BUPRENORPHINE HEPATOTOXICITY

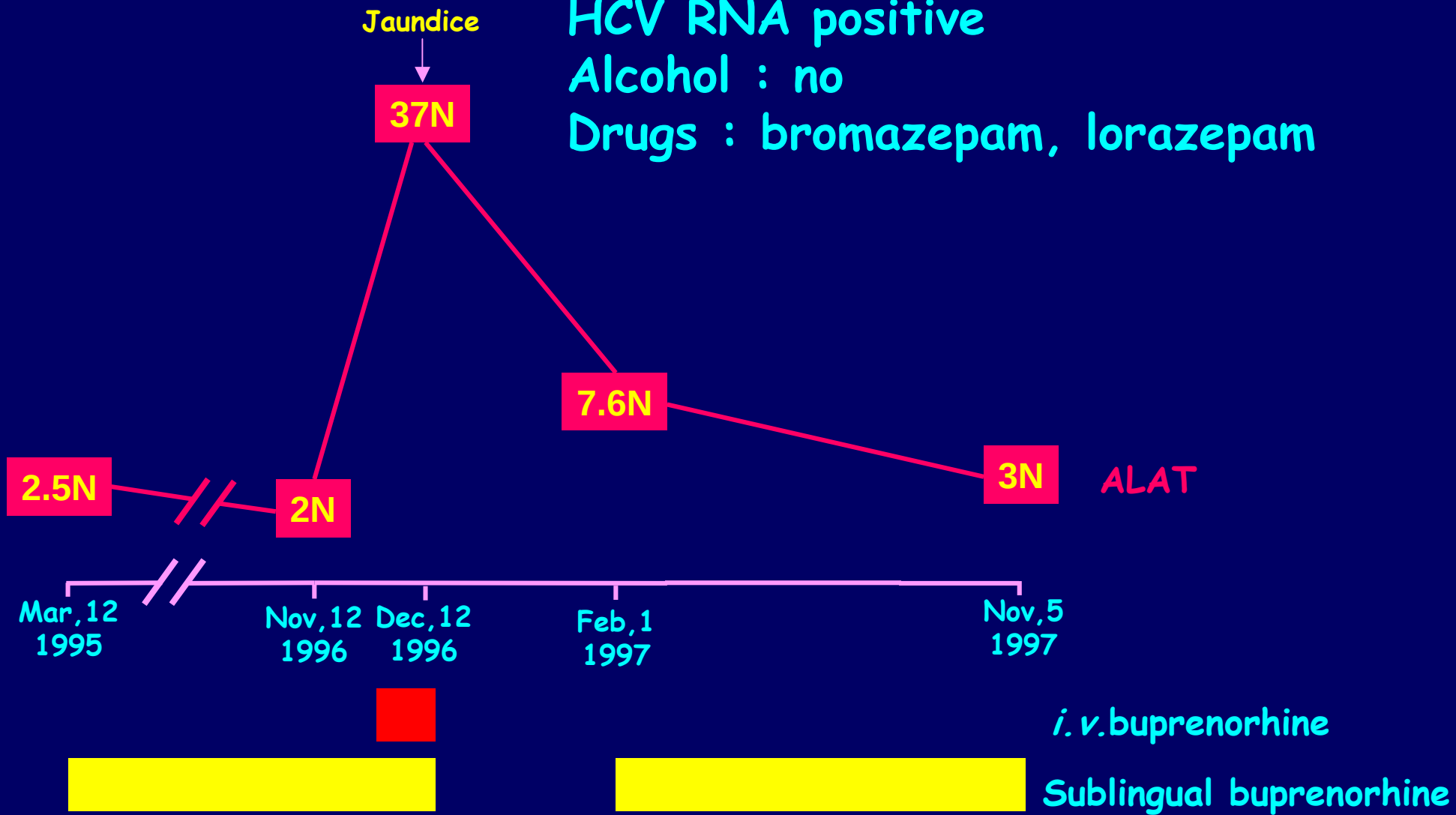
A. Berson, Inserm U773, CRB3, Bichat

-Is buprenorphine hepatotoxic ?

-Mechanism(s) of hepatotoxicity ?

Clinical report:

27-year-old male, former heroin addict
HCV RNA positive
Alcohol : no
Drugs : bromazepam, lorazepam



Subutex® hepatotoxicity (n=13)

Wisniewski et al. Gastroenterol Clin Biol 2001
Berson et al. J Hepatol 2001
Hervé et al.Eur J Gastroenterol 2004

