Was ist Immunonutrition?

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Ernährung - Immunkompetenz

Ernährungsstatus

- **Mangelernährung (Eiweißkatabolismus)**
- **Überernährung (Adipositas)**

Makro-Mikronährstoffe

Zufuhrweg

1. Warum Immunonutrition

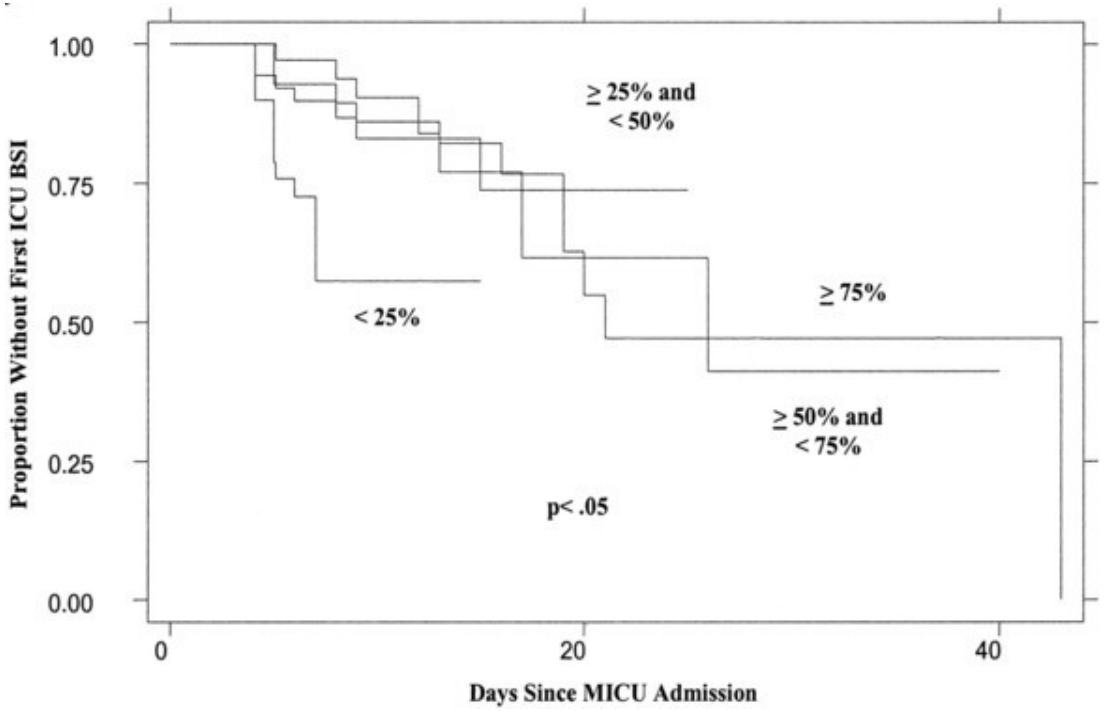
The Delayed Hypersensitivity Response and Host Resistance in Surgical Patients. 20 years later

- **4292 patients**
- **mortality of DTH reactive patients: 2.9 %**
- **Anergic patients: 20.9 % ($p<0.0000001$)**
- **Lack of T cells**
- **Only a mild malnutrition in anergic patients**
- **PN failed to correct the DTH response**

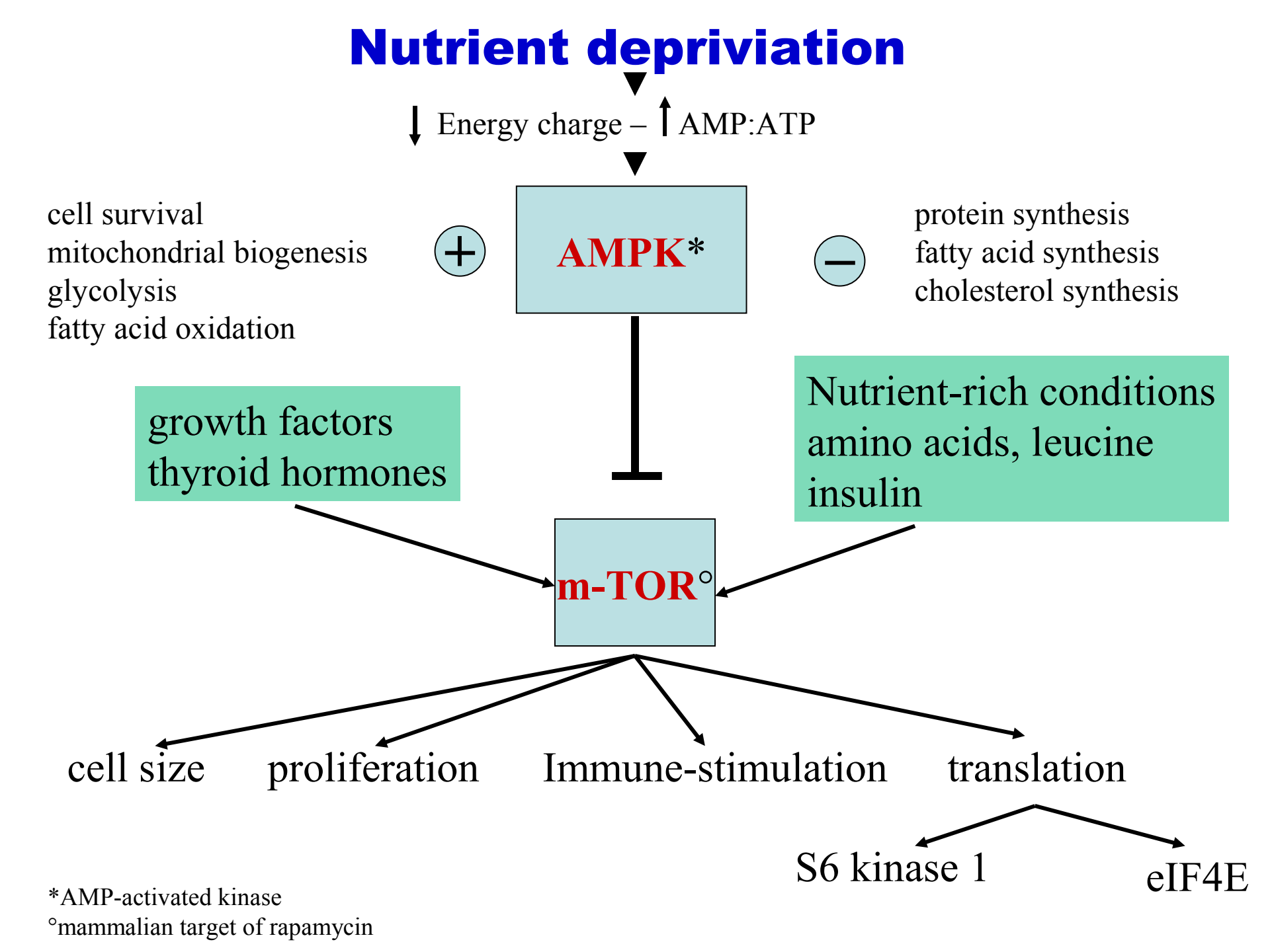
N.V. Christou et al, *Ann Surg* 1995: 222; 534

Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit

- 138 adult patients not taking food by mouth for more than 96 h after medical ICU admission

