

Nouvelles Approches Thérapeutiques de l'Hypertension Portale

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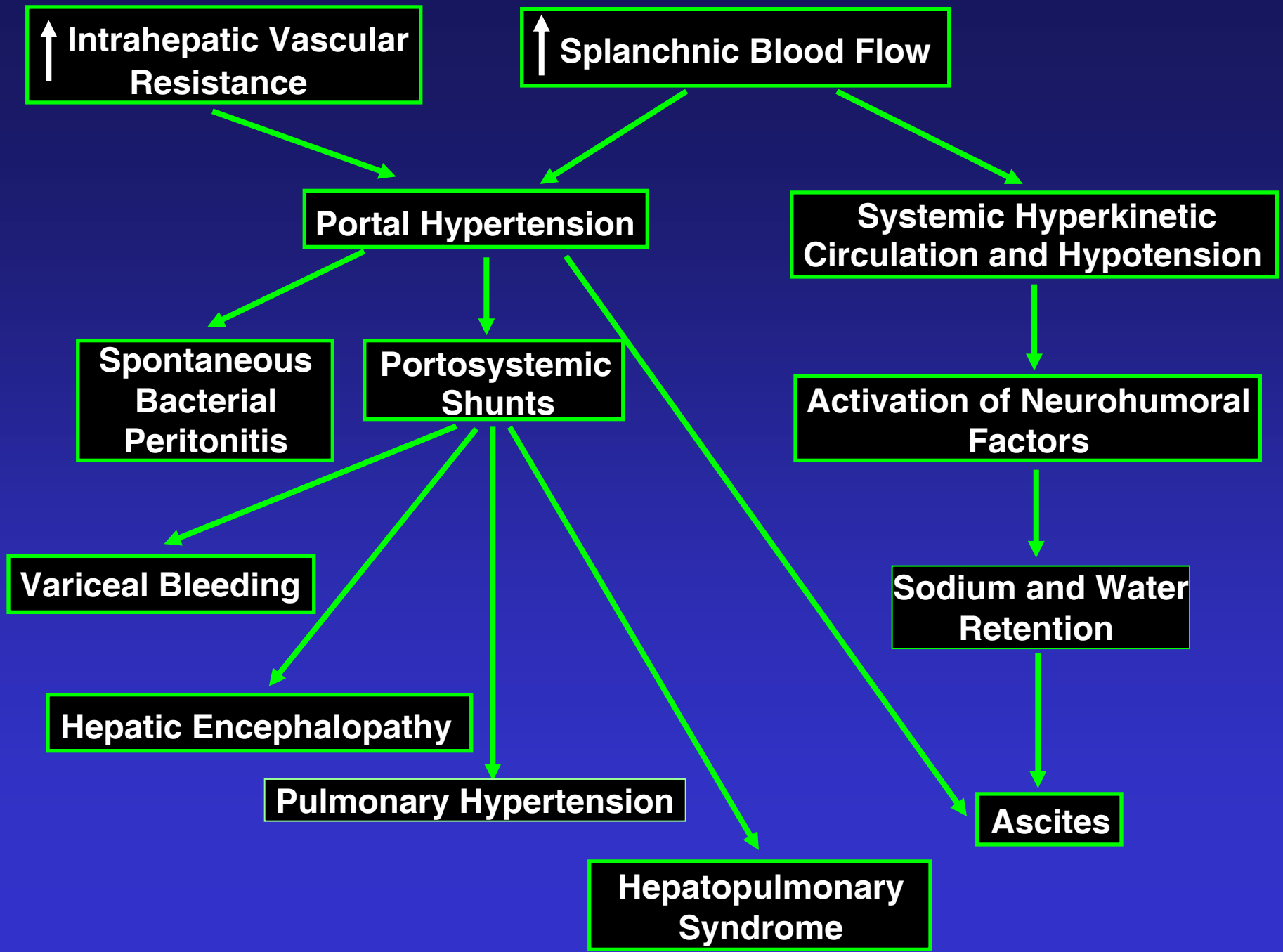
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Genève 29 novembre 2007



Portal Hypertension

- 1. Prevention of varices**
 - 2. New pharmacological approaches**
 - 3. Portal hypertension and bacterial translocation**
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Propranolol in the Prevention of Large Esophageal Varices*

	Propranolol (n=102)	Placebo (n=104)
Large varices (%)	31	14**
Variceal bleeding (%)	3	4
Mortality rate (%)	9	10

* 2 years

** p<0.05

Calés et al. Eur J Gastroenterol Hepatol 1999;11: 744-51.

Timolol in the Prevention of Esophageal Varices*

	<u>Timolol (n=108)</u>	<u>Placebo (n=105)</u>
Varices (%)	39	37
Variceal bleeding (%)	3	3
Mortality rate (%)	9	14

* 4 years

Groszmann et al N Engl J Med 2006;353:2254-6.

Nadolol in the Prevention of Aggravation of Small Esophageal Varices*

	<u>Nadolol (n=83)</u>	<u>Placebo (n=78)</u>
Large varices (%)	20	51**
Variceal bleeding (%)	12	22°
Mortality rate (%)	50	53

* 5 years ** p<0.001, °p<0.02

Merkel et al. Gastroenterology 2004;127:476-84.

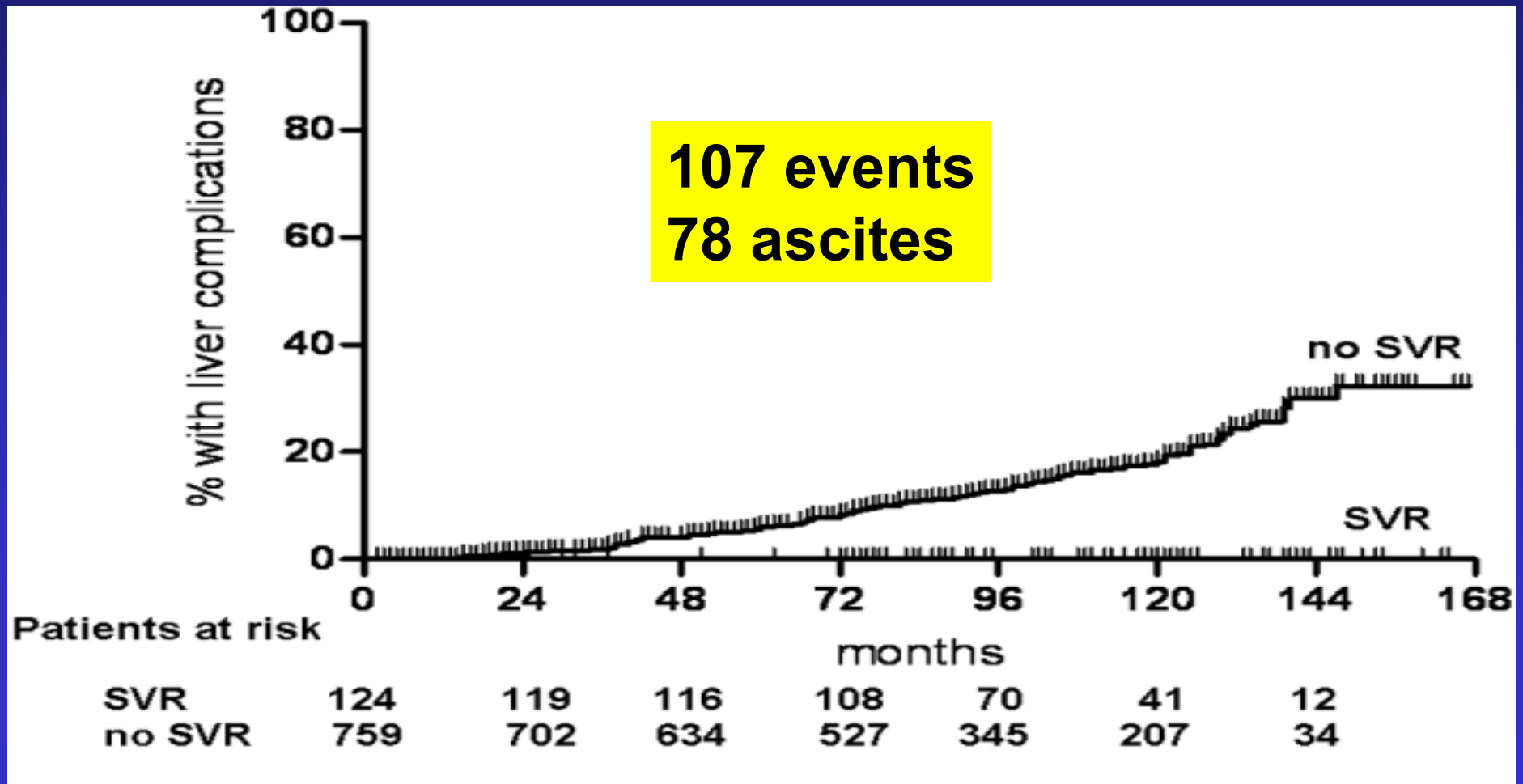
Inhibition of VEGF Receptor-2 and Porto-Systemic Shunts in Rats

	<u>Vehicle</u>	<u>SU5416</u>
Portal pressure (mm Hg)	14 ± 1	15 ± 1
Formation of shunts (%)	61 ± 6	29 ± 6*
Portal-collateral resistance (U)	4 ± 1	26 ± 5**

*P=0.003, **P=0.01.

Fernandez et al. J Hepatol 2005;43:98-103.

Sustained Virological Response (SVR) to Interferon- α Is Associated With Improved Outcome in Patients With Compensated HCV-Related Cirrhosis



Prevention of the Development of Large Varices Conclusions

β -blockers cannot be recommended.

Further studies in selected patients are needed.