Age: 30 years; 2 F/11 M

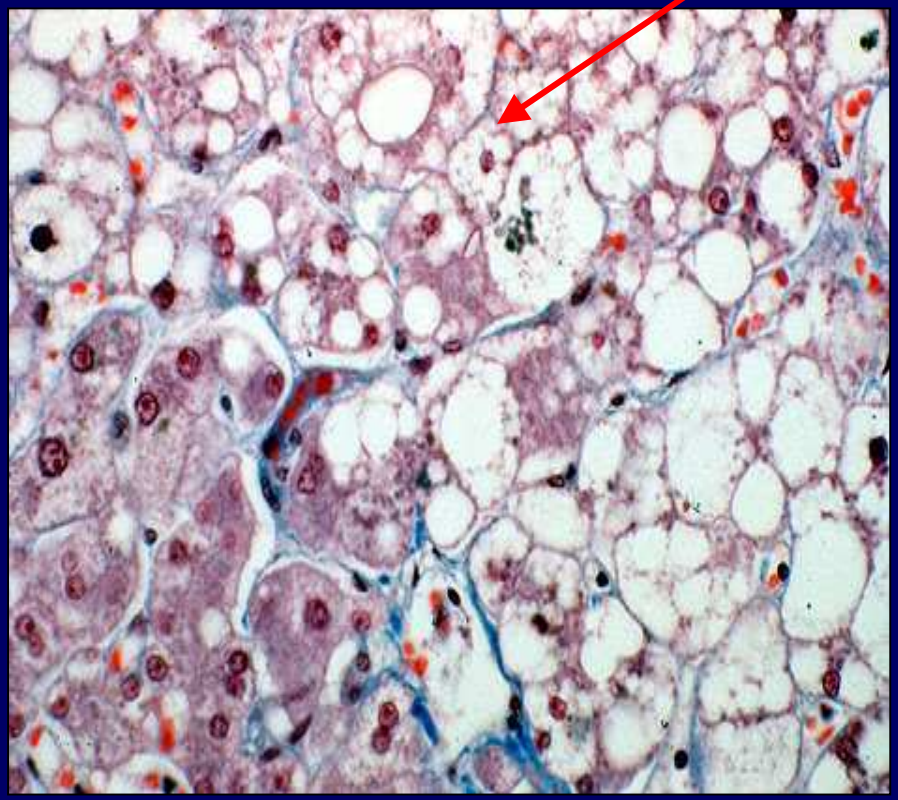
ALAT: 50 N
Alkaline phosphatase: 2 N

Favourable outcome: 13/13

Histology: microvesicular steatosis, necrosis

Liver histology

Microvesicular steatosis

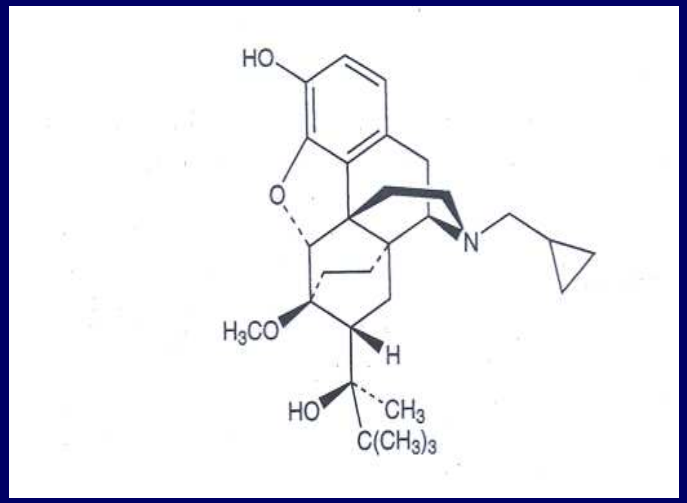


Subutex® hepatotoxicity
Associated factors

i.v. Injection (8/13)
Drug intake (9/13)
Viral infection

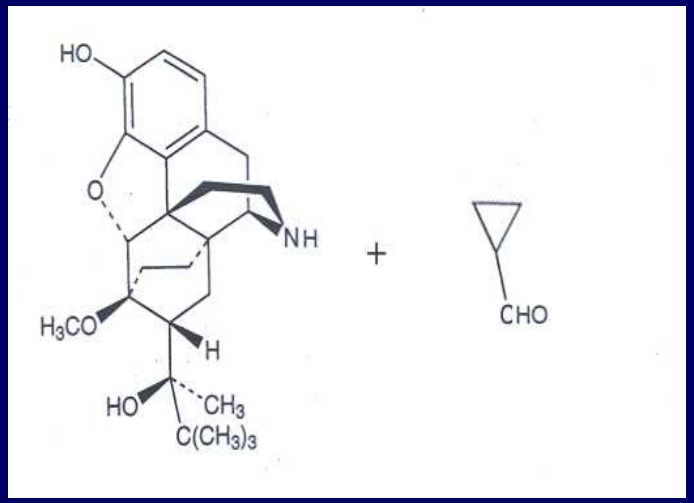
- -HCV+ (13/13); HCV Rna+ (9/13)
- -HBs Ag+ (1/13)
- -HIV+ (1/13)