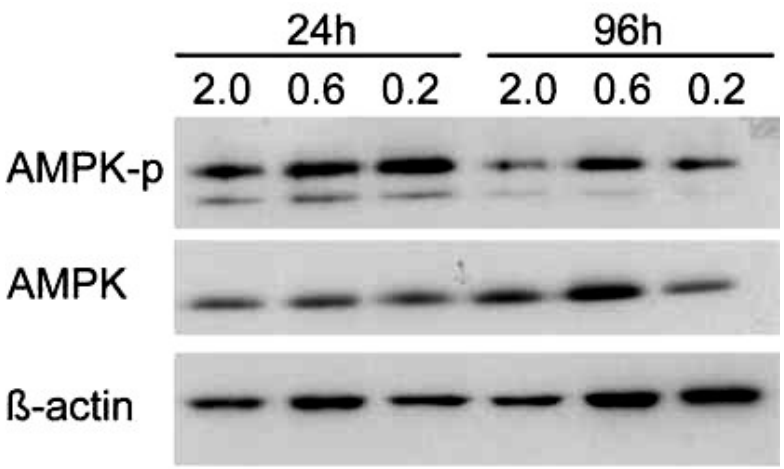


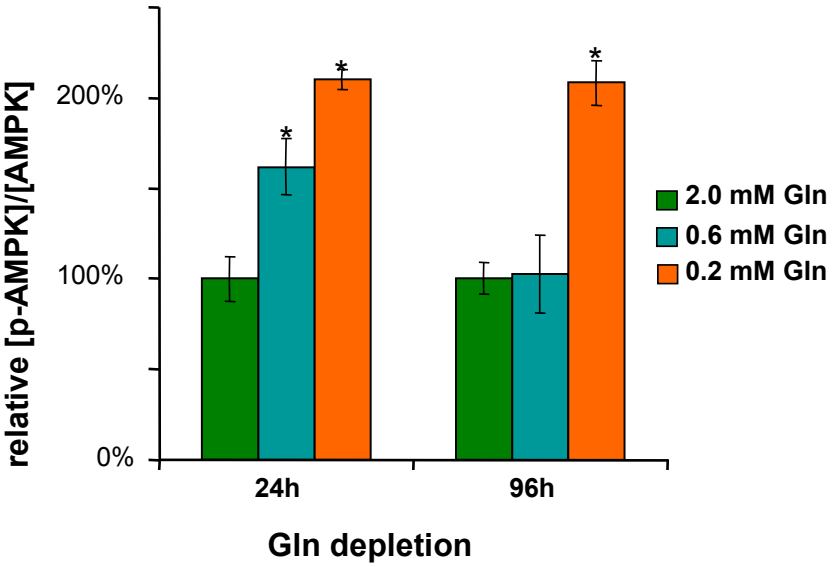
L Rubinson et al, *Crit Care Med* 2004; 32: 350


Nutrient depriviation
Energy charge –
AMP:ATP
cell survival
mitochondrial biogenesis
glycolysis
fatty acid oxidation
AMPK*
protein synthesis
fatty acid synthesis
cholesterol synthesis
growth factors
thyroid hormones
Nutrient-rich conditions
amino acids, leucine
insulin
m-TOR°
cell size
proliferation
Immune-stimulation
translation
S6 kinase 1
eIF4E
*AMP-activated kinase
°mammalian target of rapamycin