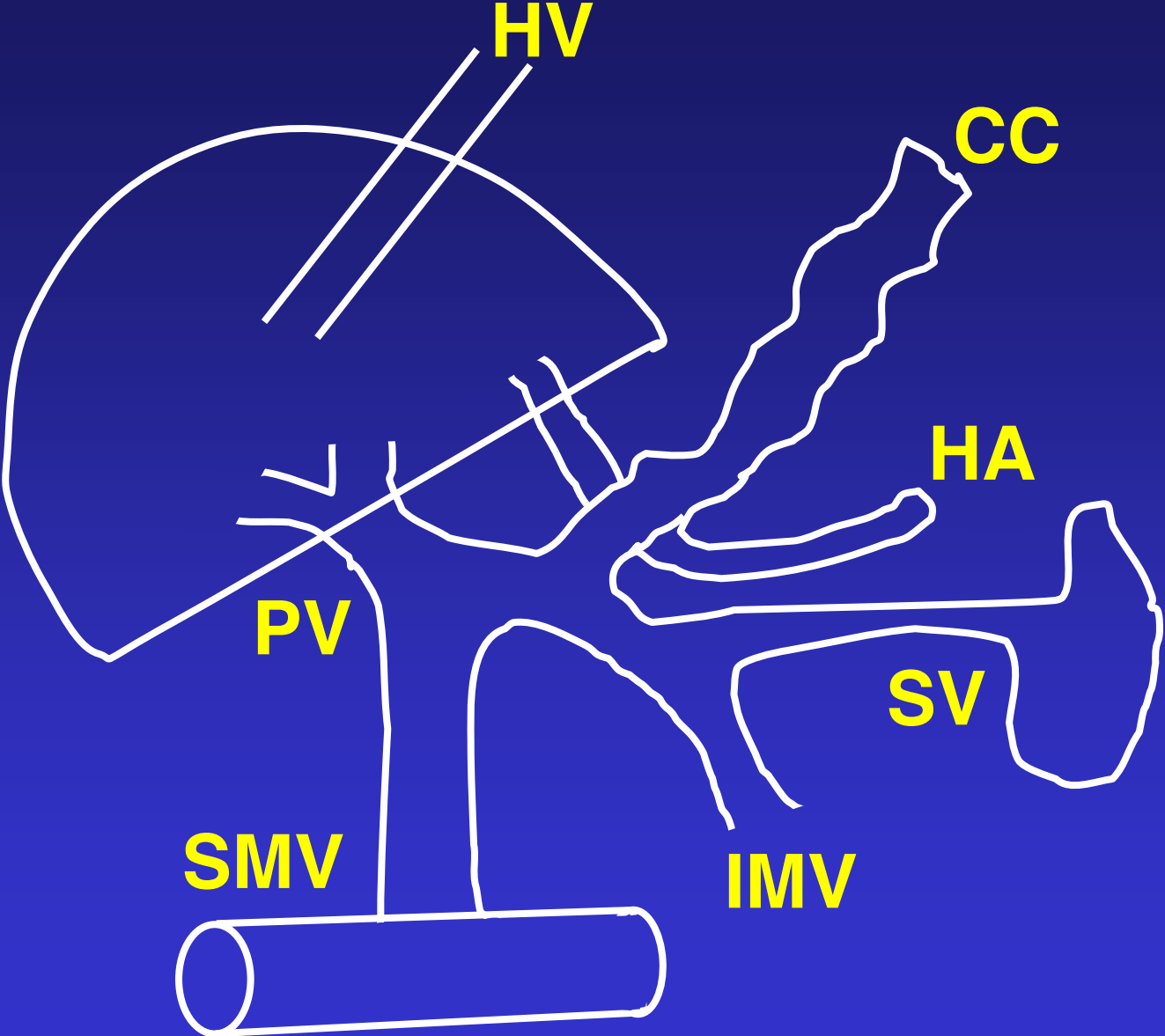
Modulation of angiogenesis may be a potential target in the prevention of porto-systemic shunts and varices.

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-

Drugs That Decrease Portal Hypertension

Angiotensin	Tertatolol	Molsidomine	Mersalyl
Octapressin	Timolol	Nitroglycerin	Spironolactone
Terlipressin	Atenolol	Iso-5-Mononitrate	Ketanserin
Vasopressin	Bexatolol	Iso-dinitrate	Ritanserin
Endothelin 1	Levomoprolol	Phenoxybenzamine	Lantreotide
Methoxamine	Metoprolol	Prazosin	Modustatin
Synephrine	ICI 118 551	Enapril	Octreotide
Clonidine	Glibenclamide	Anti-glucagon	Somatostatin
Reserpine	Bay K 8644	Tetandrine	Vapreotide
LA propranolol	Naftazone	<i>Fructus aurantii</i>	Parathyroid hormone
Mepindolol	L-NAME	Pentifylline	BN 52021
Nadolol	Terbutaline	Pentoxifylline	Losartan
Penbutolol	Bosentan	Canrenoate potassium	Irbesartan
Propranolol	Tezosentan	Chlorothiazide	Candesartan
Sotalol	Linsidomine	Furosemide	Sildenafil