Buprenorphine: pharmacological data



Buprenorphine

CYP3A

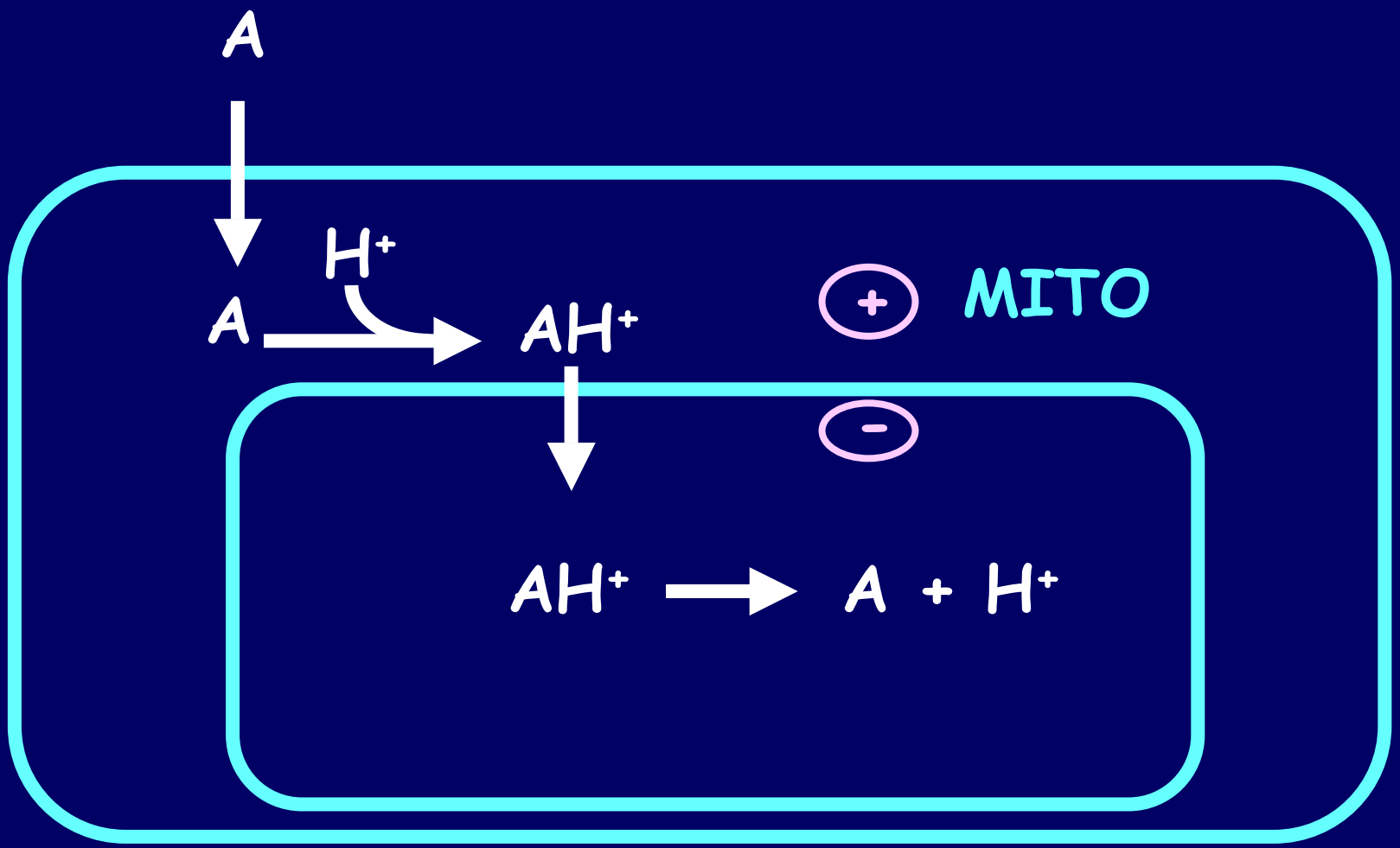


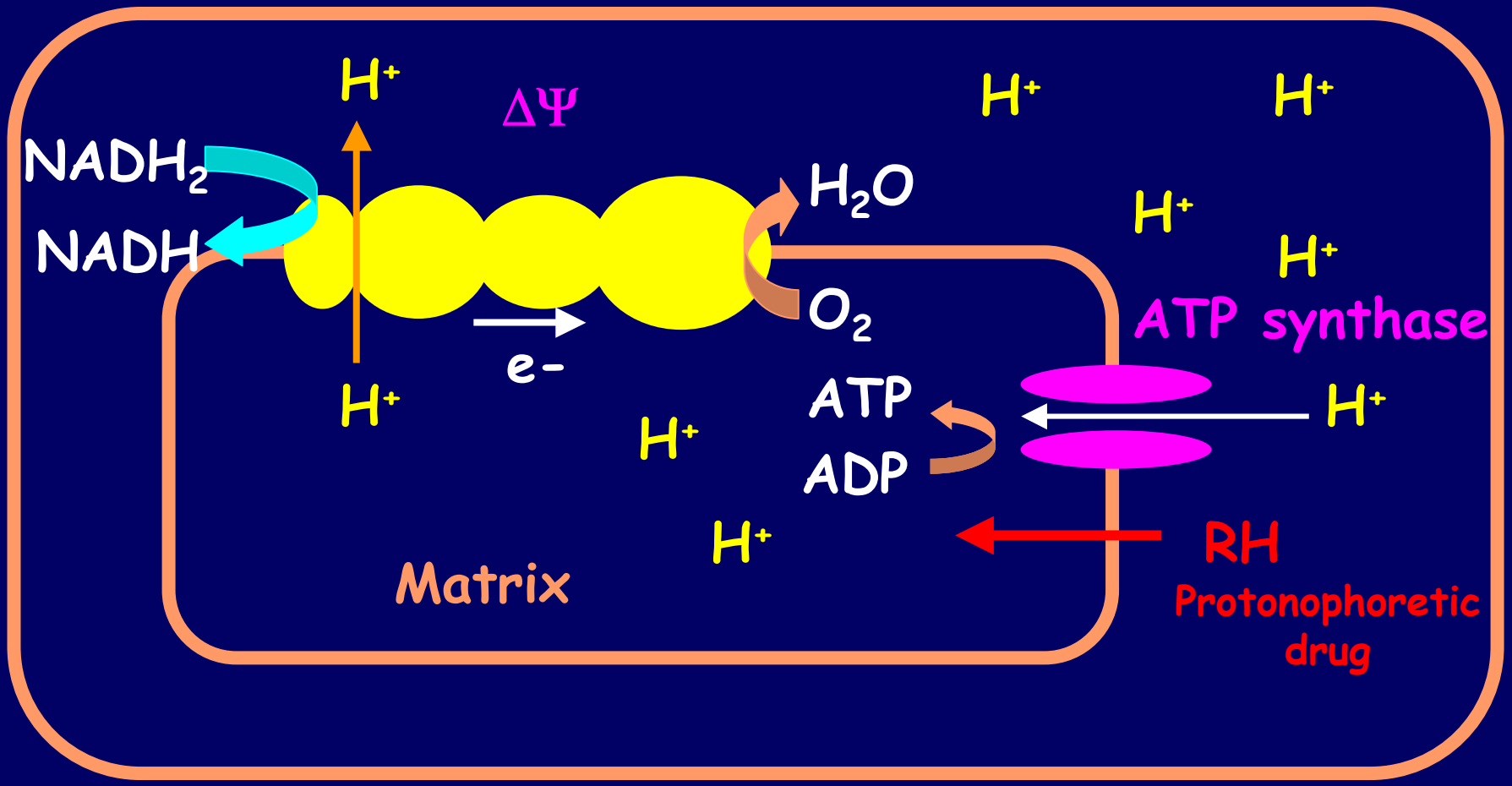
Norbuprenorphine
Cyclopropanecarboxaldehyde

Plasma concentration

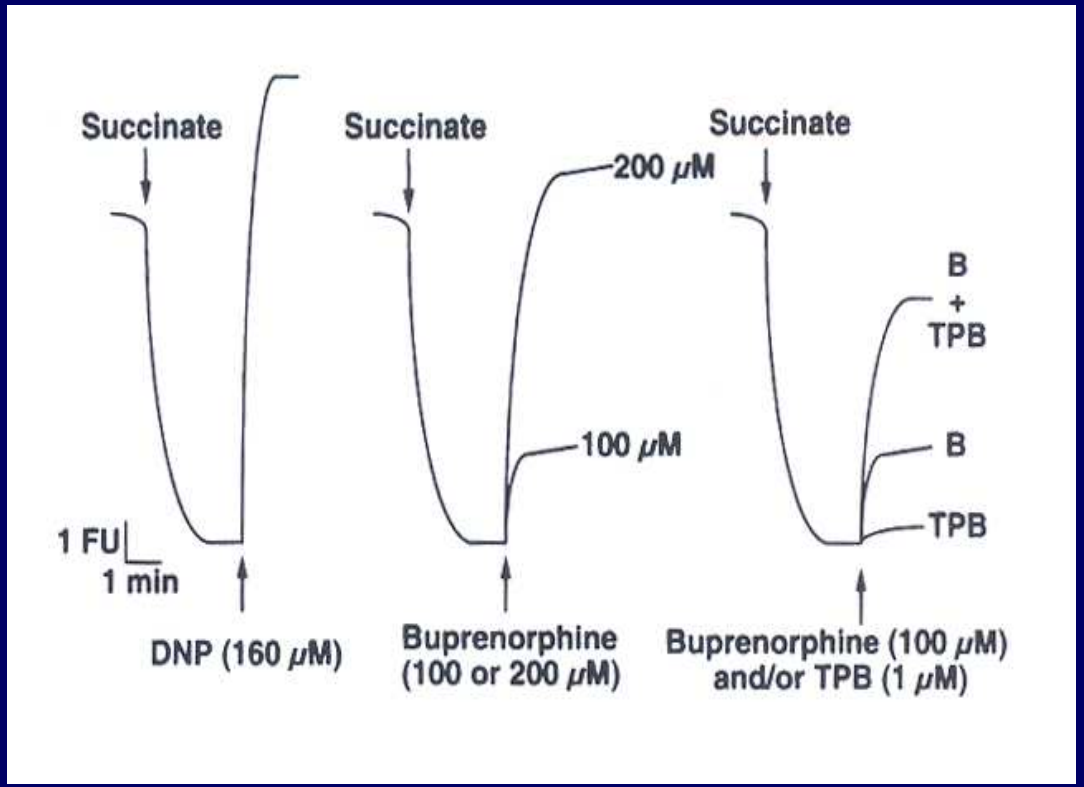
- Sublingual administration (8 mg): 0.02 µM
- *i.v.* administration (rat): x 80

Cationic amphiphilic drugs
(amiodarone, tamoxifen)



