Clinical Environmental Medicine
new science and praxis in Complex Multisystem Illnesses (CMI)

Pathomechanisms, immunology (NEIS), therapy of illnesses associated to the environment

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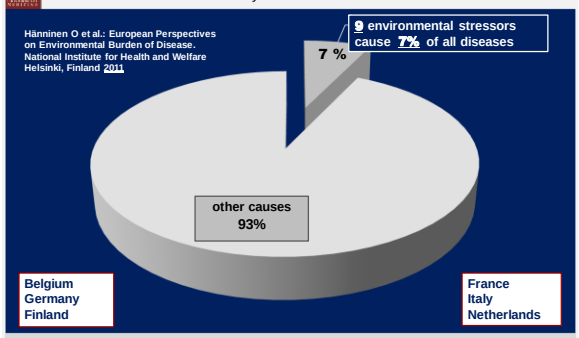
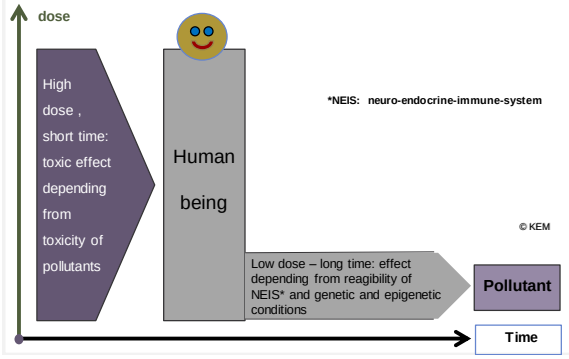
Incidence of diseases in 6 coutries of EU caused by 9 environmental stressors



* Environmental burden: benzene, formaldehyde, dioxins/furans/PCB, lead, ozone, transportation noise, second-hand smoke, particulate matter, radon

Different effect of low dose/long time and high dose/short time exposure



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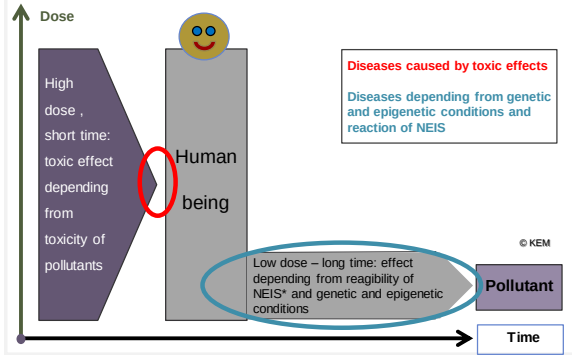
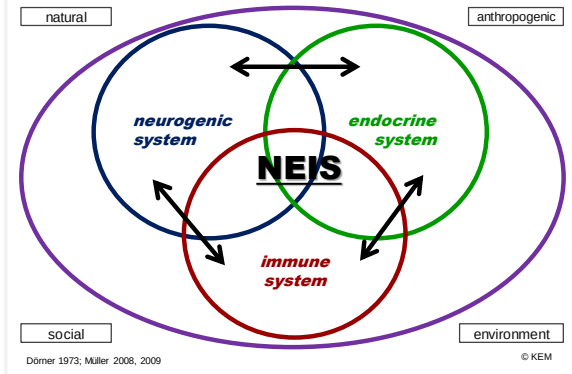
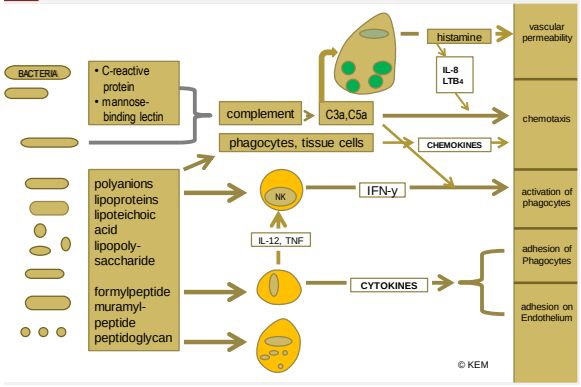


Interaction of neuroendocrine-immune system (NEIS)
NEIS: actor – not only reactor



Protection without antigen specific B and T cells – old enemies
Roitt et al. 2006



Protection without antigen specific B and T cells – new enemies

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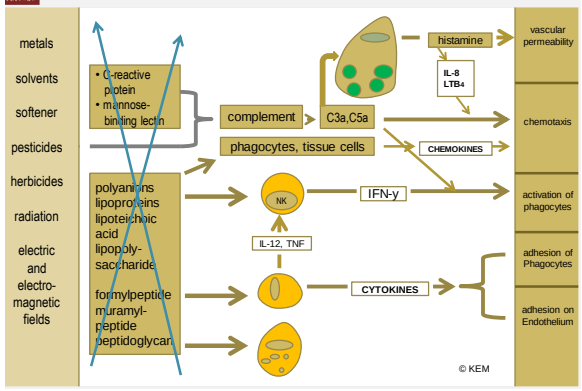
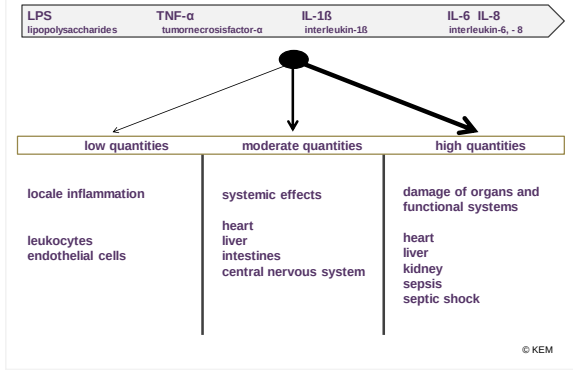


LPS induced cascade of cytokines

Dependance of clinical manifestation from quantity of cytokines
(Abbas, Lichtman, Pober (1994): Cellular and Molecular Immunology. Saunders)



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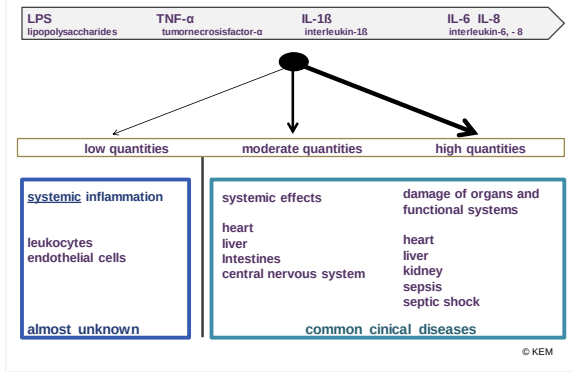
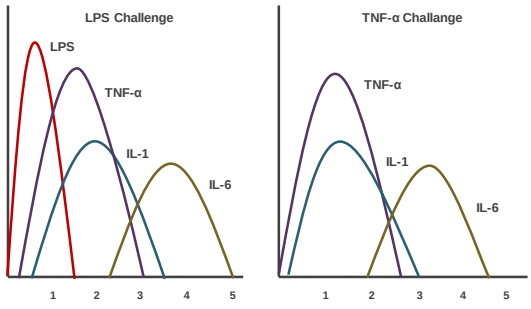


Expression of cytokines by LPS und TNF (Roitt 2006)
„Immunologic engrams“ and induktion of „montonous“ and chronic reactions
LPS = Lipopolysaccharide; TNF = Tumornekrosefaktor



Hours after having started the reaction

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Expression of cytokines by LPS und TNF (Roitt 2006)
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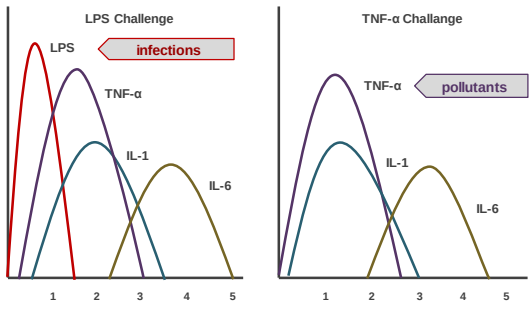