Drugs that Decrease Portal Blood flow

Agonists of AT_1 , V_{1a} and ET receptors

α_1 -adrenoceptor agonists

α_2 -adrenoceptor agonists

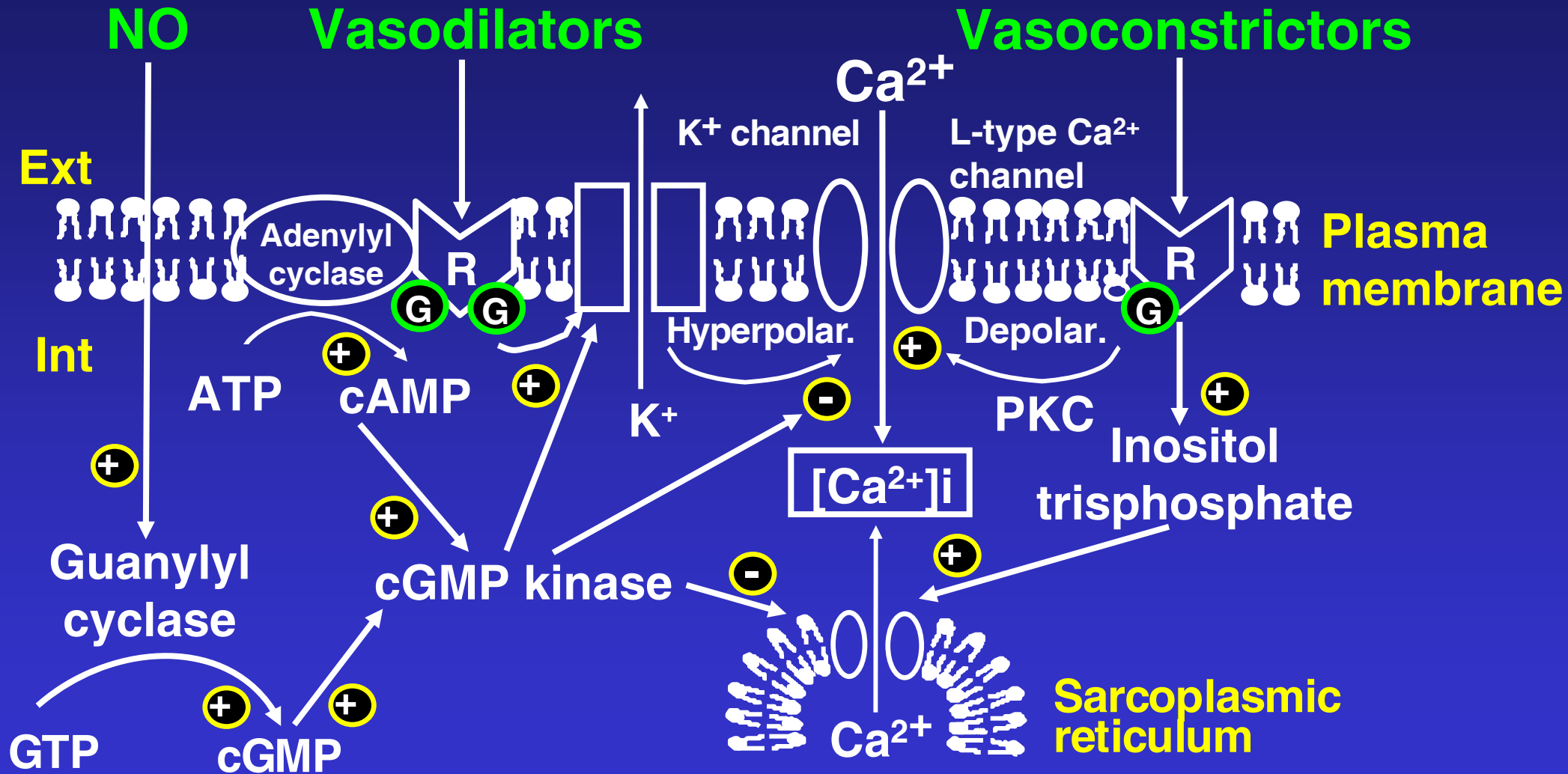
β -adrenoceptor antagonists

Blockers of ATP sensitive K^+ channels

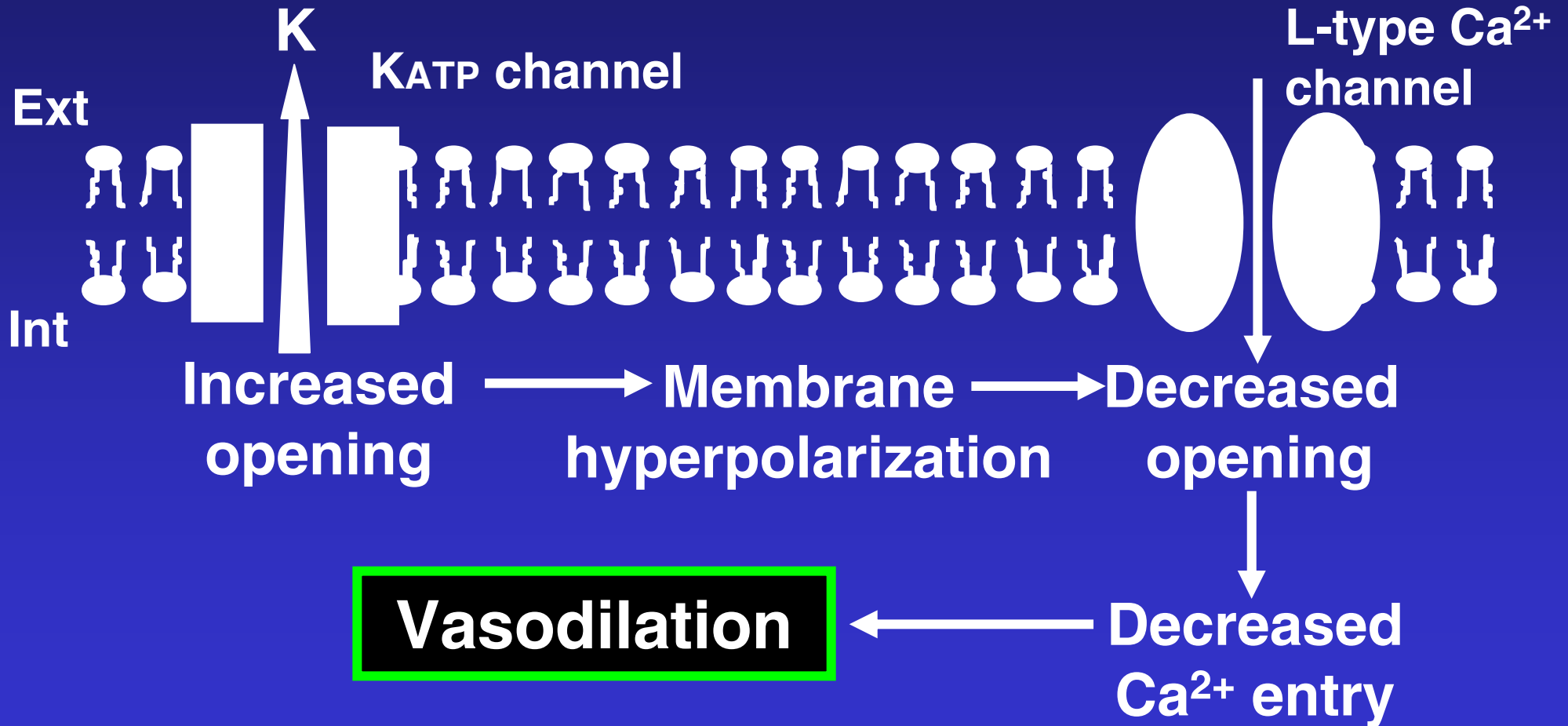
Calcium channel activator

Inhibitors of NO synthase

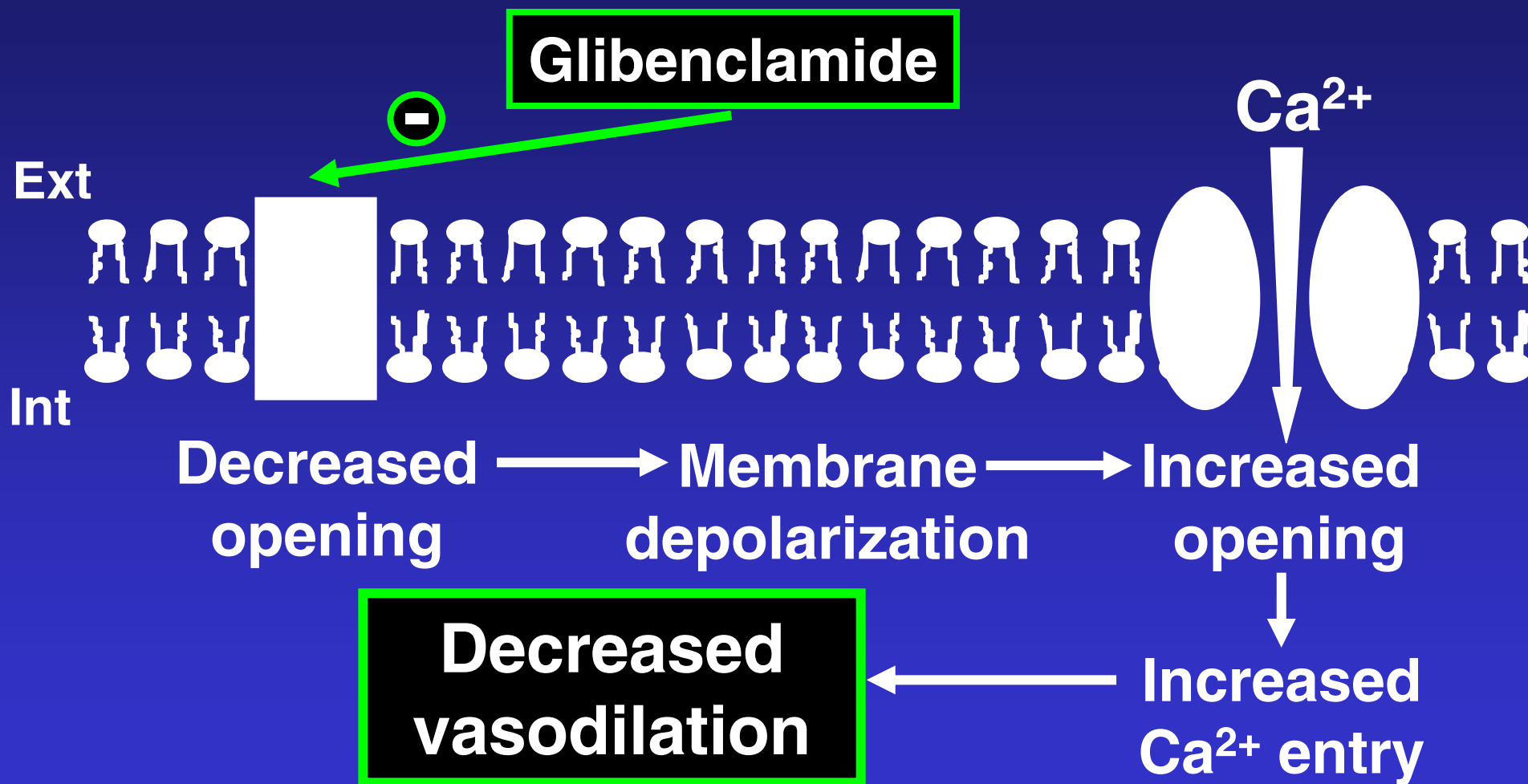