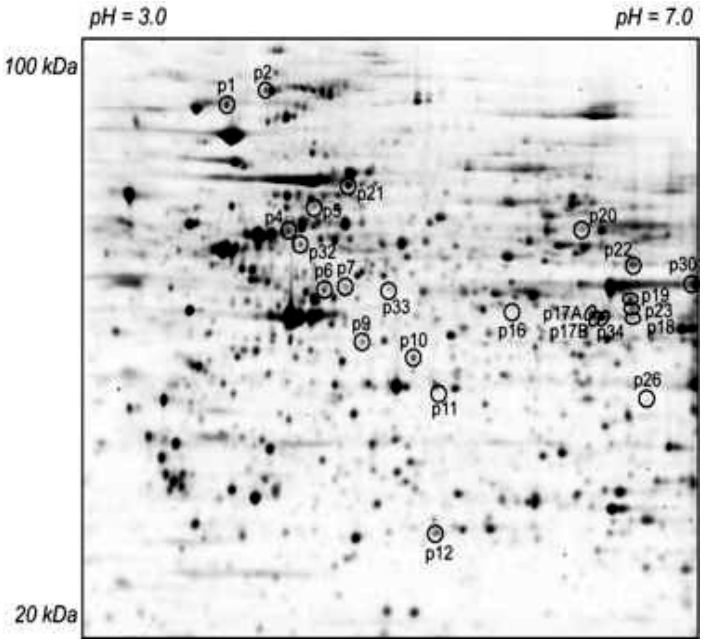
4 days of Gln depletion

AMPK phosphorylation

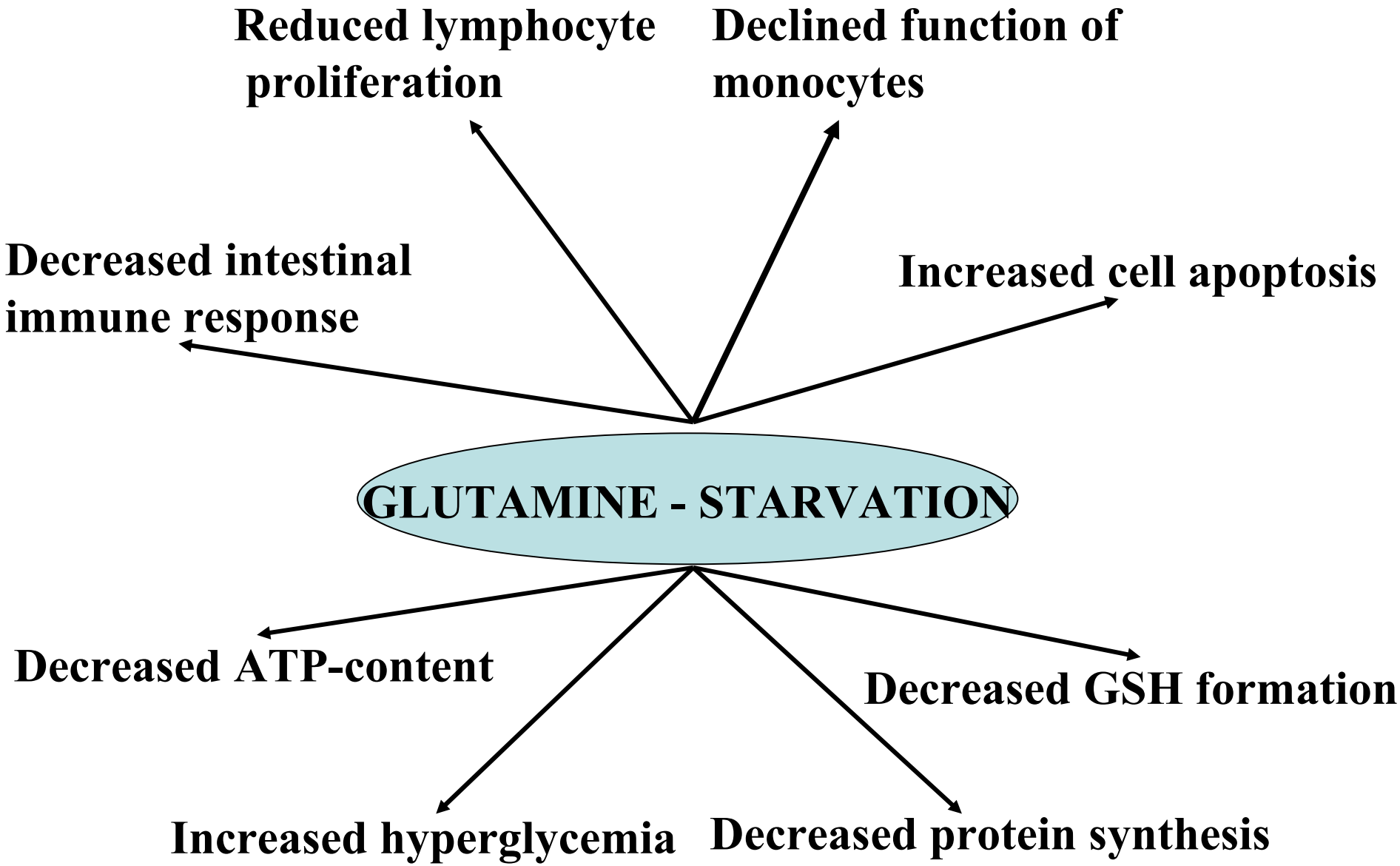




Altered protein expression after 4 days of Gln depletion



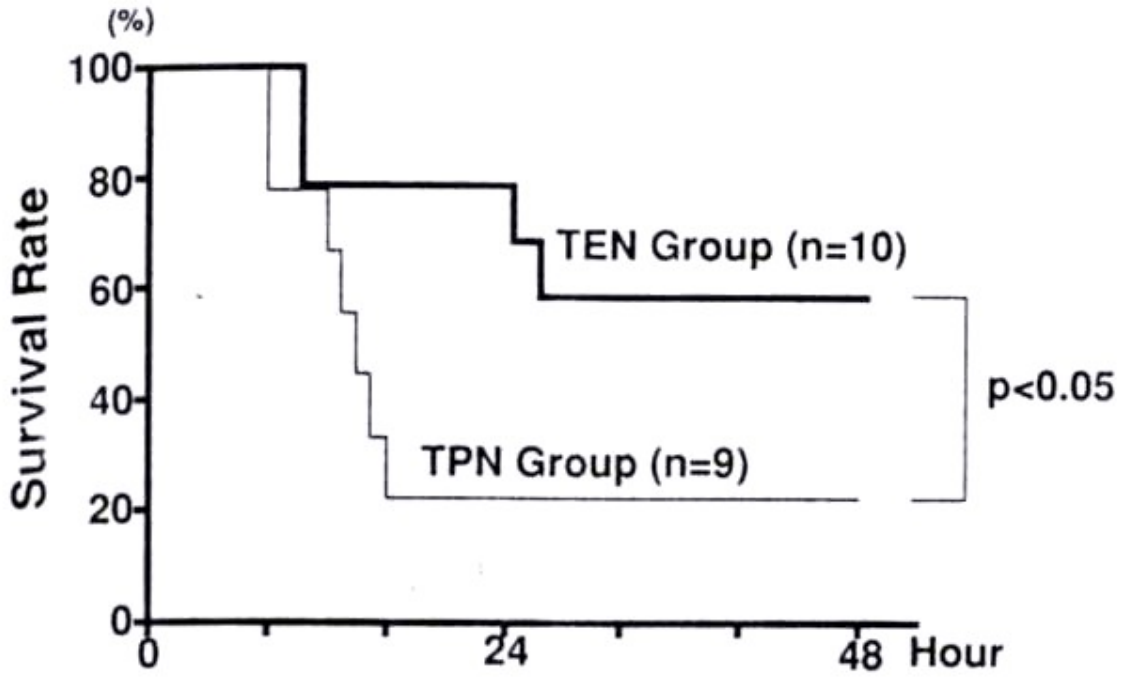
Spot ID	SwissProt Acc. Nr.	Protein Name	spot position	
			MW [kDa]	pI
p1	-			
p2	P34932	Heat shock 70 kDa protein 4 (Hsp-4)	100	5.2
p4	Q12874	Splicing factor 3A subunit 3 (SAP 61)	60	5.3
p5	-			
p6	P52597	Heterogeneous nuclear ribonucleoprotein F (hnRNP F)	45	5.5
p7	-			
p11	Q96C86	Scavenger mRNA decapping enzyme (DcpS)	35	6.0
p12	-			
p14	P40925	Malate dehydrogenase (MDH)	35	6.5
p16	-			
p17A	P49411	Elongation factor Tu, (EF-Tu)	42	6.5
p17B	P49411	Elongation factor Tu, (EF-Tu)	42	6.5
p18	-			
p19	P52209	6-phosphogluconate dehydrogenase (PGDH)	45	6.8
p20	-			
p21	P08133	Annexin 6 (A6)	70	5.5
p22	P00367 P25705	Glutamate dehydrogenase 1 (GDH) ATP Synthase α-chain (ATP-Sα)	55 55	6.6 6.6
p23	P62195	26S protease regulatory subunit 8 (p45/SUG)	42	6.6
p26	-			
p30	-			
p32	-			
p33	-			
p34	P22234	Phospho ribosyl amino imidazole-succino carboxamide synthase (PUR6)	42	6.5


Reduced lymphocyte proliferation
Declined function of monocytes
Decreased intestinal immune response
Increased cell apoptosis
GLUTAMINE - STARVATION
Decreased ATP-content
Decreased GSH formation
Increased hyperglycemia
Decreased protein synthesis

2. Immunantwort in Abhängigkeit vom Zufuhrweg

Route of Nutritional Supply Influences Local, Systemic, and Remote Organ Responses to Intraperitoneal Bacterial Challenge

Ming-Tsan Lin et al., Ann Surg 223: 84; 1996



Survival rate after E. coli peritoneal challenge

Cytokine Production in Dependence on Route of Nutritional Supply

Peritoneal Fluid:	***TPN***	**↑ TNF**
	EN	**↑ IFN-γ**
Bronchoalveolar Lavage Fluid:	***EN***	**↑ IFN-γ**
Blood:	***EN***	**↑ IFN-γ**

3. Was ist ein “Immunonutrient” ?

- **Ein Nutrient, das in einer Menge einer parenteralen oder oral/enteralen Diät zugesetzt ist, die immunmodulierend wirkt.**

- **Die Immunmodulation kann immun -stimulierend oder -supprimierend sein**

Welche immunmodulierenden Nährstoffe werden in der klinischen Erährung eingesetzt?

- Glutamin
- Arginin
- schwefel- hältige Aminosäuren
- Verzweigtkettige Aminosäuren
  ω-3 Fettsäuren
- Nukleotide
- Antioxidative Vitamine
- Mikronährstoffe
- (Proteine, Glukose)

Glucose and immunological reactions

Cytokines

The presence of glucose leads to a **higher resting cytokine** production; **after stimulation**, this **cytokine production is impaired** compared to the situation without glucose.

M Morohoshi et al. *Ann NY Acad Sci* 1995; 748:562
D Reinhold et al. *Horm Metab Res* 1996; 28:267

Phagocytosis

Impairment of phagocytosis is found in PMNs isolated from poorly regulated patients and **better regulation** of the DM leads to an **improved function**.

M Delamaire et al. *Diabetic Met* 1997; 14:29
JD Bagdade et al. *Diabetes Care* 1997; 20:392

Oxidative burst

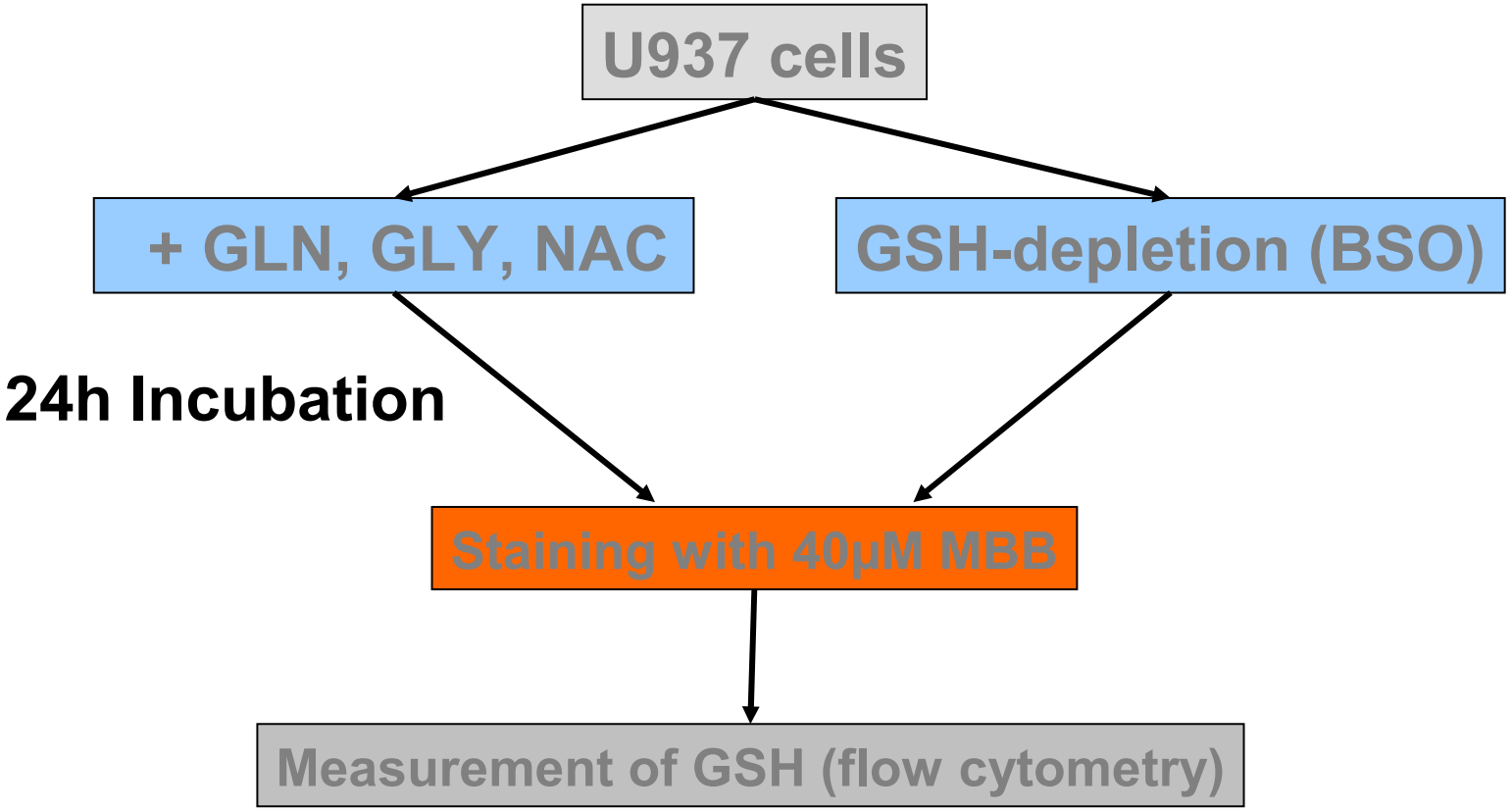
Oxidative burst is higher or the same in PBMC of diabetic patients; **after stimulation, oxidative burst in PBMC is lower** than that of control patients.