Hours after having started the reaction

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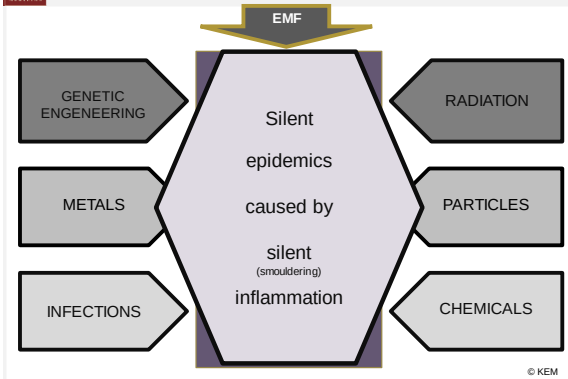
The new „enemies“ – causing new diseases:
Chronic Multisystem Illnesses (CMI)



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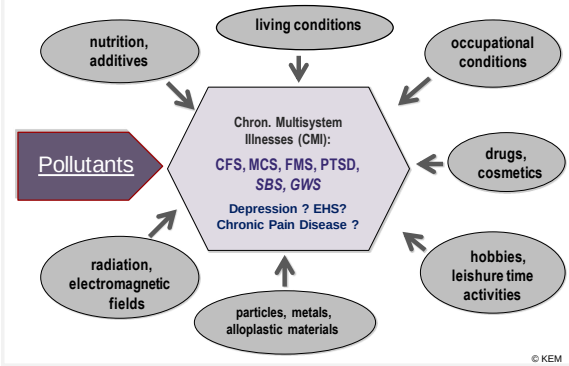
CMI and environmental influences



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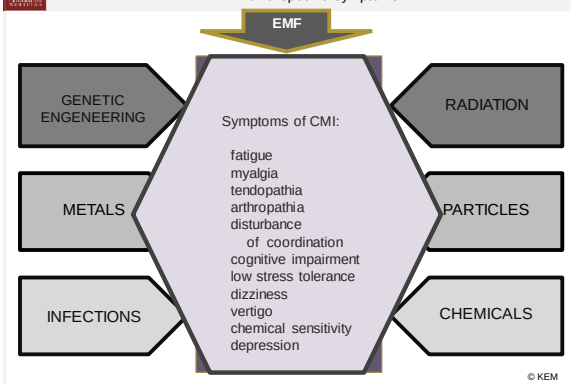
The new „enemies" – causing new diseases: with unspecific symptoms



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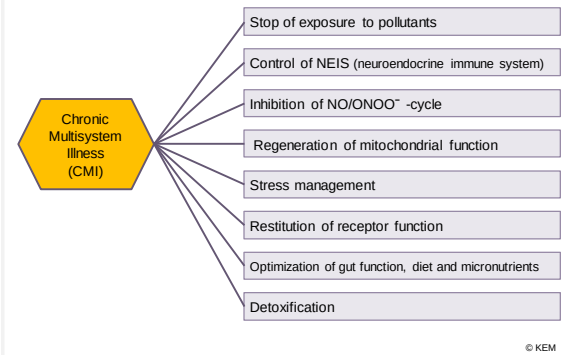
Therapeutic targets in clinical environmental medicine



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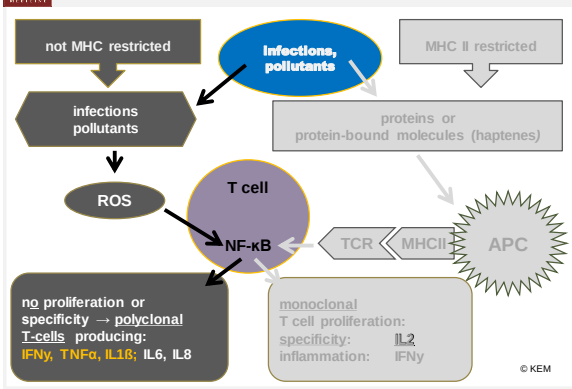
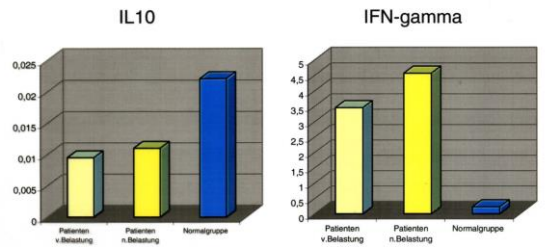
Unspecific immune reaction



Cytokine profile in MCS patientens (F. Bartram)



Interferon-γ (IFN-γ) and susceptibility

Roitt I., Brostoff J., Male D.:
Immunology. Sixth Edition, 2001. Mosby; Edinburgh, London, New York, Toronto.

..... IFN γ makes cells abnormally susceptible to intracellular pathogenes .....

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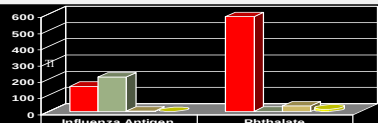
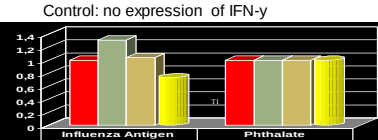
Expression of IFN-y caused by phthalates

Silent (smouldering) inflammation caused by phthalates



	Influenza Antigen	Phthalate
IFN-gamma	155	584
IL 2	213	1,13
IL 10	2,85	34,66
Quotient IFN-g/IL2/IL10	0,26	14,91

Control: no expression of IFN-y



	Influenza Antigen	Phthalate
IFN-gamma	1	1
IL 2	1,31	1
IL 10	1,04	1
Quotient IFN-g/IL2/IL10	0,73	1

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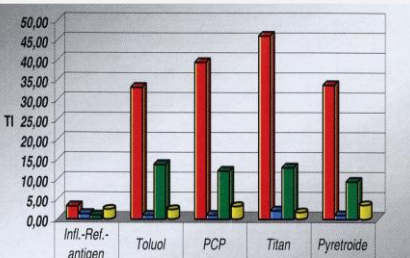
Inflammation caused by various pollutants



	Infl.-Ref.-antigen	Toluol	PCP	Titan	Pyretroide
IFN-gamma	3,29	33,13	39,40	46,05	33,71
IL2	1,34	1,00	1,00	2,13	1,00
IL10	1,00	13,78	12,17	13,00	9,45
Quotient IFN-g/IL2/IL10	2,46	2,40	3,24	1,66	3,57

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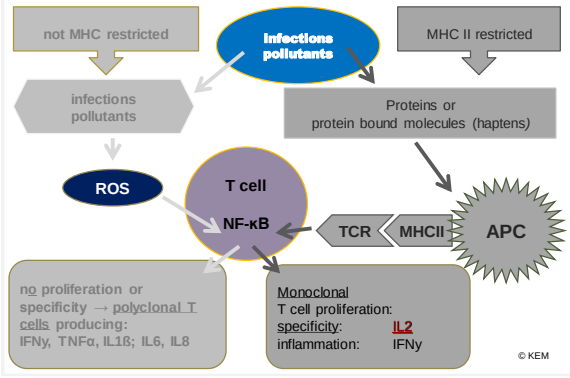
Specific immune reaction