Vasoactive Signal Transduction



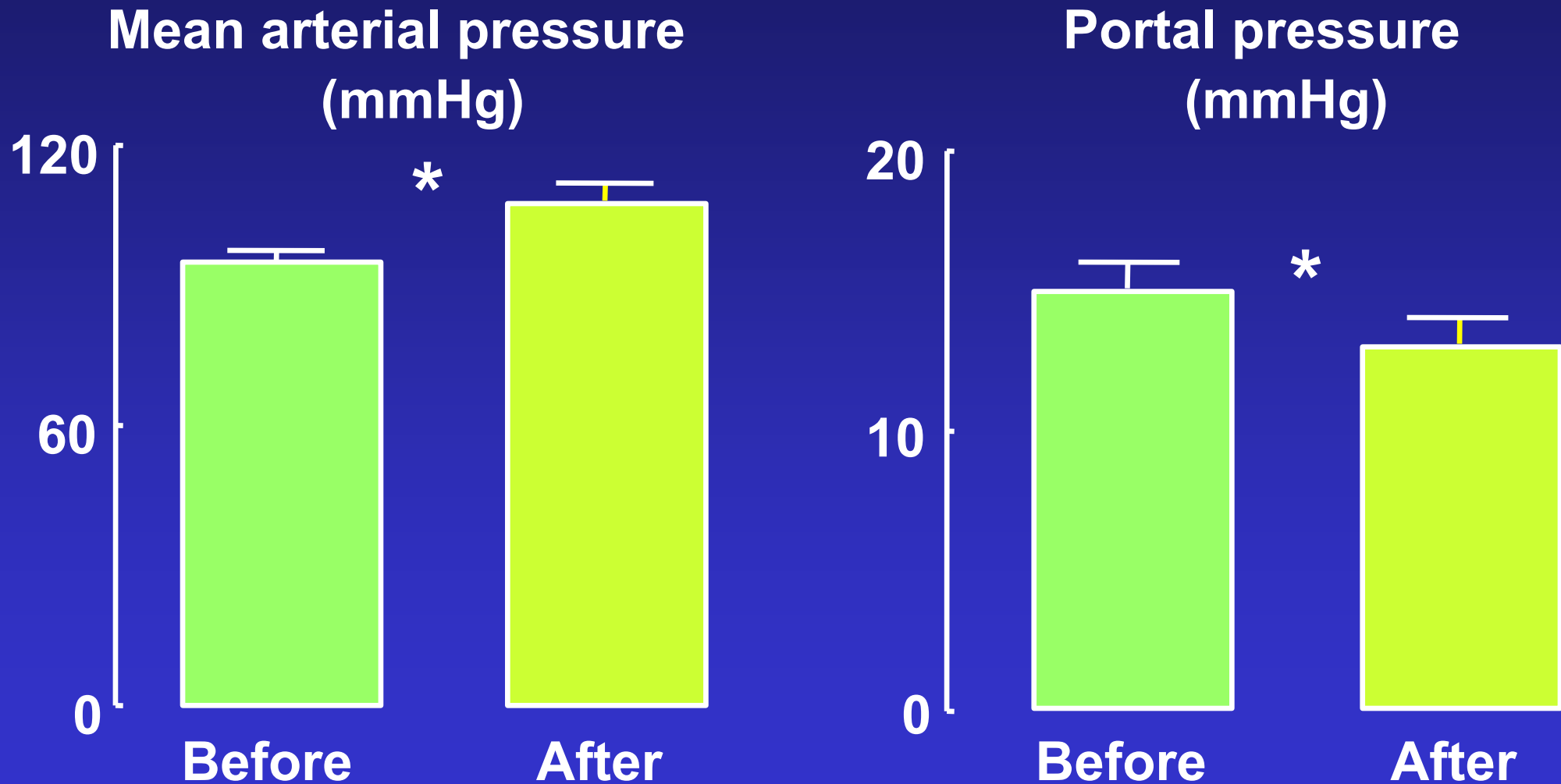
Vascular Tone in Cirrhosis

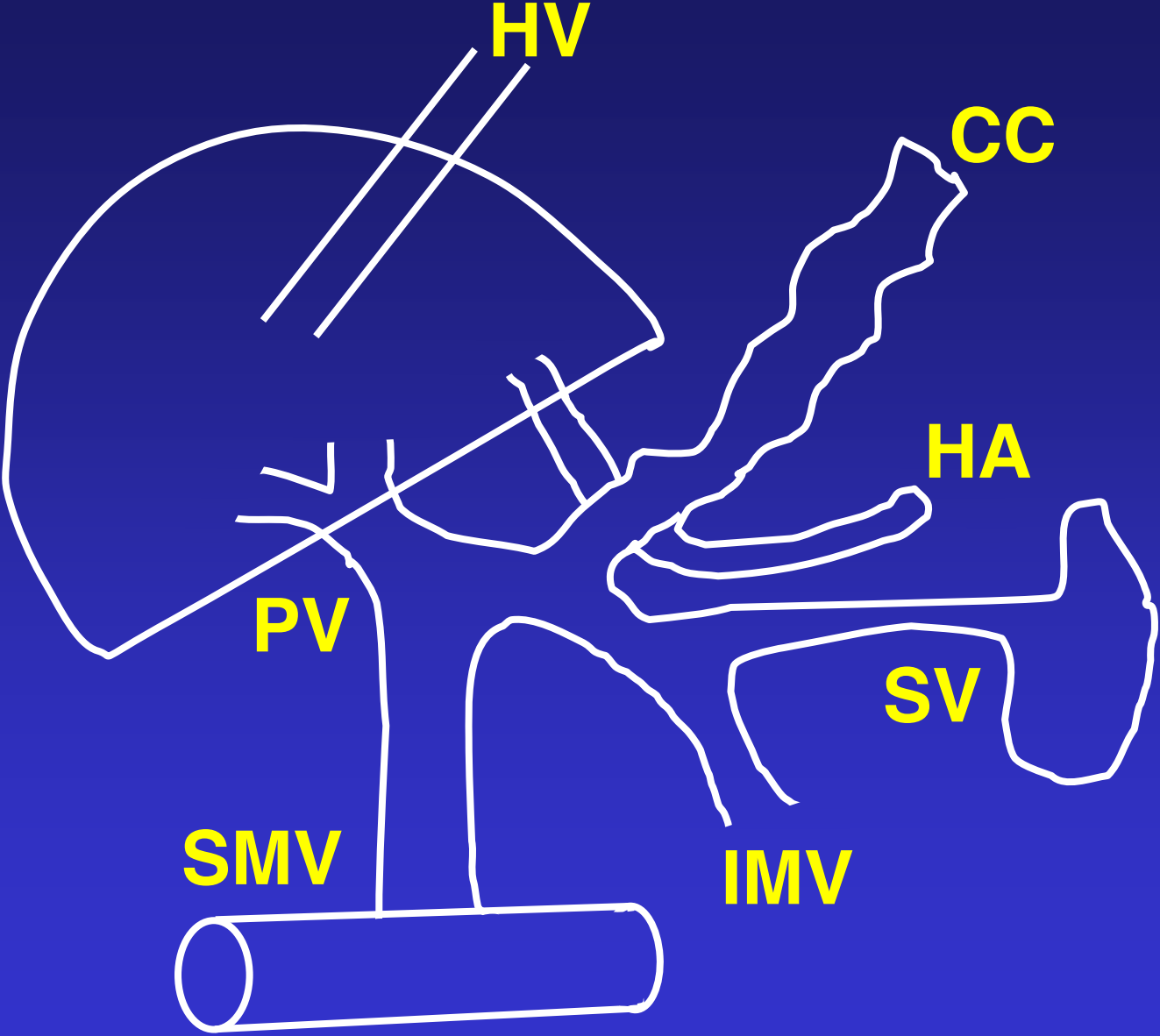


Effect of Glibenclamide on Vascular Tone in Cirrhosis

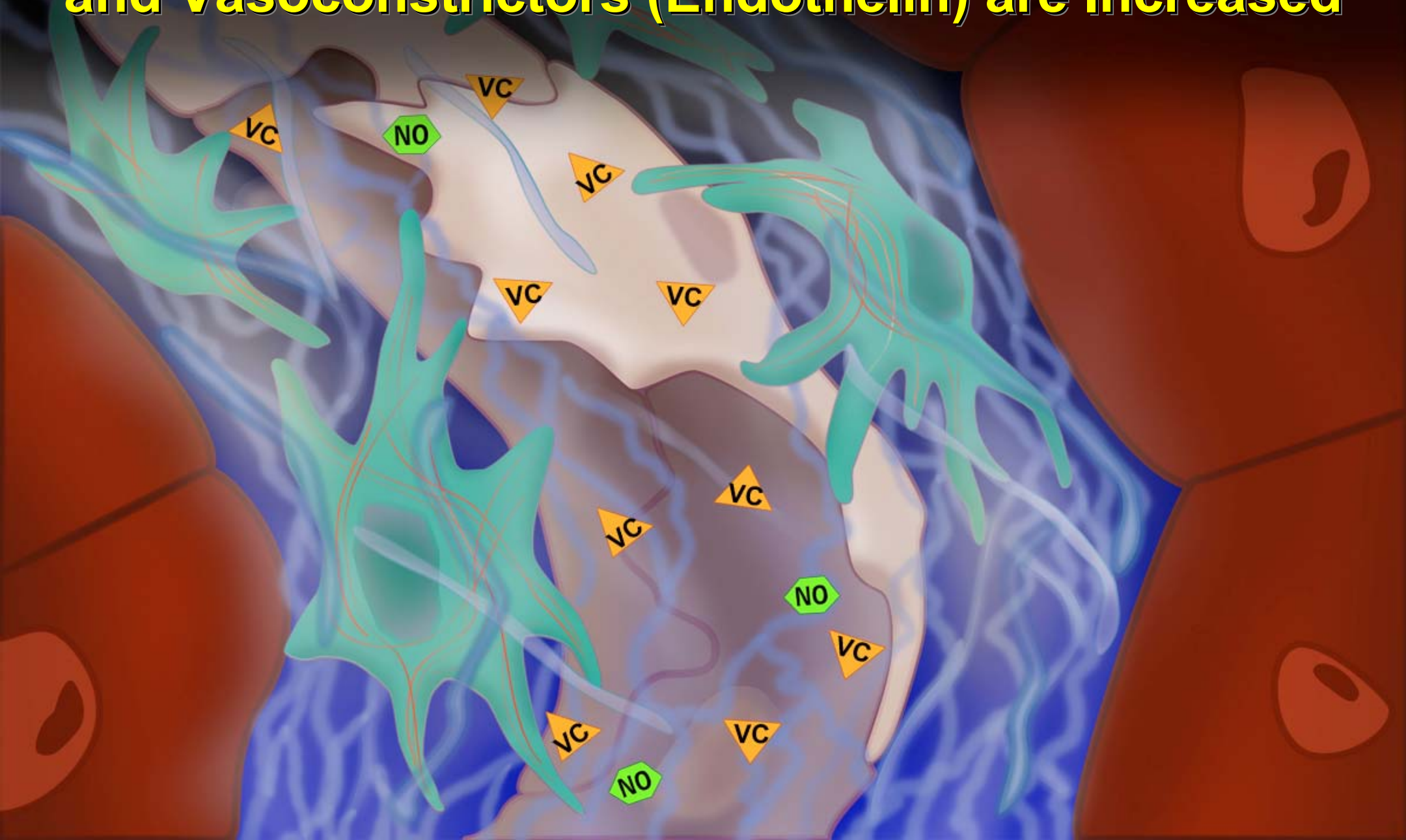


Effects of Glibenclamide in Rats with Cirrhosis





In Cirrhosis, Nitric Oxide (NO) Activity is Reduced and Vasoconstrictors (Endothelin) are Increased