W Marhoffer et al. *Diabetes Care* 1992; 15:256
SV Shah et al. *J Clin Enodcrinol Metab* 1983; 57:740

4. Verhalten sich Immunonutrients wie Pharmaka?

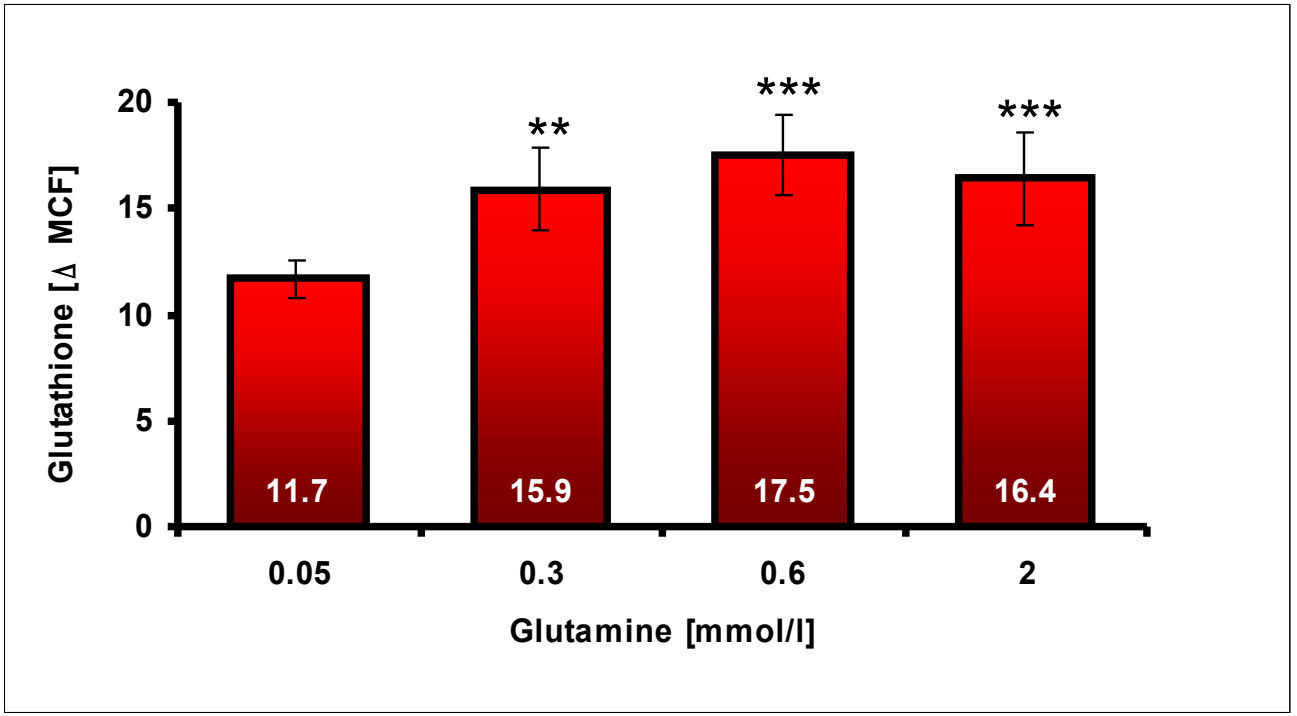
Kinetik von Immunonutrients am Beispiel von Glutamin und Glyzin in einem Zellkultursystem

Experimental design



B Wessner, E Roth et al, *Clin Nutr*, 2003

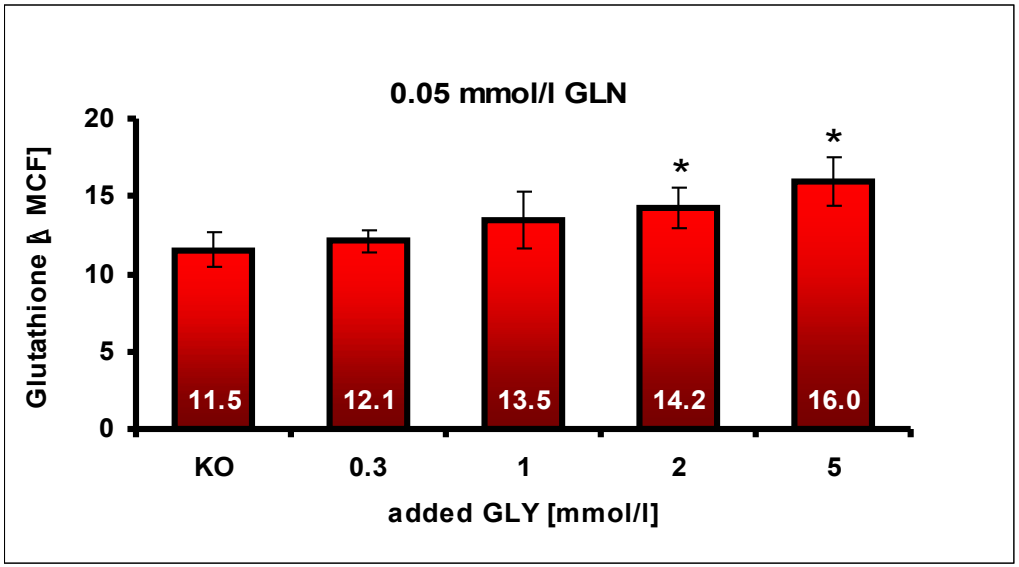
Influence of Glutamine on GSH-content of U937 cells



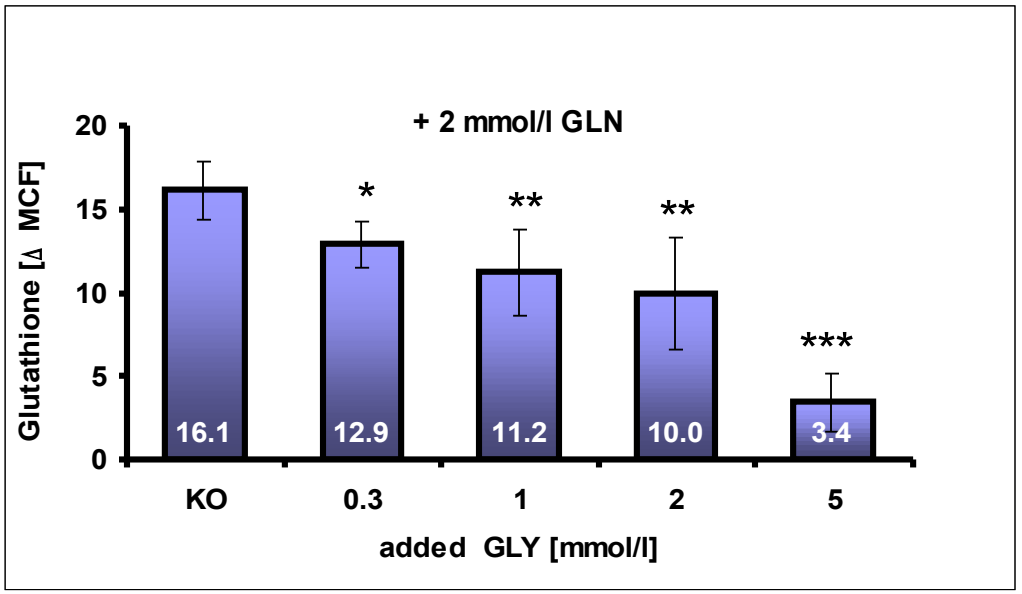
B Wessner, E Roth et al, *Clin Nutr*, 2003