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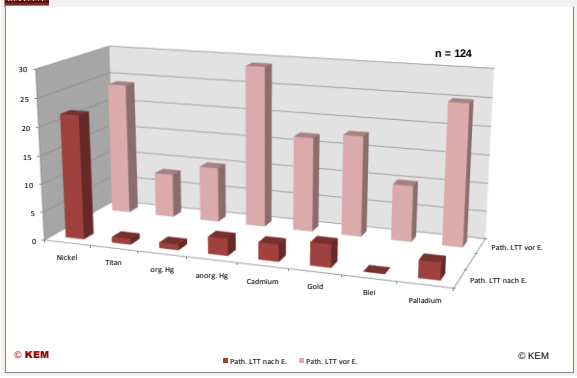
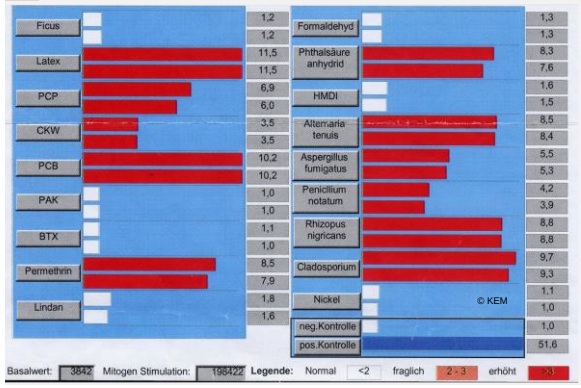
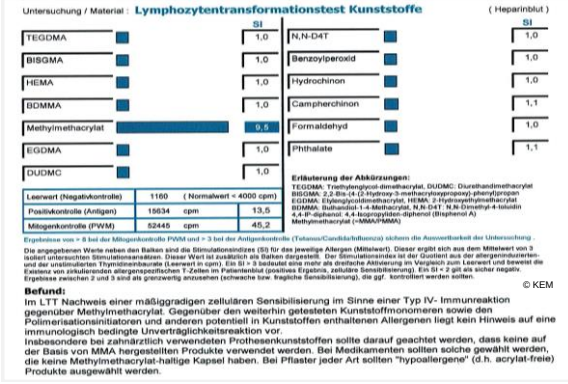
Stimulation index (SI) of lymphocyte transformation test (LTT) before and after removal of metals



T cell sensitization caused by various pollutants and moulds



T cell sensitization to methyl methacrylate


Untersuchung / Material : **Lymphozytentransformationstest Kunststoffe** (Heparinblut)

	SI		SI
TEGDMA	1,0	N,N-D4T	1,0
BISGMA	1,0	Benzoylperoxid	1,0
HEMA	1,0	Hydrochinon	1,0
BDMMA	1,0	Campherchinon	1,1
Methylmethacrylat	9,5	Formaldehyd	1,0
EGDMA	1,0	Phthalate	1,1
DUDMC	1,0		

Leerwert (Negativkontrolle)	1160	(Normalwert < 4000 cpm)
Positivkontrolle (Antigen)	15634	cpm 13,5
Mitogenkontrolle (PWM)	52445	cpm 45,2

Erläuterung der Abkürzungen:
TEGDMA: Triethylenglycol-dimethacrylat, DUDMC: Diurethandimethacrylat
BISGMA: 2,2-Bis-(4-(2-Hydroxy-3-methacryloxypropoxy)-phenyl)propan
EGDMA: Ethylenglycoldimethacrylat, HEMA: 2-Hydroxyethylmethacrylat
BDMMA: Butandiol-1,4-Methacrylat, N,N-D4T: N,N-Dimethyl-4-toluidin
4,4-IP-diphenol: 4,4-Isopropyliden-diphenol (Bisphenol A)
Methylmethacrylat (=MMA/*MMA)

Ergebnisse von > 8 bei der Mitogenkontrolle PWM und > 3 bei der Antigenkontrolle (Tetanus/Candida/Influenza) sichern die Auswertbarkeit der Untersuchung .

Die angegebenen Werte neben den Balken sind die Stimulationsindizes (SI) für das jeweilige Allergen (Mittelwert). Dieser ergibt sich aus dem Mittelwert von 3 isoliert untersuchten Stimulationsansätzen. Dieser Wert ist zusätzlich als Balken dargestellt. Der Stimulationsindex ist der Quotient aus der allergeninduzierten und der unstimulierten Thymidineinbaurate (Leerwert in cpm). Ein SI > 3 bedeutet eine mehr als dreifache Aktivierung im Vergleich zum Leerwert und beweist die Existenz von zirkulierenden allergenspezifischen T-Zellen im Patientenblut (positives Ergebnis, zelluläre Sensibilisierung). Ein SI < 2 gilt als sicher negativ. Ergebnisse zwischen 2 und 3 sind als grenzwertig anzusehen (schwache bzw. fragliche Sensibilisierung), die ggf. kontrolliert werden sollten.

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Befund:
Im LTT Nachweis einer mäßiggradigen zellulären Sensibilisierung im Sinne einer Typ IV- Immunreaktion gegenüber Methylmethacrylat. Gegenüber den weiterhin getesteten Kunststoffmonomeren sowie den Polimerisationsinitiatoren und anderen potentiell in Kunststoffen enthaltenen Allergenen liegt kein Hinweis auf eine immunologisch bedingte Unverträglichkeitsreaktion vor.
Insbesondere bei zahnärztlich verwendeten Prothesenkunststoffen sollte darauf geachtet werden, dass keine auf der Basis von MMA hergestellten Produkte verwendet werden. Bei Medikamenten sollten solche gewählt werden, die keine Methylmethacrylat-haltige Kapsel haben. Bei Pflaster jeder Art sollten "hypoallergene" (d.h. acrylat-freie) Produkte ausgewählt werden.

T cell proliferation caused by Borrelia burgdorferi

Untersuchung / Material : **Lymphozytentransformationstest LTT Borrelien** (Heparinblut)

Testansätze - Borrelienantigene

	SI
Borr. sensu stricto	5,1
Borr. afzelii	7,1
Borr. garinii	6,4
Borr. OspC	9,9
Positivkontrolle (Antigen)	14,9
Mitogenkontrolle (PWM)	71,3
Leerwert (Negativkontrolle) 1750 (Normalwert < 4000 cpm)	

Hinweise zur Untersuchungsmethode:
Die Zahlen rechts neben der Balkengrafik sind die Stimulationsindizes (SI) für das jeweilige Borrelienantigen, dass den Patientenzellen zugesetzt wird (Mittelwert von 3-fach Ansätzen).
Der Stimulationsindex ist der Quotient aus der Antigeninduzierten- und der unstimulierten Thymidineinbaurate (Leerwert in cpm, angegeben ist der Mittelwert von 3 Paralleluntersuchungen). Ein SI > 3 bedeutet eine mehr als dreifache zelluläre Aktivierung durch das Antigen im Vergleich zum Leerwert und beweist die Existenz von zirkulierenden Borrelien-spezifischen T-Zellen im Patientenblut (positives Ergebnis). Ein SI < 2 gilt als sicher negativ. Ergebnisse zwischen 2 und 3 sind als grenzwertig anzusehen (schwache bzw. fragliche Sensibilisierung), die ggf. kontrolliert werden sollte.

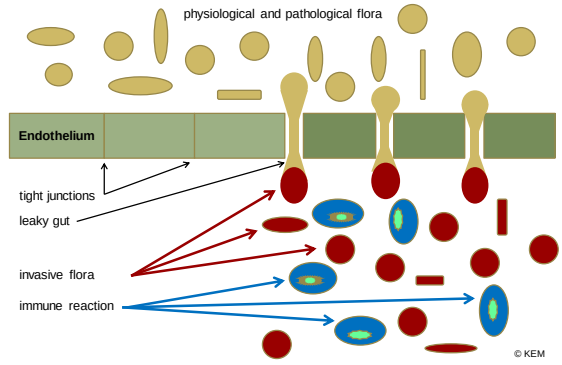
Die Positivkontrolle dient ausschließlich dem Nachweis der Reaktionsfähigkeit der Lymphozyten. Hier wird eine Tetanus / Influenza / Candida -Mischantigenprobe als Recall-Antigen verwendet, bei dem eine T-zelluläre Sensibilisierung immer vorhanden ist.
PWM ist als Mitogen Indikator für die Vitalität der Immunzellen bei Probeneingang im Labor.