Drugs that Decrease Hepatic Vascular Resistance

β_2 -adrenoceptor agonists

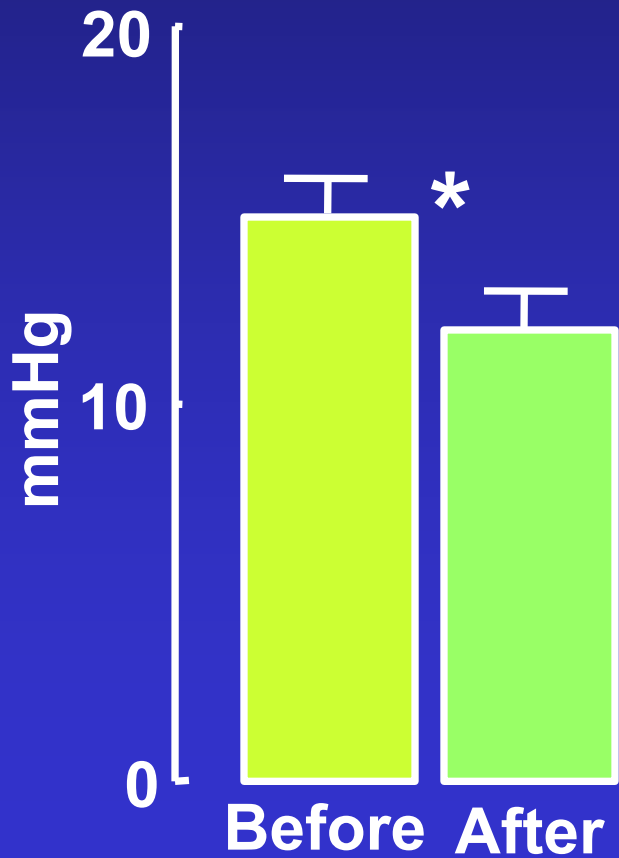
Dual ET_A - ET_B receptor
antagonists

ET_A -receptor antagonist

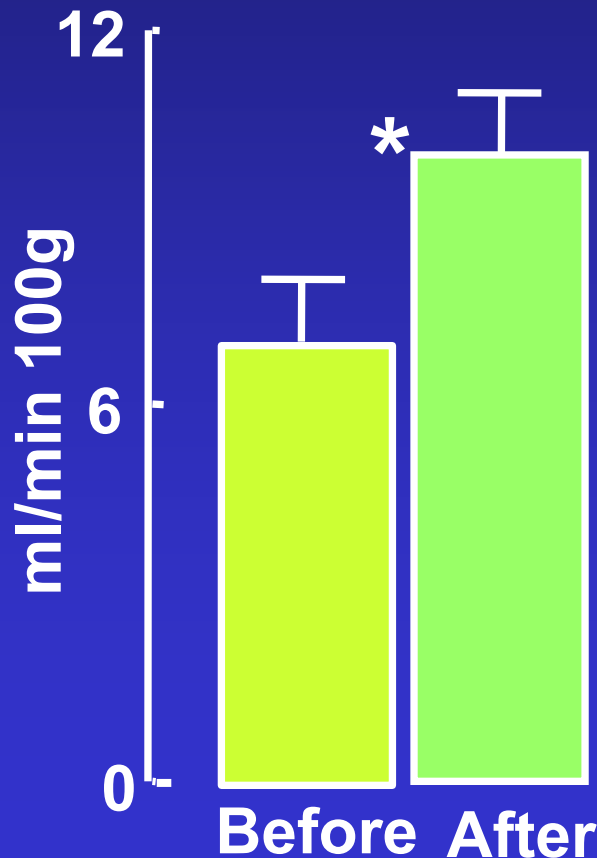
Nitrovasodilators

Effects of Bosentan in Rats With Cirrhosis

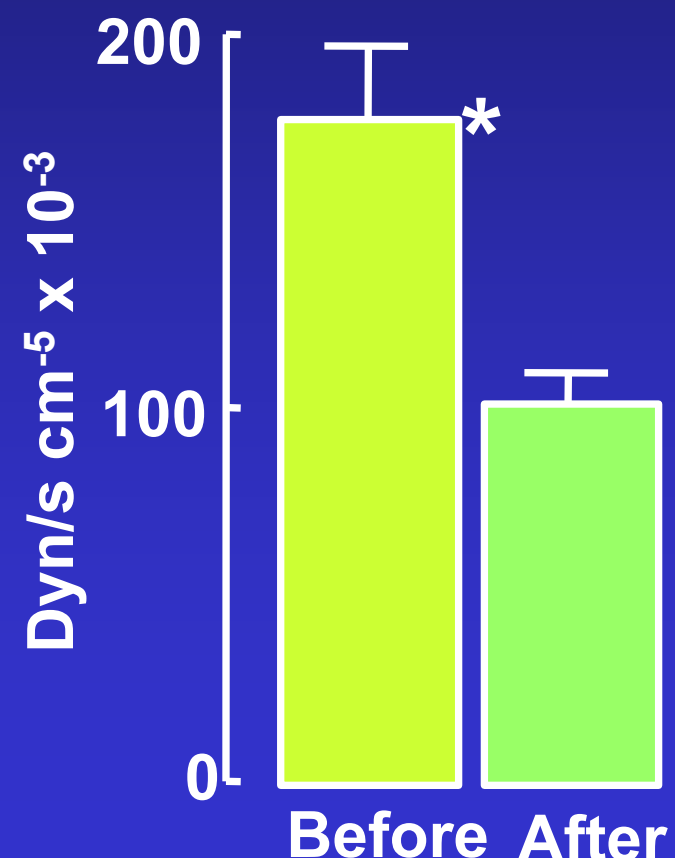
Portal pressure



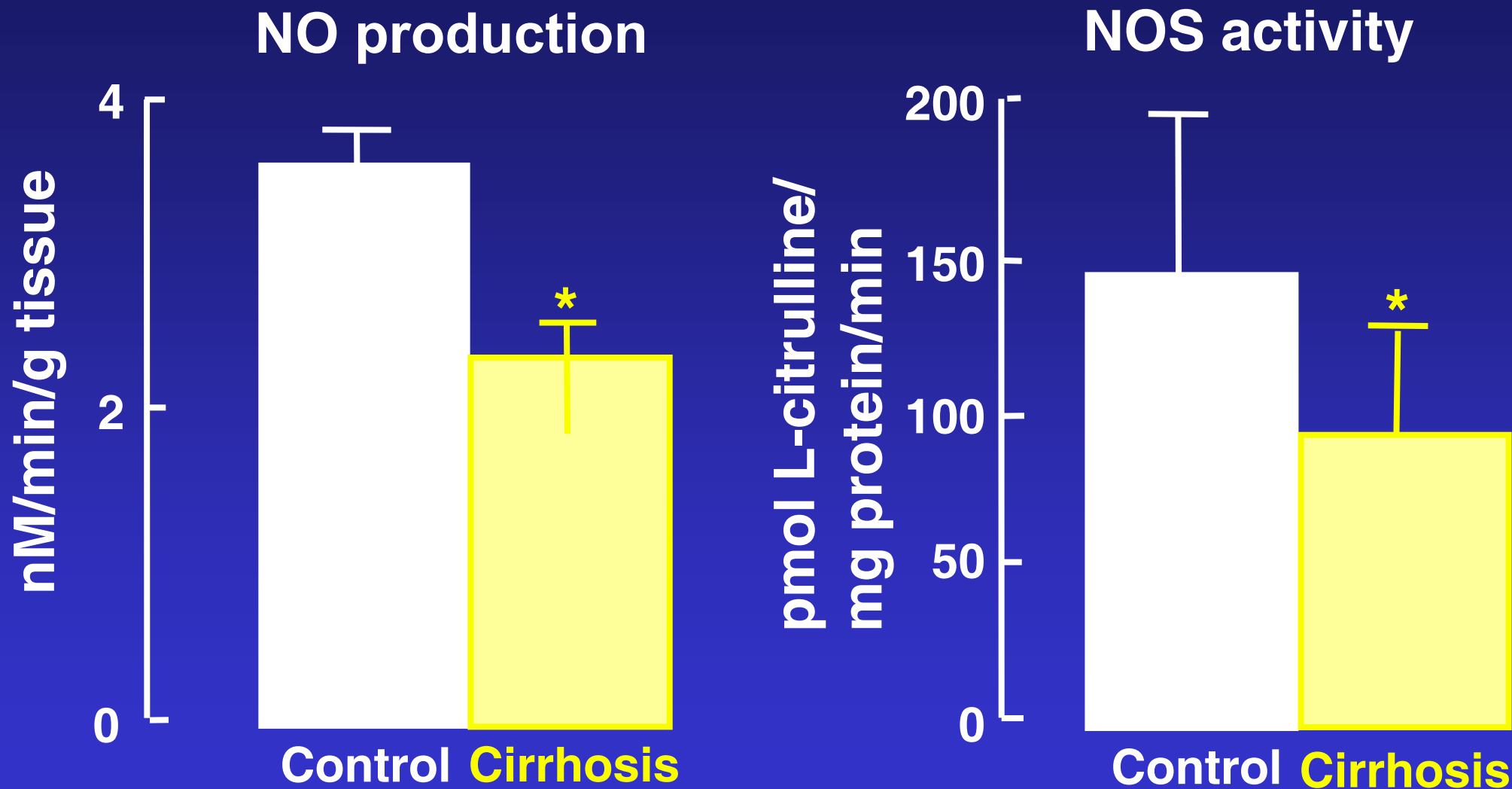
Portal tributary blood flow



Intrahepatic and collateral vascular resistance



Intrahepatic NO in Cirrhosis



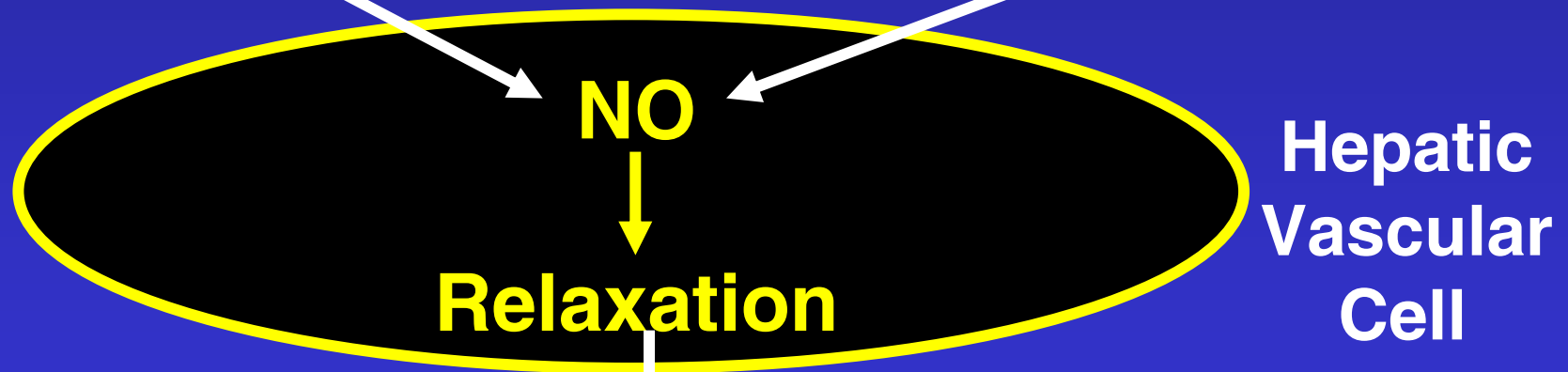
NO Administration in the Cirrhotic Liver

Pharmacological Vectors

Viral Vectors

NO Release

NOS Release



Decreased Portal Pressure

Pharmacological NO Delivery in the Cirrhotic Liver

First author

Substances

Moal*

V-PYRRO/NO

Fiorucci**

NCX-1000

*World J Gastroenterol 2006;12:6639-45.

**Proc Natl Acad Sci USA 2001;98:8897-902.

Human eNOS Gene Transfer in Cirrhotic Rats

	Cirrhosis	
	<u>Control</u>	<u>Transfected</u>
Portal pressure (mmHg)	11.4±5.1	7.7±3.4*
Arterial pressure (mmHg)	102±3.8	101±17

Van de Casteele et al. Gut 2002;51:440-5.

Effects of Intra-Portal Administration of Linsidomine in Patients with Cirrhosis

	Before	After
Portal pressure (mm Hg)	32.3± 6.4	28.6±6.5*
HVPG (mm Hg)	19.9±5.1	15.9±4.8**

P<0.05, **p<0.01. Baudi et al. EASL Paris 2005.