** p < 0.01 vs 0.05mM GLN
*** p<0.001 vs 0.05mM GLN

Glycine + Glutamine



Low GLN

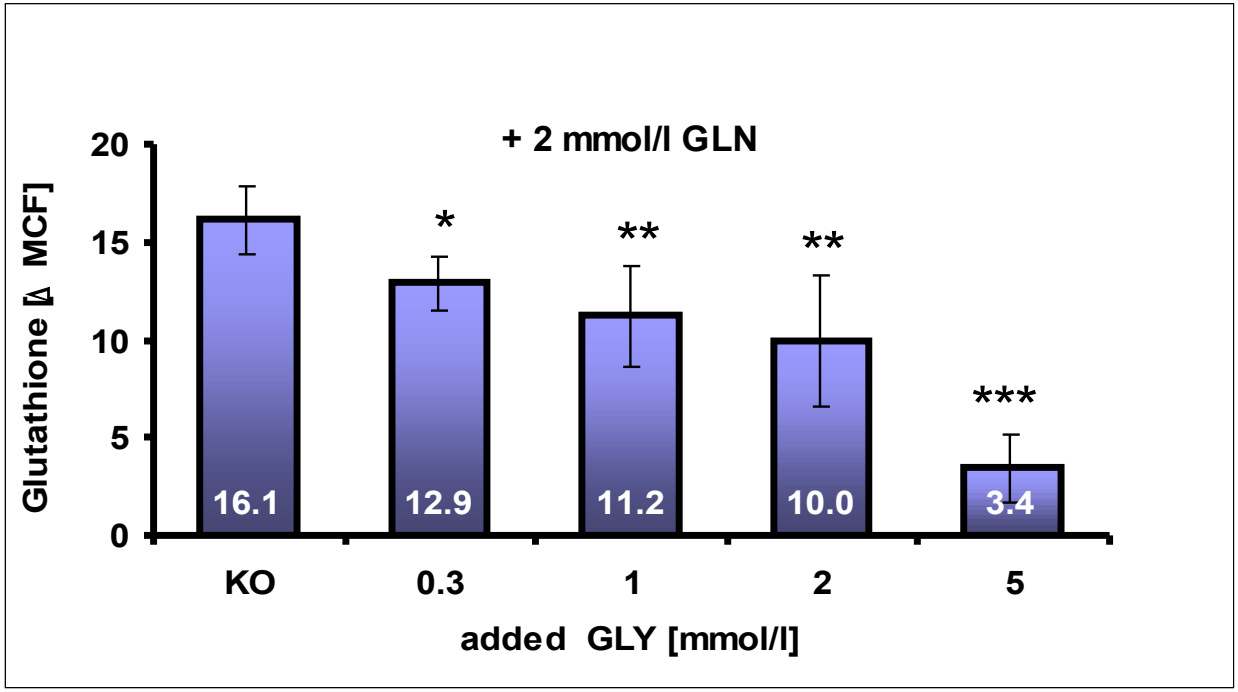


High GLN

* p < 0.05 vs KO
** p < 0.01 vs KO
*** p < 0.001 vs KO

0.02 vs KO

Glycine + high Glutamine: decreases ic glutamine concentration



B Wessner, E Roth et al, *Clin Nutr*, 2003

* p < 0.05 vs KO
** p < 0.01 vs KO
*** p < 0.001 vs KO

Effect of Different Combinations of Dietary Additives on Bacterial Translocation and Survival in Gut-Derived Sepsis

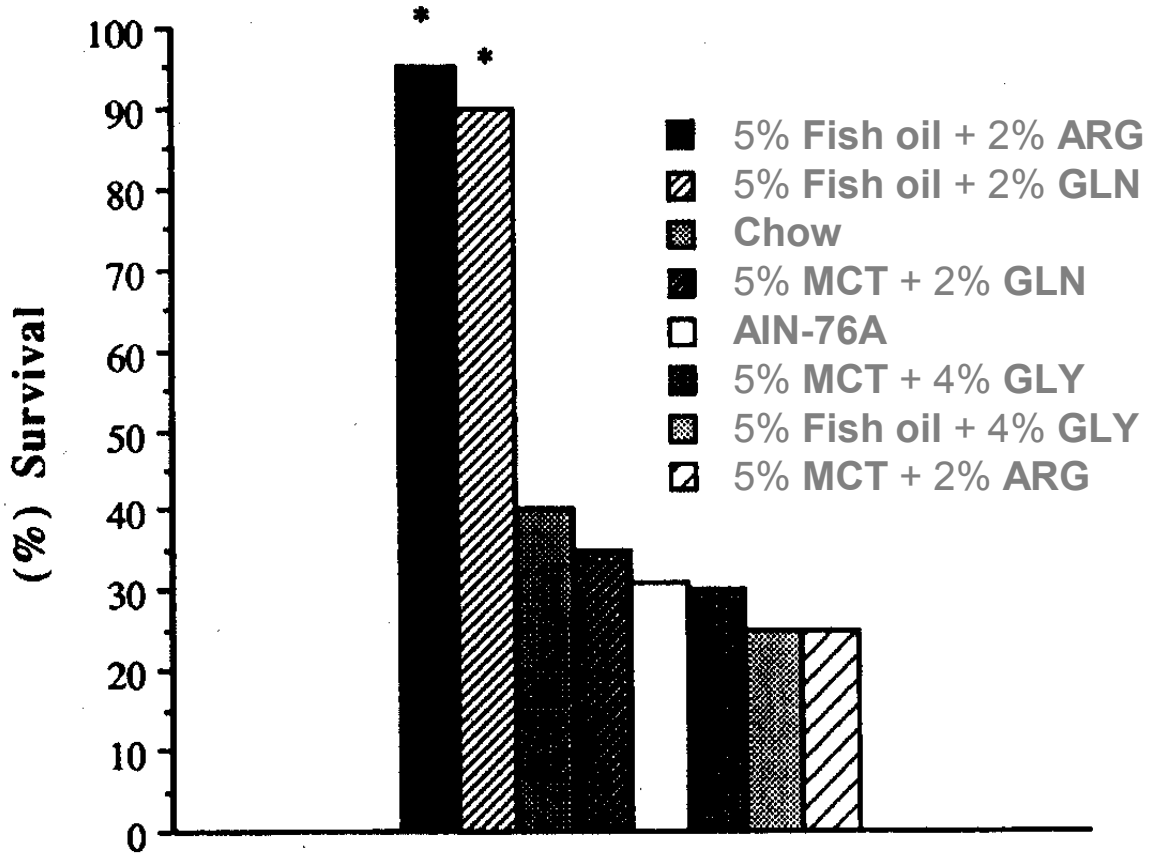


FIG. 3. Survival rate of transfused, gavaged, and burned mice fed with different pellet diets. *$p < .0001$ *vs* all other groups.

R Gennari, W Alexander et al, *JPEN* 1995

Zusammenfassung-Pharmakokinetik

- **Der Effekt von Immunonutrients ist dosisabhängig**

- **Die Kombination von Immunonutrients muss sorgfältig sowohl auf synergistische als auch antagonistische Wirkung untersucht werden**

D.K. Heyland:

... We included studies that compared enteral nutrition with <u>some</u> combination of arginine, glutamine, nucleotides, ω - 3 fatty acids

	IMPACT	Optimental
Arginine (g/L)	**12.5 (14)**	**5.5**
Nucleic acids (g/L)	**1.23**	**0**
ω - 3 PUFAs (g/L)	**1.7**	**4.83**
ω - 6 : ω - 3 ratio	**1.5 : 1**	**0.86 : 1**
Osmolarity	**375**	**560**
Vitamin E	**60**	**250**
Vitamin C	**80**	**215**
Selenium (µg/L)	**100**	**50**

DK Heyland et al, *JAMA* 2001

LOW FREE ARG

Aus Metaanalysen, die unterschiedlich zusammengesetzte Therapielösungen vergleichen, sind keine Schlussfolgerungen zulässig