Stimulationsindizes von > 8 bei der Mitogenkontrolle PWM und > 3 bei der Antigenkontrolle (Tetanus/Cand./Influenza) sichern die Auswertbarkeit der Untersuchung

Befund:
Es zeigen sich positive LTT-Reaktionen auf Borrelienantigene. Dieser Befund ist verdächtig für eine derzeit aktive Borrelieninfektion.
Besonders entscheidend für die Therapieindikation ist jedoch das gegenwärtig bestehende klinische Bild (Serologie ?). Wenn therapiert wird, sollte die Kontrolluntersuchung mit dem LTT frühestens 4-6 Wochen nach Therapieende erfolgen. Nach erfolgreicher Behandlung sind die SI-Werte für Borrelienantigene deutlich rückläufig bis unauffällig zu erwarten.

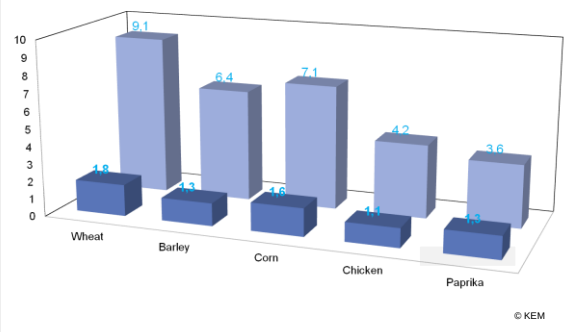
Leaky gut

(GALT = gut associated lymphoid tissue)



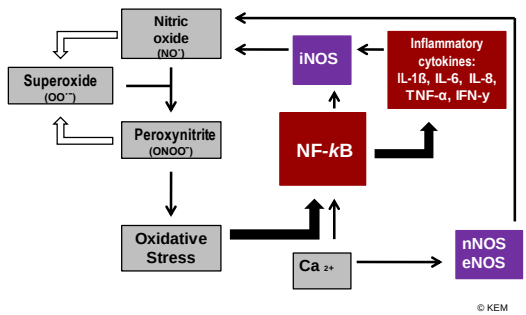
T cell mediated food allergy → Colon irritabile?

Stimulation index (SI) before and one year after elimination diet



Circulus vitiosus – NO/ONOO⁻ cycle

„Vicious cycle" n. M. Pall 2007



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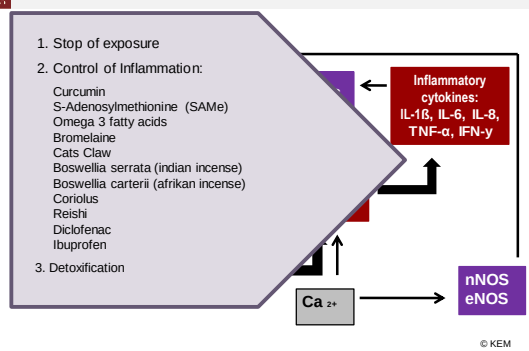
iNOS=inducible Nitric Oxide Synthase ; nNOS=neural NOS; eNOS=endothelial NOS

Circulus vitiosus - Inflammation

„Vicious cycle" n. M. Pall 2007



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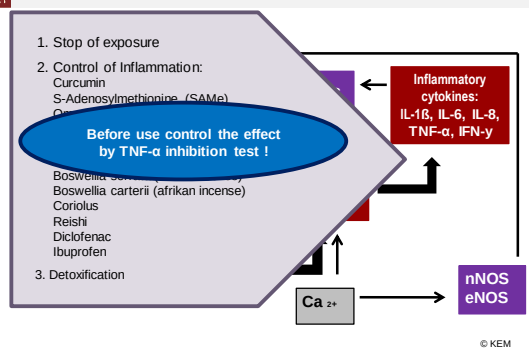
iNOS=inducible Nitric Oxide Synthase ; nNOS=neural NOS; eNOS=endothelial NOS

Circulus vitiosus – Control of effects

„Vicious cycle" n. M. Pall 2007



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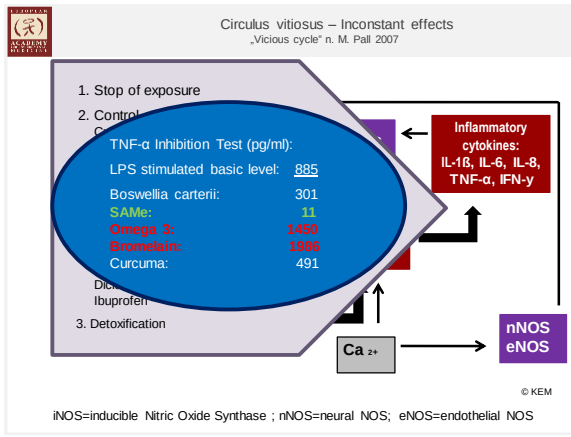

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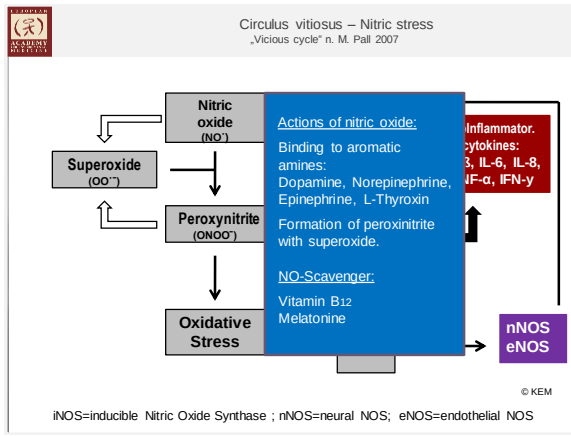

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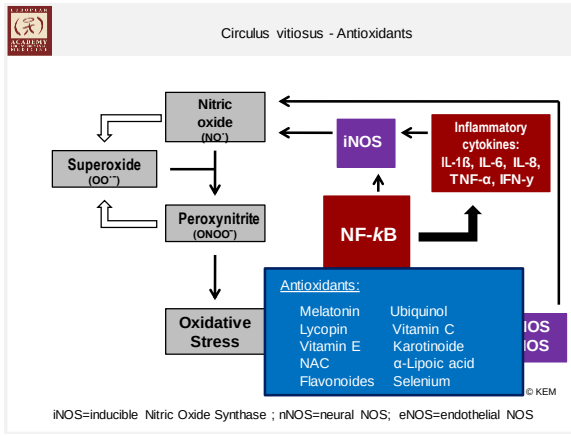
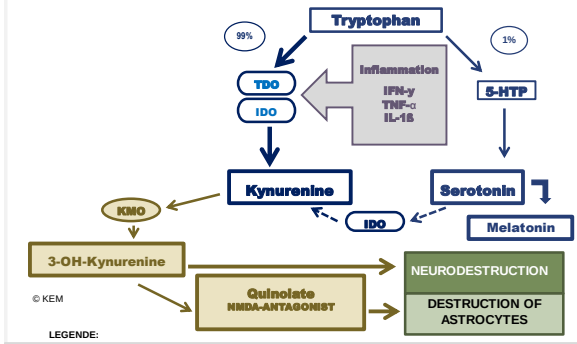
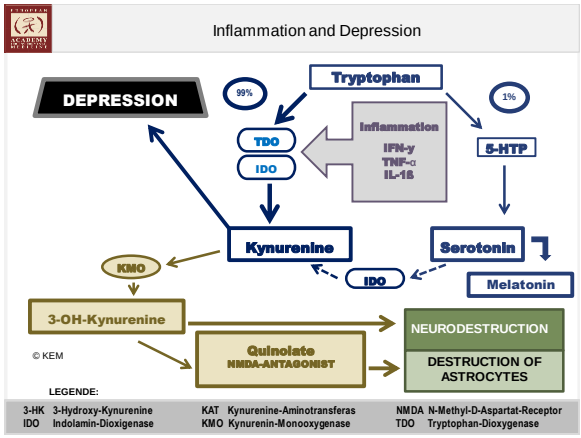


iNOS=inducible Nitric Oxide Synthase ; nNOS=neural NOS; eNOS=endothelial NOS

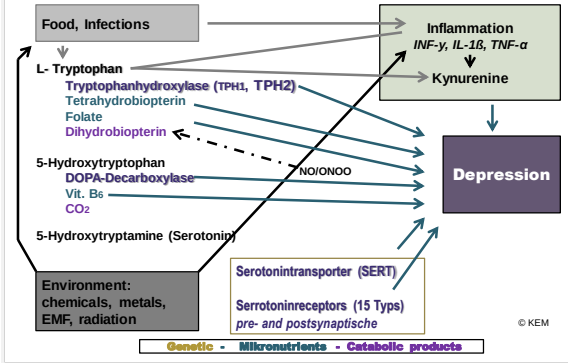
Inflammation and …….