Drugs With Unclear Mechanism of Action

α -adrenoceptor antagonists

Angiotensin converting enzyme inhibitors

Anti-glucagon

Calcium channels antagonists

Chinese medicine

Dimethylxanthine

Diuretics

5-hydroxytryptamine receptor antagonists

Growth hormone inhibiting factors

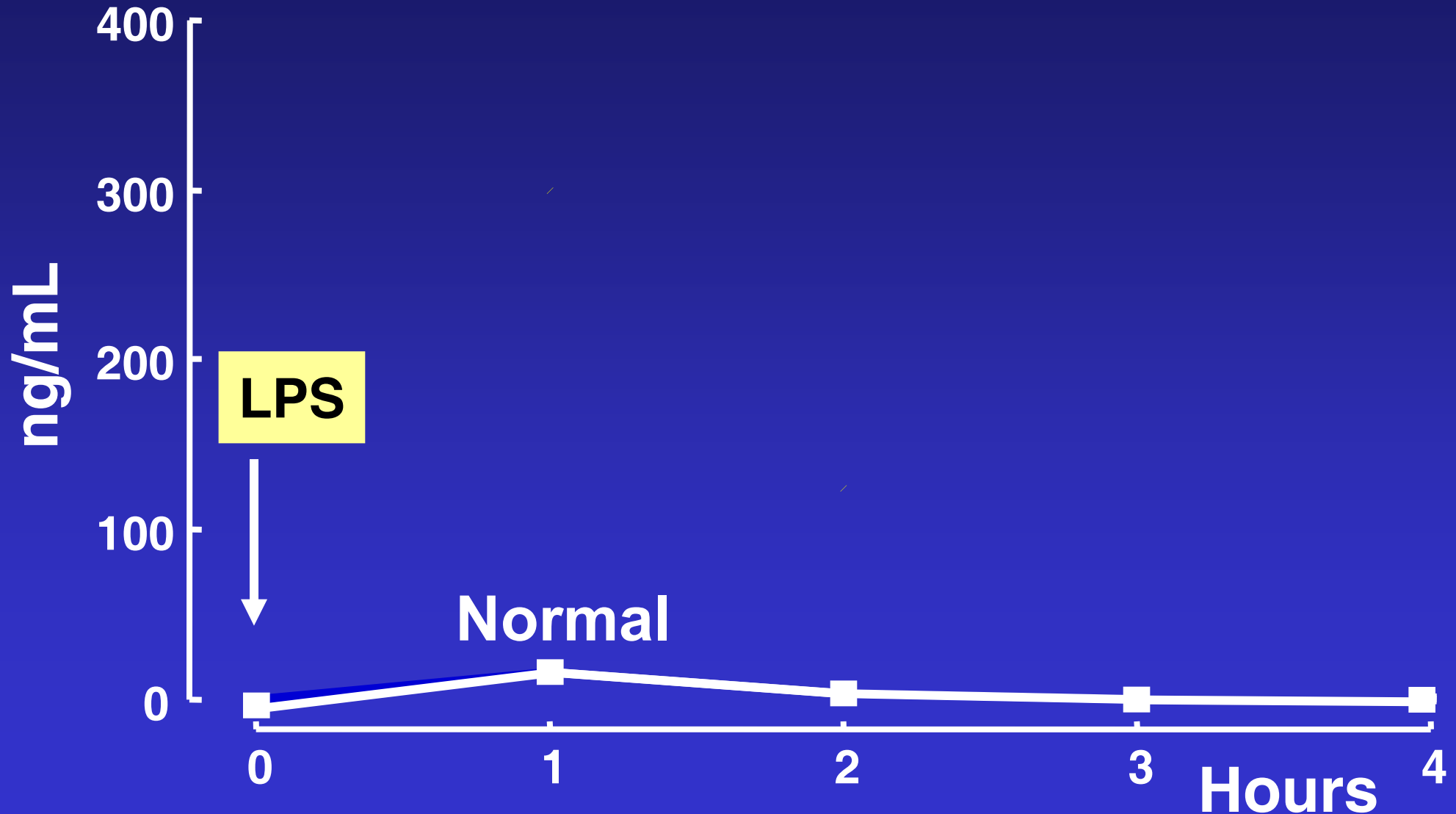
Parathyroid hormone

Platelet-activating factor

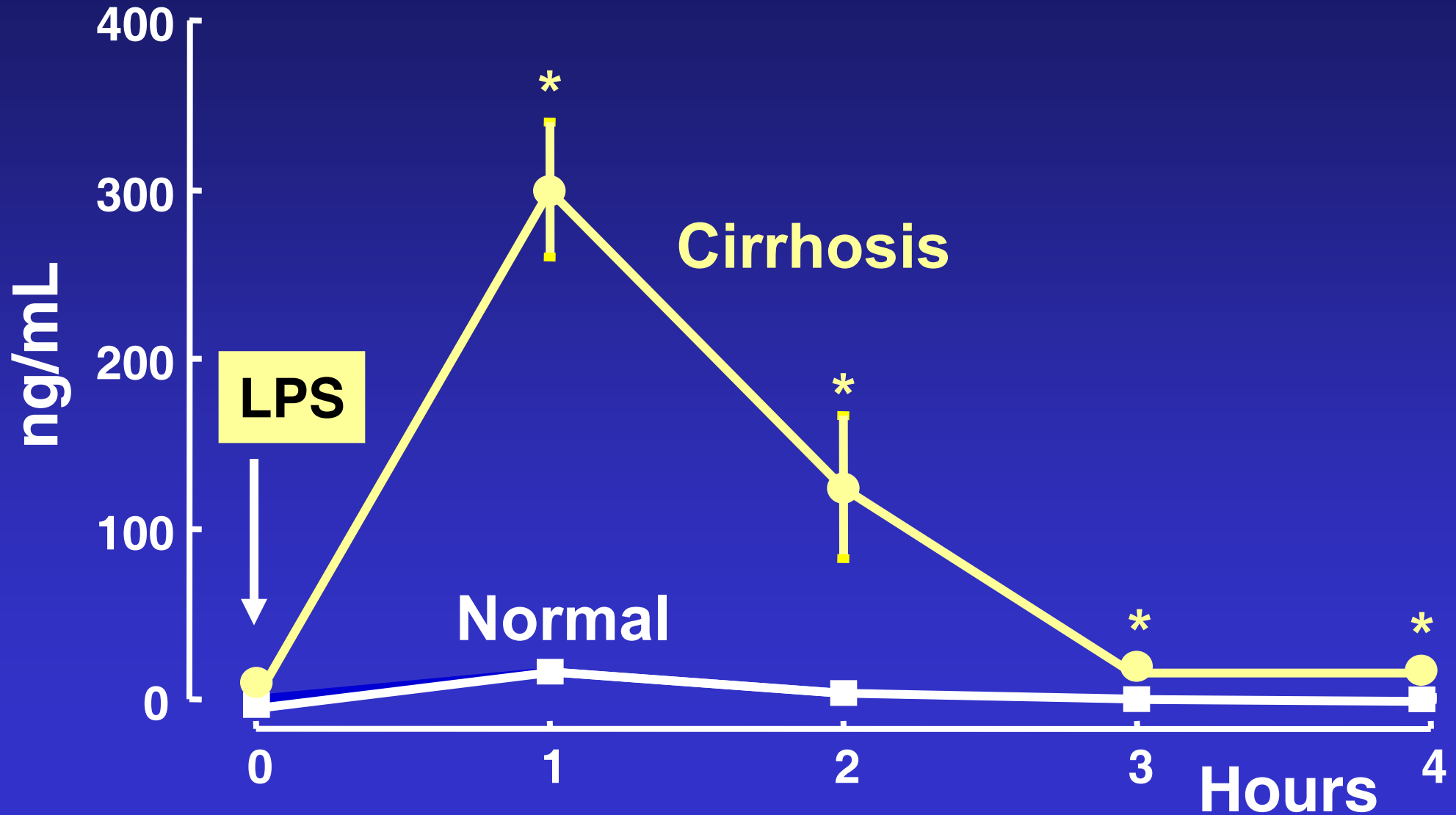
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LPS Induces Marked Increases in Plasma TNF- α Concentrations in Normal Rats



LPS Induces Marked Increases in Plasma TNF- α Concentrations in Cirrhotic Rats



Liver failure

Portal hypertension

Bacterial translocation

LPS

?

TNF α

Aortic eNOS

Aortic iNOS

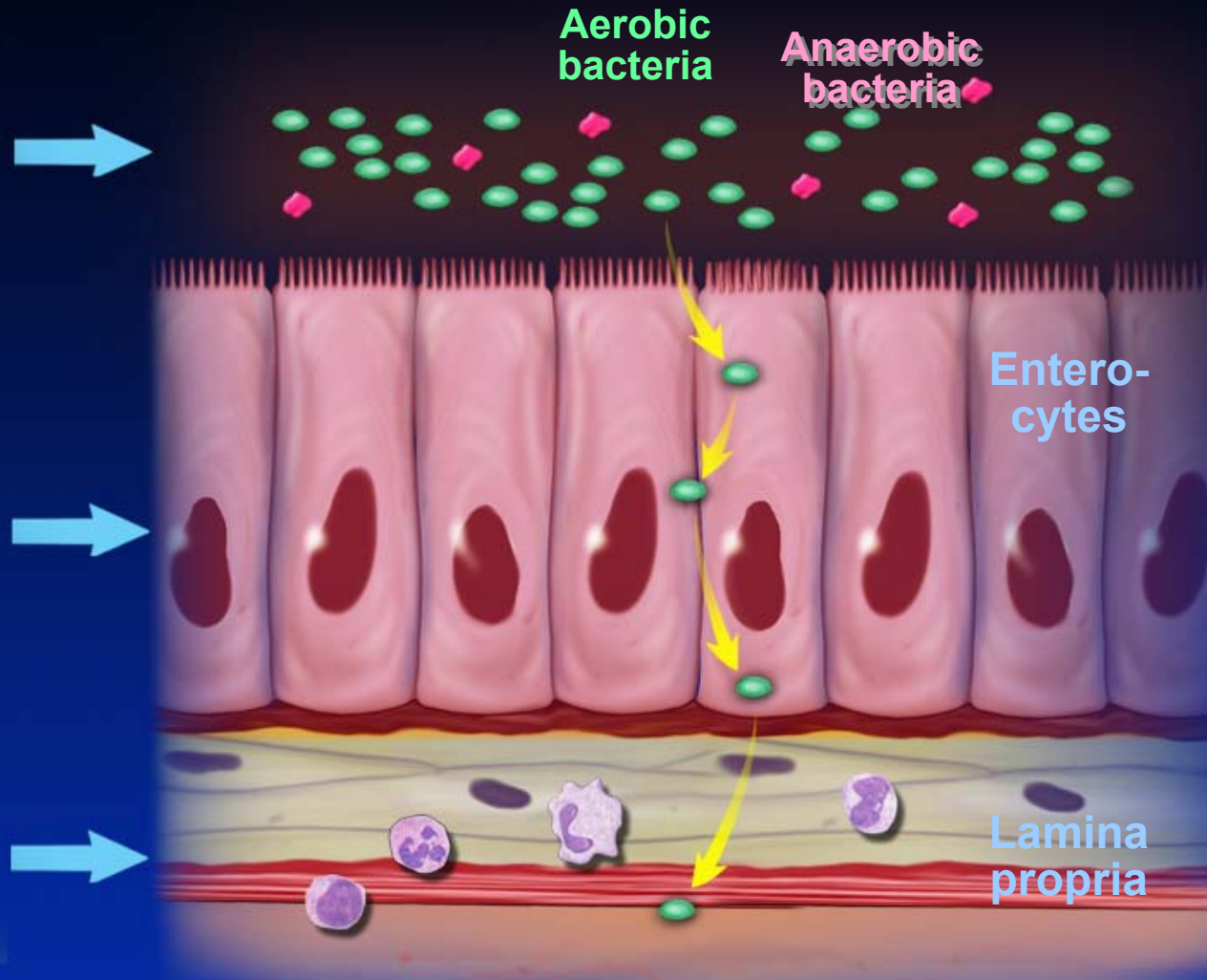
Hepatic necrosis

Mechanisms of Bacterial Translocation

Intestinal Bacterial Overgrowth
Dysmotility Delayed transit time
Nutrition?

Intestinal Permeability
Mucosal Hypoxia, Acidosis
ATP depletion, NO, LPS, TNF

Impaired Immunity
Impaired chemotaxis,
migration, phagocytic
function, complement
deficiency



Terlipressin

Propranolol

Norfloxacin

↓ Bacterial translocation

LPS

↓ TNF α

Aortic iNOS

No hepatic necrosis

?

?

Tezosentan

Effects of Propranolol on SBP in Patients with Cirrhosis

	<u>SBP</u>	<u>Number of Patients</u>	<u>%</u>
Propranolol +	6	33	18
Propranolol -	33	101	33

2 years

Cholongitas et al. J Gastroenterol Hepatol 2006;21:581-7.

Terlipressin

Propranolol

Norfloxacin

?

↓ Bacterial translocation

LPS

↓ TNF α

Aortic iNOS

No hepatic necrosis

Tezosentan

?

Effects of Norfloxacin on Rat Plasma and Aortic Cytokine Levels

	Cirrhosis		
	<u>Control</u>	<u>Untreated</u>	<u>Treated</u>
Plasma			
TNF- α (pg/ml)	3.3 \pm 0.6	48.2 \pm 14.1 [*]	11.6 \pm 1.7
Aortic (densitometry)			
TNF- α	100%	220 \pm 20 [*]	112 \pm 10
IL-6	100%	190 \pm 20 [*]	110 \pm 08
IFN- γ	100%	180 \pm 15 [*]	115 \pm 10

*P<0.01 (control vs cirrhosis) **P<0.01 (untreated vs treated)