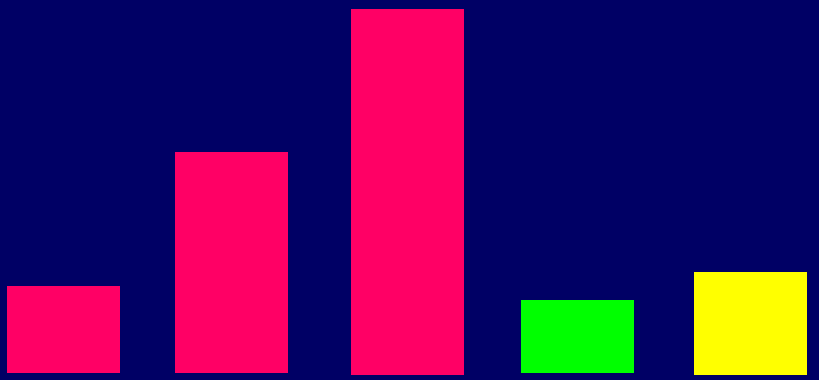


Mitochondrial membrane potential

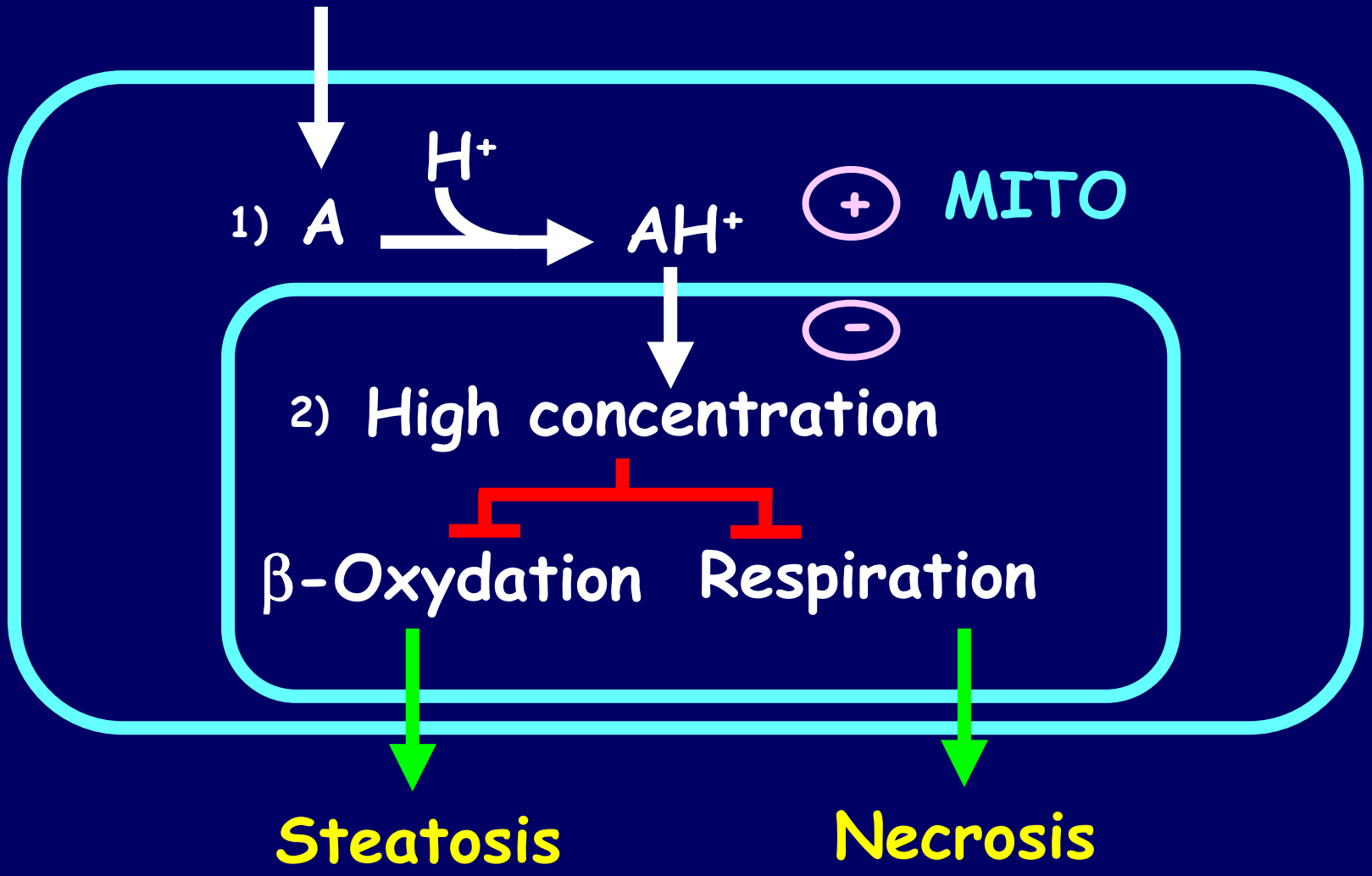


State 4 respiration

(control percent)



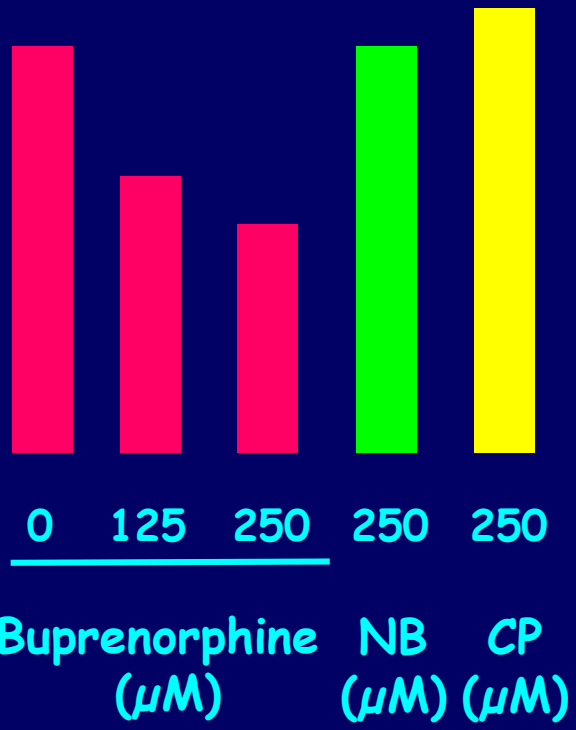
Cationic amphiphilic drugs (amiodarone, tamoxifen)



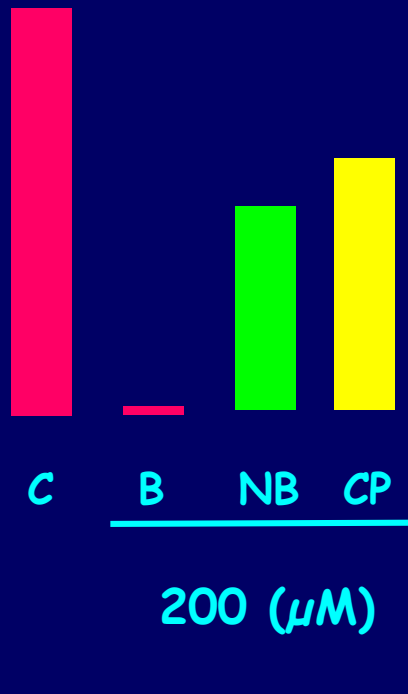
Mitochondrial/medium concentration

	Residual concentration in medium (μM)	Concentration in mitochondria (μM)	Mitochondria/ medium concentration ratio
B after 0.5 min	15.8 ± 0.7	225 ± 28	14.2
NorB after 0.5 min	19.0 ± 0.6	77 ± 4	4.0
B after 5 min	16.3 ± 0.3	203 ± 19	12.4
NorB after 5 min	18.9 ± 0.7	74 ± 4	3.9