5. Immunmodulatoren – Experimentelle Substrate

Lipoic acid

Curcumin

Green Tea Extract

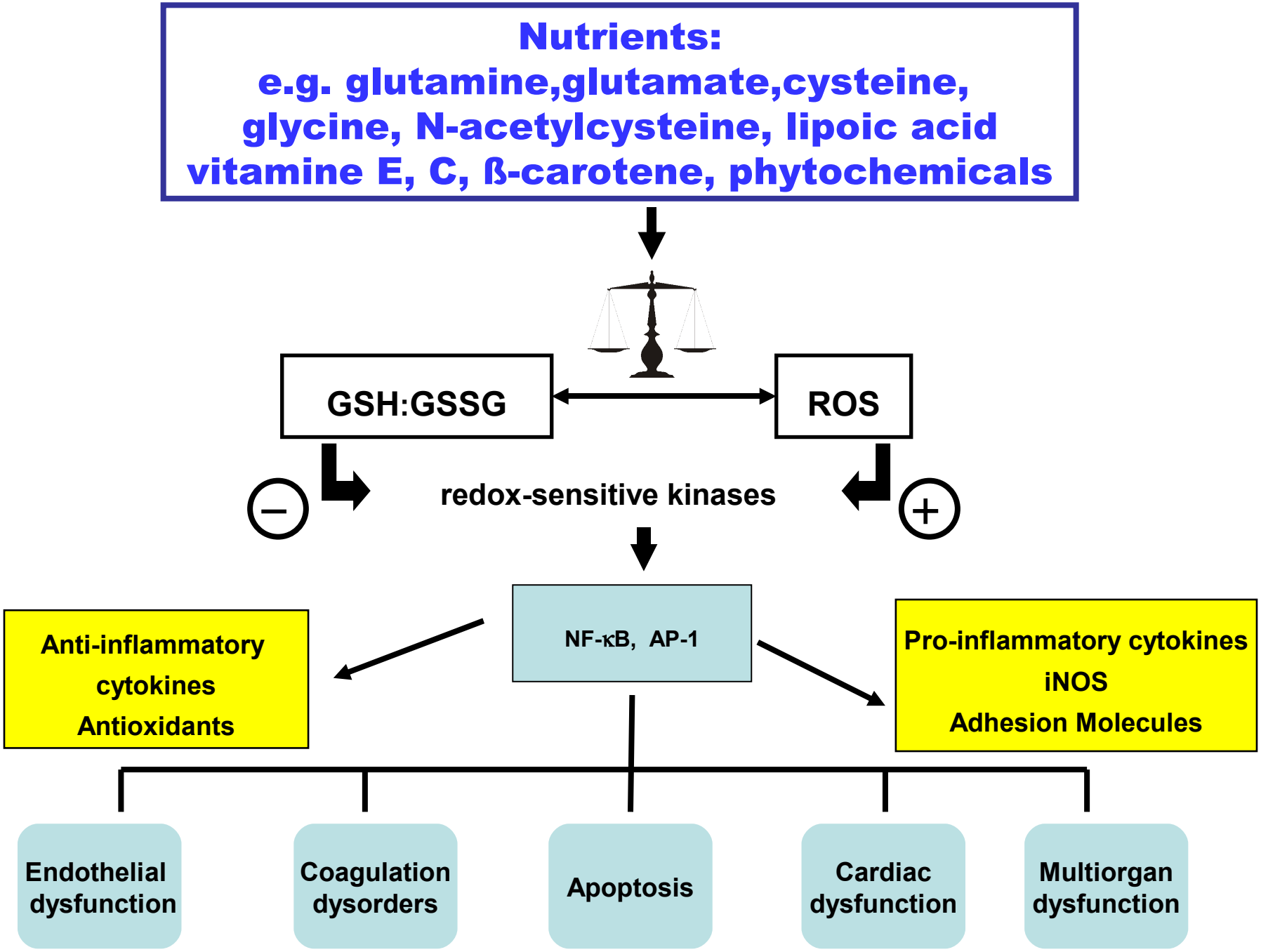
Thymoquinone

Sesamin

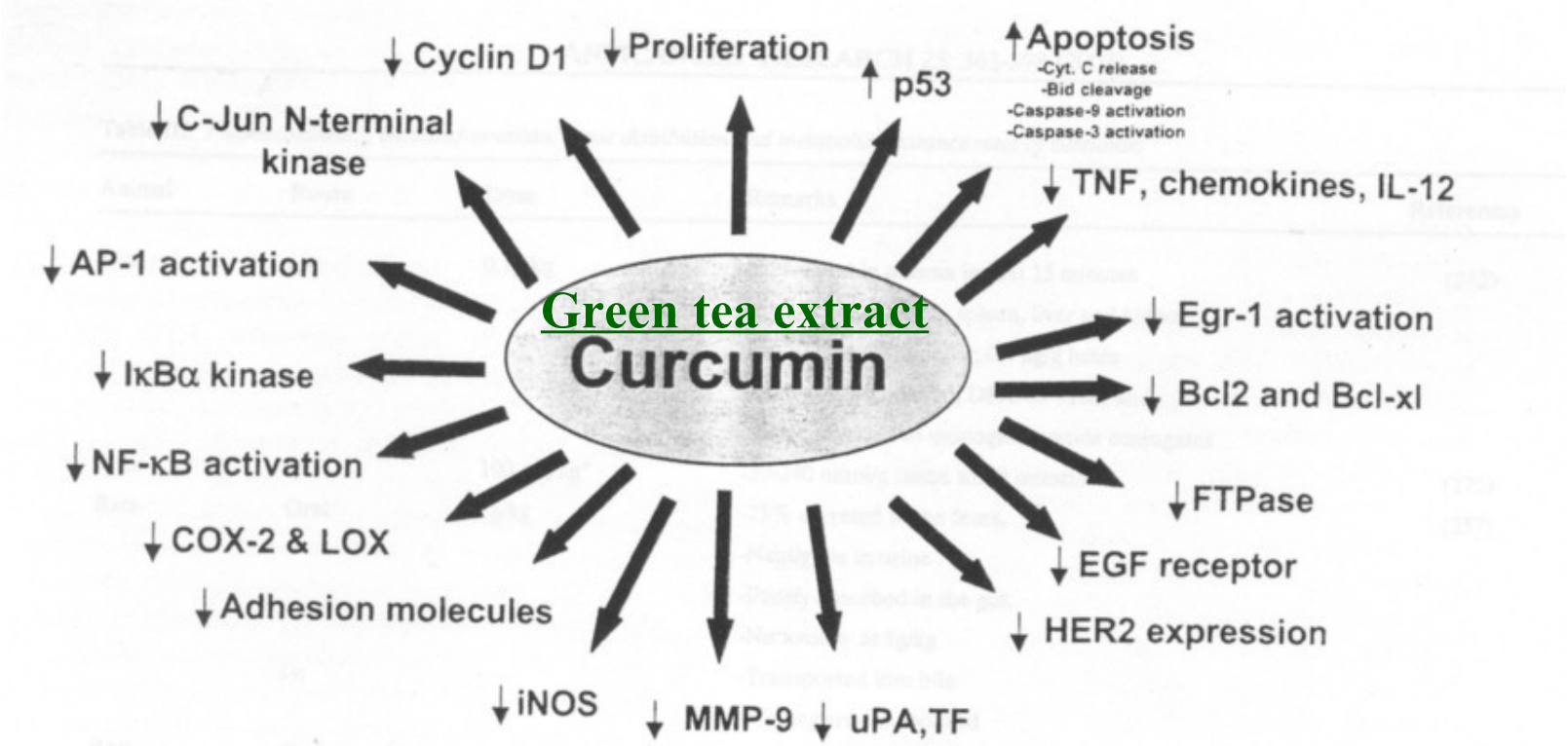
Kahweol

Cafestol

S-adenosyl-L-methionine (SAM)