Terlipressin

Propranolol

Norfloxacin

↓ Bacterial translocation

LPS

↓ TNF α

Aortic iNOS

No hepatic necrosis

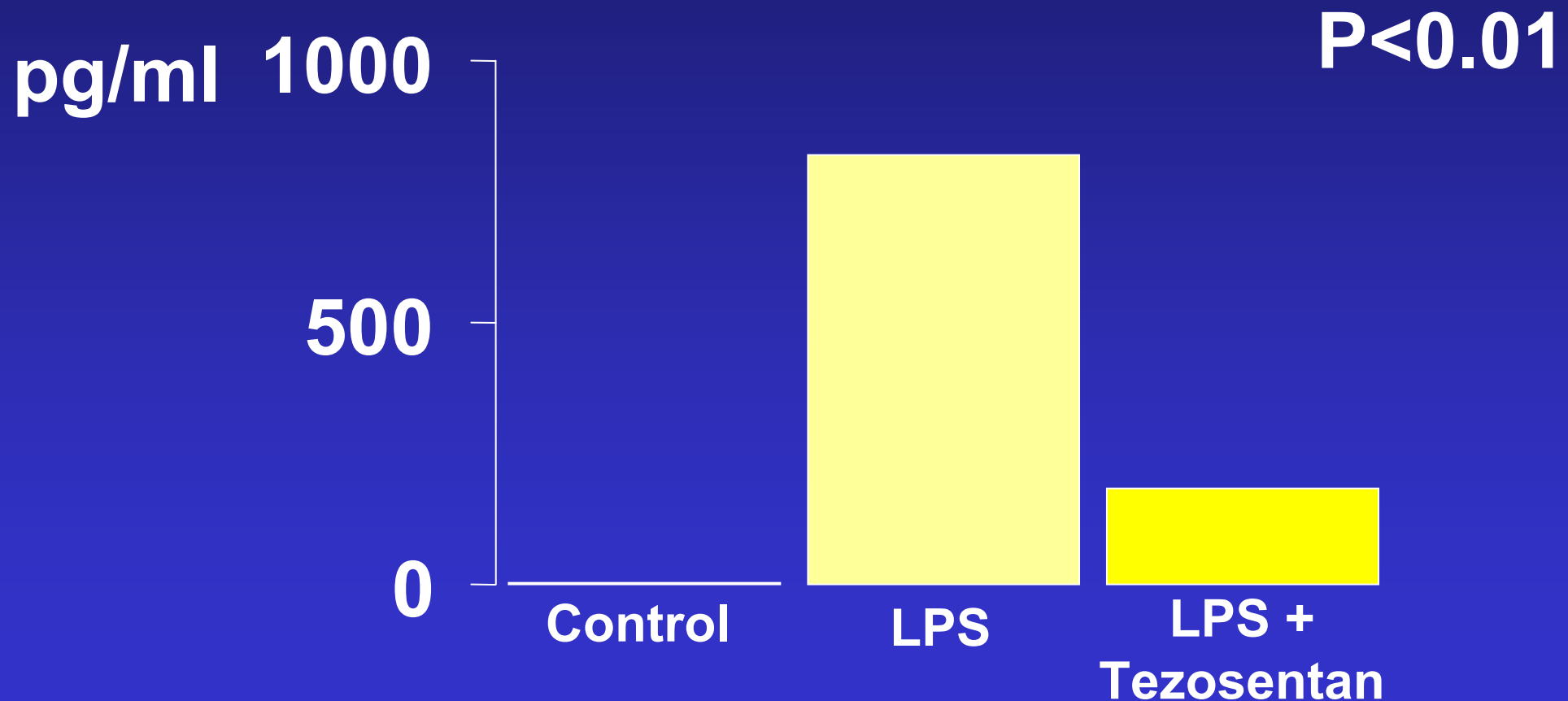
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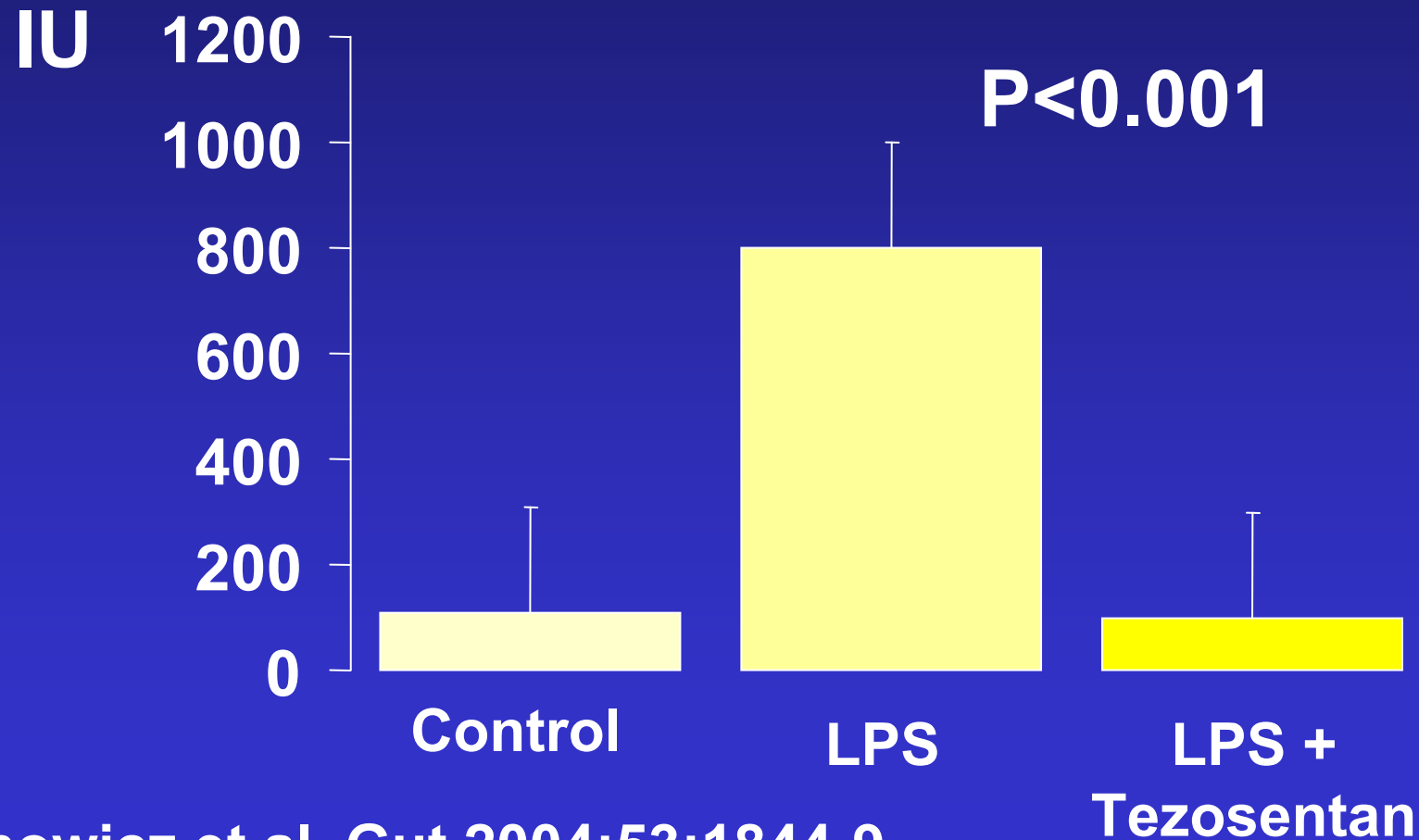
Tezosentan

Effect of Tezosentan on Plasma TNFalpha in Endotoxin Challenged Cirrhotic Rats



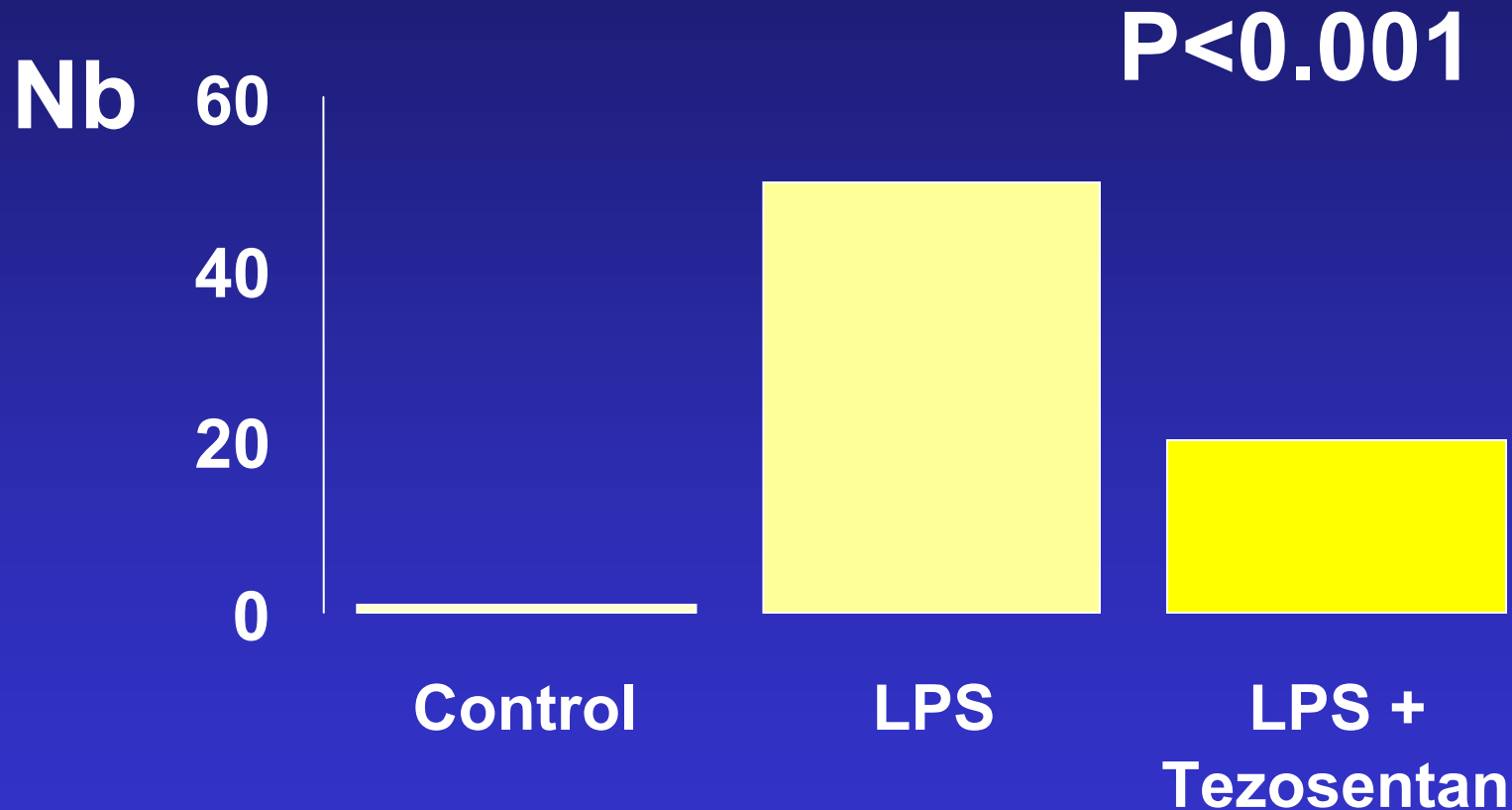
Urbanowicz et al. Gut 2004;53:1844-9.