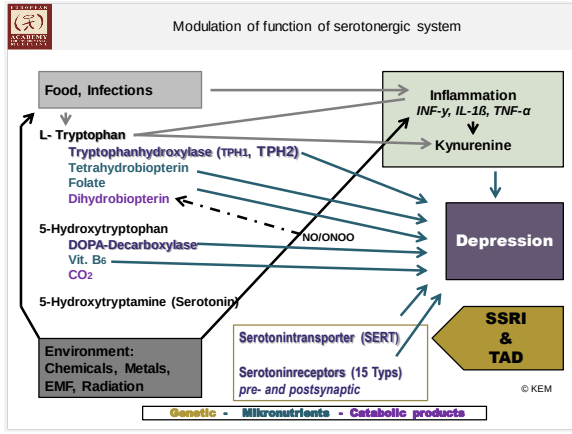


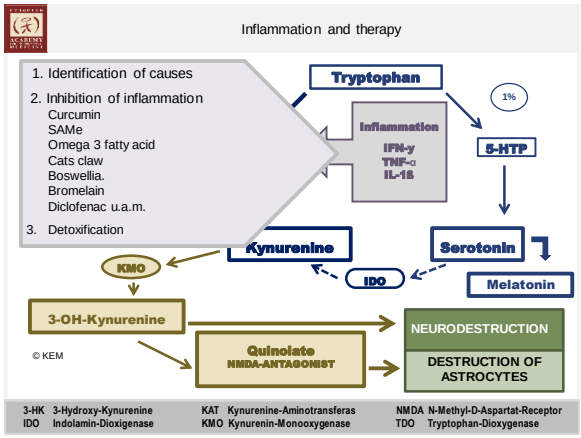
Inflammation and Depression

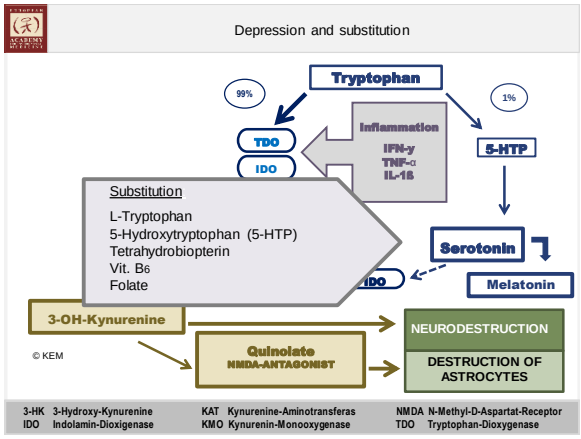


Modulation of function of serotonergic system



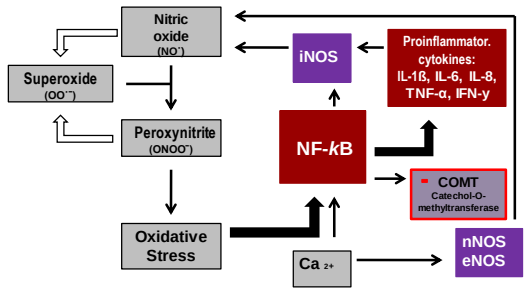

Modulation of function of serotonergic system
Food, Infections
L- Tryptophan
Tryptophanhydroxylase (TPH1, TPH2)
Tetrahydrobiopterin
Folate
Dihydrobiopterin
5-Hydroxytryptophan
DOPA-Decarboxylase
Vit. B6
CO2
5-Hydroxytryptamine (Serotonin)
Environment: Chemicals, Metals, EMF, Radiation
Inflammation
INF-y, IL-1ß, TNF-α
Kynurenine
NO/ONOO
Depression
SSRI & TAD
Serotonintransporter (SERT)
Serotoninreceptors (15 Typs)
pre- and postsynaptic
© KEM
Genetic - Mikronutrients - Catabolic products


Inflammation and therapy
1. Identification of causes
2. Inhibition of inflammation
Curcumin
SAMe
Omega 3 fatty acid
Cats claw
Boswellia.
Bromelain
Diclofenac u.a.m.
3. Detoxification
Tryptophan
1%
Inflammation
IFN-y
TNF-α
IL-1ß
5-HTP
Kynurenine
Serotonin
KMO
IDO
Melatonin
3-OH-Kynurenine
NEURODESTRUCTION
Quinolate
NMDA-ANTAGONIST
DESTRUCTION OF ASTROCYTES
© KEM
3-HK 3-Hydroxy-Kynurenine
IDO Indolamin-Dioxigenase
KAT Kynurenine-Aminotransferas
KMO Kynurenin-Monooxygenase
NMDA N-Methyl-D-Aspartat-Receptor
TDO Tryptophan-Dioxygenase


Depression and substitution
Tryptophan
99%
1%
TDO
IDO
Inflammation
IFN-y
TNF-α
IL-1ß
5-HTP
Substitution
L-Tryptophan
5-Hydroxytryptophan (5-HTP)
Tetrahydrobiopterin
Vit. B6
Folate
Serotonin
IDO
Melatonin
3-OH-Kynurenine
NEURODESTRUCTION
Quinolate
NMDA-ANTAGONIST
DESTRUCTION OF ASTROCYTES
© KEM
3-HK 3-Hydroxy-Kynurenine
IDO Indolamin-Dioxigenase
KAT Kynurenine-Aminotransferas
KMO Kynurenin-Monooxygenase
NMDA N-Methyl-D-Aspartat-Receptor
TDO Tryptophan-Dioxygenase

Circulus vitiosus – Inhibition of COMT

„Vicious cycle" n. M. Pall 2007



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iNOS=inducible Nitric Oxide Synthase ; nNOS=neural NOS; eNOS=endothelial NOS

What has changed?

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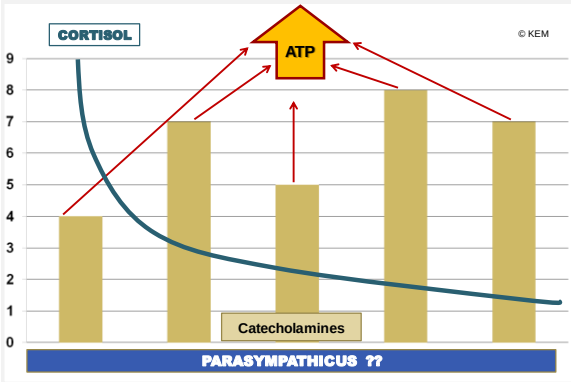
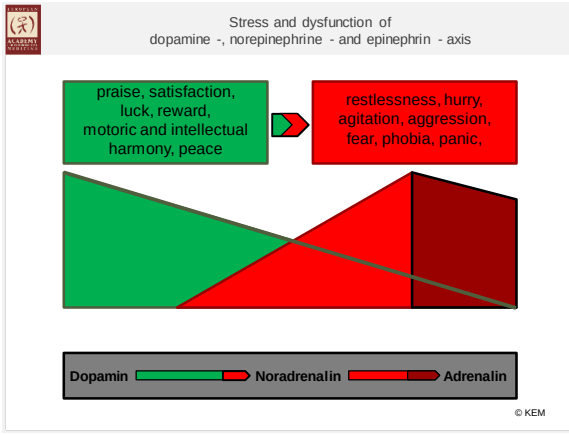
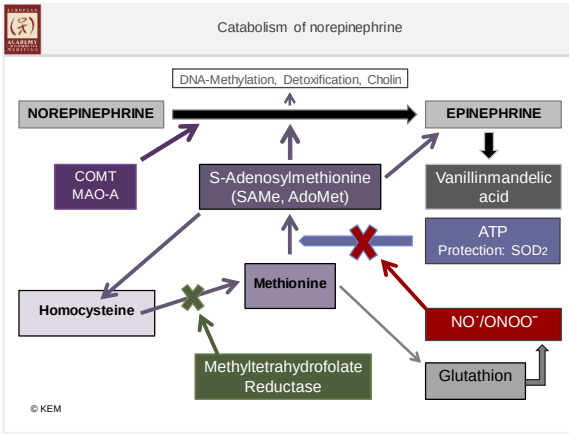
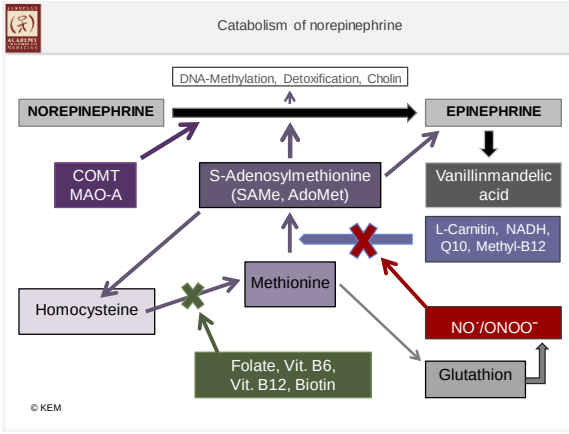
Catecholamines are dominating every days life