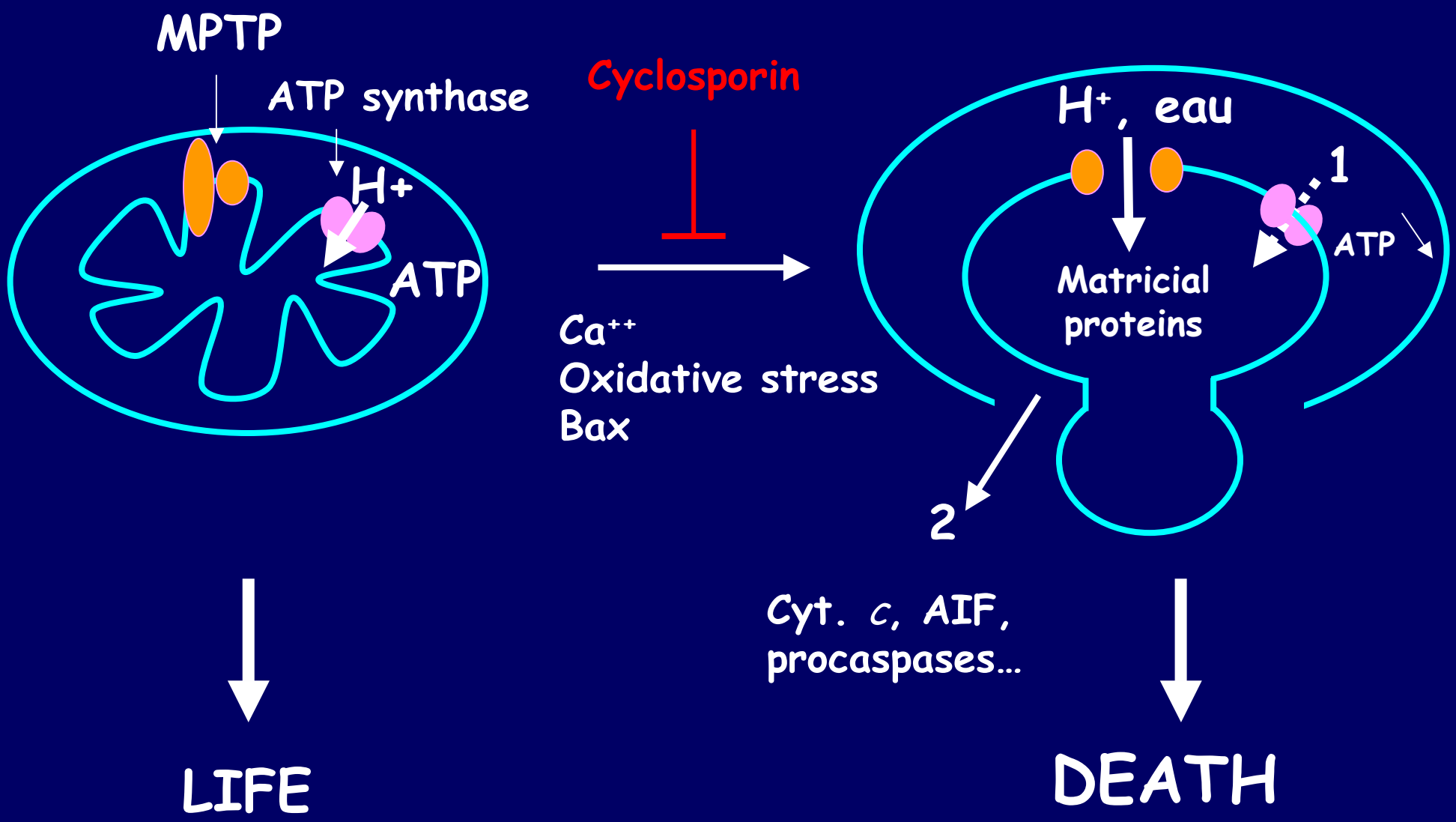
State 3 respiration *(control percent)*



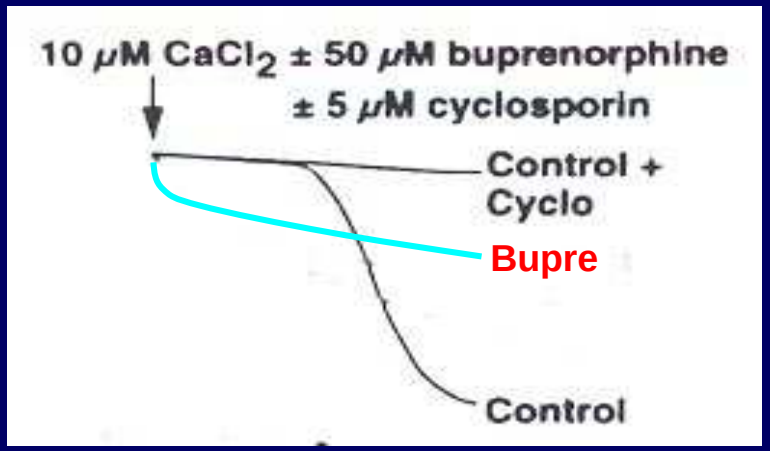
Mitochondrial β-oxidation *(control percent)*

