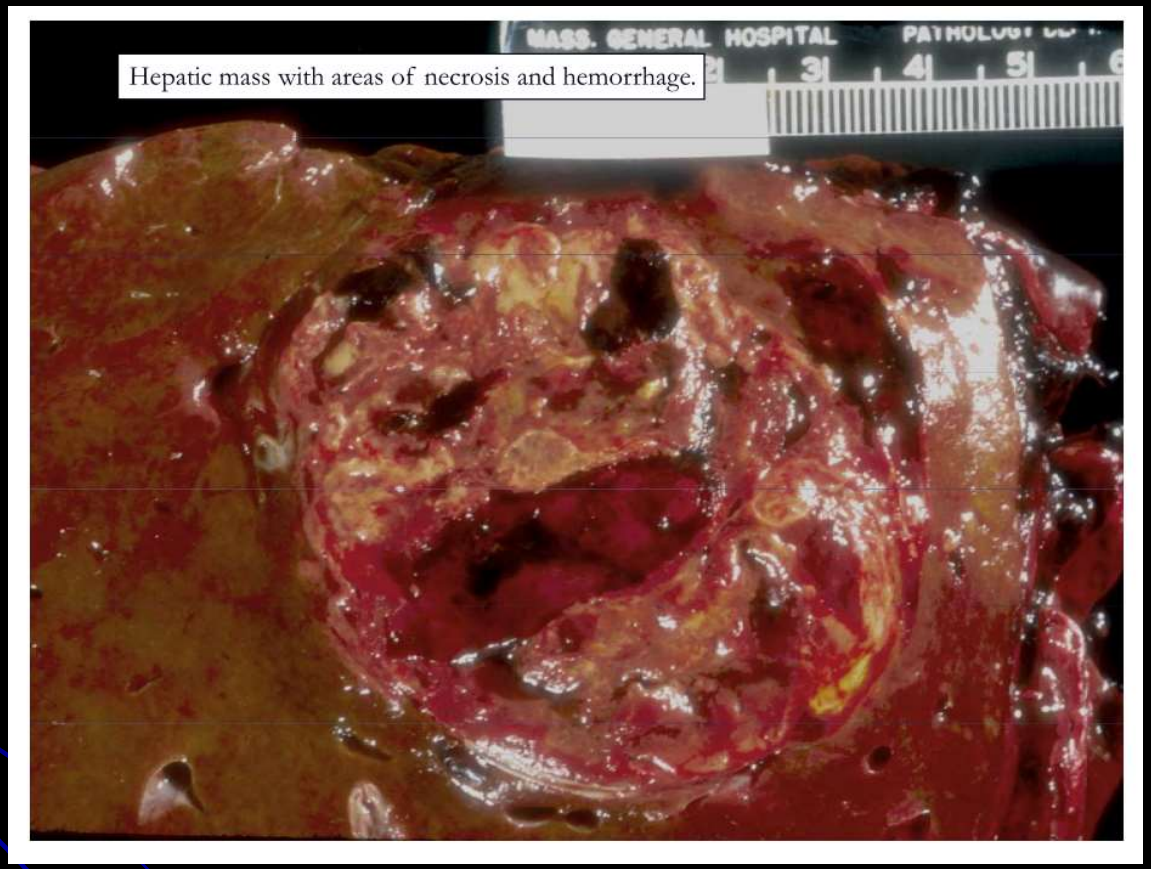
Hipótese do Hapteno ou Neoantígeno



Idiosyncratic Drug Reactions and Forms of Liver Injuries

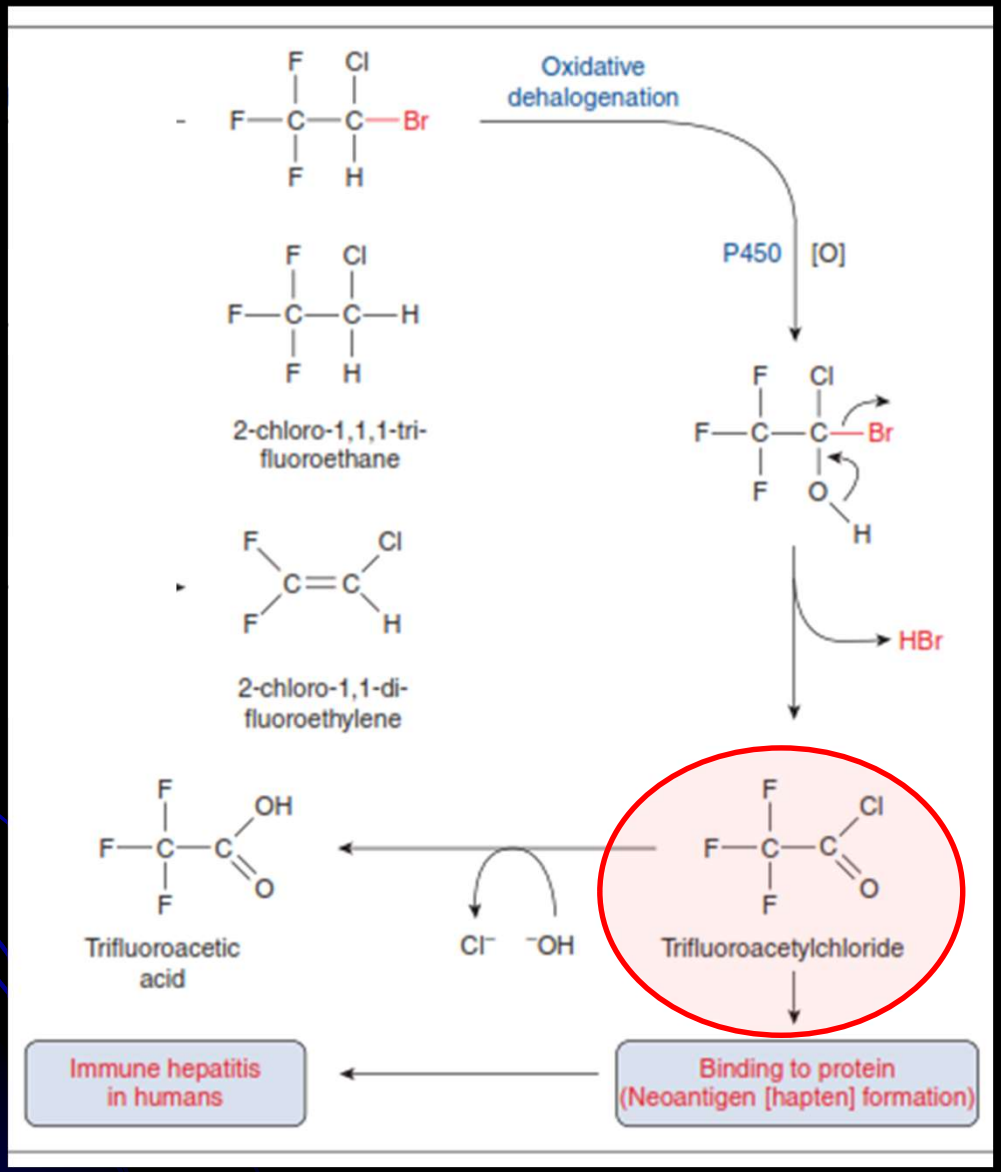
Drugs	Forms of Liver Injuries
Isoniazid, trazodone, diclofenac, nefazodone, venlafaxine, lovastatin	Hepatocellular necrosis
Chlorpromazine, estrogen, erythromycin, and other macrolides	Cholestasis
Phenytoin, sulfamethoxazole	Immunoallergic reaction
Diltiazem, sulfonamides, quinidine	Granulomatous hepatitis
Didanosine, tetracycline, valproic acid	Acute steatosis
Nitrofurantoin, methyldopa, lovastatin, minocycline	Autoimmune hepatitis
Methotrexate	Fibrosis
Oral contraceptives, anabolic steroids	Hepatic tumor
Amoxicillin/clavulanate, carbamazepine, cyclosporine, methimazole	Mixed hepatocellular/ cholestatic injury

- 70 year old woman with retinal detachment treated with scleral buckling using halothane anesthesia followed by nausea and vomiting X 3d