Effects of Tezosentan on ALAT in Endotoxin Challenged Cirrhotic Rats



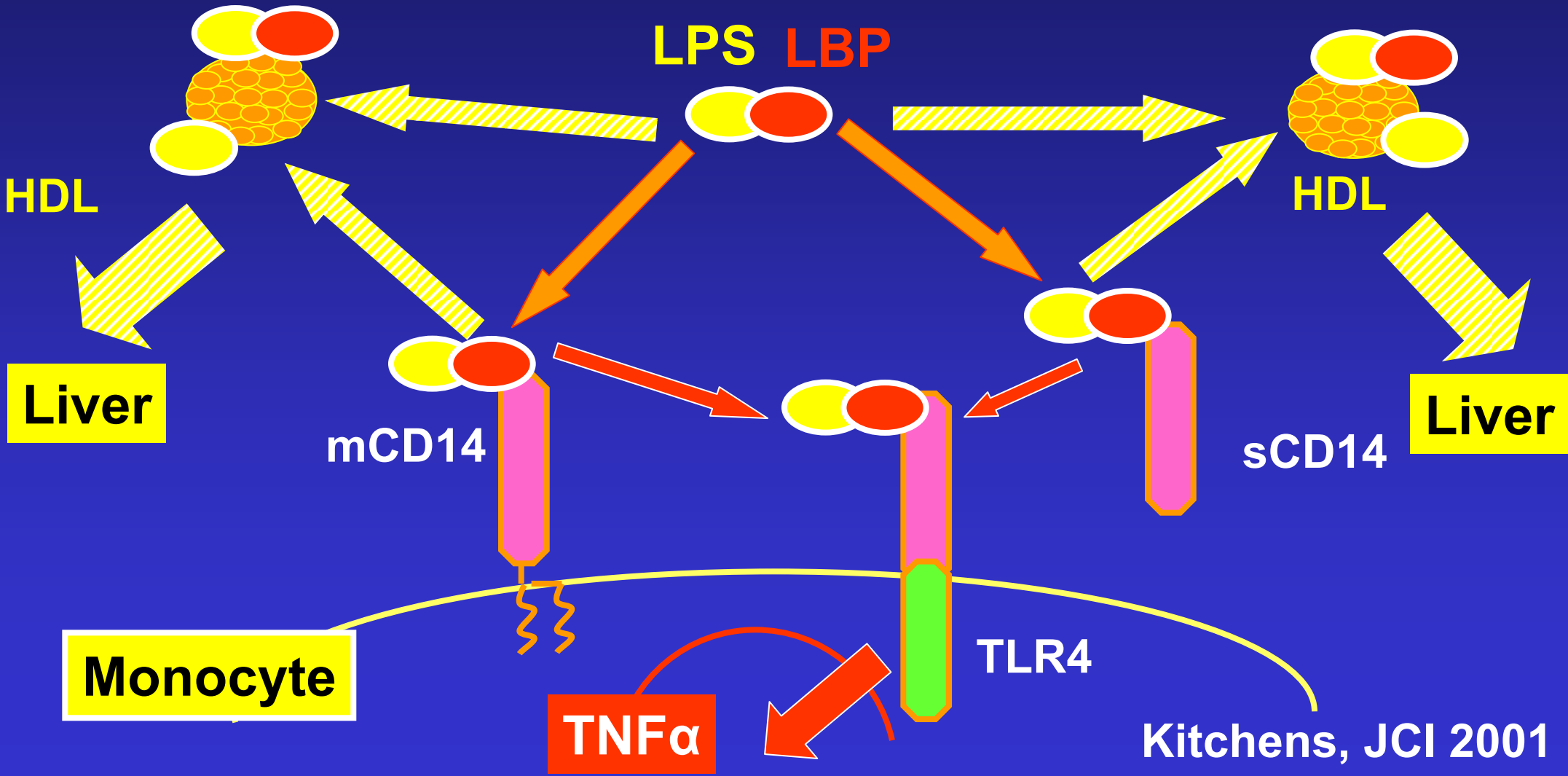
Urbanowicz et al. Gut 2004;53:1844-9.

Effects of Tezosentan on 4 h- Mortality in Endotoxin Challenged Cirrhotic Rats

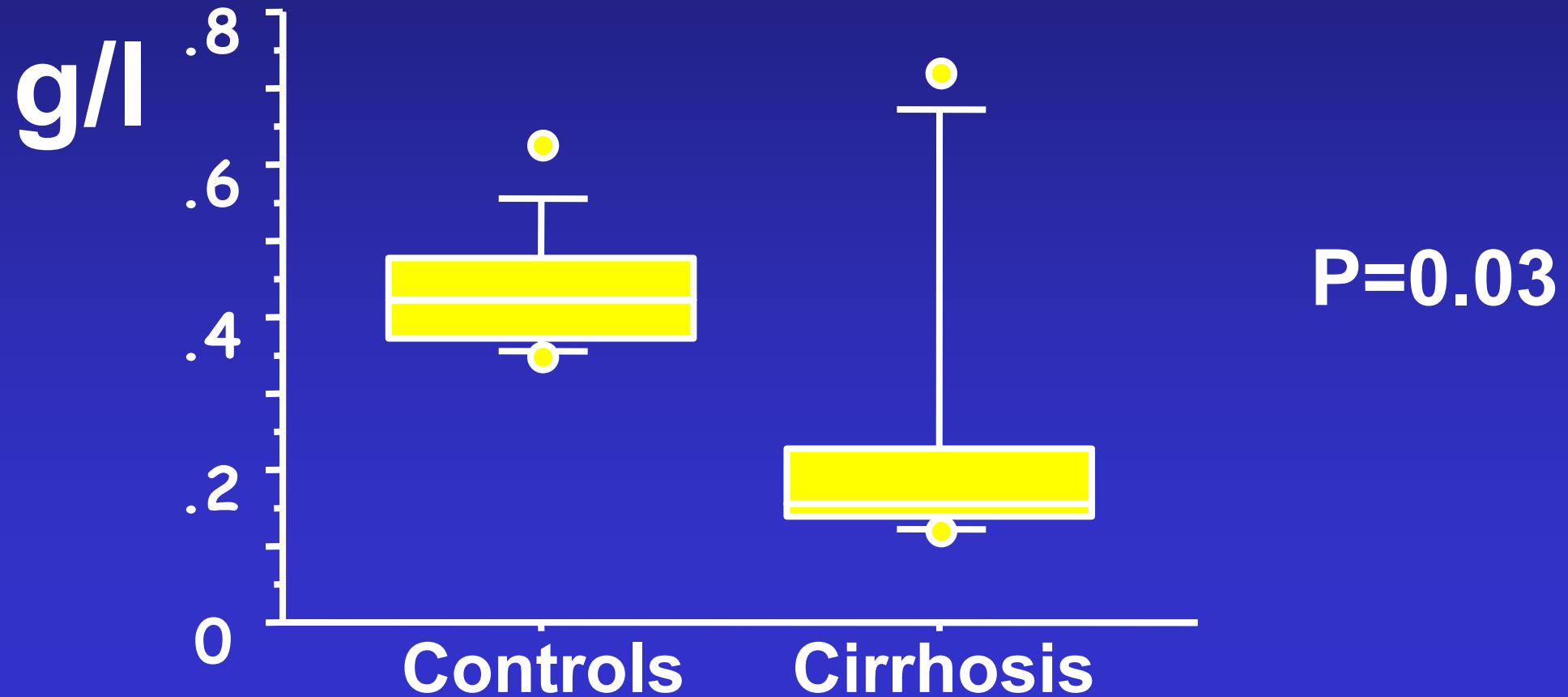


Urbanowicz et al, Gut 2004;53:1844-9.

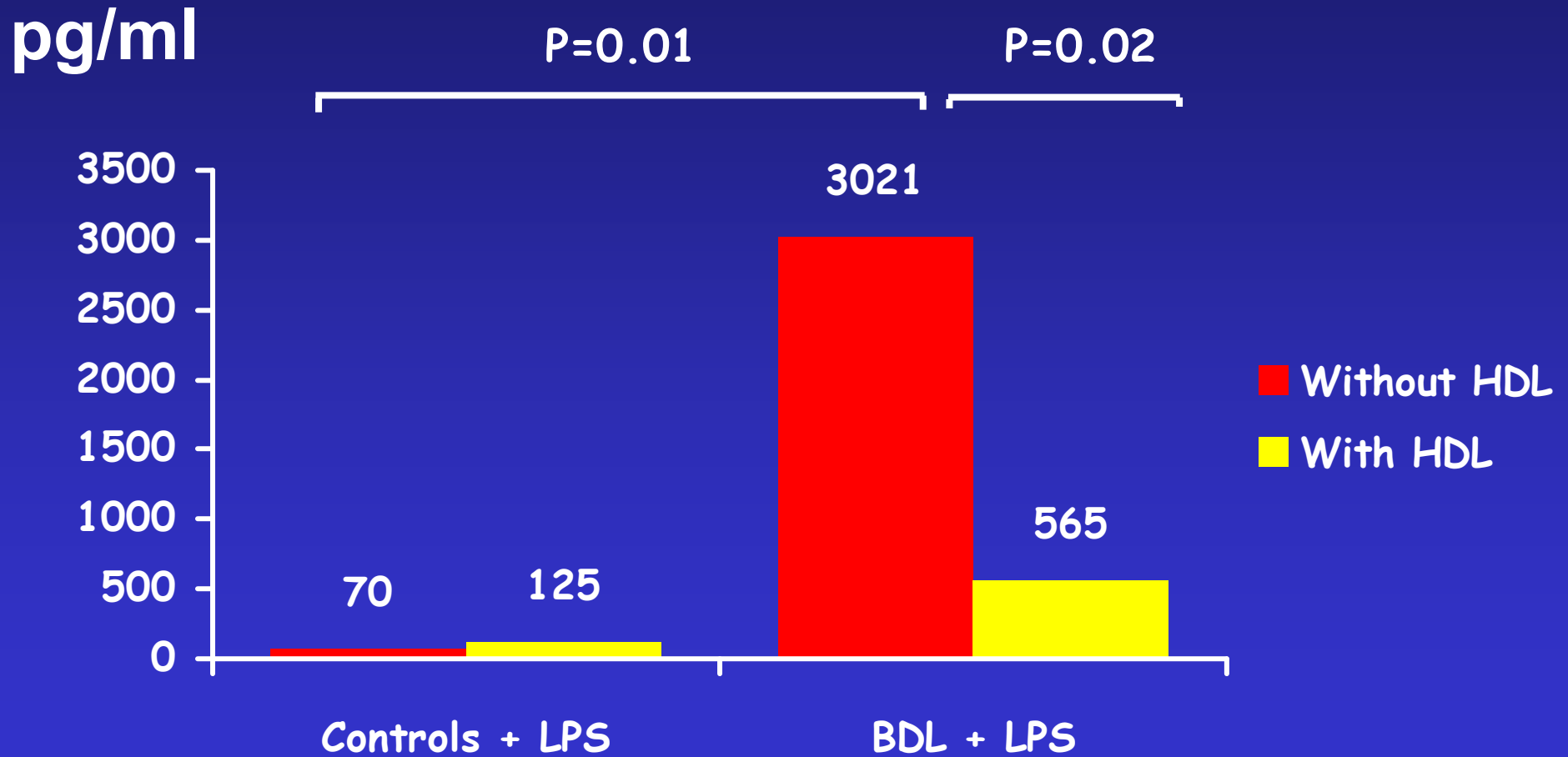
Anti-inflammatory Effect of rHDL by LPS Neutralization



Plasma HDL Levels



Plasma TNF α Levels



Conclusions

New ideas, hypotheses, and approaches are needed to further our understanding of the mechanisms of portal hypertension and its complications.