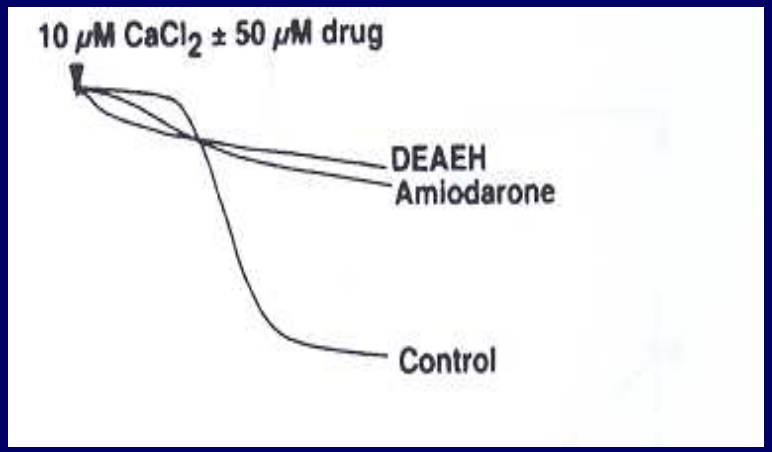


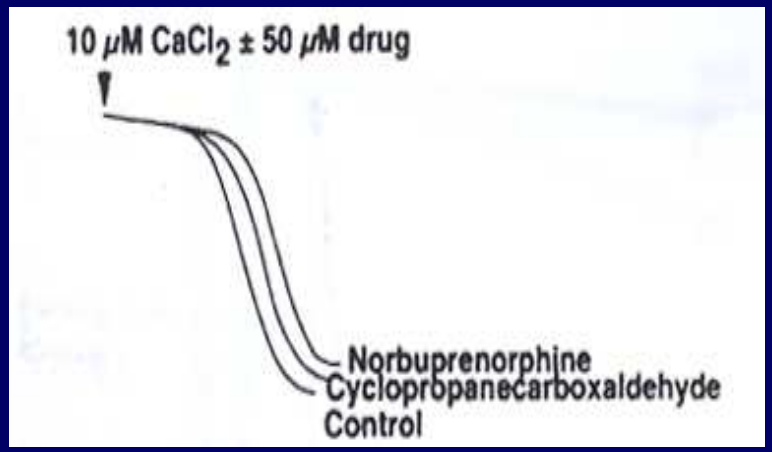
Mitochondrial Permeability Transition Pore



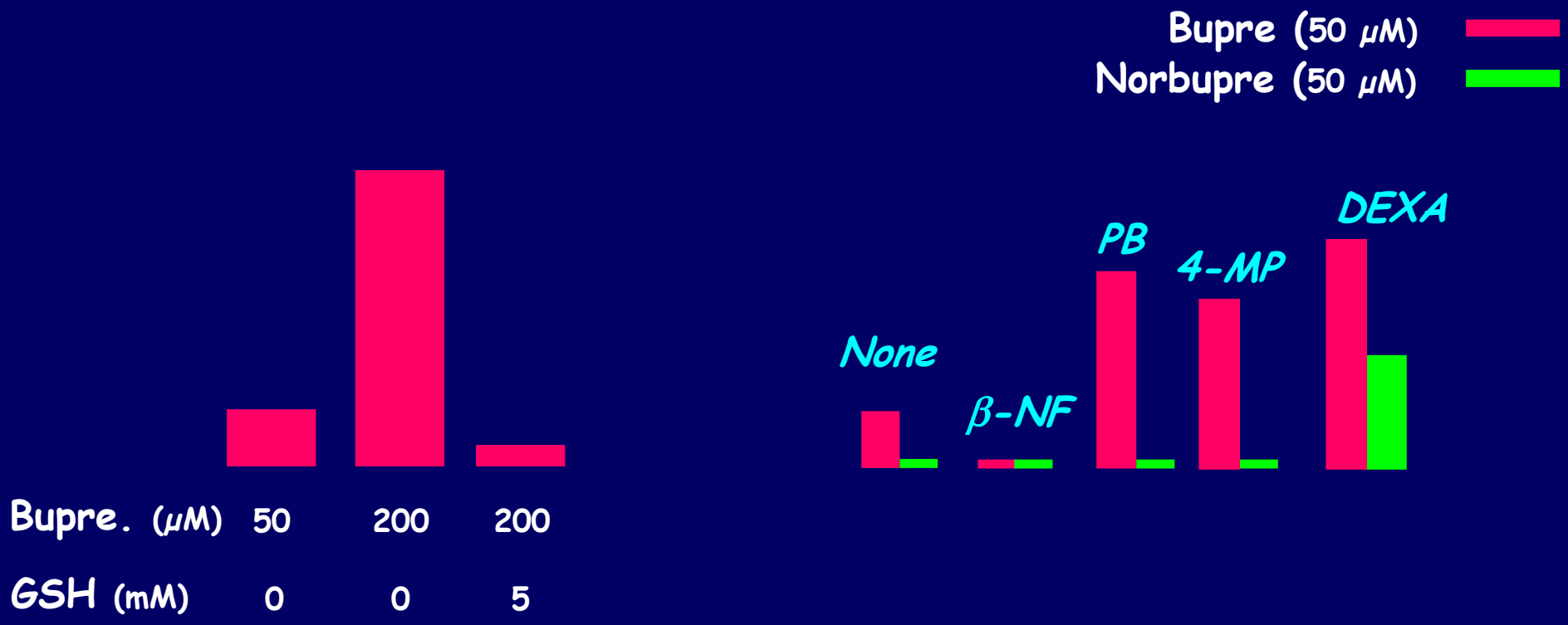
Mitochondrial permeability transition





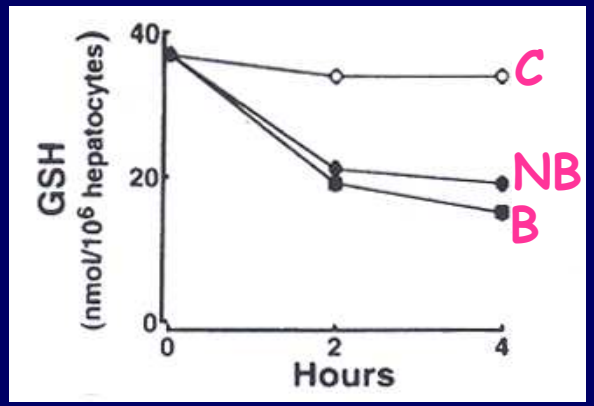


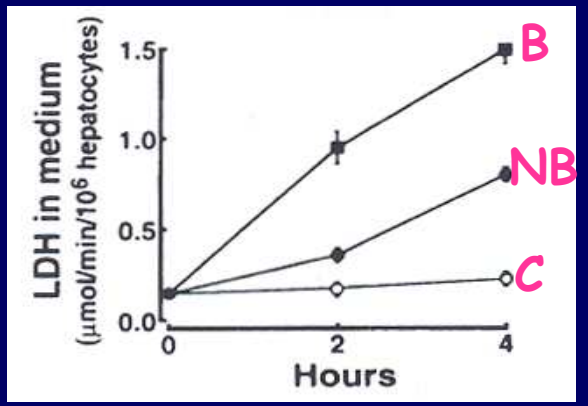
NADPH-dependent covalent binding to rat liver microsomes