- Two months later, admitted to the hospital due to recurrent retinal detachment; had another scleral buckling with halothane
- On 7th day, developed jaundice, bilirubin 14, AST 220
- On 8th day, confusion, drowsiness, AST 1350
- Over the next several days, coma, multiorgan failure, death



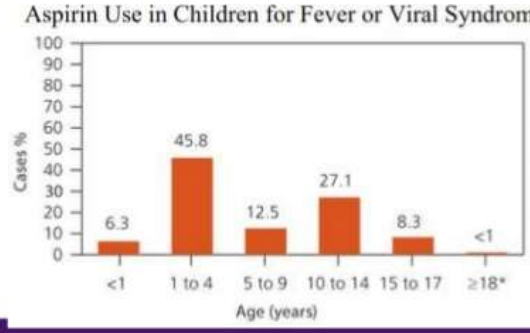
exame anátomo-patológico

Halotano


Oxidative dehalogenation
P450
[O]
2-chloro-1,1,1-tri-fluoroethane
2-chloro-1,1-di-fluoroethylene
HBr
Trifluoroacetic acid
Cl⁻
⁻OH
Trifluoroacetylchloride
Immune hepatitis in humans
Binding to protein (Neoantigen [hapten] formation)

Aspirin and Reye's Syndrome

- Reye syndrome is an acute, non-inflammatory encephalopathy and hepatotoxicity that follows an acute viral illness. It is associated with salicylates treatment



a incidência anual varia de 0,16 a 0,88 para 100.000 crianças