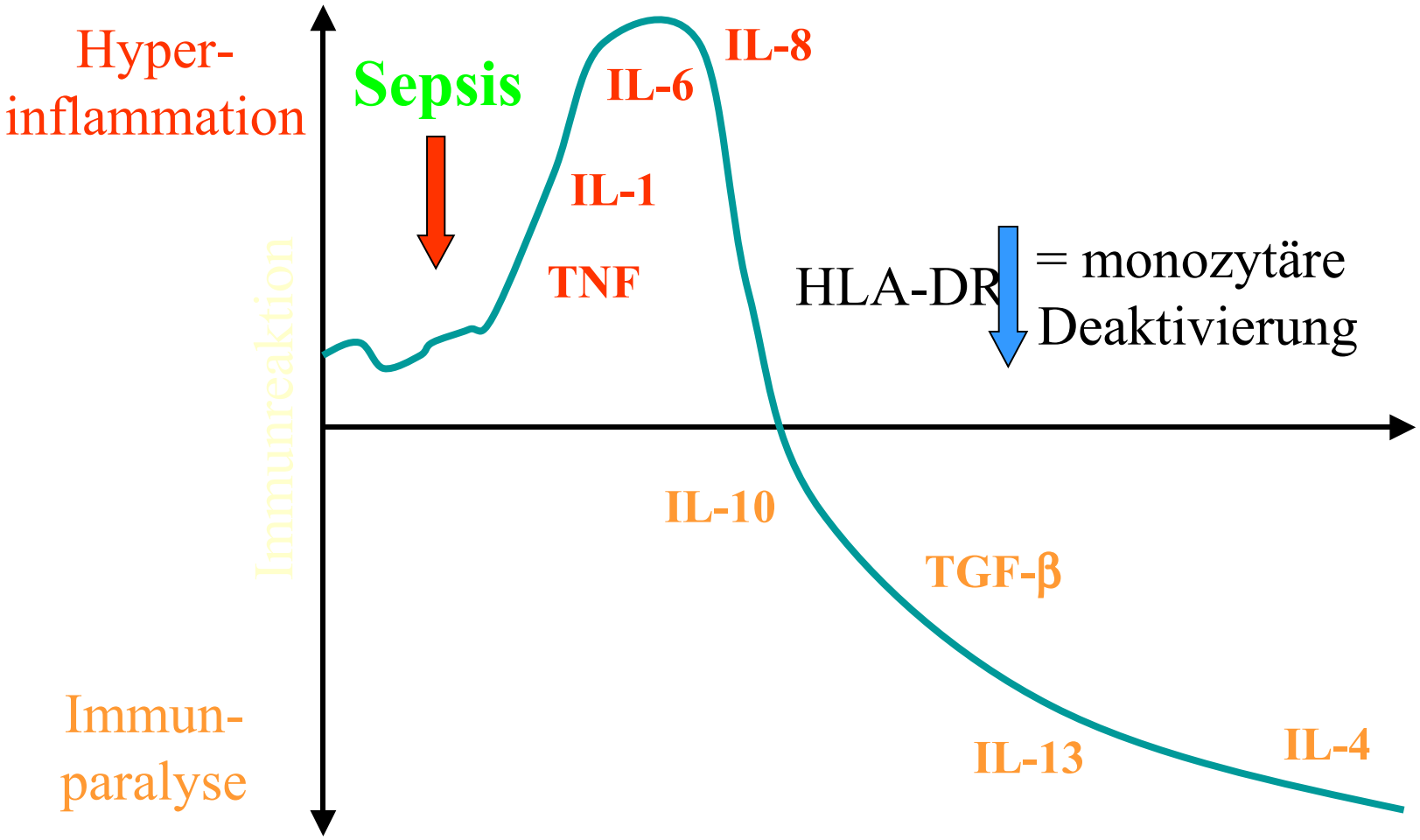

Nutrients:
e.g. glutamine,glutamate,cysteine,
glycine, N-acetylcysteine, lipoic acid
vitamine E, C, ß-carotene, phytochemicals
GSH:GSSG
ROS
redox-sensitive kinases
NF-κB, AP-1
Anti-inflammatory
cytokines
Antioxidants
Pro-inflammatory cytokines
iNOS
Adhesion Molecules
Endothelial
dysfunction
Coagulation
dysorders
Apoptosis
Cardiac
dysfunction
Multiorgan
dysfunction

Influence of curcumin on signal transduction



6. Gabe von Immunonutrients in Abhängigkeit vom pathophysiologischen Zustand

Zwei-Phasen-Modell der Sepsis



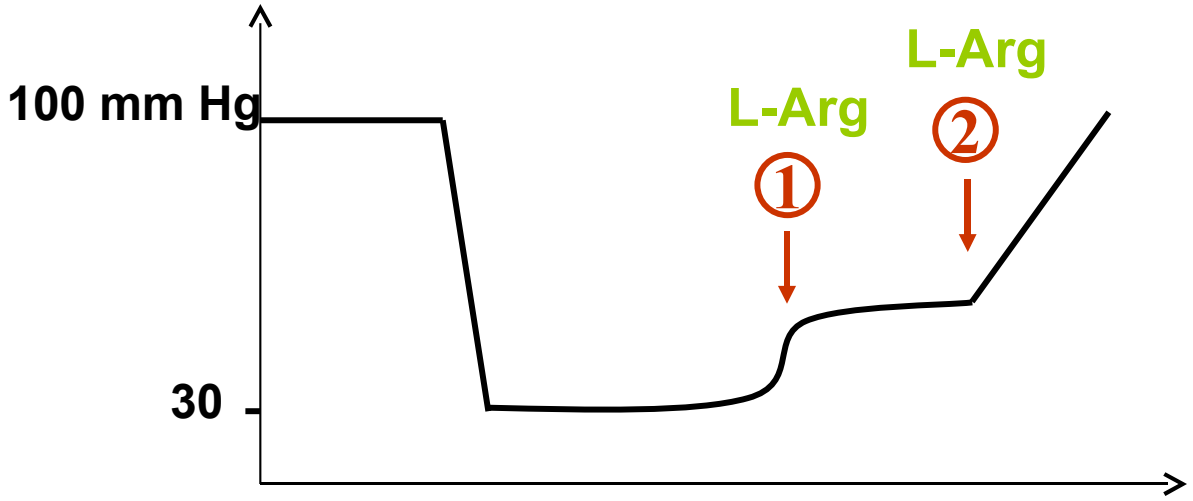
- **Modulation of hemorrhagic shock by intestinal mucosal N^G-nitro-L-arginine and L-arginine in the anesthetized rat** (D Mailman, *Shock 1999;12:155)*

  - **reduced survival by arginine analoga**
  - **improved survival by L-arginine**

- **Significance of NO in hemorrhage-induced hemodynamic alterations, organ injury and mortality in rats** (YM Yao et al., *Am J Phys 1996;270: H1616)*

  - **improved survival by arginine analoga**

NO and formation of peroxynitrite: Dichotomy of Arginine in Hemorrhagic Shock



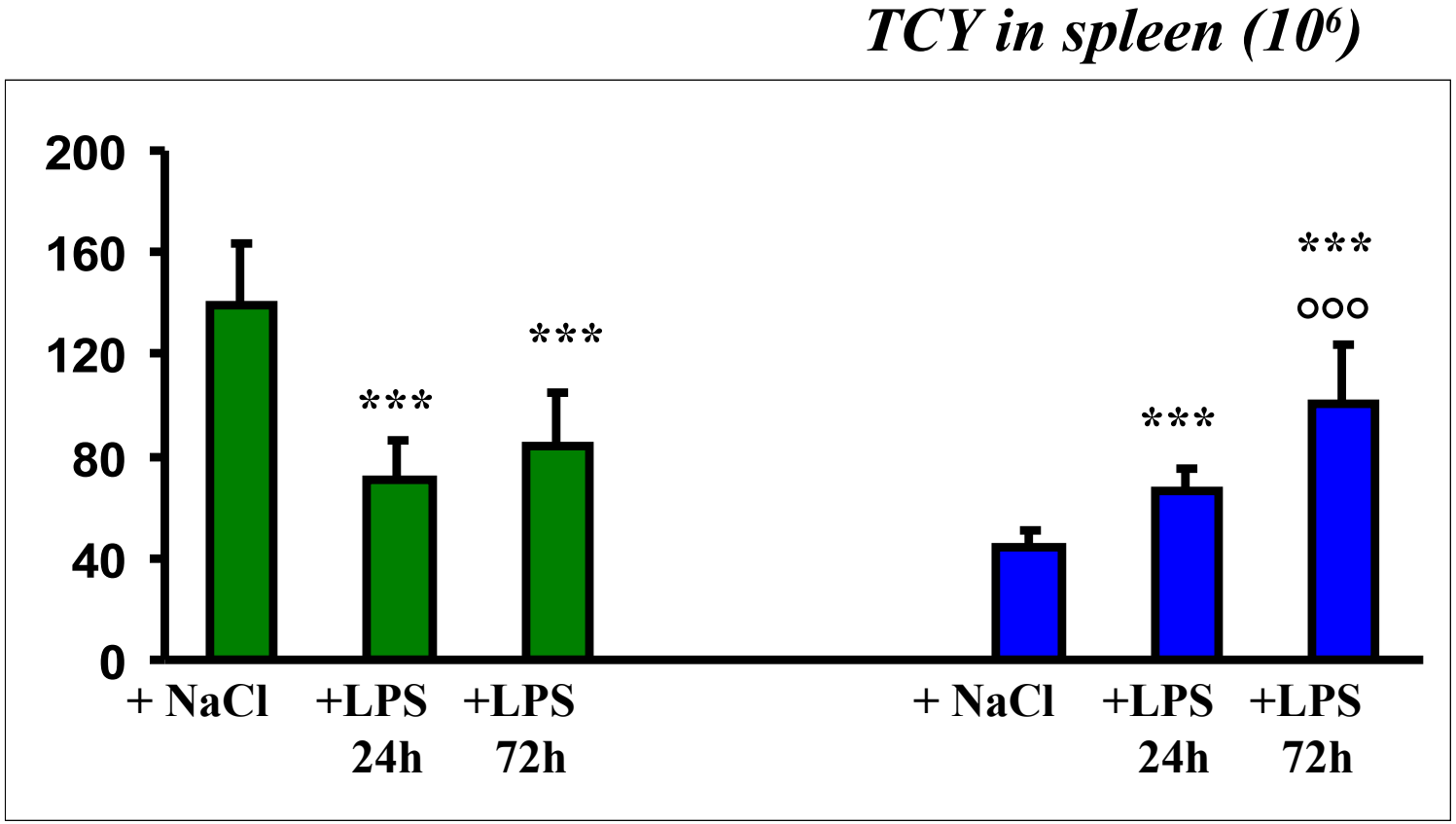
① $NO^{\cdot} + O_2^{\cdot -} \rightarrow ONOO^{2-} + H^+$