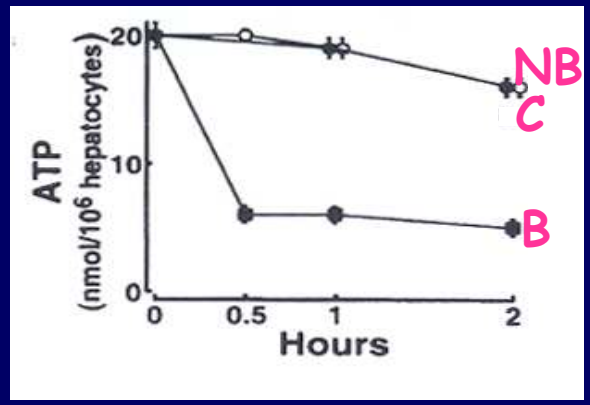


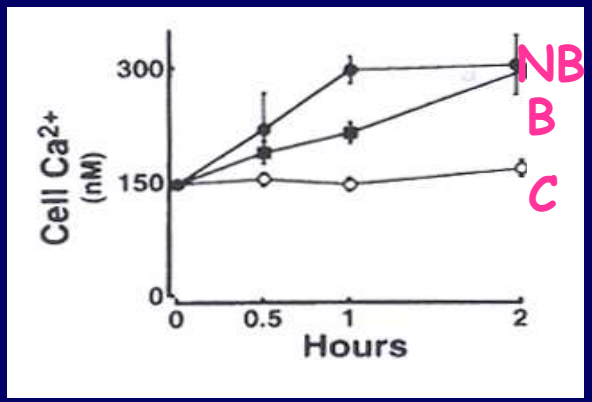
Effects on isolated hepatocytes

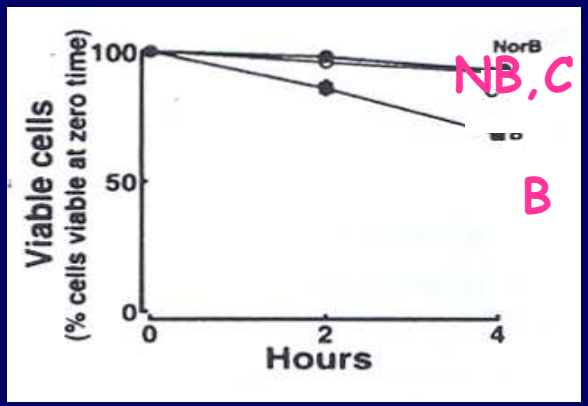
B: Buprenorphine 200 µM
NB: Norbuprenophine 200 µM
C: Cyclopropanecarboxaldehyde 200 µM