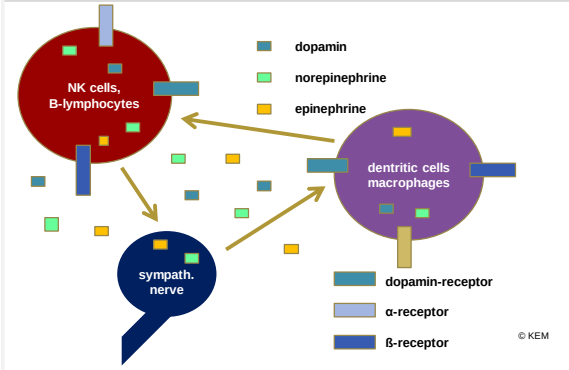



Stress and dysfunction of
dopamine -, norepinephrine - and epinephrin - axis
praise, satisfaction, luck, reward, motoric and intellectual harmony, peace
restlessness, hurry, agitation, aggression, fear, phobia, panic,
Dopamin
Noradrenalin
Adrenalin
© KEM

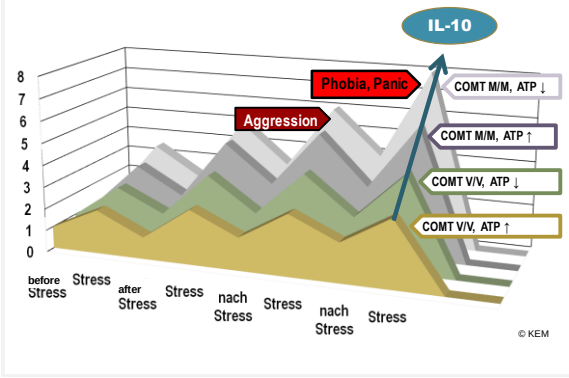

Catabolism of norepinephrine
DNA-Methylation, Detoxification, Cholin
NOREPINEPHRINE
EPINEPHRINE
COMT
MAO-A
S-Adenosylmethionine (SAMe, AdoMet)
Vanillinmandelic acid
ATP
Protection: SOD2
Homocysteine
Methionine
NO˙/ONOO⁻
Methyltetrahydrofolate Reductase
Glutathion
© KEM


Catabolism of norepinephrine
DNA-Methylation, Detoxification, Cholin
NOREPINEPHRINE
EPINEPHRINE
COMT
MAO-A
S-Adenosylmethionine (SAMe, AdoMet)
Vanillinmandelic acid
L-Carnitin, NADH, Q10, Methyl-B12
Homocysteine
Methionine
NO˙/ONOO⁻
Folate, Vit. B6, Vit. B12, Biotin
Glutathion
© KEM

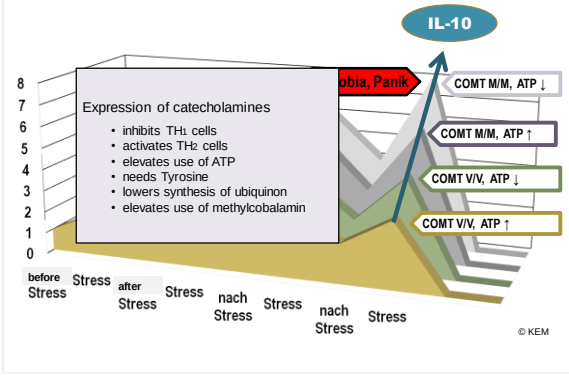
Secretion of catecholamines and receptor expression on immune cells - interaction with sympathetic nerve system



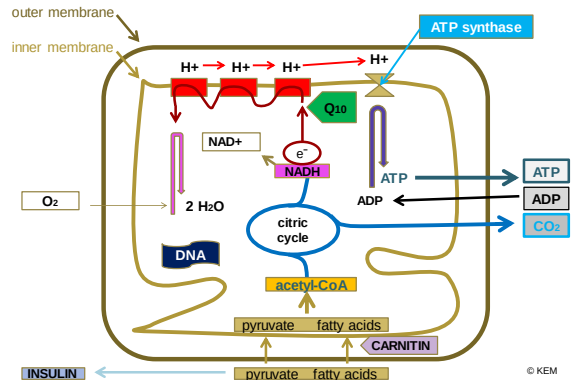
Stress reaction: COMT- polymorphism, ATP synthesis and immune function



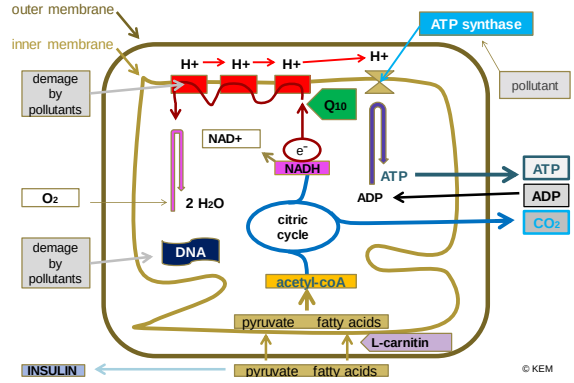
Stress reaction: COMT- polymorphism, ATP and immune function



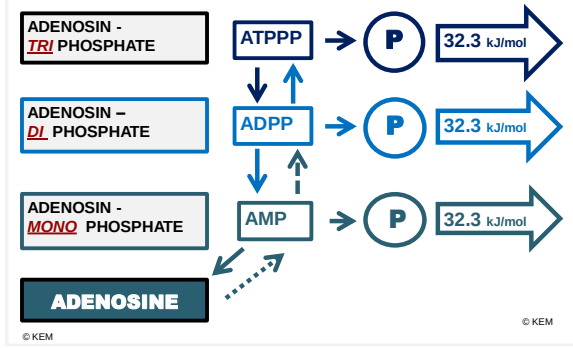
Function and structure of mitochondria

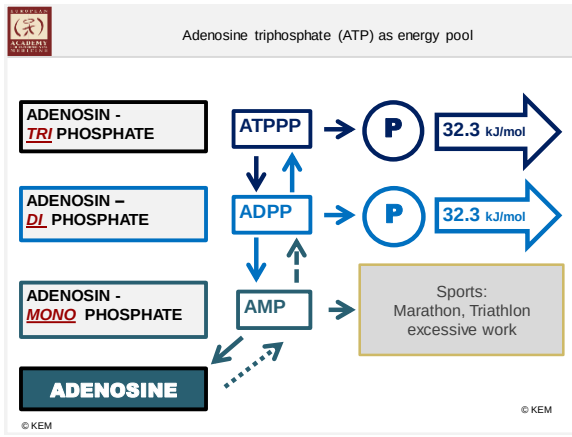


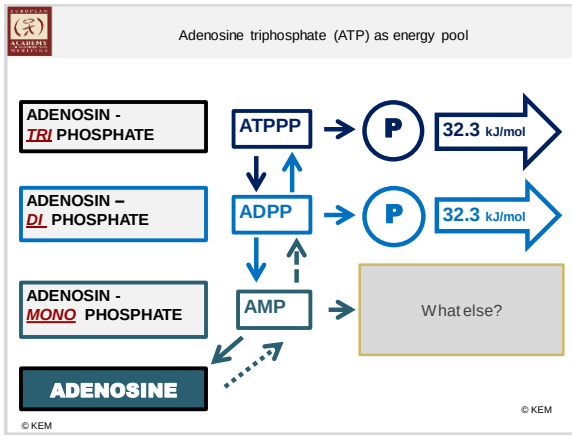
Damage of function and structure of mitochondria