peroxynitrite = cytotoxic

② $NO^{\cdot}$ = cytoprotective

7. Organspezifische Immunmodulation

Lipopolysaccharide causes atrophy of Peyer´s Patches



Manhart N. Roth E et al. Shock 2000; 14:478-483

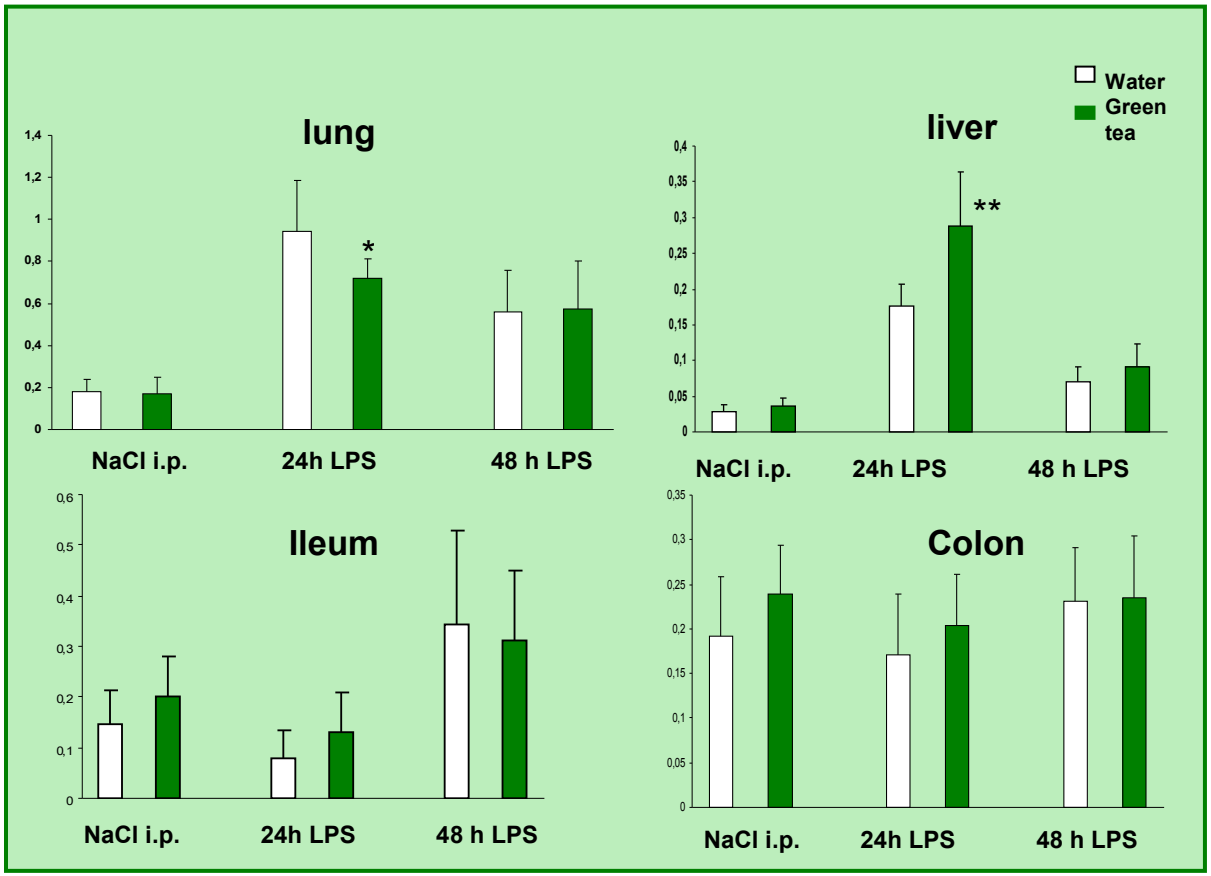
Green tea polyphenol administration partly ameliorates chemotherapy-induced side effects in the small intestine of mice

Wessner B, Manhart N. Roth E et al. J. Nutr 2007;137:634

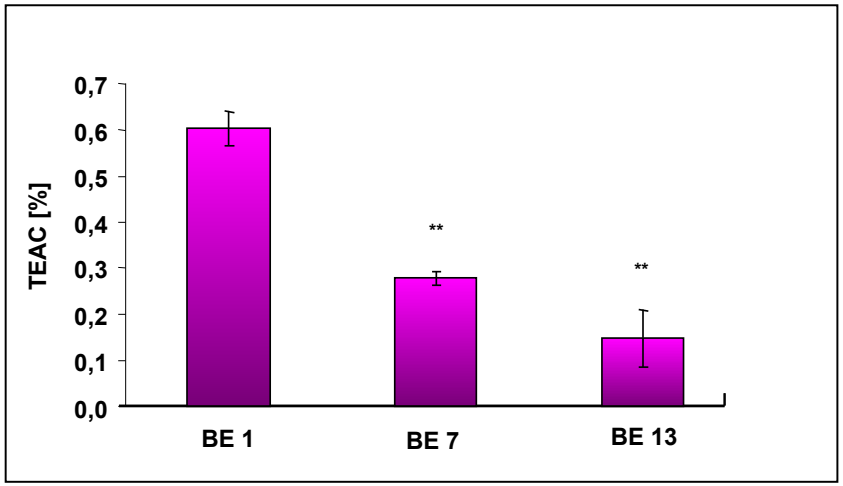
Green tea polyphenols increase lymphocyte numbers and diminish oxidative stress in the Peyers patches of endotoxemic mice

Manhart N, Wessner B, Roth E et al.

Myeloperoxidase activity



Antioxidativ ist nicht gleich anti-inflammatorisch



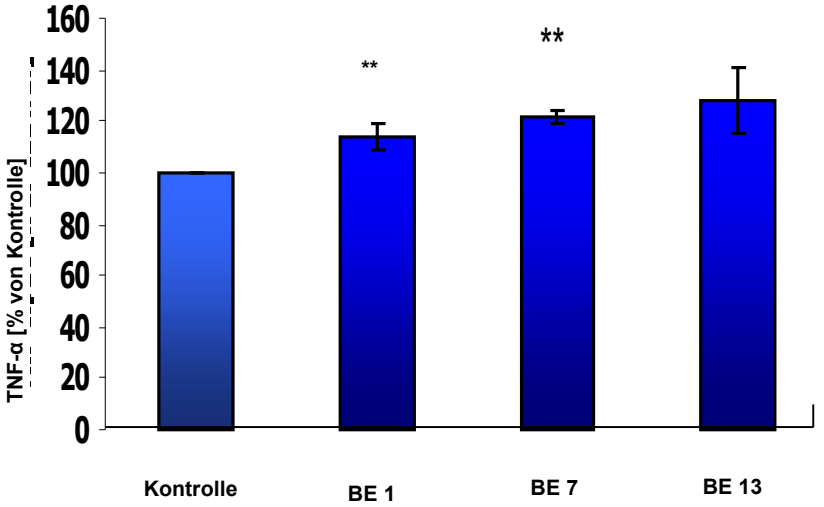


Abbildung 1
Anti-oxidative Kapazität der Basilikumextrakte
** p < 0.01
Daten aus 3 unabhängigen Experimenten

Abbildung 2
Einfluss der Basilikumextrakte auf die TNF-α Sekretion von LPS stimulierten U937 Zellen
** p < 0.01 vs. Kontrolle
Daten aus 4 unabhängigen Experimenten

Petra Riedl, Poster 10.2; Ernährung 2008

Zusammenfassung

- Hohe Korrelation zwischen Anergie und Mortalität bei Intensivpatienten
- Mangelernährung –Substratmangel führt zu einer Immunsuppression
- Immunonutrients folgen den Gesetzen der Pharmakokinetik
- Einsatz von Immunonutrients in Abhängigkeit der Immunlage
- Immunonutrients wirken organspezifisch
- Zentrale Angriffspunkte der Immunonutrients sind
  - das Redoxpotential +Transkriptionsfaktor NfkB
  - das AMPK/m-TOR System
  - die Signalkaskade