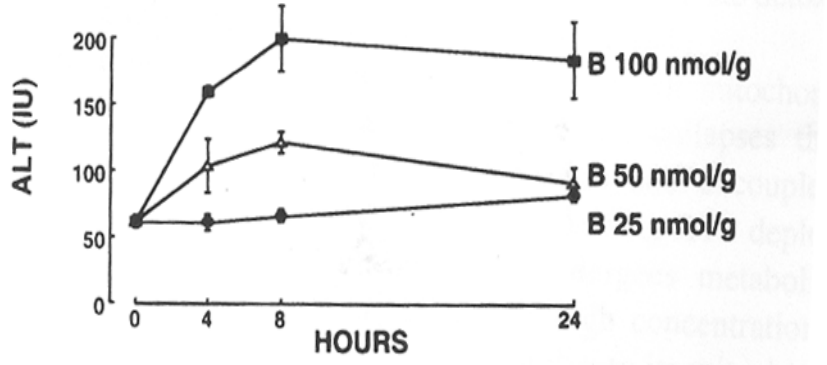


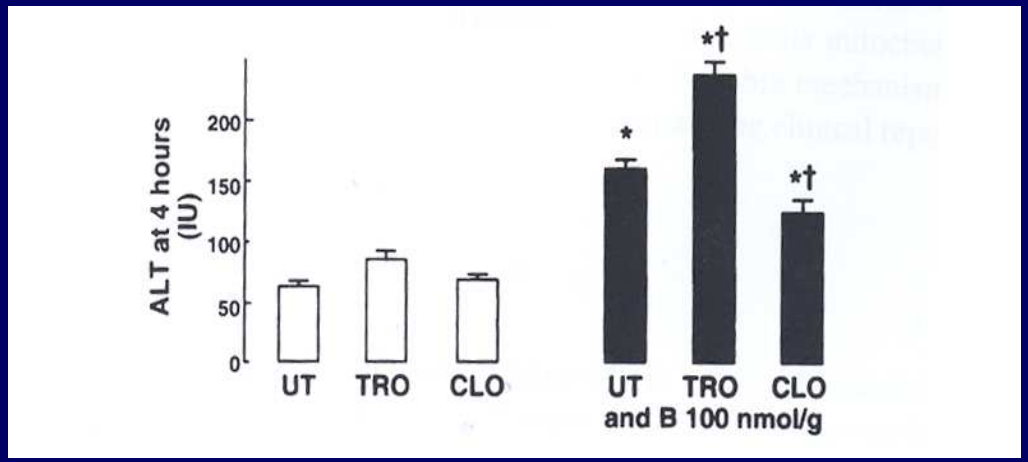


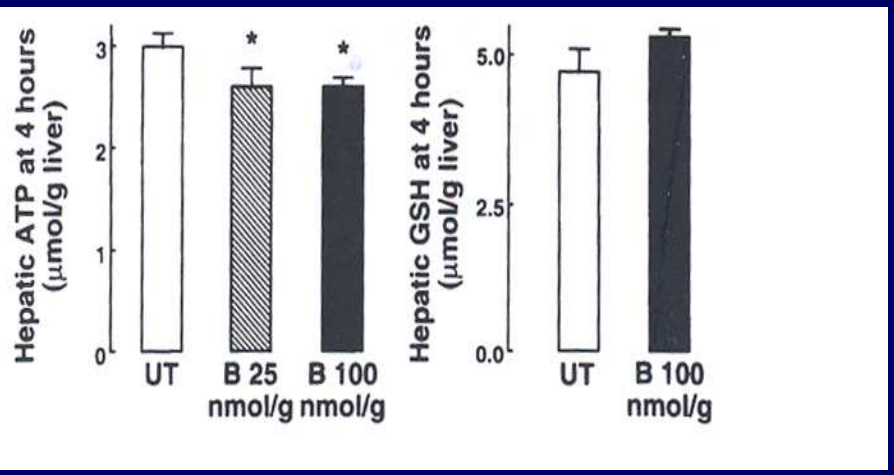


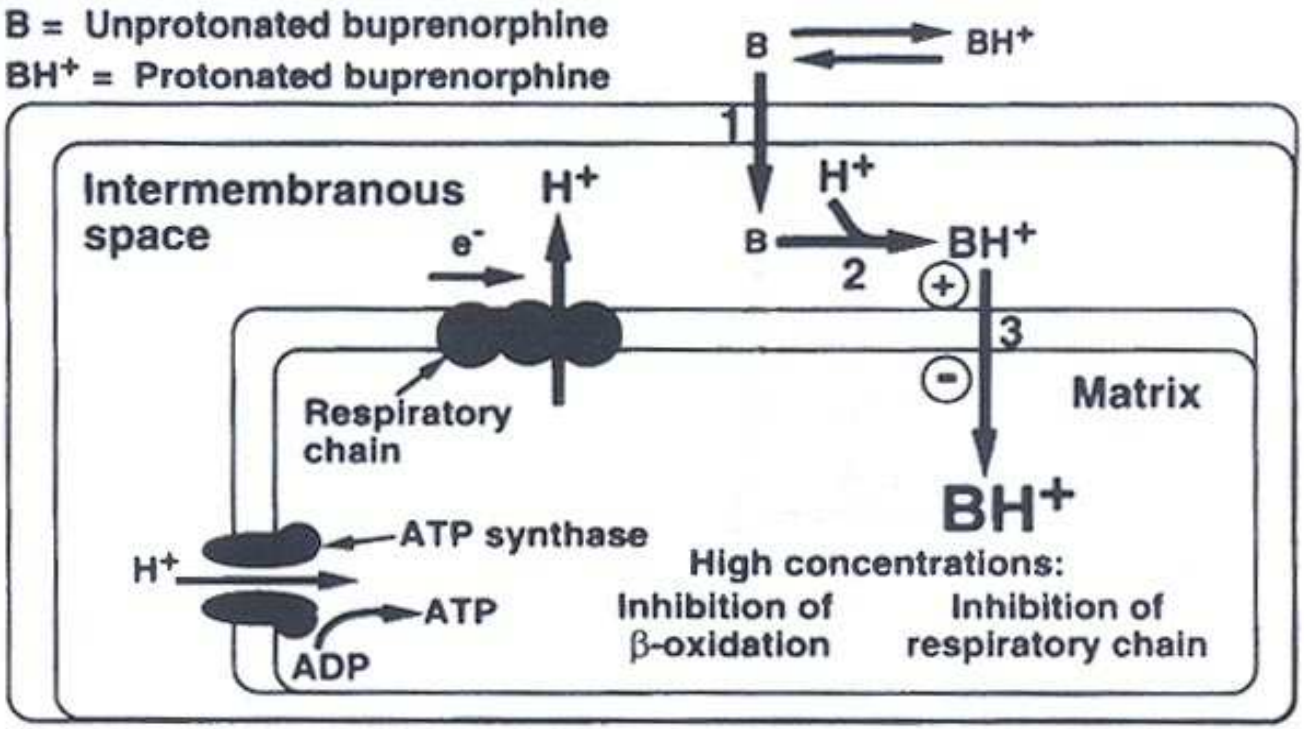


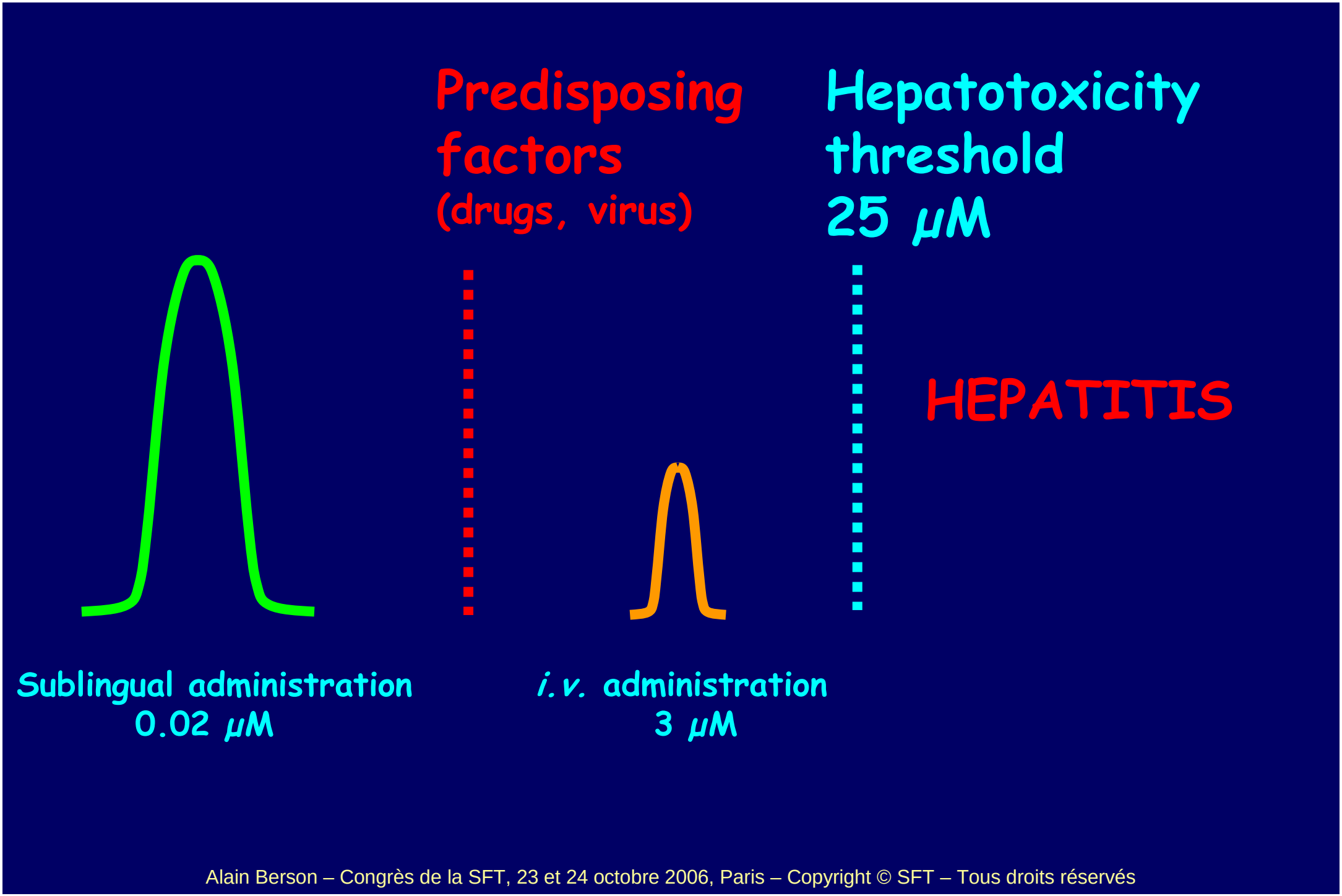
Effects of buprenorphine in mice (*i.p.* injection)











Mitochondrial dysfunction by xenobiotics

Mitochondrial respiration

Direct:

amphiphilic cationic drugs, acetaminophen (ROS)…

mtDNA impairment:

NRTIs, α-interferon, ethanol, tacrine, tamoxifen…

β-oxidation

Salycylic acid, valproate, tetracyclines, tianepetine, NSAIDs …

Respiration and β-oxidation

Amphiphilic cationic drugs

Viral infection and drug hepatotoxicity

Aspirin → Reye syndrome ← Viral infection (measles)

Anti-tuberculous
HAART
Azathioprine
Ibuprofen
→ Hepatitis ← HBV HCV

Mechanisms ?

Buprenorphine

HEPATOPROTECTION

Decreases VHB and VHC transmission

HEPATOTOXICITY

Misuse *(i.v.* injection)
HCV, HBC, HIV
Ethanol
Drugs