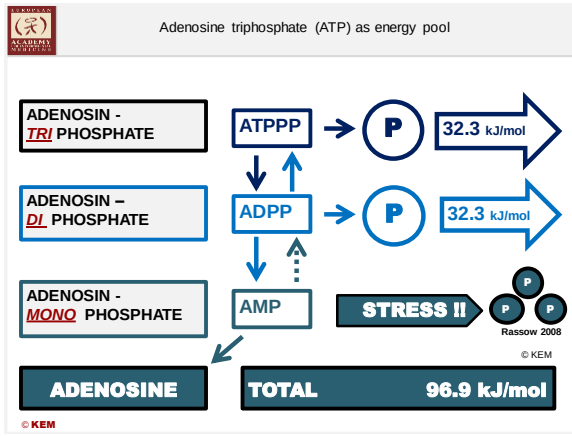


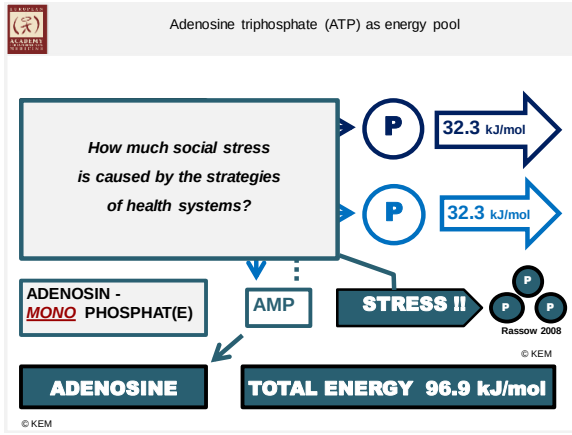
Adenosine triphosphate (ATP) as energy pool

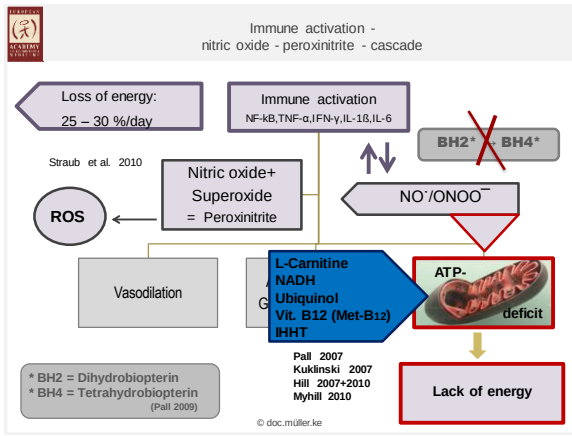


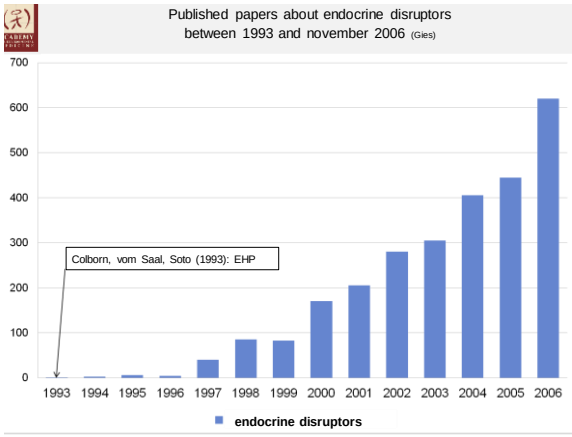

Adenosine triphosphate (ATP) as energy pool
ADENOSIN - TRI PHOSPHATE
ADENOSIN – DI PHOSPHATE
ADENOSIN - MONO PHOSPHATE
ADENOSINE
ATPPP
ADPP
AMP
P
32.3 kJ/mol
Sports: Marathon, Triathlon excessive work
© KEM
© KEM

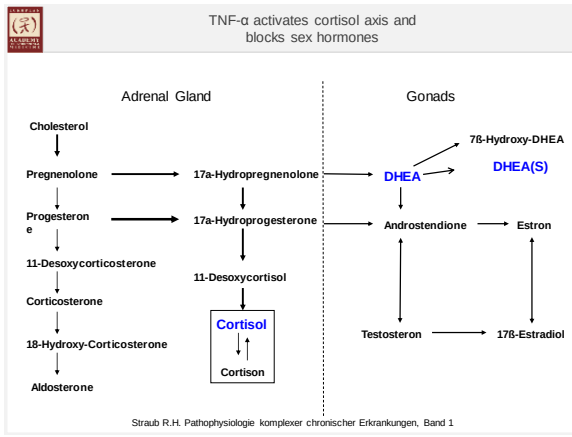

Adenosine triphosphate (ATP) as energy pool
ADENOSIN - TRI PHOSPHATE
ADENOSIN – DI PHOSPHATE
ADENOSIN - MONO PHOSPHATE
ADENOSINE
ATPPP
ADPP
AMP
P
32.3 kJ/mol
What else?
© KEM
© KEM

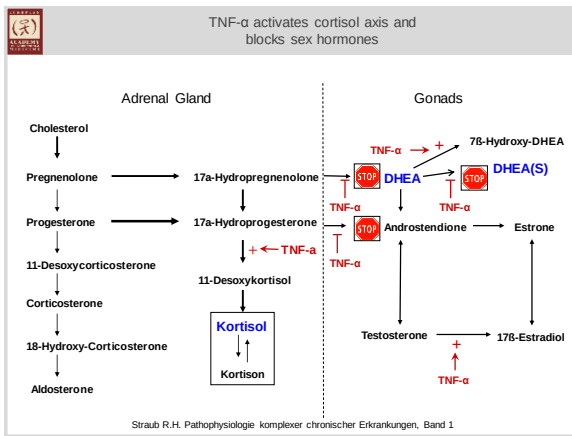

Adenosine triphosphate (ATP) as energy pool
ADENOSIN - TRI PHOSPHATE
ADENOSIN – DI PHOSPHATE
ADENOSIN - MONO PHOSPHATE
ADENOSINE
ATPPP
ADPP
AMP
P
32.3 kJ/mol
STRESS !!
Rassow 2008
© KEM
TOTAL 96.9 kJ/mol
© KEM

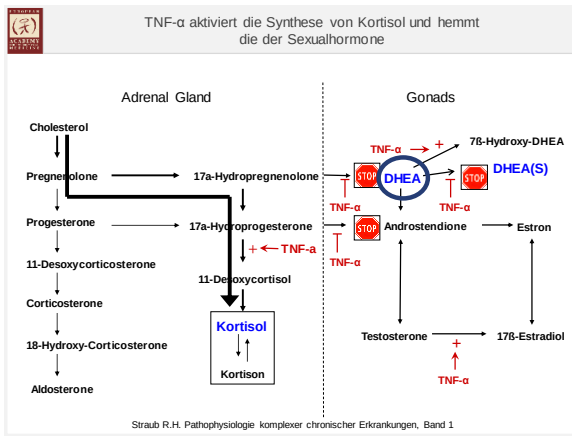

Adenosine triphosphate (ATP) as energy pool
How much social stress
is caused by the strategies
of health systems?
P
32.3 kJ/mol
P
32.3 kJ/mol
ADENOSIN -
MONO PHOSPHAT(E)
AMP
STRESS !!
P
P
P
Rassow 2008
© KEM
ADENOSINE
TOTAL ENERGY 96.9 kJ/mol
© KEM

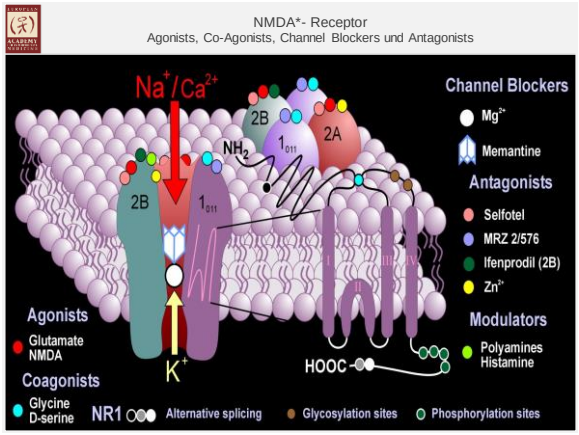

Immune activation -
nitric oxide - peroxinitrite - cascade
Loss of energy:
25 – 30 %/day
Immune activation
NF-kB,TNF-α,IFN-γ,IL-1ß,IL-6
BH2*
BH4*
Straub et al. 2010
Nitric oxide+
Superoxide
= Peroxinitrite
NO˙/ONOO⁻
ROS
Vasodilation
L-Carnitine
NADH
Ubiquinol
Vit. B12 (Met-B12)
IHHT
ATP-
deficit
Pall 2007
Kuklinski 2007
Hill 2007+2010
Myhill 2010
Lack of energy
* BH2 = Dihydrobiopterin
* BH4 = Tetrahydrobiopterin
(Pall 2009)
© doc.müller.ke

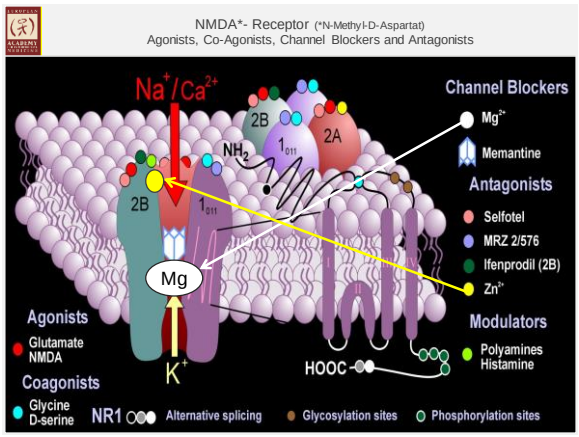

Published papers about endocrine disruptors
between 1993 and november 2006 (Gies)
700
600
500
400
300
200
100
0
Colborn, vom Saal, Soto (1993): EHP
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006
endocrine disruptors

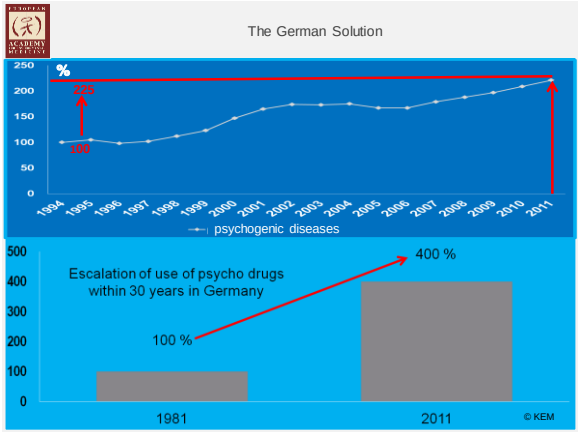

TNF-α activates cortisol axis and blocks sex hormones
Adrenal Gland
Gonads
Cholesterol
Pregnenolone
17a-Hydropregnenolone
DHEA
7ß-Hydroxy-DHEA
DHEA(S)
Progesteron e
17a-Hydroprogesterone
Androstendione
Estron
11-Desoxycorticosterone
11-Desoxycortisol
Corticosterone
Cortisol
Cortison
18-Hydroxy-Corticosterone
Testosteron
17ß-Estradiol
Aldosterone
Straub R.H. Pathophysiologie komplexer chronischer Erkrankungen, Band 1


TNF-α activates cortisol axis and blocks sex hormones
Adrenal Gland
Gonads
Cholesterol
TNF-α
7ß-Hydroxy-DHEA
Pregnenolone
17a-Hydropregnenolone
DHEA
DHEA(S)
STOP
Progesterone
17a-Hydroprogesterone
Androstendione
Estrone
+ TNF-α
11-Desoxycorticosterone
11-Desoxykortisol
Corticosterone
Kortisol
Kortison
18-Hydroxy-Corticosterone
Testosterone
17ß-Estradiol
Aldosterone
Straub R.H. Pathophysiologie komplexer chronischer Erkrankungen, Band 1


TNF-α aktiviert die Synthese von Kortisol und hemmt die der Sexualhormone
Adrenal Gland
Gonads
Cholesterol
TNF-α
7ß-Hydroxy-DHEA
Pregnenolone
17a-Hydropregnenolone
DHEA
DHEA(S)
STOP
Progesterone
17a-Hydroprogesterone
Androstendione
Estron
+ TNF-α
11-Desoxycorticosterone
11-Desoxycortisol
Corticosterone
Kortisol
Kortison
18-Hydroxy-Corticosterone
Testosterone
17ß-Estradiol
Aldosterone
Straub R.H. Pathophysiologie komplexer chronischer Erkrankungen, Band 1


NMDA*- Receptor
Agonists, Co-Agonists, Channel Blockers und Antagonists
Na+/Ca2+
2B
2A
NH2
1011
2B
1011
K+
HOOC
Channel Blockers
Mg2+
Memantine
Antagonists
Selfotel
MRZ 2/576
Ifenprodil (2B)
Zn2+
Modulators
Polyamines
Histamine
Agonists
Glutamate
NMDA
Coagonists
Glycine
D-serine
NR1
Alternative splicing
Glycosylation sites
Phosphorylation sites


NMDA*- Receptor (*N-Methyl-D-Aspartat)
Agonists, Co-Agonists, Channel Blockers and Antagonists
Na+/Ca2+
2B
2A
NH2
1011
2B
1011
Mg
K+
HOOC
Channel Blockers
Mg2+
Memantine
Antagonists
Selfotel
MRZ 2/576
Ifenprodil (2B)
Zn2+
Modulators
Polyamines
Histamine
Agonists
Glutamate
NMDA
Coagonists
Glycine
D-serine
NR1
Alternative splicing
Glycosylation sites
Phosphorylation sites


The German Solution
%
225
100
250
200
150
100
50
0
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
psychogenic diseases
500
400
300
200
100
0
Escalation of use of psycho drugs
within 30 years in Germany
400 %
100 %
1981
2011
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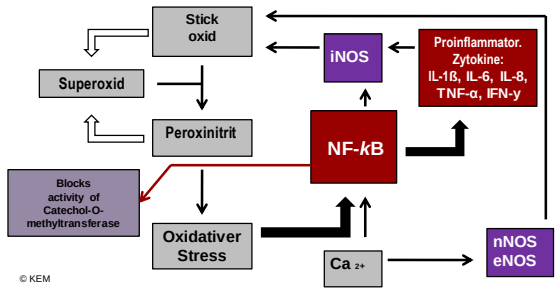
EUROPEAN ACADEMY FOR ENVIRONMENTAL MEDICINE

END

Circulus vitiosus – stress regulaion

„Vicious cycle" n. M. Pall 2007



iNOS=induzierbare; nNOS=neurogene; eNOS=endotheliale Stickoxidsynthase